

BHIVA guidelines for the treatment of HIV-1 positive adults with antiretroviral therapy 2012

30th April 2012

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1. Introduction

1.1 Scope and purpose

The overall purpose of these guidelines is to provide guidance on best clinical practice in the treatment and management of adults with HIV infection with antiretroviral therapy (ART). The scope includes guidance on the initiation of ART in those previously naïve to therapy, support of patients on treatment, management of patients experiencing virological failure and recommendations in specific patient populations where other factors need to be taken into consideration. The guidelines are aimed at clinical professionals directly involved with and responsible for the care of adults with HIV infection and at community advocates responsible for promoting the best interests and care of HIV positive adults. They should be read in conjunction with other published BHIVA guidelines

1.2 Methodology

1.2.1 Guideline development process

BHIVA revised and updated the association's guideline development manual in 2011 [1]. BHIVA has adopted the modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for the assessment, evaluation and grading of evidence and the development of recommendations [2,3]. Full details of the guideline development process including conflict of interest policy are outlined in the manual.

The scope, purpose and guideline topics were agreed by the Writing Group. Questions concerning each guideline topic were drafted and a systematic literature review undertaken by an information scientist. Details of the search questions and strategy (including the definition of populations, interventions and outcomes) are outlined in Appendix 2. BHIVA adult ART guidelines were last published in 2008 [4]. For the 2012 guidelines the literature search dates were 1st January 2008 to 16th September 2011 and included Medline, Embase and the Cochrane library. Abstracts from selected conferences (see Appendix 2) were searched between 1st January 2009 and 16th September 2011. For each topic and health care question, evidence was identified and evaluated by Writing Group members with expertise in the field. Using the modified GRADE system (Appendix 1), panel members were responsible for assessing and grading the quality of evidence for predefined outcomes across studies and developing and grading the strength of recommendations. An important aspect of evaluating evidence is an understanding of the design and analysis of clinical trials including the use of surrogate marker data.

For a number of questions, GRADE evidence profile and summary of findings tables were constructed, using predefined and rated treatment outcomes (Appendix 3), to help achieve consensus for key recommendations and aid transparency of the process. Prior to final approval by the Writing Group, the guidelines were published on line for public consultation and external peer review commissioned.

1.2.2 Patient involvement

BHIVA views the involvement of patient and community representatives in the guideline development process as essential. The Writing Group included two patient representatives appointed through the UK HIV Community Advisory Board (UK CAB) who were involved in all aspects of the guideline development process. In addition two meetings with patients and community representatives were held to discuss and receive feedback and comment on the proposed guideline recommendations. The first was held prior to the Writing Group's consensus meeting and the second as part of the public consultation process.

1.2.3 GRADE

The GRADE Working Group [3] has developed an approach to grading evidence that moves away from initial reliance on study design to consider the overall quality of evidence across outcomes. BHIVA has adopted the modified GRADE system for the association's guideline development.

The advantages of the modified GRADE system are: (i) the grading system provides an informative, transparent summary for clinicians, patients and policy makers by combining an explicit evaluation of the strength of the recommendation with a judgment of the quality of the evidence for each recommendation; (ii) the two-level grading system of recommendations has the merit of simplicity and provides clear direction to patients, clinicians and policy makers.

A Grade 1 recommendation is a strong recommendation to do (or not do) something, where the benefits clearly outweigh the risks (or vice versa) for most, if not all patients. Most clinicians and patients should and would want to follow a strong recommendation unless there is a clear rationale for an alternative approach. A strong recommendation usually starts with the standard wording 'we recommend'.

A Grade 2 recommendation is a weaker or conditional recommendation, where the risks and benefits are more closely balanced or are more uncertain. Most clinicians and patients would want to follow a weak or conditional recommendation but many would not. Alternative approaches or strategies may be reasonable depending on the individual patient's circumstances, preferences and values. A weak or conditional recommendation usually starts with the standard wording 'we suggest'.

The strength of a recommendation is determined not only by the quality of evidence for defined outcomes but also the balance between desirable and undesirable effects of a treatment or intervention, differences in values and preferences and where appropriate resource use. Each recommendation concerns a defined target population and is actionable.

The quality of evidence is graded from A to D and for the purpose of these guidelines is defined as the following:

Grade A evidence means high-quality evidence that comes from consistent results from well-performed randomised controlled trials (RCTs), or overwhelming evidence of some other sort (such as well-executed observational studies with consistent strong effects and exclusion of all potential source of bias). Grade A implies confidence that the true effect lies close to the estimate of the effect.

Grade B evidence means moderate-quality evidence from randomised trials that suffer from serious flaws in conduct, inconsistency, indirectness, imprecise estimates, reporting bias, or some combination of these limitations, or from other study designs with special strengths such as observational studies with consistent effects and exclusion of most potential source of bias.

Grade C evidence means low-quality evidence from controlled trials with several very serious limitations or observational studies with limited evidence on effects and exclusion of most potential source of bias.

Grade D evidence on the other hand is based only on case studies, expert judgment or observational studies with inconsistent effects and a potential for substantial bias, such that there is likely to be little confidence in the effect estimate.

1.2.4 Good practice points

In addition to graded recommendations, the BHIVA Writing Group has also included good practice points (GPP), which are recommendations based on the clinical judgment and experience of the working group. GPPs emphasise an area of important clinical practice for which there is not, nor is there likely to be, any significant research evidence. They address an aspect of treatment and care that is regarded as such sound clinical practice that health care professionals are unlikely to question it and where the alternative recommendation is deemed unacceptable. It must be emphasised that GPPs are not an alternative to evidence-based recommendations.

1.2.5 Dissemination and implementation

The following measures have/will be undertaken to disseminate and aid implementation of the guidelines:

- E-publication on the BHIVA website and the journal *HIV Medicine*
- Publication in *HIV Medicine*
- Shortened version detailing concise summary of recommendations
- E-learning module accredited for CME
- Educational slide set to support local and regional educational meetings
- National BHIVA audit programme

1.2.6 Guideline updates and date of next review

The guidelines will be next fully updated and revised in 2014. The Writing Group will however continue to meet regularly to consider new information from high quality studies and publish amendments and addendums to the current recommendations prior to the full revision date where this is thought to be clinically important to ensure continued best clinical practice.

1.3 Treatment aims

The primary aim of ART is the prevention of the mortality and morbidity associated with chronic HIV infection at low cost of drug toxicity. Treatment should improve the physical and psychological well being of people living with HIV infection. The effectiveness and tolerability of ART has improved significantly over the last 15 years, with the overwhelming majority of patients attending HIV services in the UK and receiving ART experiencing long-term virological suppression and good treatment outcomes [5] which compare very favourably with other developed countries.

Recent data has shown that the life expectancy in the UK of someone living with HIV infection has improved significantly over recent years but is still about 13 years less than that of the UK population [6]. For someone aged 20 years starting ART, life expectancy increased from 30.0 to 45.8 years from 1996–9 to 2006–8. The impact of starting ART late is large with up to 15 years of reduced life expectancy if ART is started later than the current BHIVA guidelines recommend. Other data has shown for HIV positive men who have sex with men (MSM) living in a developed country with extensive access to HIV care and assuming a high rate of HIV diagnosis the projected life expectancy was 75 years [7]. The authors concluded that the greatest risk of excess mortality is due to delays in HIV diagnosis. Decreasing late diagnosis, starting ART earlier at recommended CD4 count levels, maintaining patients in care and reducing long-term drug toxicity and non-AIDS co-morbidities are crucial to further improving life expectancy and the well being of people living with HIV infection.

A further aim of treatment is the reduction in the sexual transmission of HIV and for some patients may be the primary aim. The use of ART to prevent mother to child transmission is universally accepted and best practice is addressed in the BHIVA pregnancy guidelines. Recently, the size of the effect of ART on reducing the risk of sexual transmission of HIV has been estimated at greater than 95% [8,9]. At a population level, ART may be potentially important in reducing the incidence of HIV infection. ART is usually started for the health benefit of the individual, but in certain circumstances it may be beneficial to start ART to primarily reduce the risk of onward sexual transmission of HIV.

1.4 Resource use

ART is extremely cost effective and compares favourably with the cost of management of many other chronic diseases. Estimates of the cost effectiveness of antiretroviral therapy have been assessed in studies in North America and Europe [10–12]. Their findings have been consistent with an estimated incremental cost effectiveness ratio of about US\$20,000 per quality adjusted life year for combination antiretroviral therapy compared to no therapy based on drug costs and treatment patterns in the USA and Europe [13].

The number of people living with HIV in the UK continues to increase and by the end of 2010 was estimated to be 91,500 of whom 24% were undiagnosed. Of those diagnosed, 69,400 accessed HIV services in 2010 of whom 82% were on ART [5]. With ongoing HIV transmission, increased HIV testing and a reduction in the undiagnosed fraction the number of people diagnosed with HIV and accessing HIV services will continue to increase. It has been estimated that the annual population treatment and care costs rose from £104 million in 1997 to £483 million in 2006, rising to a projected annual cost of £721 million in 2013 [14]. It is likely this

estimated projected cost is an overestimate due to various factors including earlier diagnosis and a lower proportion of patients with symptoms. However in the current economic climate containing and reducing annual costs without affecting the current high standards of care and treatment outcomes will be an immense challenge to commissioners, health care professionals and patients alike. A collaborative approach is required.

In the UK, higher annual treatment and care costs have been associated with late diagnosis and initiation of ART at lower CD4 counts than the BHIVA guidelines recommend [15,16]. In addition to earlier diagnosis and initiation of ART, reducing inpatient episodes, decreasing drug toxicity, preventing HIV-associated co-morbidities and innovations in models of care are likely to have a beneficial effect on annual costs. However the cost of antiretroviral drugs remains the major factor contributing to treatment and care costs. With the future availability of generic drugs and the introduction of a standard tariff for HIV services (in England) clinicians and patients will be faced with difficult choices about the value and benefit of different antiretroviral drugs.

The BHIVA Writing Group recognises that cost of drugs is an important issue in the choice of ART regimens. There is limited cost effectiveness data in the UK comparing different antiretroviral drugs and for this reason the Writing Group did not include cost effectiveness as an outcome in ART comparisons. However the Writing Group believes that decreasing the risk of virological failure, drug resistance and drug-associated toxicity are likely to have a beneficial impact on long-term cost effectiveness and resource use. In the setting of equivalent virological efficacy, determining the acceptable threshold at which differences in the risk of toxicity, tolerability and convenience outweigh differences in resource use and cost will be important. These thresholds may differ amongst clinicians and patients alike.

In developing the recommendations in these guidelines the Writing Group has taken into account differences in critical treatment outcomes between different drug regimens in determining preferred and alternative treatment regimens. The Writing Group recognises and supports that commissioning arrangements and local drug costs will and should influence ART choice where outcomes, across a range of clinical measures, are equivalent between individual drugs in the treatment of defined patient populations. The Writing Group however believes that reducing treatment costs should not be at the cost of an increased risk of poorer treatment outcomes and quality of care, not least as these are likely to have a detrimental impact on long-term cost.

1.5 Implications for research

In reviewing quality of evidence, guidelines will identify areas of treatment and care where there is either an absence of evidence or limited confidence in the size of effect to influence choice of treatments or determine treatment and management strategies. For this reason it is not the intention of these guidelines to stifle clinical research but help promote continued research with the aim to further improve clinical care and treatment outcomes. The Writing Group supports the development and provision of HIV clinical trials within the UK and participation in a clinical trial should be open and offered to patients where appropriate.

1.6 References

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2. Recommendations and auditable outcomes

2.1 Recommendations (GRADE)

Patient involvement in decision making (Section 3)

<ul style="list-style-type: none"> • 3 . 1 	<ul style="list-style-type: none"> • We recommend patients are given the opportunity to be involved in making decisions about their treatment. 	<ul style="list-style-type: none"> • GPP
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When to start (Section 4)

Chronic infection

<ul style="list-style-type: none"> • 4 . 1 	<ul style="list-style-type: none"> • We recommend patients with chronic infection start ART if the CD4 count is ≤ 350 cells/μL: it is important not to delay treatment initiation if the CD4 cell count is close to this threshold. 	<ul style="list-style-type: none"> • 1A
<ul style="list-style-type: none"> • 	<ul style="list-style-type: none"> • We recommend patients with the following conditions start ART: • AIDS diagnosis (e.g. Kaposi's sarcoma) irrespective of CD4 cell count. • HIV-related co-morbidity including HIVAN, ITP, symptomatic HIV-associated neurocognitive disorders irrespective of CD4 cell count. • Co-infection with hepatitis B virus if the CD4 count is ≤ 500 cells/μL (see Section 8.2.2 Hepatitis B) • Co-infection with hepatitis C virus if the CD4 count is ≤ 500 cells/μL (Section 8.2.3 Hepatitis C) • Non-AIDS defining malignancies requiring immunosuppressive radiotherapy or chemotherapy (Section 8.3.2 When to start ART: non-AIDS-defining malignancies) 	<ul style="list-style-type: none"> • 1A • 1C • 1B • 1C • 1C
<ul style="list-style-type: none"> • 	<ul style="list-style-type: none"> • We suggest patients with the following conditions start ART: • Co-infection with hepatitis B virus if the CD4 count is > 500 cells/μL and treatment of hepatitis B is indicated (see Section 8.2.2 Hepatitis B) 	<ul style="list-style-type: none"> • 2B

Patients presenting with AIDS or a major infection

• 4 . 2	• We recommend patients presenting with an AIDS-defining infection, or with a serious bacterial infection and a CD4 count <200 cells/μL, start ART within 2 weeks of initiation of specific antimicrobial chemotherapy.	• 1B
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Treatment of primary HIV infection

• 4 . 3	<ul style="list-style-type: none"> We recommend patients presenting with primary HIV infection and meeting any one of the following criteria start ART: Neurological involvement Any AIDS-defining illness Confirmed CD4 cell count <350 cells/μL 	<ul style="list-style-type: none"> 1D 1A • 1C
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Treatment to reduce transmission

• 4 . 4	• We recommend the evidence that treatment with ART lowers the risk of transmission is discussed with all patients, and an assessment of the current risk of transmission to others is made at the time of this discussion.	• GPP
•	• We recommend following discussion, if a patient with a CD4 count above 350 cell/μL wishes to start ART to reduce the risk of transmission to partners, this decision is respected and ART is started.	• GPP

What to start (Section 5)

5.1	We recommend therapy naïve patients start ART containing two NRTIs and either a ritonavir-boosted protease inhibitor, or a NNRTI or an integrase inhibitor	1A									
	Summary recommendations for choice of ART:										
	<table border="1"> <thead> <tr> <th></th> <th>PREFERRED</th> <th>ALTERNATIVE</th> </tr> </thead> <tbody> <tr> <td>NRTI backbone</td> <td>Tenofovir and emtricitabine</td> <td>Abacavir and lamivudine^{1,3}</td> </tr> <tr> <td>Third Agent</td> <td>Atazanavir/ritonavir Darunavir/ritonavir Efavirenz</td> <td>Lopinavir/ritonavir Fosamprenavir/ritonavir Nevirapine²</td> </tr> </tbody> </table>		PREFERRED	ALTERNATIVE	NRTI backbone	Tenofovir and emtricitabine	Abacavir and lamivudine ^{1,3}	Third Agent	Atazanavir/ritonavir Darunavir/ritonavir Efavirenz	Lopinavir/ritonavir Fosamprenavir/ritonavir Nevirapine ²	
	PREFERRED	ALTERNATIVE									
NRTI backbone	Tenofovir and emtricitabine	Abacavir and lamivudine ^{1,3}									
Third Agent	Atazanavir/ritonavir Darunavir/ritonavir Efavirenz	Lopinavir/ritonavir Fosamprenavir/ritonavir Nevirapine ²									

	Raltegravir	Rilpivirine ³	
<p>Abacavir is contraindicated if HLA B*5701 positive</p> <p>Nevirapine is contra-indicated if baseline CD4 greater than 250/400 cells/μL in women/men.</p> <p>Use recommended only if baseline viral load less than 100,000 copies/ml: Rilpivirine as a third agent, abacavir + lamivudine as NRTI back bone</p> <p>The presence or future risk of co-morbidities and potential adverse effects need to be considered in the choice of antiretroviral drugs in individual patients.</p>			

Which NRTI backbone

5.3	We recommend therapy naïve patients start combination ART containing tenofovir and emtricitabine as the NRTI backbone.	1A
	We suggest abacavir and lamivudine is an acceptable alternative NRTI backbone in therapy naïve patients who prior to starting ART have baseline viral load of \leq 100,000 copies/ml	2A
	Abacavir must not be used in patients who are HLAB*5701 positive.	1A

Which third agent?

5.4	We recommend therapy-naïve patients start combination ART containing either atazanavir/ritonavir, or darunavir/ritonavir, or efavirenz, or raltegravir as the third agent. (1A)	1A
	We suggest in therapy-naïve patients lopinavir/ritonavir and fosamprenavir/ritonavir are acceptable alternative protease inhibitors, and nevirapine and rilpivirine are acceptable alternative NNRTIs .	2A

Novel ART strategies

5.5	We recommend against the use of protease inhibitor monotherapy as initial therapy for treatment-naïve patients.	1C
	We recommend against the use of protease inhibitor-based dual antiretroviral therapy with a single NRTI, NNRTI, CCR5 receptor antagonist, or integrase inhibitor as an initial therapy for treatment-naïve patients.	1C

Supporting patients on therapy (Section 6)

Adherence

Interventions to increase adherence to treatment

6.1.1	We recommend adherence and potential barriers to it are assessed and discussed with the patient whenever ART is prescribed or dispensed	GPP
	We recommend adherence support should address both perceptual barriers (e.g. beliefs and preferences) and/ or practical barriers (e.g. limitations in capacity and resources) to adherence	GPP

Pharmacology

Drug interactions

6.2.1	We recommend that potential adverse pharmacokinetic interactions between antiretroviral drugs and other concomitant medications are checked before administration (with tools such as www.hiv-druginteractions.org)	GPP
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Therapeutic drug monitoring (TDM)

6.2.2	We recommend against the unselected use of TDM	GPP
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Stopping therapy: pharmacological considerations

6.2.3	We recommend patients stopping ART containing a NNRTI in combination with a NRTI backbone replace all drugs with a protease inhibitor (lopinavir/ritonavir) for four weeks.	1C
	We recommend patients stopping a PI-containing regimen stop all drugs simultaneously and no replacement is required (1C)	1C

Switching ART in virological suppression

Switching ARVs in combination ART

6.3.2	We recommend in patients on suppressive ART regimens, consideration is given to differences in side effect profile, drug–drug interactions and drug resistance patterns before switching any ARV component.	GPP
	We recommend in patients with prior NRTI resistance mutations, against switching a ritonavir boosted PI to either a NNRTI or an INI as the third agent.	1B

Protease inhibitor monotherapy

6.3.3	We recommend continuing standard combination ART as the maintenance strategy in virologically suppressed patients (1C). There is insufficient data to recommend PI/r monotherapy in this clinical situation.	1C
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Stopping therapy

6.4	We recommend against treatment interruption or intermittent therapy in patients stable on a virally suppressive ART regimen	1A
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Managing virological failure (Section 7)

Blips, low level viraemia and virological failure

7.2	In patients on ART: A single viral load of 50–400 copies/ml preceded and followed by an undetectable viral load is usually not a cause for clinical concern We recommend a single viral load >400 copies/ml is investigated further, as it is indicative of virological failure We recommend in the context of repeated viral blips, resistance testing is attempted	GPP 1C 1D
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Patients with no or limited drug resistance

7.3	We recommend patients experiencing virological failure on first-line ART with WT virus at baseline and without emergent resistance mutations at failure, switch to a PI/r-based combination ART regimen.	1C
	We recommend patients experiencing virological failure on first-line ART with WT virus at baseline and limited emergent resistance mutations (including two-class NRTI/NNRTI) at failure, switch to a new PI/r-based regimen with the	1C

	addition of at least one preferably two active drugs	
•	We recommend patients experiencing virological failure on first-line PI/r – two NRTI based regimen with major protease mutations, switch to a new active PI/r with the addition of at least one, preferably two active agents of which one has a novel mechanism of action	1C
•	We recommend against switching a PI/r to raltegravir or a NNRTI as the third agent in patients with historical or existing RT mutations associated with NRTI resistance or past virological failure on NRTIs	1B

Patients with triple-class (NNRTI, NRTI, PI) virological failure with or without triple-class resistance

7.4	We recommend patients with persistent viraemia and with limited options to construct a fully suppressive regimen are discussed/referred for expert advice (or through virtual clinic referral).	GPP
	We recommend patients with triple-class resistance switch to a new ART regimen containing at least two and preferably three fully active agents with at least one active PI/r such as darunavir/ritonavir or tipranavir/ritonavir and one agent with a novel mechanism (CCR5 receptor antagonist or integrase/fusion inhibitor) with etravirine an option based on viral susceptibility	1C

Patients with limited or no therapeutic options when a fully viral suppressive regimen cannot be constructed

7.5	We recommend accessing newer agents through research trials, expanded access and named patient programmes	GPP
	We suggest continuing/commencing NRTIs as this may contribute partial ARV activity to a regimen, despite drug resistance	2C
	We recommend the use of lamivudine or emtricitabine to maintain a mutation at codon position 184 of the reverse transcriptase gene .	1B
	We recommend against discontinuing or interrupting ART	1D
	We recommend against adding a single, fully active ARV because of the risk of further resistance	1D
	We recommend against the use of maraviroc to increase the CD4 count in the absence of CCR5 tropic virus.	1C

ART in specific populations (Section 8)
HIV with tuberculosis co-infection: when to start

8.1.1.	Timing of initiation of antiretroviral therapy during TB therapy		1B
	CD4 count cells/ μ L	When to start HAART	
	<100	As soon as practical within two weeks after starting TB therapy	
	100–350	As soon as practical, but can wait until after completing two months TB treatment, especially when there are difficulties with drug interactions, adherence and toxicities	
	>350	At physician's discretion	

HIV with tuberculosis: what to start

8.1.2.	We recommend efavirenz in combination with tenofovir and emtricitabine as first-line antiretroviral therapy in TB/HIV co-infection	1C
	We recommend that when rifampicin is used with efavirenz in patients over 60kg, the efavirenz dose is increased to 800mg daily. Standard doses of efavirenz are recommended if the patient weighs less than 60kg	1C
	We recommend that rifampicin is not used with nevirapine or ritonavir-boosted protease inhibitors	1C
	We recommend that where effective ART necessitates the use of ritonavir-boosted protease inhibitors that rifabutin is used instead of rifampicin	1C

HIV and viral hepatitis co-infection: summary of when to start recommendations

CD4 cells/ μ L	HBV requiring Rx ¹	HBV not requiring Rx	HCV with immediate plan to start HCV Rx ¹	HCV with no immediate plan to start HCV Rx
>500	Start ART in some patients (2C) (Include tenofovir and emtricitabine)	Defer ART	Defer ART	Defer ART
\leq 500	Start ART (1B)	Start ART (1B)	350–500	Start ART (1C)

	(Include tenofovir and emtricitabine)	(Include tenofovir and emtricitabine)	Start ART after HCV treatment commenced (1C) <350 Start ART before HCV treatment (1B). Discuss with HIV and viral hepatitis specialist	
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¹See viral hepatitis Guidelines for indications to treat hepatitis B and C

Hepatitis B: when to start

8.2.2.1	We recommend patients with HIV and hepatitis B virus co-infection who have a CD4 count between 350–500 cells/ μ L start ART	1C
	We suggest patients with HIV and hepatitis B virus co-infection who have a CD4 count >500 cells/ μ L and who require treatment for their hepatitis B start ART	2C

Hepatitis B: what to start

8.2.2.2	We recommend patients with HIV and hepatitis B virus co-infection who start ART include tenofovir and emtricitabine as part of their ART regimen, if there are no contraindications for either drug	1A
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Hepatitis C: when to start ART

8.2.3.1	We recommend patients with HIV and hepatitis C virus co-infection be assessed for HCV treatment (GPP)	GPP
	We recommend patients with HIV and hepatitis C virus co-infection and CD4 count between 350-500 cells/ μ L start ART: (i) immediately if HCV treatment is deferred, (ii) after initiation of HCV treatment if this is starting immediately. ¹	1C
	We recommend patients with HIV and hepatitis C virus co-infection and CD4 count <350 cells/ μ L start ART before HCV treatment	1B

Hepatitis C: what to start

8.2.3.2	We recommend that potential pharmacokinetic interactions between antiretrovirals and anti-hepatitis agents are checked prior to administration (with tools such as: http://www.hep-druginteractions.org)	GPP
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HIV-related cancers: when to start

8.3.1.	We recommend starting ART in HIV positive patients with Kaposi sarcoma (1A
	We recommend starting ART in HIV positive patients with non-Hodgkin lymphoma	1B
	We suggest starting ART in HIV positive patients with cervical cancer	1C
	We recommend starting ART in HIV positive patients who are commencing radiotherapy or chemotherapy for cervical cancer	1D
8.3.2	We suggest starting ART in HIV positive patients with non-AIDS defining malignancies	2C
	We recommend starting ART in HIV positive patients who are commencing immunosuppressive radiotherapy or chemotherapy for non-AIDS defining malignancies	1C

HIV related cancers: what to start

8.3.3	We recommend that potential pharmacokinetic interactions between antiretrovirals and systemic anticancer therapy are checked prior to administration (with tools such as: http://www.hiv-druginteractions.org)	GPP
	We suggest avoiding ritonavir-boosted ART in HIV positive patients who are to receive cytotoxic chemotherapy agents that are metabolised by the CYP450 enzyme system	2C
	We recommend against the use of atazanavir in HIV positive patients who are to receive irinotecan	1C
	We suggest avoiding antiretroviral agents in HIV positive patients who are to receive cytotoxic chemotherapy agents that have overlapping toxicities	2C

HIV-associated neurocognitive impairment: when to start

8.4.2	We recommend patients with symptomatic HIV-associated neurocognitive	1C
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	disorders start ART irrespective of CD4+ lymphocyte count	
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HIV-associated neurocognitive impairment: what to start

8.4.3	We recommend patients with HIV-associated NC disorders start standard combination ART regimens.	1C
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HIV-associated neurocognitive impairment: modification of antiretroviral therapy

8.4.4	<p>In patients with ongoing or worsening NC impairment despite ART we recommend the following best practice management</p> <ul style="list-style-type: none"> • Best practice management should include • Re-assessment for confounding conditions • Assessment of CSF HIV RNA, CSF HIV genotropism and genotyping of CSF HIV RNA • In subjects with detectable CSF HIV RNA, modifications to antiretroviral therapy should be based on plasma and CSF genotypic and genotropism results 	<ul style="list-style-type: none"> • GPP
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Chronic kidney disease: when to start

8.5.1	We recommend patients with HIV-associated nephropathy (HIVAN) start ART immediately irrespective of CD4 cell count	1C
	We recommend patients with end-stage kidney disease who are suitable candidates for renal transplantation start ART irrespective of CD4 cell count (1C)	1C

Chronic kidney disease: what to start

8.5.2	We recommend against the use of antiretroviral drugs that are potentially nephrotoxic, in patients with stages 3–5 CKD if acceptable alternative antiretroviral agents are available.	GPP
	We recommend dose adjustment of renally cleared antiretroviral drugs in patients with reduced renal function.	GPP

Cardiovascular disease: what to start

8.6.4	We suggest avoiding: abacavir, fosamprenavir/ritonavir and	2C
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	lopinavir/ritonavir in patients with a high CVD risk, if acceptable alternative antiretroviral drugs are available.	
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Women: when to start

8.7.2	We recommend therapy naïve HIV positive women who are not pregnant start ART according to the same indicators as in men (See Section 3: When to Start)	1A
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Women: what to start

8.7.3	We recommend therapy naïve HIV positive women start ART containing two NRTIs and either a ritonavir-boosted protease inhibitor, or a NNRTI or an integrase inhibitor, as per therapy naïve HIV positive men.	1A
	We recommend therapy naïve HIV positive women start ART with preferred or alternative NRTI backbone and third agent as per therapy naïve HIV positive men (See Section 5.1: What to start: summary recommendations). Factors such as potential side effects, co-morbidities, drug interactions, patient preference and dosing convenience need to be considered in selecting ART in individual women.	1A
	We recommend both HIV positive women of child bearing potential and health care professionals who prescribe ART are conversant with the benefits and risks of ARV agents for both the health of the HIV positive women and for that of an unborn child	GPP
	We recommend that potential pharmacokinetic interactions between antiretrovirals, hormonal contraceptive agents and hormone replacement therapy are checked prior to administration (with tools such as: http://www.hiv-druginteractions.org)	GPP

2.2 Summary of auditable measures

Percentage of patients who confirm they have been given the opportunity to be involved in making decisions about their treatment

Proportion of patients with CD4 count <350 cells/ μ L not on ART

Proportion of patients with CD4 count >350 cells/ μ L and an indication to start ART on ART

Proportion of patients presenting with an AIDS defining infection or with a serious bacterial infection and a CD4 count <200 cells/ μ L started on ART within 2 weeks of initiation of specific antimicrobial chemotherapy.

Proportion of patients presenting with primary HIV infection and either neurological involvement or an AIDS defining illness or confirmed CD4 count <350 cells/ μ L started on ART

Record in patient's notes of discussion, treatment with ART lowers risk of HIV transmission and an assessment of current risk of transmission.

Proportion of therapy naïve patients not starting ART containing 2 NRTIs and either a PI/r or a NNRTI or an INI (preferred or alternative agents)

Proportion of patients starting ART with either tenofovir/emtricitabine or abacavir/lamivudine as the NRTI backbone

Proportion of patients starting ART with either atazanavir/r, or darunavir/r, or efavirenz or raltegravir as the third agent

Proportion of patients with undetectable VL <50 copies/ml at six months and at 12 months after starting ART

Proportion of patients who switch therapy in the first 6 and 12 months

Record in patient's notes of HLA B5701 status prior to starting abacavir

Record in patient's notes of discussion and assessment of adherence and potential barriers to, prior to starting a new ART regimen and whilst on ART

Record in patient's notes of provision or offer of adherence support

Record in patient's notes of potential adverse pharmacokinetic interactions between antiretroviral drugs and other concomitant medications

Proportion of patients with undetectable viral load on ART who on stopping a regimen containing a NNRTI in combination with a NRTI backbone, are switched to a PI/r for four weeks.

Number of patients with an undetectable VL on current regimen and documented prior NRTI resistance who have switched a PI/r to either a NNRTI or an INI as the third agent

Number of patients on PI/r monotherapy as ART maintenance strategy in virologically suppressed patients and record of rationale

Record in patient's notes of resistance result at ART initiation (if available) and at first viral load >400 copies/ml and/or before switch

Record in patient's notes of adherence assessment and tolerability/toxicity to ART, in patients' experiencing virological failure or repeated viral blips

Number of patients experiencing virological failure on current ART regimen

Proportion of patients experiencing virological failure switched to a new suppressive regimen within 6 months

Proportion of patients on ART with prior documented HIV drug resistance with VL <50 copies/ml

Record of patients with three class virological failure with or without three class resistance referred/discussed in MDT with expert advice

Proportion of patients with TB and CD4 count <100 cells/ μ L started on ART within 2 weeks of starting Tb therapy

Proportion of patients with active TB on anti-tuberculosis therapy started on ART containing efavirenz and tenofovir and emtricitabine

Proportion of patients with HIV and hepatitis B virus co-infection with CD4 counts <500 cells/ μ L on ART

Proportion of patients with HIV and hepatitis B virus co-infection starting tenofovir and emtricitabine as part of their first ART regimen

Proportion of patients with HIV and Hepatitis C virus co-infection and CD4 counts <500 cells/ μ L on ART

Record in patient's notes of potential pharmacokinetic interactions between antiretrovirals and ant-viral hepatitis C agents

Proportion of patients with an AIDS defining malignancy on ART

Proportion of patients with a non-AIDS defining malignancy on ART

Record in patient's notes of potential pharmacokinetic drug interactions between antiretrovirals and systemic anti-cancer therapy

Proportion of patients with symptomatic HIV associated neurocognitive disorders on ART

Proportion of patients with HIV associated NC disorders on ART containing two NRTIs and either a NNRTI or a PI/r or a INI

Proportion of patients with HIV associated nephropathy (HIVAN) started on ART within 2 weeks of diagnosis of CKD

Number of patients with CKD stages 3-5 on ARVs that are potentially nephrotoxic and record of rationale

Record in patient's notes of the calculated dose of renally cleared ARVs in patients with CKD stage 3 or greater

Number of patients with high CVD risk on either abacavir or fosamprenavir/ritonavir or lopinavir/ritonavir and record of rationale

Proportion of HIV positive women with CD4 cell count <350 cells/ μ L not on ART

3. Patient involvement in decision making

3.1 Recommendations

We recommend patients are given the opportunity to be involved in making decisions about their treatment. (GPP)

Provision of treatment support resources should include in-house, independent and community information providers and peer support resources.

Auditable measure

Percentage of patients who confirm they have been given the opportunity to be involved in making decisions about their treatment

3.2 Rationale

Patients should be given the opportunity to be involved in making decisions about their treatment [1]. Studies show that trust, a good quality relationship and good communication skills between doctor and patient are associated with better adherence and treatment outcomes in HIV and in other disease areas [2–6].

Studies have shown that patient beliefs about the necessity, efficacy and side-effects of antiretroviral therapy (ART), the practicability of taking it, and their beliefs about their ability to adhere to therapy all affect adherence [7–9].

Before prescribing ART (treatment initiation or switching), clinicians should assess:

- Patients' readiness to take therapy;
- Their knowledge of its mode of action and efficacy, and perceptions of their personal need for ART;
- Concerns about taking ART or specific antiretroviral drugs including potential adverse effects;
- Concerns with possible adverse social consequences such as, for instance, disclosure or interference with lifestyle;
- Their confidence that they will be able to adhere to the medication (self-efficacy);
- Psychological or neurocognitive issues that could impact on adherence
- Socioeconomic factors which could impact on adherence including, but not limited to, poverty, housing, immigration status or domestic violence.

Community advocacy and peer support are helpful in supporting patient's understanding and confidence around treatments and help the patient's readiness and decision to start therapy. Community organisations in the UK have been instrumental in providing a range of patient information resources and peer support services including published and web based information

materials, telephone advice lines, treatment advocates and peer support groups, working in collaboration with health care professionals. They are an important and essential adjunct to clinic based services and are helpful in addressing the issues discussed below.

A number of patient factors may affect adherence, adverse effects and treatment outcomes. Depression is significantly associated with low adherence [10,11] and some studies report an independent association between depression and mortality in people with HIV [12]. Adherence can be improved by treating depression [13], so all patients should be screened for depression before starting therapy, using simple screening tools such as the Arroll two-question quick screen [14]. Patients should also be screened for anxiety and for cognitive impairment.

Current problematic alcohol and recreational drug use are also associated with low adherence [15–17], though a history of injecting drug use, or even active use, is not necessarily so [18]. Patients should be asked about alcohol and recreational drug use and offered support to moderate or manage it if desired.

Conversely, adherence has been associated with positive experiences of quality of life such as having a meaningful life, feeling comfortable and well cared for, using time wisely, and taking time for important things [19]. Patient self-management skills and courses that teach them have been associated with both improved adherence and better clinical outcomes in a number of studies [20–22] and it may be helpful to patients to inform them of these and other psychological support options locally available, in line with the *BPS/BHIVA Standards for psychological support for adults living with HIV* [23].

A patient's socioeconomic status has a more direct effect on adherence and other healthcare behaviours, than clinicians realise. For instance a US study found that poverty had a direct effect on adherence, largely due to food insufficiency [24]. A 2010 report on poverty in people with HIV in the UK found that one in six people with HIV was living in extreme poverty, in many cases due to unsettled immigration status [25]. Clinicians should be aware of patients' socioeconomic status and refer to social support where necessary.

Clinicians should establish what level of involvement the patient would like and tailor their consultation style appropriately. Clinicians should also consider how to make information accessible and understandable to patients (e.g. with pictures, symbols, large print and different languages)[1] including linguistic and cultural issues. Youth is consistently associated with lower adherence to ART, loss to follow-up and other negative healthcare behaviours [26] and some studies have found an independent association between poorer adherence and attendance and female gender [27], so information and consultation style should be age- and gender-appropriate for the patient.

If there is a question about the patient's capacity to make an informed decision, this should be assessed using the principles in the Mental Capacity Act 2005 [28].

Patients presenting at the clinic may be at different stages of readiness to take therapy [29] and clinicians' first task is to assess their readiness, by means of open questions rather than closed, before supporting and furthering patients' decisions on therapy. However if a patient presents in circumstances that necessitates starting ART immediately e.g. with certain AIDS diagnoses or very low CD4 counts then doctors should prescribe ART and provide support for the patient's adherence, especially through the first few weeks. Recognising symptoms that patients attribute

to ART side effects might avoid loss of adherence and deterioration of trust in the patient-provider relationship [30,31].

Supporting patients requires good communication not just between clinician and patient but also between all health care staff involved with their care including those in their HIV services, their GP and any clinicians involved in management of co-morbid conditions. Patients should be offered copies of letters about them sent to their GP and other physicians. The advantages of HIV status disclosure to the patient's GP, should be discussed and considered best practice, as several situations require consensual clinical decision making. A patient's decision not to disclose their status to their GP should, however, always be respected, subject to the clinician's duty to protect vulnerable individuals.

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4. When to start

4.1 Chronic infection

4.1.1 Recommendations

- We recommend patients with chronic infection start ART if the CD4 count is ≤ 350 cells/ μL [1A]: it is important not to delay treatment initiation if the CD4 cell count is close to this threshold.

The absolute risk of disease progression is significantly higher for a given CD4 count in older people (see Table 2.1), so consideration should be given to starting at higher CD4 counts in older persons. Evidence from cohort studies suggest that the risk of disease progression is significantly higher once the CD4 count falls below 350 cells/ μL , so it is important not to delay unnecessarily the initiation of ART if the CD4 count is close to this threshold.

- We recommend patients with the following conditions start ART:
- AIDS diagnosis (e.g. Kaposi's sarcoma) irrespective of CD4 cell count [1A];
- HIV-related co-morbidity including HIVAN [1C], ITP, [1C], symptomatic HIV-associated neurocognitive disorders irrespective of CD4 cell count [1C]
- Co-infection with hepatitis B virus if the CD4 count is ≤ 500 cells/ μL [1B] (see Section 8.2.2 Hepatitis B)
- Co-infection with hepatitis C virus if the CD4 count is ≤ 500 cells/ μL [1C] (Section 8.2.3 Hepatitis C)
- Non-AIDS defining malignancies requiring immunosuppressive radiotherapy or chemotherapy [1C] (Section 8.3.2 When to start ART: non-AIDS-defining malignancies)
- We suggest patients with the following conditions start ART:
- Co-infection with hepatitis B virus if the CD4 count is > 500 cells/ μL and treatment of hepatitis B is indicated [2B] (see Section 8.2.2 Hepatitis B)

Auditable measures

Proportion of patients with CD4 count < 350 cells/ μL not on ART

Proportion of patients with CD4 count > 350 cells/ μL and an indication to start ART not on ART

4.1.2 Rationale

To date there have been no published randomised trials that directly assess whether treatment-naïve people with higher CD4 counts should initiate ART immediately rather than defer until the CD4 count falls to ≤ 350 cells/ μL ; whilst the START trial is addressing this question, results are not expected until 2015. Only one trial [1] has randomized people with a CD4 count > 350 cells/ μL , but this used a comparator arm of delay of initiation of ARVs until the CD4 count has fallen

below 250 cells/ μ L, and thus is likely to over-estimate the apparent benefits of immediate treatment compared with starting at <350 cells/ μ L. There have been a number of observational studies that have attempted to address this issue [2–9], which have produced conflicting findings. Some of these studies have failed to take into account the lead-time between an individual's CD4 count falling below the threshold for treatment and the date of starting treatment [8]; as this may introduce serious bias into treatment comparisons, these results do not resolve the question whether it is better to start ART at higher CD4 cell counts.

Where studies have used methods that take the lead-time into account, the statistical methods used are novel and different approaches have been used. The analyses reached substantially different conclusions on the mortality benefits of early ART initiation in people with a CD4 count >350 cells/ μ L, and particularly in those with CD4 count >500 cells/ μ L. Critically, none of these methods are able fully to adjust for potential confounding, which might well be large in this scenario and could create a bias that is in the same direction in all studies. Thus, we do not believe that the evidence is currently sufficiently strong to recommend a change in guidelines.

Table 2.1

Table 1 Predicted 6-month risk of AIDS in antiretroviral therapy-naïve patients according to current age [(a) 25 years, (b) 35 years, (c) 45 years and (d) 55 years], CD4 cell count, viral load and whether antiretroviral therapy is initiated immediately or deferred

Treatment	Viral load (copies/mL)	Risk (%)									
		CD4 count (cells/ μ L)									
		50	100	150	200	250	300	350	400	450	500
<i>(a)</i>											
Deferred	3000	6.8	3.7	2.3	1.6	1.1	0.8	0.6	0.5	0.4	0.3
Initiated		2.3	1.2	0.8	0.5	0.4	0.3	0.2	0.2	0.1	0.1
Deferred	10000	9.6	6.3	3.4	2.3	1.6	1.2	0.9	0.7	0.5	0.4
Initiated		3.2	1.8	1.1	0.8	0.5	0.4	0.3	0.2	0.2	0.1
Deferred	30000	13.3	7.4	4.7	3.2	2.2	1.6	1.2	0.9	0.7	0.6
Initiated		4.4	2.5	1.6	1.1	0.7	0.5	0.4	0.3	0.2	0.2
Deferred	100000	18.6	10.6	6.7	4.6	3.2	2.4	1.8	1.4	1.1	0.8
Initiated		6.2	3.5	2.2	1.5	1.1	0.8	0.6	0.5	0.4	0.3
Deferred	300000	25.1	14.5	9.3	6.3	4.5	3.3	2.5	1.9	1.5	1.2
Initiated		8.4	4.8	3.1	2.1	1.5	1.1	0.8	0.6	0.5	0.4
<i>(b)</i>											
Deferred	3000	8.5	4.7	3.0	2.0	1.4	1.0	0.8	0.6	0.5	0.4
Initiated		2.8	1.6	1.0	0.7	0.5	0.3	0.3	0.2	0.2	0.1
Deferred	10000	12.1	6.7	4.3	2.9	2.0	1.5	1.1	0.9	0.7	0.5
Initiated		4.0	2.2	1.4	1.0	0.7	0.5	0.4	0.3	0.2	0.2
Deferred	30000	16.6	9.3	5.9	4.0	2.8	2.1	1.6	1.2	0.9	0.7
Initiated		5.5	3.1	2.0	1.3	0.9	0.7	0.5	0.4	0.3	0.2
Deferred	100000	23.1	13.2	8.5	5.8	4.1	3.0	2.3	1.7	1.3	1.1
Initiated		8.0	4.5	2.8	1.9	1.4	1.0	0.8	0.6	0.4	0.4
Deferred	300000	30.8	18.0	11.7	8.0	5.7	4.2	3.1	2.4	1.9	1.5
Initiated		10.3	6.0	3.9	2.7	1.9	1.4	1.0	0.8	0.6	0.5
<i>(c)</i>											
Deferred	3000	10.7	5.9	3.7	2.5	1.8	1.3	1.0	0.7	0.6	0.5
Initiated		3.6	2.0	1.2	0.8	0.6	0.4	0.3	0.2	0.2	0.2
Deferred	10000	15.1	8.5	5.4	3.6	2.6	1.9	1.4	1.1	0.8	0.7
Initiated		5.0	2.8	1.8	1.2	0.9	0.6	0.5	0.4	0.3	0.2
Deferred	30000	20.6	11.7	7.5	5.1	3.6	2.6	2.0	1.5	1.2	0.9
Initiated		6.9	3.9	2.5	1.7	1.2	0.9	0.7	0.5	0.4	0.3
Deferred	100000	28.4	16.5	10.6	7.3	5.2	3.8	2.9	2.2	1.7	1.3
Initiated		9.5	5.5	3.5	2.4	1.7	1.3	1.0	0.7	0.6	0.4
Deferred	300000	37.4	22.4	14.6	10.1	7.2	5.3	4.0	3.1	2.4	1.9
Initiated		12.5	7.5	4.9	3.4	2.4	1.8	1.3	1.0	0.8	0.6
<i>(d)</i>											
Deferred	3000	13.4	7.5	4.7	3.2	2.3	1.7	1.2	0.9	0.7	0.6
Initiated		4.5	2.5	1.6	1.1	0.8	0.6	0.4	0.3	0.2	0.2
Deferred	10000	18.8	10.7	6.8	4.6	3.3	2.4	1.8	1.4	1.1	0.8
Initiated		6.3	3.6	2.3	1.5	1.1	0.8	0.6	0.5	0.4	0.3
Deferred	30000	25.4	14.6	9.4	6.4	4.6	3.3	2.5	1.9	1.5	1.2
Initiated		8.5	4.9	3.1	2.1	1.5	1.1	0.8	0.6	0.5	0.4
Deferred	100000	34.6	20.5	13.3	9.2	6.5	4.8	3.6	2.8	2.2	1.7
Initiated		11.5	6.8	4.4	3.1	2.2	1.6	1.2	0.9	0.7	0.6
Deferred	300000	44.8	27.5	18.2	12.6	9.1	6.7	5.0	3.9	3.0	2.4
Initiated		14.9	9.2	6.1	4.2	3.0	2.2	1.7	1.3	1.0	0.8

Table 2.1 foot note: Predicted risk of AIDS if ART is deferred is taken from [10]. The predicted 6-month risk if ART is initiated is based on the assumption that the rate with immediate therapy initiation is one-third the rate without therapy initiation. This (probably conservative) value is based on considering evidence from multiple sources, including references [11–16]

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4.2 Patients presenting with AIDS or a major infection

4.2.1 Recommendation

- We recommend patients presenting with an AIDS-defining infection, or with a serious bacterial infection and a CD4 count <200 cells/ μ L, start ART within two weeks of initiation of specific antimicrobial chemotherapy (1B).

Auditable measure

Proportion of patients presenting with an AIDS defining infection or with a serious bacterial infection and a CD4 count <200 cells/ μ L started on ART within 2 weeks of initiation of specific antimicrobial chemotherapy

4.2.2 Rationale

This recommendation is largely based on the ACTG 5164 study that demonstrated fewer AIDS progressions/deaths and improved cost-effectiveness when ART was commenced within 14 days (median 12 days; IQR 9–13 days) compared to after completion of treatment for the acute infection (median 45 days; IQR 41–55 days) [1,2]. Those with tuberculosis as the primary infection were excluded from this study, and the majority of patients enrolled had pneumocystis pneumonia (PCP), followed by lesser proportions with cryptococcal meningitis and bacterial infections. The patients were well enough to give informed consent and to take oral medications, and therefore the findings may not be generalisable to those who are severely unwell or requiring intensive care. Previous observational data suggest a survival benefit for HIV positive patients who are started on ART whilst in the intensive care unit [3,4], but the data are insufficient to make a recommendation in this group [3,4]

There was no increase in the incidence of immune reconstitution disorders (IRD) or adverse events generally with early ART initiation in ACTG 5164 [1,5]. However those with intracranial opportunistic infections (OI) (such as cryptococcal meningitis [6]) may be more prone to severe IRDs with early ART initiation and increased observation of these patients may be warranted (though it is still recommended to initiate ART around two weeks after the commencement of OI therapy assuming the patient is stable). Those presenting with tuberculosis and malignancies are discussed in Section 8.

4.2.3 References

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4.3 Treatment of primary HIV infection

4.3.1 Recommendations

- We recommend patients presenting with primary HIV infection and meeting any one of the following criteria start ART:
- Neurological involvement [1D]
- Any AIDS-defining illness [1A]
- Confirmed CD4 cell count <350 cells/ μ L [1C]

Auditable measure

Proportion of patients presenting with primary HIV infection and either neurological involvement or an AIDS defining illness or confirmed CD4 count <350 cells/ μ L started on ART

4.3.2 Rationale

The scientific rationale for treating with ART in primary HIV infection (PHI) is as follows:

1. Preservation of specific anti-HIV CD4+ T lymphocytes that would otherwise be destroyed by uncontrolled viral replication, the presences of which are associated with survival in untreated individuals [1].

2. Reduction in morbidity associated with high viraemia and profound CD4 depletion during acute infection [2–4].

3. Reduction in the enhanced risk of onward transmission of HIV associated with PHI [5–10].

Treatment of patients with primary HIV infection who present with AIDS-defining illnesses, neurological disease or a CD4 count of < 350 is consistent with the recommendations for patients with chronic infection. The rationale for treating patients with neurological disease is that ART may lead to regression of otherwise irreversible neurological disease (although there is no high quality evidence for this effect of treatment in primary infection). Data from the CASCADE collaboration [11] showed that in patients with primary infection who had at least one CD4 count of <350 cells μ /L in the first 6 months of infection had a significantly greater mortality than those whose CD4 counts remained above this threshold, which supports early treatment in patients with lower CD4 counts.

Multiple observational studies have shown encouraging but inconclusive results following short course ART initiated in PHI for individuals in whom ART would not otherwise be indicated [12,13]. There have been three RCTs comparing the role of interrupted ART initiated in PHI on time to reach CD4 <350 cells/ μ L or the need for initiation of lifelong ART [14–16]. Overall there was a modest benefit in terms of delaying the decline in CD4 count or time from seroconversion to requiring initiation of lifelong ART following a 48 [16] or 60 [15] week course of ART. A posthoc analysis from the SPARTAC trial [16] showed a non significant trend towards benefit in time to CD4 count <350 cells/ μ L when ART was initiated closer to the time of infection (HR 0.48 p = 0.09). This randomised study supported cohort studies in which a more rapid rate of CD4+ cell loss was seen in individuals presenting within 12 weeks of a negative HIV antibody test [17,18].

For this reason, we suggest that the following are discussed with those presenting with a very short test interval (\leq 12 weeks) in particular those with severe symptoms of seroconversion; such as rash, fever, weight loss, persistent lymphadenopathy, diarrhoea >4 days, malaise, headaches or laboratory evidence of acute HIV infection (e.g. as defined in SPARTAC [16]).

A 48 week course of ART showed a benefit in surrogate markers of HIV disease progression; delaying CD4 decline and lowering viral set point up to 60 weeks after stopping therapy; (there was no such benefit from 12 week ART); in those individuals presenting within 12 weeks of infection this effect was more marked; there is no clear evidence of long-term clinical benefit of ART in this setting.

No study has examined whether ART started during or soon after PHI should be continued long-term, but most clinicians would recommend that irrespective of indication to start ART, once initiated, it should be continued indefinitely. Discontinuation of ART in the context of treatment of primary HIV infection was not commonly associated with morbidity, however [15,16]

Initiation of a PI-based regimen is recommended if therapy is started prior to the availability of a genotype result based on the prevalence of transmitted rates of drug resistance in the UK [19].

There is no specific evidence to support the role of ART in PHI to prevent onward transmission of virus but there is little reason to consider that ART is any less effective in reducing infectivity at this time, so long as viral suppression has been achieved [20].

Patients with recently diagnosed primary HIV infection may be in a particularly vulnerable psychological state, and thus ill-prepared to commit to starting long-term treatment.

4.3.3 References

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4.4. Treatment to reduce transmission

4.4.1 Recommendations

- We recommend the evidence that treatment with ART lowers the risk of transmission is discussed with all patients, and an assessment of the current risk of transmission to others is made at the time of this discussion. (GPP)
- We recommend following discussion, if a patient with a CD4 count above 350 cell/ μ L wishes to start ART to reduce the risk of transmission to partners, this decision is respected and ART is started. (GPP)

Auditable measures

Record in patient's notes of discussion, treatment with ART lowers risk of HIV transmission and an assessment of current risk of transmission.

The discussion should include the following:

The decision to start ART is the patient's choice and must not be due to the pressure from partners or others.

ART lowers rather than eliminates the risk of transmission: other prevention strategies including male and female condoms continue to be recommended to address concerns of any residual risk of transmission

For a patient with a CD4 count above 350 cells/ μ L, it is uncertain whether any benefits of immediate treatment to their own health will be outweighed by any harm.

Condoms both, male and female, continue to be recommended as protection from other sexually transmitted infections (STIs) and unplanned pregnancy.

There are risks associated to interrupting ART, once started, should generally continued indefinitely.

The evidence that ART lowers the risk of transmission mainly relates to vaginal sex. Although ART is highly likely to reduce the risk transmission for anal sex, the residual risk could be higher than seen in studies for vaginal sex. There are currently few data to inform this.

High and consistent adherence to ART is required to maintain viral suppression and minimise transmission risk.

Taking ART does not result in immediate complete viral suppression; it usually takes several months to achieve an undetectable viral load in blood.

The use of ART to reduce transmission risk is a particularly important consideration in sero-discordant heterosexual couples wishing to conceive and it is recommended that the HIV positive partner is on fully-suppressive ART.

4.4.2 Rationale

The potential effect of HIV treatment to reduce the risk of onward sexual transmission should be discussed with all patients as a part of safer sex messages in general. The discussion should include the HIV status of their partner (s) and whether ART is indicated for their own health.

This discussion should make clear that there is good evidence from one RCT (HPTN 052) [1] that ART treatment can markedly reduce (by 96%) the risk of transmission to HIV negative partners. This is supported by the secondary outcomes of another trial [2] that also found a marked reduction in transmission from partners taking ART (by 92%). It is important to note that only 3% of the couples in HPTN 052 were men who have sex with men (MSM) and the Partners in Prevention study was conducted entirely in heterosexual couples. The evidence base thus relates mainly to the risk of transmission for vaginal sex in heterosexual couples, it seems likely that a reduction in risk will also be seen for anal sex, but this is the subject of ongoing studies.

Prior to these randomized controlled studies the evidence base for treatment to reduce transmission was based on a number of cohort studies which found that transmission between heterosexual couples where the HIV-positive partner had an undetectable viral load on treatment was very rare or did not occur [3–7].

Viral suppression due to ART is usually as effective in reducing viral load in semen [8] and in the rectum [9] as in plasma. This suggests that in the absence of other facilitators of transmission such as STIs, ART would be expected to be as effective in reducing infectiousness in MSM and other populations as it is in heterosexuals. Indirect evidence comes from a study of MSM

attending HIV treatment services where ART was associated with a 96% reduction in HIV transmission [10].

Condoms should still be recommended, to protect from other sexually transmitted infections, and also to lower further any residual risk of transmission.

Patients should be informed that taking ART does not result in immediate viral suppression. Studies have shown that the mean time to suppression of viral load to <50 copies/ml in patients taking ART is about 90 days, and that a proportion may take nine months or more [11]. Patients should also be informed about the possibility of virological failure leading to transmission of HIV. Decisions on condom use and safer sex should always be based on a recent viral load test result and not on an assumption that taking ART implies non-infectiousness.

For sero-discordant heterosexual couples wishing to conceive irrespective of the method used for conception, the HIV positive partner will need to be on ART with an undetectable plasma viral load, regardless of his/her CD4 count or clinical status. This is likely to reduce the risk of transmission sufficiently to be the only risk reduction method some couples will want, but additional measures such as sperm washing, artificial insemination and potentially PrEP to the HIV negative partner have either been recommended in previous guidance [12] or are currently being assessed for couples wishing to address concerns of any residual risk of transmission.

Details of the use of ART to prevent mother to child transmission are covered in the pregnancy guidelines [13].

4.4.3 References

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5. What to start

5.1 Summary recommendations

- We recommend therapy naïve patients start ART containing two NRTIs and either a ritonavir-boosted protease inhibitor, or a NNRTI or an integrase inhibitor (1A)
- Summary recommendations for choice of ART:

	PREFERRED	ALTERNATIVE
NRTI backbone	Tenofovir and emtricitabine	Abacavir and lamivudine 1,3
Third Agent	Atazanavir/ritonavir Darunavir/ritonavir Efavirenz Raltegravir	Lopinavir/ritonavir Fosamprenavir/ritonavir Nevirapine ² Rilpivirine ³

1. Abacavir is contraindicated if HLA B*5701 positive
2. Nevirapine is contra-indicated if baseline CD4 greater than 250/400 cells/ μ L in women/men.
3. Use recommended only if baseline viral load less than 100,000 copies/ml: rilpivirine as a third agent, abacavir + lamivudine as NRTI back bone

The presence or future risk of co-morbidities and potential adverse effects need to be considered in the choice of antiretroviral drugs in individual patients.

Summary auditable measures

Proportion of therapy naïve patients not starting ART containing 2 NRTIs and either a PI/r or a NNRTI or an INI (preferred or alternative agents)

Proportion of patients starting ART with either tenofovir/emtricitabine or abacavir/lamivudine as the NRTI backbone

Proportion of patients starting ART with either atazanavir/r, or darunavir/r, or efavirenz or raltegravir as the third agent.

Proportion of patients with undetectable VL <50 copies/ml at six months and at 12 months after starting ART

Proportion of patients who switch therapy in the first 6 and 12 months

Record in patient's notes of HLA B5701 status prior to starting abacavir

5.2 Introduction

For the 'which NRTI backbone' and 'which third agent' questions evidence profiles and summary of findings tables were constructed to assess quality of evidence across pre-defined treatment outcomes (Appendix 3). Evidence from RCTs and systematic reviews was identified from a systematic literature review (Appendix 2). Outcomes were scored and ranked (critical, important, not important) by members of the writing committee. The following were ranked as critical outcomes: viral suppression at 48/96 weeks, protocol defined virological failure, drug resistance, quality of life, discontinuation for adverse events and grade 3/4 adverse events (overall), rash and ALT/AST elevation.

Treatments were compared and differences in critical outcomes assessed. Where there were differences, consensus opinion was sought to determine whether the difference in size of effect was above the threshold for clinical decision-making. If conflicting differences were detected, the balance of outcomes was based on consensus opinion of the committee.

A treatment was defined as preferred or alternative to indicate strong or conditional recommendations and the decision based on the assessment of critical outcomes and the balance of desirable and undesirable effects in a general ART naïve patient population. 'Preferred' indicates a strong recommendation that most clinicians and patients would want to follow unless there is a clear rationale not to do so. 'Alternative' indicates a conditional recommendation and is an acceptable treatment option for some patients and might in selected patients be the preferred option.

Factors including potential side effects, co-morbidities, patient preference, drug interactions need to be taken into account when selecting an ART regimen in individual patients and may include both preferred and alternative treatment options.

For guidance on assessment of patients prior to initiation of ART and monitoring of patients on ART the reader should consult the BHIVA guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals 2011 (<http://www.bhiva.org/Monitoring.aspx>).

5.3 Which NRTI backbone

5.3.1 Recommendations

- We recommend therapy naïve patients start combination ART containing tenofovir and emtricitabine as the NRTI backbone. (1A)
- We suggest abacavir and lamivudine is an acceptable alternative NRTI backbone in therapy naïve patients who prior to starting ART have baseline viral load of $\leq 100,000$ copies/ml (2A)
- Abacavir must not be used in patients who are HLAB*5701 positive. (1A)

5.3.2 Rationale

Three randomised controlled trials have compared tenofovir-emtricitabine (TDF-FTC) with abacavir-lamivudine (ABC-3TC) as the NRTI backbone in combination with: different third

agents: atazanavir/ritonavir (ATV/r) or efavirenz (EFV) [1–5], efavirenz [6–8] and lopinavir/ritonavir (LPV/r) [9].

Assessment of virological efficacy as a critical outcome was complicated by different definitions across the three studies. In our analysis for GRADE (see Appendix 3.1), there was no difference in rates of virological suppression at 48 weeks or 96 weeks but the analysis excluded the largest of the three trials (ACTG5202) and the quality of evidence for this outcome was assessed as low or very low. Assessment of the risk of protocol defined virological failure at 48 weeks favoured TDF-FTC (RR 0.76, 95% CI 0.53–1.07), the effect was not statistically significant and the heterogeneity in the analysis was relatively high (I^2 46%). Assessment of protocol defined virological failure at 96 weeks showed a significant difference favouring TDF-FTC (RR 0.73, 95% CI 0.59–0.92). Data were only available from one study [3] for this analysis, however this was by far the largest of the three trials and the quality of evidence assessment for this outcome was rated as high. The difference in virological failure was assessed by the committee to be large enough to be above the clinical threshold for decision-making. The difference equates to a number needed to treat to prevent one case of virological failure of approximately 20 patients treated for one year.

The results of ACTG5202 [1–3] are complicated by the early termination of those individuals with a baseline viral load of >100,000 copies/ml at the recommendation of the data and safety monitoring board (DSMB) due to significantly inferior performance in those subjects receiving ABC-3TC. No difference in virological efficacy between the TDF-FTC and ABC-3TC arms was seen in those in the lower viral load stratum (baseline viral load <100,000 copies/ml). The subsequent 96-week analysis, after discontinuation of those subjects in the higher viral load stratum, may therefore underestimate the difference between the two backbones. HLA B5701 screening was not routine in ACTG5202 and this potentially may have influenced some of the safety endpoints, but appears not to have influenced the primary virological outcome. In the higher viral load strata the number of patients with suspected hypersensitivity reactions was equal between both arms and virological failure in these patients was infrequent.

With regard to the assessment of the other critical and important outcomes including drug resistance, discontinuation for adverse events and lipodystrophy, no difference was shown between TDF-FTC and ABC-3TC. No data were available to assess quality of life outcomes. For grade 3/4 adverse events (all) and grade 3/4 ALT/AST elevation there were trends that favoured TDF-FTC (see Appendix 3.1).

Although the rate of drug resistance was not different between the NRTI backbones, the number developing drug resistance was higher numerically in those receiving ABC-3TC, given the higher rate of virological failure.

The only outcome that significantly favoured ABC-3TC was bone mineral density but no difference in bone fractures was identified

It is the view of the writing committee that given the favourable virological outcomes TDF-FTC compared to ABC-3TC and the lack of other significant differences in critical and important adverse event outcomes, TDF-FTC is recommended as the preferred NRTI backbone of choice. ABC-3TC is an acceptable alternative option in patients with a baseline viral load <100,000 copies/ml, but must only be used after ensuring a patient is HLA B*5701 negative.

When selecting a NRTI backbone, factors such as potential side effects, co-morbidities, patient preference and cost should also be considered. Observational studies have variably reported associations between ABC and cardiovascular disease [10–12], and TDF may cause renal disease [13]. These aspects will be discussed in more detail in Section 8. However, based on the balance of current evidence we suggest ABC is not used in individuals at high risk of cardiovascular disease (see Section 8.6 Cardiovascular disease) and TDF is not used in patients with stage 3-5 chronic kidney disease or at high risk of progression of CKD (see Section 8.5 Chronic kidney disease) if acceptable alternative ARVs are available.

5.3.4 Not recommended

The writing committee believes there is no routine role for other NRTI backbones in the treatment of ART-naïve patients. Zidovudine-lamivudine may be considered in certain specific circumstances e.g. pregnancy, (see BHIVA pregnancy guidelines [14]) but should not be given routinely due to the proven association with mitochondrial toxicity, particularly lipoatrophy with zidovudine. There is no place for the use of stavudine or didanosine containing regimens as initial therapy, due to the associations with significant mitochondrial and hepatic toxicities.

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5.4 Which third agent?

5.4.1 Recommendations

- We recommend therapy-naïve patients start combination ART containing either atazanavir/ritonavir, or darunavir/ritonavir, or efavirenz, or raltegravir as the third agent. (1A)
- We suggest in therapy-naïve patients lopinavir/ritonavir and fosamprenavir/ritonavir are acceptable alternative protease inhibitors, and nevirapine and rilpivirine are acceptable alternative NNRTIs (2A).
- Nevirapine must only be used according to CD4 criteria and rilpivirine should only be used in patients with baseline viral load <100,000 copies/ml.

5.4.2 Rationale

The 2008 BHIVA guidelines recommended EFV as the preferred third agent in view of significantly better virological outcomes compared to LPV/r [1]. A similar outcome was subsequently reported in a smaller randomised study of patients commencing ART with advanced disease, as defined by a CD4 count of <200 cells/ μ L [2].

Since the 2008 guidelines, a number of comparative studies against either EFV or LPV/r have been reported, investigating alternative third agents.

Comparison with EFV: Atazanavir/ritonavir [3–9]; raltegravir [10–13]; rilpivirine [14–16]

Comparison with LPV/r: Atazanavir/ritonavir [17]; Darunavir/ritonavir [18–20]

For the current guidelines, evidence for agreed treatment outcomes for each potential third agent was compared to EFV, either directly or indirectly depending on the available evidence (Appendix 3).

ATV/r and raltegravir (RAL) have been compared directly with EFV in randomised control trials. For critical virological efficacy and safety outcomes, no differences were identified between EFV and either ATV/r or RAL. For these outcomes the quality of evidence was rated as high or moderate.

There was a difference in the rate of drug resistance favouring ATV/r (RR 3.94, 95% CI 2.37–6.56; $P < 0.00001$) but the overall rate of emergent drug resistance was low for both treatments. This difference is a class effect and has previously been reported for other NNRTIs and PI/rs.

Differences were also identified in the rate of grade 3/4 CNS events and the rate of lipid abnormalities favouring both ATV/r and RAL. These differences may well influence choice between preferred third agents for individual patients.

There are no randomised controlled trials comparing DRV/r versus EFV directly. Thus an indirect comparison was undertaken using data from studies comparing DVR/r versus LPV/r [18–20] and LPV/r versus EFV [1,2] to assess outcomes between the two treatment options. Some differences between these studies were identified in terms of comparability and are outlined in Appendix 3. Overall these differences were judged to be insufficient to invalidate an indirect comparison between EFV and DRV/r.

Comparing DRV/r and LPV/r there were clinically significant differences in the critical outcomes virological suppression, discontinuation due to adverse events and serious adverse events in favour of DRV/r but no differences in the critical outcomes virological failure and drug resistance. Comparing EFV and LPV/r there was clinically significant differences in the critical outcomes virological failure and suppression at 96 weeks in favour of EFV but no differences in the critical outcomes drug resistance and discontinuation due to adverse events. In addition there were significant differences in some adverse events favouring EFV over LPV/r.

Rilpivirine (RPV) has been compared directly with EFV in randomised control trials [14–16]. With respect to critical virological outcomes there was no difference in virological suppression but there were differences in drug resistance (RR 0.38, 95% CI 0.20–0.72, $P = 0.003$) and virological failure (RR 0.55, 95% CI 0.29–1.02, $P = 0.06$), both in favour of EFV. Pooled analyses by the investigators of the two RCTs showed the risk of virological failure with RPV was highest in patients with a baseline viral load of $>100,000$ copies/ml [16]. For critical safety outcomes there was a difference in the proportion discontinuing for adverse events in favour of RPV (RR 2.29, 95% CI 1.15–4.57, $P = 0.02$) but no difference in serious adverse events. Rilpivirine also had better lipid profile outcomes.

In summary it is the view of the writing committee that EFV, given its performance across multiple well-controlled randomised trials and the wealth of clinical experience, should remain a preferred third agent. In addition because of similar critical treatment outcomes, it is the view of the committee that ATV/r, DRV/r and RAL are also recommended as preferred third agents.

For RPV versus EFV there were conflicting differences in critical outcomes. RPV was associated with fewer discontinuations for adverse events but the virological failure and resistance

outcomes favoured EFV. It was the opinion of the committee that on balance the virological and resistance outcomes outweighed the adverse event outcomes. For this reason RPV is recommended as an alternative third agent, but only in patients with baseline viral load <100,000copies/ml.

As in the 2008 guidelines nevirapine (NVP) remains an alternative third agent, based on the associated CD4 cell count restrictions that limit its use plus the higher risk of moderate to severe rash/hepatitis and discontinuation for adverse events compared to other agents [21,22].

LPV/r is listed as an alternative third agent based on comparison of virological outcomes with EFV [1,2] and DRV/r [18,19], which have been previously discussed. Fosamprenavir/ritonavir is also listed as an alternative third agent as it has been shown to be non-inferior to LPV/r in terms of virological efficacy [23].

When selecting a third agent from either the preferred or alternative options, factors such as potential side effects, dosing requirements, dosing convenience, patient preference, co-morbidities, drug interactions and cost should be considered.

Neuropsychiatric side effects have commonly been reported in patients treated with EFV and patients with a history of psychiatric disorders appear to be at a greater risk of serious psychiatric adverse events [24]. In patients with a current or a history of psychiatric disorders including depression, anxiety and suicidal ideation caution should be exercised in prescribing EFV and strong consideration given to using an acceptable alternative third agent.

EFV may be used in pregnancy and the reader is directed to the BHIVA pregnancy guidelines 2012, for full discussion on this issue. Further discussion of choice of ART in selected populations is outlined in Section 8 ART in specific populations.

5.4.3 Not recommended

Saquinavir/ritonavir (SQV/r) is not listed as preferred or alternative options. SQV/r has been reported as non-inferior to LPV/r in terms of virological and safety outcomes [25] However a higher pill burden, the availability of alternative PI/rs and a recent update to the summary of product characteristics (SPC) requiring dose escalation and careful ECG monitoring due to its association with QT interval prolongation are the reasons SQV/r is no longer listed as a preferred or an alternative option in the treatment of ART-naïve patients with chronic infection.

The CCR5 antagonist maraviroc (MVC) and unboosted atazanavir are not licensed in Europe for initial ART and as such are not recommended.

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5.5 Novel ART strategies

5.5.1 Recommendation

- We recommend against the use of protease inhibitor monotherapy as initial therapy for treatment-naïve patients. (1C)

5.5.2 Rationale

Data on use of PI monotherapy as initial ART is limited. In one RCT comparing LPV/r versus LPV/r plus zidovudine and lamivudine, the use of PI monotherapy as initial ART was associated with lower rates of virological suppression at 48 weeks and with the emergence of PI mutations [1].

There were no significant differences in tolerability. For this reason PI monotherapy is not recommended as initial ART. However as with other novel strategies there may be specific circumstances where a rationale for its use may be made.

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5.5.4 Recommendation

- We recommend against the use of protease inhibitor-based dual antiretroviral therapy with a single NRTI, NNRTI, CCR5 receptor antagonist, or integrase inhibitor as an initial therapy for treatment-naïve patients. (1C)

5.5.5 Rationale

A number of studies have assessed the use of protease inhibitor-based dual antiretroviral therapy as initial therapy in treatment-naïve patients. Many of these are either open label, not powered to demonstrate non-inferiority compared to triple therapy, single arm studies or have only been reported as conference abstracts.

The combination of a NNRTI with a PI/r has been shown to have similar virological efficacy compared to triple combination regimens in one study [1] There were no significant differences in time to either virological or regimen failure with a combination of LPV/r and EFV compared to either two NRTIs and EFV or two NRTIs and LPV/r. There was however an increased rate of drug resistance in the NRTI sparing arm, with the emergence of more NNRTI associated resistance mutations than the comparator arms. An increased rate of grade 3/4 toxicities was observed, predominantly LDL cholesterol and triglyceride elevations.

Comparison of a dual therapy regimen containing one NRTI with a PI/r (TDF and LPV/r vs two NRTIs and LPV/r) failed to demonstrate non-inferiority of the dual therapy arm compared to standard triple therapy combination [2].

The use of dual therapy with the CCR5-receptor antagonist maraviroc (MVC) in combination with a PI/r has been assessed in one RCT but was not designed to show non-inferiority [3] The comparative efficacy of the integrase inhibitor RAL plus a PI/r is being compared to standard triple therapy in several ongoing and/or unpublished studies [4–8]. Reports from one study [4,5] suggest similar rates of virological suppression at 48 and 96 weeks. However in a single arm study investigating RAL in combination with DRV/r, a significantly increased risk of virological failure with emergent integrase inhibitor resistance was seen in patients with baseline viral load >100,000 copies/ml compared to those with a baseline viral load <100,000 copies/ml [9]. Further data are required. There is a need to wait the results of ongoing randomised trials.

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6. Supporting patients on therapy

6.1 Adherence

6.1.1 Interventions to increase adherence to treatment

6.1.1.1 Recommendations

We recommend adherence and potential barriers to it are assessed and discussed with the patient whenever ART is prescribed or dispensed (GPP)

We recommend adherence support should address both perceptual barriers (e.g. beliefs and preferences) and/or practical barriers (e.g. limitations in capacity and resources) to adherence (GPP)

Auditable measures

Record in patient's notes of discussion and assessment of adherence and potential barriers to, prior to starting a new ART regimen and whilst on ART

Record in patient's notes of provision or offer of adherence support

6.1.1.2 Rationale

Low adherence to ART is associated with drug resistance, progression to AIDS [1] and death [2–4]. Given the multiple adverse consequences of treatment failure (risk of disease progression, increase in complexity and costs of treatment and risk of HIV transmission) engaging patients in treatment decisions and the monitoring and support of adherence are of paramount importance [5] (see Section 3: Patient involvement in decision making).

Non-adherence is best understood as a variable behaviour with intentional and unintentional causes. Most people taking medication are non-adherent some of the time. Unintentional non-adherence is linked to limitations in capacity or resources that reduce the ability to adhere to the treatment as intended. Intentional non-adherence is the product of a decision informed by beliefs, emotions and preferences [6].

BHIVA recommendations on the monitoring of adherence to ART are available [7]. NICE has published detailed guidance on the assessment and support of adherence to medication in chronic diseases; key recommendations for adherence support are shown in Box 1 [8].

Box 1. Summary of NICE guidance on adherence support [8]

- A 'no blame' approach is important to facilitate open and honest discussion
- A patient's motivation to start and continue with prescribed medication is influenced by the way in which they judge their personal need for medication (necessity beliefs), relative to their concerns about potential adverse effects. Delayed uptake and non-adherence are associated with doubts about personal need for ART and concerns about taking it [9,10]
- Interventions to support adherence should be individualised to address specific relevant perceptual and practical barriers. A three-step 'Perceptions and Practicalities Approach' (PAPA) [9] may be helpful:
 1. Identify and address any doubts about personal need for ART
 2. Identify and address specific concerns about taking ART
 3. Identify and address practical barriers to adherence
- Because evidence is inconclusive, only use interventions to overcome practical problems if there is a specific need. Interventions might include:
 - suggesting patients record their medicine-taking
 - encouraging patients to monitor their results
 - simplifying the dosing regimen
 - using a multi-compartment medicines system.
 - If side effects are a problem:
 - discuss benefits, and long-term effects and options for dealing with side effects
 - consider adjusting the dosage, switching to another combination or other strategies such as changing the dose timing or formulation.
- Patient's experience of taking ART and their needs for adherence support may change over time.
 - Patients' knowledge, understanding and concerns about medicines and the benefits they perceive should be reviewed regularly at agreed intervals.

6.1.2 Should the choice of first-line ART combination be affected by risk of non-adherence?

6.1.2.1 Recommendation

In patients where there is clinical concern that doses may be missed intermittently, there is insufficient evidence to recommend a PI/r over EFV-based regimens. However where there is a risk of frequent prolonged treatment interruptions EFV-based regimens may be associated with more frequent selection for drug resistance compared to ritonavir boosted PIs.

6.1.2.2 Rationale

Clinicians are poor at both predicting future adherence to ART in naïve subjects [11] and at detecting non-adherence during ART [12,13]. However in a case where a clinician or patient has concerns about a patient's future adherence, should this influence the choice of first-line therapy?

The consequences of low adherence depend on drug pharmacokinetics, potency, fitness of resistant strains and genetic barrier to resistance [14]. Hence both the level and pattern of non-adherence must be considered.

Large randomized controlled trials of first-line therapy may not be able to inform this choice as subjects likely to be non-adherent are often excluded from such trials. On the other hand observational studies often select patients already established on ART [15,16] where the observed effects of non-adherence on treatment outcome are likely to differ from those in patients starting ART de novo. This selection bias may exclude those who have either experienced early virological failure, disease progression (or even death) or have defaulted from care. In addition most studies either predate the use of boosted PI regimens in first-line therapy [15,17] or include large numbers of patients on unboosted PI regimens.

Two different outcomes may be considered: virological suppression and selection of drug resistance.

Effect of adherence on viral suppression

There are no data from RCTs that directly address this question. Among subjects reporting <95% adherence in a RCT comparing LPV/r with once daily DRV/r, virological failure was more likely in the LPV/r arm [18].

Among initially virological suppressed patients, adherence <95% is associated with an increased risk of failure [16] and very low adherence (<50%) results in virological rebound irrespective of regimen [5,16,19]. However virological suppression has been observed with only moderate adherence (50–75%) among patients on NNRTIs [5, 16,19] and virological failure has been reported to be significantly more likely among all patients on unboosted PI-based regimens where adherence was <95% [16]. However this finding may have been confounded by the once daily dosing in the EFV group. A further study [20] examined only patients with undetectable viraemia and found no difference in rates of virological rebound for patients on ritonavir boosted PIs v NNRTIs.

Effect of adherence on selection of drug resistance

The effect of level of non-adherence on selection of drug resistance varies by class. This was first described for unboosted PI regimens where moderate to high adherence was associated with increased risk of resistance [21]. The incidence of resistance in studies of boosted PI regimens is low [18,22–26] but is observed with adherence just below 80–95% [15,27]. In contrast, for first generation NNRTIs the selection for resistance has been associated with very low average adherence (<50%) [14,28]

Effect of pattern of non-adherence

The pattern of non-adherence may also be important. A number of small observational studies have examined short intermittent treatment interruptions (2–7 days) in patients with prolonged virological suppression. For EFV, cycles of two days off per week appeared no more likely to result in treatment failure than continuous therapy, as long the treatment interruption was not prolonged [29,30]. However cycles of 7 or 28-day treatment interruption resulted in failure of EFV and selection of resistance [31,32]. For ritonavir boosted PIs, one study found that average

adherence, rather than duration of treatment interruption, was associated with virological response [33].

6.1.3 Dosing frequency

A recent overview of systematic reviews of consumer-oriented medication interventions found that simplified dosing regimens improved adherence in the majority of studies in several reviews [34]. Another review of adherence interventions found that reducing dosing to once daily had some effect on adherence but no effect on treatment outcome was observed [35]. NICE [8] reviewed several RCTs of interventions to reduce dose frequency and found that adherence may increase with once daily dosing. For ART regimens, a meta-analysis of once versus twice daily ART regimens found that in the sub-group of treatment-naïve trials, once daily ART was associated with a significantly improved adherence and virological outcome [36].

Therefore once daily dosing is a reasonable intervention to reduce unintentional non-adherence to ART.

6.1.4 Fixed-dose combinations

In examining whether fixed-dose combination formulations (FDCs) of drugs improve adherence or treatment outcome, only studies comparing the same drugs with same dose frequency given as combination or separate pills were considered. No meta-analyses have been published on this subject for ART. A meta-analysis of nine RCTs and cohort studies in a range of diseases found the use of FDCs was associated with a significant reduction in the risk of non-adherence [36]. Gupta [37] reported a meta-analysis of cohort studies and found that use of FDCs for antihypertensives was associated with increased adherence but with no improvement on the control of blood pressure.

A retrospective study of a pharmacy database found no benefit in persistence on first-line ART for any FDC over separate agents [38]. A prospective observational study found that patients reported higher adherence over the preceding month (but not week) after switching from separate components to Atripla, however reporting bias cannot be excluded [39].

Patients may preferentially adhere less closely to one component of a regimen than others and FDCs may prevent this. While a minority of patients in one RCT of treatment strategies did report such 'differential' adherence, this was not associated with outcome for currently used first-line strategies [40].

Therefore FDCs can increase adherence. In patients with low adherence use of FDCs must be weighed against other treatment characteristics such as effectiveness, tolerability and resistance profile.

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6.2 Pharmacology

More than for any other infection, patients receiving ART require their doctor to have a clear understanding of the basic principles of pharmacology in order to ensure effective and appropriate prescribing. This is especially the case in four therapeutic areas.

6.2.1 Drug interactions

6.2.1.1 Recommendations

- We recommend that potential adverse pharmacokinetic interactions between antiretroviral drugs and other concomitant medications are checked before administration (with tools such as www.hiv-druginteractions.org) (GPP)

Auditable measure

Record in patient's notes of potential adverse pharmacokinetic interactions between antiretroviral drugs and other concomitant medications

6.2.1.2 Rationale

The importance of considering the potential for drug interactions in patients receiving ART cannot be overemphasised. Drug–drug interactions may involve positive or negative interactions between antiretroviral agents, or between these and drugs used to treat other coexistent conditions. A detailed list is beyond the remit of these guidelines but clinically important interactions to consider when co-administering with antiretroviral drugs include interactions with the following drugs: methadone, oral contraceptives, anti-epileptics, antidepressants, lipid-lowering agents, acid-reducing agents, certain antimicrobials (e.g. clarithromycin, minocycline and fluconazole), some anti-arrhythmics, tuberculosis therapy, anti-cancer drugs, immunosuppressants, phosphodiesterase inhibitors and anti-HCV therapies. Most of these interactions can be managed safely (i.e. with/without dosage modification, together with enhanced clinical vigilance) but in some cases (e.g. rifampicin and PIs, proton-pump inhibitors and atazanavir, and didanosine and HCV therapy) the nature of the interaction is such that co-administration must be avoided.

Importantly, patient education on the risks of drug interactions including over-the-counter or recreational drugs should be undertaken, and patients should be encouraged to check with pharmacies or their health care professionals before commencing any new drugs, including those prescribed in primary care.

Large surveys report that around 1 in 3-4 patients receiving antiretroviral therapy is at risk of a clinically significant drug interaction [1–6]. This suggests that safe management of HIV drug interactions is only possible if medication recording is complete, and if physicians are aware of the possibility that an interaction might exist. Incomplete or inaccurate medication recording has resulted from patient self-medication, between hospital and community health services [7] and within hospital settings particularly when multiple teams are involved, or when medical records are fragmented (e.g. with separate HIV case sheets) [8].

More worryingly, one survey in the UK reported that even when medication recording is complete, physicians were only able to correctly identify a third of clinically significant interactions involving HIV drugs [4]. In addition to HIV specialist and local drug information pharmacists, the University of Liverpool's comprehensive drug interaction website (www.hiv-druginteractions.org) is an excellent and highly recommended resource for information relating to potential drug interactions. Additional information resources also include the electronic medicines compendium (www.medicines.org.uk/emc) and medical information departments of pharmaceutical companies.

Communication with GPs and other medical specialties involved in patient care is fundamental in minimising the risk of adverse drug–drug interactions. All clinic letters should carry as a standard header or footer advice to check for interactions, and links to resources, such as www.hiv-druginteractions.org, to address the potential for drug interactions.

6.2.2 Therapeutic drug monitoring (TDM)

6.2.2.1 Recommendation

- We recommend against the unselected use of TDM (GPP)

TDM may be of clinical value in specific populations (e.g. children, pregnant women) or selected clinical scenarios (e.g. malabsorption, drug interactions, suspected non adherence to therapy).

6.2.2.2 Rationale

TDM has been shown to be valuable in optimising the management of certain patients; however, the general utility of this test in patients receiving ART has been poorly assessed. With the marked improvement in efficacy and tolerability of modern anti-retroviral regimens, the role of TDM in clinical management has also evolved. A Cochrane review of randomized controlled trials [9] suggests little value when used unselectively. However, TDM may aid the management of vulnerable populations or complex clinical situations:

1. Monitoring adherence. Whilst detection of drug at therapeutic or even high plasma concentrations does not exclude low adherence, absence of measurable drug, or else very low levels of drug strongly suggests lack of medication intake, particularly in the absence of evidence of significant malabsorption. Here, TDM should rarely be interpreted in isolation, but rather integrated with virological rebound particularly in the absence of any resistance mutations, and other features in the history which suggest risk for low treatment adherence.
2. Optimising treatment in vulnerable patients (e.g. children, pregnant women and patients with extremes of BMI,) or else in specific clinical situations (e.g. liver and renal impairment, treatment failure, drug interactions both foreseen and unanticipated, malabsorption, suspected non adherence, and unlicensed once-daily dosing regimens). In these scenarios, the aim is to optimise dosing based either on known efficacy or toxicity cut-offs, or else to achieve the range of plasma concentrations encountered in patients without these factors, who have been recruited to PK studies at licensed treatment doses which are known to be both safe and efficacious.
3. Managing drug interactions (see above). Where the HIV drug has the potential to be adversely affected by another drug, and the combination is unavoidable, TDM may be used either to manage that interaction, or else discount a significant interaction in a particular patient.
4. Other situations. Knowledge of plasma drug concentrations may be clinically useful when evaluating whether there is scope for treatment simplification, or else confirming or refuting impaired drug absorption as a reason for virological failure.

More detailed recommendations for the use of TDM are available in the BHIVA Monitoring Guidelines 2011 [10]. As for all other investigations, it is essential that TDM is undertaken correctly, especially with regard to timing (undertaken when steady-state has been achieved). A consensus has been achieved for defining targets [11] for many ARVs. With many newer agents,

evidence for a defined minimum target for efficacy is either weak or lacking, and evidence for an upper toxicity cut-off for most ARVs is lacking.

6.2.3 Stopping therapy: pharmacological considerations

6.2.3.1 Recommendations

- We recommend patients stopping ART containing a NNRTI in combination with a NRTI backbone replace all drugs with a protease inhibitor (lopinavir/ritonavir) for four weeks. (1C)
- We recommend patients stopping a PI-containing regimen stop all drugs simultaneously and no replacement is required (1C)

Auditable measure

Proportion of patients with a undetectable viral load on ART who on stopping a regimen containing a NNRTI in combination with a NRTI backbone are switched to a ritonavir boosted PI for four weeks.

6.2.3.2 Rationale

In general, treatment interruptions are not recommended for most patients. Whatever the reason for stopping ART (e.g. drug toxicity, inter-current illness, after pregnancy, or patient choice), pharmacological issues must be considered in order for a clinician to give guidance. The half-life of each drug included in the regimen is critical. There is the potential for monotherapy or dual therapy if antiretroviral drugs with different half-lives are stopped simultaneously. NNRTI and NRTI resistance mutations have been detected following discontinuation of previously suppressive regimens [12] and may have the potential to affect the likelihood of viral re-suppression on restarting a NNRTI based ART regimen.

There is limited data on which to base recommendations for how to protect against development of resistance in the period immediately following treatment cessation. Several discontinuation strategies have been proposed [13], and choice is influenced by clinical considerations, patient wishes and pharmacological principles. Options include: (1) simultaneous stopping all drugs in a regimen containing drugs with similar half lives, (2) a staggered stop, discontinuing the drug with the longest half life first in a regimen containing drugs with short and long half lives; or (3) replacing all drugs with a drug with a short half life and high genetic barrier to resistance (i.e. a protease inhibitor). There is no randomised comparison of these three strategies. However in one study lower numbers of emergent resistance mutations was seen in patients switching to a PI compared to those undertaking a simultaneous or staggered stop [12]. Therapeutic plasma concentrations of EFV can also be detected up to three weeks after stopping the drug in some patients and thus a staggered stop of one week may potentially be inadequate to prevent emergence of NNRTI mutations [14]. The optimal duration of replacement with a PI is not known, but four weeks is probably advisable.

6.2.4 Switching therapy: pharmacological considerations

6.2.4.1 Recommendations

Data on how to switch away from EFV to an alternative ‘third’ agent are either non-existent, or of low or very low quality. Based on pharmacological principles, there is little rationale for any strategy other than straightforward substitution when switching to a PI/r, or RAL.

Pharmacokinetic studies show that straightforward substitution with ETV and RPV may result in slightly lower concentrations of either drug for a short period following switching, but limited virological data suggest that risk of virological failure with this strategy is low. Different strategies for switching to NVP have been proposed, but no comparative data are available to guide the choice of strategy. Limited data suggest that the dose of MVC should be doubled in the week following switching (unless given together with a PI/r).

If switching away from EFV is undertaken when viral load is likely to still to be detectable (e.g. as a result of CNS intolerance within the first few weeks of starting EFV), substitution with a PI/r in preference to a within-class switch is advised.

6.2.4.2 Rationale

Switching a component of an ART regimen is frequently considered in patients to manage drug side effects or address adherence issues. ARVs which either induce or inhibit drug metabolising enzymes have the potential to affect the plasma concentrations of the new agent. This applies in particular to switching away from NNRTIs. Induction of drug metabolising enzymes by EFV is likely to persist for a period beyond drug cessation. Consideration should also be taken of whether or not viral load is maximally suppressed when planning how to switch away from EFV to an alternative agent. Broadly, strategies for switching from EFV to an alternative ‘third’ agent may be summarized as follows:

Efavirenz to nevirapine:

A pharmacokinetic study performed in HIV positive individuals suggested that patients changing from EFV to NVP should commence on 200 mg twice a day to ensure therapeutic plasma concentrations and potentially avoid selection of resistance to NVP [15]. However no patient in the NVP lead-in group experienced virological failure in the 3 month follow up period. Switching without dose escalation is in direct contrast with the information in the Viramune SPC which advises the administration of a NVP lead-in dose (200 mg once daily for two weeks) when starting NVP [16] as this has been shown to decrease the frequency of rash.

In ART experienced patients who are virologically suppressed with an undetectable plasma HIV RNA level (<50 copies/ml), the risk of hypersensitivity and/or hepatotoxicity on switching to NVP is not increased in patients with higher CD4 counts (above the gender specific CD4 count thresholds) [17] In ART experienced patients with detectable plasma HIV RNA levels, a switch to NVP is not advised.

Furthermore the need to minimise any window for developing resistance is greatest in patients who discontinue EFV early on when virological suppression has not yet been achieved. The latter scenario is made more complex when enzyme induction has not yet been fully achieved, and if doubt exists, alternative choices to switch to should be considered.

Efavirenz to etravirine:

Steady-state (14 days following the switch) etravirine (ETV) pharmacokinetic parameters are lowered by previous EFV intake in the case of both once- (C_{min} was lowered by 33%) and twice-daily (C_{min} was lowered by 37%) administration. However, ETV concentrations have been shown to increase over time following the switch and in patients with undetectable viral loads switching from EFV to ETV, standard doses of ETV can be commenced [18]. No data are to date available on what strategy to adopt in patients with active viral replication.

Efavirenz to rilpivirine:

Concentrations of RPV are lowered by previous EFV administration. However, 28 days after the switch, they returned to levels comparable with those when RPV was administered without prior EFV treatment, except for a 25% lower C_{min}. Therefore, in patients with undetectable viral loads switching from EFV to RPV, standard doses of RPV can be commenced [19]. No data is to date available on what strategy to adopt in patients with active viral replication.

Efavirenz to a PI/r:

Because of the strong inhibitory effect of ritonavir on CYP450 3A4, it is unlikely to require a modification of the PI/r dose when switching from EFV to a PI/r. Formal pharmacokinetic data are unavailable. TDM data were presented on ATV/r and showed that after stopping EFV, ATV concentrations were above the suggested minimum effective concentration in all studied subjects [20].

Efavirenz to raltegravir:

Although formal pharmacokinetic data are not available, switching EFV to RAL should not lead to clinical significant consequences, as co-administration of EFV with RAL led to a moderate to weak reduction in RAL C_{min} (21%) [21] and this may persist for two to four weeks after the switch but the degree of this reduction is unlikely to be clinically meaningful.

Efavirenz to maraviroc:

A formal pharmacokinetic study in HIV positive individuals showed that the induction effect of EFV necessitated an increase in MVC dose to 600 mg twice daily for one week following the switch [22]. Maraviroc 300 mg twice daily (standard dose) seems to be safe after this period. Although the absence of data, when switching from EFV to MVC plus a PI/r, it is likely that a dose of 150 mg twice daily is safe from the first day after the switch. Whether it is advisable to use MVC 150 mg once daily in this context or for how long a twice-daily dose should be used after the switch remains unknown.

6.2.5 References

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6.3 Switching ART in virological suppression

6.3.1 Introduction

In patients on fully viral suppressed regimens, switching individual components of the ART combination regimen is frequently considered for several reasons including: management of ARV drug toxicity or intolerance, desire for once daily dosing and reduced pill burden, management of potential drug–drug interactions, patient preference and cost [1]. Guidance on the management of the drug toxicity of individual ARVs is not within the scope of these guidelines. Guidance on interventions to support adherence including once daily dosing and fixed-dose combinations is addressed in Section 6.1 Adherence and pharmacological considerations on switching ARVs is discussed in Section 6.2.4 Switching therapy: pharmacological considerations.

Switching individual components of an ART regimen may well improve adherence and tolerability, but should not be at the cost of virological efficacy. The following guidance concerns the impact on virological efficacy of either switching the third agent or the NRTI backbone in a combination ART regimen or simplifying to boosted PI monotherapy. Evidence from a systematic literature review (Appendix 2) was evaluated, the impact on critical treatment outcomes of different switching strategies assessed. Critical outcomes included virological suppression at 48 weeks, virological failure and discontinuation from grade 3/4 events.

6.3.2. Switching ARVs in combination ART

6.3.2.1 Recommendations

- We recommend in patients on suppressive ART regimens, consideration is given to differences in side effect profile, drug–drug interactions and drug resistance patterns before switching any ARV component. (GPP)
- We recommend in patients with prior NRTI resistance mutations, against switching a ritonavir boosted PI to either a NNRTI or an INI as the third agent. (1B)

Auditable measure

Number of patients with an undetectable VL on current regimen and documented prior NRTI resistance who have switched a PI/r to either a NNRTI or an INI as the third agent

6.3.2.2 Rationale

Within class switches are usually undertaken to improve ARV tolerability. The available evidence for current recommended third agents is limited but switching PI/rs or NNRTIs in virologically suppressed patients has in a small number of studies not been associated with loss of virological efficacy [2–4]. Consideration should however be given to differences in side effect profiles, drug–drug interactions and food effect and for switching between different PIs to the prior history of major PI mutations, as this may potentially have an adverse effect on the virological efficacy of the new PI/r.

For NRTIs recent studies have mainly evaluated switching from a thymidine analogue to either TDF or ABC to manage patients with lipoatrophy or have investigated switching to one of two available NRTI fixed-dose combinations (TDF and FTC or ABC and 3TC). If screening for HLA B5701 positivity is undertaken prior to a switch to ABC, then similar virological efficacy is seen in patients switched to ABC-3TC FDC compared to a switch to TDF-FTC FDC [5]. In general, in the absence of prior resistance mutations, switching within class should result in maintaining virological suppression.

Several RCTs have assessed switching between classes (PI to a NNRTI and PI to an INI) in patients who are virologically suppressed. A meta-analysis of six trials showed non-inferiority in maintenance of virological suppression when switching from a PI (both ritonavir boosted and unboosted) to NVP compared to continuing the PI but was associated with more discontinuations due to liver toxicity [6]. Previous treatment failure on a NRTI containing regimen has been associated with an increased risk of virological failure when switching from a PI to a NNRTI based regimen [7]. A recent cohort analysis showed similar rates of virological failure at 12 months in patients switching from a first-line PI/r to either EFV or NVP compared to continuing on the PI/r. [8]. If switching to NVP, consideration should be given to the risk of hypersensitivity reactions and hepatotoxicity. Similar rates have been reported in virologically suppressed compared to ART naïve patients stratified for CD4 count and gender [9,10]. For patients without prior NRTI or NNRTI resistance mutations switching from a PI/r to any of the current licensed NNRTIs is likely to maintain virological efficacy and choice of NNRTI will depend on side effect profile, tolerability and patient preference.

Switching from a PI/r to the integrase inhibitor, RAL, in virologically suppressed patients has been evaluated in three RCTs. Two studies have shown that a prior history of NRTI resistance mutations increases the risk of subsequent virological failure on switching compared to continuing on a PI/r [11,12]. This association was not seen in a third trial [13]. However it is not surprising that switching from an ARV with a high genetic barrier to one with a low genetic barrier to resistance may potentially increase the risk of virological failure if the activity of the NRTI backbone has been compromised by prior NRTI resistance.

There is limited data on switching from a NNRTI to an alternative third agent in virologically suppressed patients however consideration must be given to prior treatment history and potential PK interactions. The latter is discussed in more detail in Section 6.2.4 Switching therapy: pharmacological considerations.

6.3.2.3 References

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6.3.3. Protease inhibitor monotherapy

6.3.3.1 Recommendation

- We recommend continuing standard combination ART as the maintenance strategy in virologically suppressed patients (1C). There is insufficient data to recommend PI/r monotherapy in this clinical situation.

Auditable measure

Number of patients on PI/r monotherapy as ART maintenance strategy in virologically suppressed patients and record of rationale

6.3.3.2 Rationale

For the assessment and evaluation of evidence, GRADE tables were constructed (Appendix 3). Virological suppression, drug resistance and serious adverse events were defined as critical outcomes. From the systematic literature review (Appendix 2) 10 RCTs were identified, investigating the use of either LPV/r or DRV/r in stable, virologically suppressed patients without active hepatitis B co-infection [1–14].

Assessment of virological suppression showed significantly fewer patients on PI monotherapy maintaining virological suppression compared to those continuing on standard combination ART (RR 0.95 95% CI 0.9,0.99), although the difference was small. A similar result has previously been reported in a meta-analysis [15]. Viral load rebound is usually at low level, and is easily reversed by re-introduction of NRTIs. The long-term consequences of this viral rebound and re-suppression are unknown. There were no differences in the frequency of emergence of viral resistance, or of serious adverse events, though few patients developed drug resistance and thus the confidence in the estimate of this effect is low. One potential concern is the development of CNS disease in patients on PI monotherapy [6,11] however we did not identify a difference in this outcome though the quality of the evidence is low. Further data are required.

Overall there is no significant clinical benefit of PI monotherapy compared to standard combination ART, which might offset the disadvantage of a lower rate of viral suppression with

PI monotherapy. For this reason PI monotherapy should not be used in unselected patient populations for maintaining virological suppression where standard ART is an acceptable alternative. There may be potential benefits of PI monotherapy, in terms of drug resistance, long-term drug toxicity and cost [16] but further data are required. The ongoing 'Protease Inhibitor monotherapy versus Ongoing Triple therapy in the long-term management of HIV infection' (PIVOT) trial has been designed to address these issues [17]. The primary end point is drug resistance.

We recognise that PI monotherapy may well be an acceptable option in some specific patient populations but there are few data to provide recommendations. Clinicians, might consider PI monotherapy in patients who are unable to tolerate NRTIs due to toxicities or as a short term measure to manage or bridge complex clinical scenarios (e.g. stopping certain NNRTI containing regimens or managing toxicity overdose or acute illness) Where PI monotherapy is considered, DRV/r (dosed once or twice daily) or LPV/r (dosed twice daily) should be used. ATV/r monotherapy is not recommended as it has been associated with higher rates of virological failure [18,19]. PI monotherapy is not recommended in patients with active hepatitis B co-infection.

6.3.3.3 References

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6.4 Stopping therapy

6.4.1 Recommendation

- We recommend against treatment interruption or intermittent therapy in patients stable on a virally suppressive ART regimen (1A)

Auditable measure

Proportion of patients with a CD4 count <350 cells/ μ L not on ART

6.4.2 Rationale

Several RCTs have investigated the efficacy of CD4 count guided intermittent therapy as a potential strategy to reduce long-term risk of drug toxicity and drug resistance [1–4]. In the

largest of these, patients were randomised to either CD4 count guided intermittent therapy (stopping ART once CD4 count above 350 cells/ μ L, restarting when CD4 count falls to 250 cells/ μ L) compared to a continuous ART [1]. The trial showed intermittent therapy was associated with a significantly higher rate of opportunistic disease and all cause mortality and a higher rate of major cardiovascular, renal or hepatic disease. The effect was seen at all CD4 count levels. The study showed for the first time that continuous ART with virological suppression is associated with a reduction in the risk of non-AIDS co-morbidities and all cause mortality as well as HIV disease progression. For this reason treatment interruption or intermittent therapy is not recommended.

Once ART has been started in a patient with HIV infection, it should be continued. Temporary interruptions of 1–2 days can usually be managed and are unlikely to be associated with adverse outcomes. Longer interruptions of ART should only be considered in exceptional circumstances. These may include:

- After pregnancy, in women who have taken ART during pregnancy to prevent mother-to-child transmission, but do not otherwise require treatment.
- After early initiation of ART (CD4 counts >500 cells/ μ L) e.g. when started to reduce infectiousness.
- Severe drug toxicity e.g. hepatotoxicity
- Severe psychological distress

Guidance on pharmacokinetic considerations when stopping ART is contained in Section 6.2.3 Stopping therapy: pharmacological considerations.

6.4.3 References

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7. Managing virological failure

7.1 Introduction

For detailed guidance on HIV viral load, resistance and genotropism testing, the reader should consult the BHIVA monitoring guidelines (www.bhiva.org).

The following recommendations concern the management of patients experiencing virological failure on ART. Patient populations at the time of virological failure will include those with no or limited HIV drug resistance through to those with three class failure and either no or limited treatment options. For the assessment and evaluation of evidence, priority questions were agreed and outcomes were ranked (critical, important, and not important) by members of the writing committee. For patients with no or limited HIV drug resistance the following were ranked as critical outcomes: viral suppression <50 copies/ml at 48 weeks, development of resistance, discontinuation rates for clinical and laboratory AE; for patients with three class failure/few therapeutic options: clinical progression, median CD4 count change at 48 weeks, development of new resistance. Treatments were compared where data was available and differences in outcomes assessed. Details of the search strategy and literature review are contained in Appendix 2.

In the UK, the virological failure rate on current first-line regimen in 2008-2009 was approximately 10% at one year [1]. The options for switch depend on the most recent and past ARV treatments as well as current and archived resistance results. As genotypic testing in ARV naïve is now performed routinely and is recommended practice, detection of resistance at virological failure is rarely a result of transmitted drug resistance and failure to adapt first-line treatment [2,3].

The General principles for the management of patients experiencing virological failure are outlined in boxes 1 and 2 as good practice points. Details of typical patterns of HIV drug resistance found in patients with a history of or presenting with virological failure is outlined in box 3. For guidance on HIV viral load, drug resistance and tropism testing the reader should consult the BHIVA guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals 2011 [4](www.bhiva.org/Monitoring.aspx).

Summary auditable measures

Record in patient's notes of resistance result at ART initiation (if available) and at first viral load >400 copies/ml and/or before switch

Record in patient's notes of adherence assessment and tolerability/toxicity to ART in patients' experiencing virological failure or repeated viral blips.

Number of patients experiencing virological failure on current ART regimen

Proportion of patients experiencing virological failure switched to a new suppressive regimen within 6 months

Proportion of patients on ART with prior documented HIV drug resistance with VL <50 copies/ml

Record of patients with three class virological failure with or without three class resistance referred/discussed in MDT with expert advice.

7.2 Blips, low level viraemia and virological failure

7.2.1 Recommendations

- In patients on ART:
- A single viral load of 50–400 copies/ml preceded and followed by an undetectable viral load is usually not a cause for clinical concern (GPP)
- We recommend a single viral load >400 copies/ml is investigated further, as it is indicative of virological failure (1C)
- We recommend in the context of repeated viral blips, resistance testing is attempted (1D)

7.2.2 Rationale

Blips: Optimal HIV control is ordinarily reflected by complete viral suppression with an undetectable viral load. A virological blip is variably defined but for the purposes of these guidelines the definition that has been adopted is a detectable viral load of <400 copies/ml, which is preceded and followed by an undetectable result without any change of therapy. Blips are frequent and represent random variation around a mean undetectable viral load [5–7]. Many patients have at least one at some time [8] when they are not predictive of virological failure or associated with emergent resistance in most studies [5,9,10]. Viral load assay variation and laboratory processing artefacts account for many blips (i.e. no ‘true’ increase in viral replication), which partly explains why blips do not appear to compromise long-term outcomes [9,11–12]. However, those with sustained low-level increases in viral load run a higher risk of virological failure. Most blips are low-level (median magnitude 79 copies/ml in one study [range 51–201]) and short lived (median 2.5 days [range 2–11.5]) [7]. In a retrospective study, 28.6% of patients, experienced VL increases from 50–500 copies/ml over 8 years; 71% of these were blips [8].

Review and reiteration of the importance of full adherence, as well as looking for any tolerability/toxicity issues, drug–drug/food interactions, and archived resistance should take place. However, blips do not appear to be related to inter-current illness, vaccination, baseline CD4/VL, duration of preceding suppression or level of adherence [7,14,15]. Therefore, it is the recommendation of the writing committee that a viral load result of 50–400 copies/ml preceded and followed by an undetectable viral load should not be a cause of clinical concern. In the context of repeated blips, it may then be useful to test for resistance [16,17].

Low level viraemia is defined as a repeatedly detectable but low level of viraemia (LLV) over a sustained period of time. For the purposes of these guidelines, <400 copies/ml is used although it is recognised that some patients have viral loads up to 1000 copies/ml without development of resistance and with therapeutic drug levels. LLV is observed in up to 8% of individuals [18] and is associated with an increased risk of virological rebound (>400 copies/ml) [6,19]. The likelihood

of resuppression after LLV is greater for lower magnitudes of viraemia: 41% after two consecutive viral loads of >50 copies/ml compared with 12% after two VLs >200 copies/ml [20]. LLV is associated with resistance (37% in one study [21]) that may be associated with LLV magnitude; in one analysis, maximum viral load was higher in those who developed resistance (368 vs. 143 copies/ml; P=0.008). LLV is also associated with immune activation [10]. Low-level antigenic exposure differentially affects T-cell activation and HIV specific T cell response. In cohort studies [19] and clinical trials [21] patients on PI/r-based ART are more likely to experience detectable viraemia than those on an NNRTI. In the absence of clear data, the committee believes LLV on a low genetic barrier regimen warrants prompt regimen change. This is especially true where ART combination without a boosted PI is being used [22,23]. Further evaluation should follow as for that listed in Box 1.

Failure is defined as failure to achieve a viral load of <50 copies/ml 6 months after commencing ART or following viral suppression to <50 copies/ml a viral load rebound to >400 copies/ml on two consecutive occasions. In the UK approximately 18% of those achieving an undetectable viral load in 2008-2009 experienced viral load rebound. In the same database, among drug experienced patients the overall prevalence of resistance was 44% in 2007[1]. Confirmation of virological failure at any stage should lead to the practice set out in Box 1.

Box 1: Best practice for the management of patients with virological failure

- Factors affecting adherence and drug exposure including tolerability/toxicity issues, drug–drug/food interactions, ARV potency, significant renal/liver disease, and mental health/drug dependency problems are evaluated
- Resistance testing is performed while on failing therapy or within four weeks of discontinuation
- Past ART and resistance tests are reviewed for archived mutations
- Tropism testing is performed if maraviroc is being considered
- Intensification with an additional active ARV is not recommended
- Once virologic failure is confirmed and a resistance result available, the regimen is changed as soon as possible to avoid accumulation of resistance mutations

The choice of the new ART regimen will primarily depend on the results of resistance testing and the patient's preference. Additional considerations include the results of tropism and HLAB57 testing, drug–drug/food interactions, co-morbidities and future therapy options. The goal of the new combination is to re-establish a VL <50 copies/ml.

Box 2: Best practice for the management of patients with three class virological failure

- In patients with ongoing viraemia and with few options to construct a fully suppressive regimen, referral for specialist advice and/or discussion in an MDT 'virtual' clinic
- Include at least two and preferably three fully active agents with at least one active PI/r(e.g.DRV/r) and one agent with a novel mechanism of action (CCR5 antagonist /integrase or fusion inhibitor)
- Treatment interruption is not recommended

Box 3: Typical resistance patterns on virological failure

- No resistance (wild type virus)
- 3TC/FTC resistance (M184V/I) following any first-line therapy including TDF/FTC or ABC/3TC
- NNRTI resistance (e.g. K103N or Y181C/I/V) and/or 3TC/FTC resistance (following first-line therapy with NNRTI-based including TDF/FTC or ABC/3TC)
- INI resistance (e.g. Q148 or N155H) and/or 3TC/FTC resistance (following first-line therapy with RAL based including TDF/FTC or ABC/3TC)
- Extended RT resistance (e.g. K65R/L74V, or thymidine) (following suboptimal regimens/patients with more extensive drug history associated with virological failure)
- Three class resistance (indicating NRTI, NNRTI and PI) (following multiple failing regimens)
- Limited or no therapeutic options (following multiple failing regimens including the newer drugs with novel actions)

7.3 Patients with no or limited drug resistance**7.3.1 Recommendations**

- We recommend patients experiencing virological failure on first-line ART with WT virus at baseline and without emergent resistance mutations at failure, switch to a PI/r-based combination ART regimen. (1C)
- We recommend patients experiencing virological failure on first-line ART with WT virus at baseline and limited emergent resistance mutations (including two-class NRTI/NNRTI) at failure, switch to a new PI/r-based regimen with the addition of at least one preferably two active drugs (1C)
- We recommend patients experiencing virological failure on first-line PI/r – two NRTI based regimen with major protease mutations, switch to a new active PI/r with the addition of at least one, preferably two active agents of which one has a novel mechanism of action (1C)
- We recommend against switching a PI/r to raltegravir or a NNRTI as the third agent in patients with historical or existing RT mutations associated with NRTI resistance or past virological failure on NRTIs (1B)

7.3.2 Rationale**7.3.2.1 First-line treatment failure with no resistance**

A significant minority of patients have WT virus despite failing on therapy [24–30]. Failure here is usually attributable to poor treatment adherence with drug levels that are both insufficient to maintain viral load suppression and inadequate to select out viral mutations associated with

drug resistance detectable on standard tests. Factors affecting adherence such as tolerability/toxicity issues, regimen convenience, drug-food interactions, and mental health/drug dependency problems should be fully evaluated and where possible corrected before initiation of the new regimen. Additional adherence support should be considered and careful discussion with the patient take place. TDM may be of benefit in individual patients in confirming low/absent therapeutic drug levels and enabling discussion with the patient.

A priority question the writing committee addressed was whether patients failing an NNRTI-based ART without detectable resistance should receive a PI/r- based regimen.

The absence of detectable resistance mutations does not exclude the presence of mutations in minor virus populations, especially with the NNRTIs [9–11]. This may lead to subsequent failure if the same first-line drugs, or drugs in the same class, are prescribed [31,32]. Testing for minority resistance is a specialist test and expert interpretation by a virologist is essential. There is no indication for routine minority species testing in patients failing with WT virus on therapy.

The recommendation of the writing committee is that, following NNRTI/two NRTIs virological failure when no resistance mutations exist, a switch to a PI/r-based regimen should lead to virological suppression and is unlikely to lead to emergent resistance. The decision as to whether or not to restart the same NNRTI-based combination or switch to another NNRTI, RAL or MVC (where CCR5 tropism has been confirmed) has to be individualised to the patient, their past history of virological failure, and to whether further switches in the combination are occurring.

No supportive data exists for management of virological failure when this has developed on first-line therapy with RAL/two NRTIs but the general principles set out for NNRTI-based failure would still apply. However, the high genetic barrier of PI/rs reduces the risk of low-level resistance developing.

7.3.2.2 First -line treatment failure with NNRTI resistance

Up to two-thirds of virologically failing patients harbour viruses with NNRTI and half NRTI mutations at 48 weeks [27–30, 33]: with increasing time, there will be accumulation of resistance mutations that may compromise second-line regimens [34]. Although potential options for second-line therapy after failure on an NNRTI-containing include, RAL, ETV and MVC (RPV is not licensed for this indication), evidence supports the use of a PI/r. A switch to any PI/r-based regimen should lead to virological suppression and is unlikely to lead to further emergent resistance and should be considered whenever possible. Where NRTI resistance has been documented or likely, these should be replaced and new active NRTIs or other ARVs should be incorporated. There are no direct comparisons of the boosted PIs in second-line treatment after first-line failure on an NNRTI-based regimen and choice would be individualised to the patient. Sequencing from an EFV or NVP-based regimen to ETV is not recommended [35] although remains an option when switched as part of a new combination when only K103N is present. Switching to RAL or MVC with two active NRTIs is an option but is also not recommended in a patient with historical or existing RT mutations/prior NRTI virological failure [36].

7.3.2.3 First -line treatment failure on a PI/r-based two NRTI regimen with or without PI resistance

Less than 1% of patients harbour viruses with primary PI mutations and 10–20% NRTI mutations at 48 weeks, with 75% having WT virus [27–29, 37–39]. There is currently limited data regarding the efficacy of switching to another PI/r, NNRTI, MVC, or RAL-based regimen and again the decision is individualised to the patient. However, switching to RAL, MVC, or a NNRTI in a patient with historical or existing RT mutations is not recommended because of an increased risk of virological failure and further emergence of resistance [36]. By contrast, because of the high genetic barrier of PI/rs, sequencing to a regimen that includes a new PI/r is unlikely to lead to further emergent resistance and is recommended. Where PI/r mutations exist, DRV/r is the preferred agent unless resistance is likely.

7.3.2.4 First-line treatment failure with INI based resistance

Up to one half harbour viruses with primary integrase mutations and 25% NRTI mutations at 48 weeks: approximately half have WT virus [26,33,37,40]. Again, there are no data supporting a switch to a PI/r, NNRTI, or MVC but sequencing to a new regimen which includes a PI/r is unlikely to lead to further emergent resistance and is recommended. Switching to an NNRTI or MVC with two active NRTIs is an option but is also not recommended in a patient with historical or existing RT mutations/prior NRTI virological failure. Patients experiencing virological failure on RAL should switch to a new regimen as soon as possible to reduce the risk of accumulating resistance mutations which may affect susceptibility to newer INIs such as dolutegravir.

7.4 Patients with triple-class (NNRTI, NRTI, PI) virological failure with or without triple-class resistance

7.4.1 Recommendations

- We recommend patients with persistent viraemia and with limited options to construct a fully suppressive regimen are discussed/referred for expert advice (or through virtual clinic referral). [GPP]
- We recommend patients with triple-class resistance switch to a new ART regimen containing at least two and preferably three fully active agents with at least one active PI/r such as darunavir/ritonavir or tipranavir/ritonavir and one agent with a novel mechanism (CCR5 receptor antagonist or integrase/fusion inhibitor) with etravirine an option based on viral susceptibility [1C]

7.4.2 Rationale

Risk of development of triple class virological failure is relatively low at around 9% at nine years from start of ART [41]. Until the last few years, limited treatment options have been available for people with HIV who have had virological failure with the three original classes of HIV antiretroviral drugs (triple-class virological failure) of whom many have developed triple-class resistance. Most of these patients have received suboptimal ARV treatment, often from the pre-HAART era, or have been adhered poorly to multiple regimens and have accumulated resistance. However, with the introduction of several new agents active against resistant virus, many of

which have novel sites of action, the potential for virological control akin to that achieved with naïve patients has now become a probability [42,43].

Consequent to more active ARVs and improved strategies of management, there has been substantial improvement in the proportion of people who had virological response after triple-class virological failure between 2000 and 2009 [44]. However, despite improvements in treatments, viral loads cannot be suppressed for some people. In most patients, this is a result of poor adherence but some patients do have extended drug resistance and minimal treatment options and achieving viral suppression is not possible.

The drugs now most commonly used in triple-class failure are the PI/rs, DRV/r and tipranavir/ritonavir (TPV/r), the integrase inhibitors RAL and elvitegravir (ELV) (not yet licensed), the CCR5 chemokine receptor antagonist MVC, the NNRTI ETV, and the fusion inhibitor enfuvirtide. The available data for DRV/r, TPV/r, RAL, ELV, ETV, and enfuvirtide show that they are most effective when used with other active drugs to which the virus is susceptible based on resistance testing and antiviral experience [45–53]. When used as the only effective agent, the likelihood of achieving virological suppression is significantly and the development of emergent resistance to the drug greater and a future opportunity for constructing an effective regimen is often lost.

A priority question the writing committee addressed was whether two or three fully active drugs should be included in the new regimen. In a meta-analysis of 10 trials of patient with triple-class virological failure and virological resistance where the study drug was added to optimised background therapy (OBT) and compared to placebo, associations were demonstrated with increased virological suppression (pooled OR 2.97) and larger CD4 count increases for the active agent [54]. OBT genotypic sensitivity scores (GSSs) were also associated with larger differences in virological suppression ($P < 0.001$ for $GSS = 0, \leq 1$ and ≤ 2) and CD4 cell count increase ($GSS = 0, P < 0.001$; $GSS \leq 1, P < 0.002$; $GSS \leq 2, P = 0.015$) between the two groups. In a further non-inferiority study, ELV was found to be non-inferior to RAL when accompanied by a boosted PI and a third agent [46].

This supports the use of at least two and possibly three of these agents in the new regimen and with this strategy, the goal of an undetectable viral load is now achievable even in most patients with multiregimen failure. A priority question addressed in this group was whether regimens with at least three fully active drugs should include NRTIs? The recommendation from the writing committee is that in constructing an optimized background, continuing/commencing NRTIs may contribute partial ARV activity to a regimen, despite drug resistance [56,57].

For those drugs with a novel mode of action (integrase and fusion inhibitors, and CCR5 antagonists), the absence of prior exposure indicates susceptibility although MVC is only active against patients harbouring CCR5 tropic virus. For DRV, TPV and ETV, the number and type of mutations inform the degree to which these drugs are active [57–59]. The potential for drug–drug interactions is also important. Etravirine can be paired with DRV/r (but not TPV/r) and MVC dosing is variable depending on the other drugs in the new regimen: however, RAL and enfuvirtide require no alteration.

Some patients can have a successfully suppressive fully active three-drug regimen constructed without a PI/r [60]. Nevertheless, where feasible a PI/r such as DRV/r should be included because of its protective effect on emergent resistance to the other drugs in the regimen although this can be given DRV/r 800mg/100mg once daily in treatment-experienced patients

without DRV RAMs [61]. Enfuvirtide is an option in some patients despite the inconvenience of subcutaneous injection and injection site reactions. With the availability of the newer agents, dual PI/rs are not recommended [62].

The same principles regarding reviewing adherence, tolerability/toxicity issues, drug–drug/food interactions, and mental health/drug dependency problems apply. Additional adherence support is important in these patients as the reason triple-class failure has occurred often relates to past poor adherence. Additionally, the pill burden is increased and careful discussion with the patient should take place.

7.5 Patients with limited or no therapeutic options when a fully viral suppressive regimen cannot be constructed

7.5.1 Recommendations

- We recommend accessing newer agents through research trials, expanded access and named patient programmes (GPP)
- We suggest continuing/commencing NRTIs as this may contribute partial ARV activity to a regimen, despite drug resistance (2C)
- We recommend the use of lamivudine or emtricitabine to maintain a mutation at codon position 184 of the reverse transcriptase gene (1B).
- We recommend against discontinuing or interrupting ART (1B)
- We recommend against adding a single, fully active ARV because of the risk of further resistance (1D)
- We recommend against the use of maraviroc to increase the CD4 count in the absence of CCR5 tropic virus. (1C)

7.5.2 Rationale

This usually occurs following attempts in patients with triple-class failure to achieve virological suppression with the newer agents and often indicates adherence issues have not been addressed successfully or sequential addition of the newer agents has occurred without incomplete viral suppression and selection of resistance to the new drug.

There is evidence from cohort studies that continuing therapy, even in the presence of viraemia and the absence of CD4 T-cell count increases, reduces the risk of disease progression [63,64] whereas interruption may lead to a rapid fall in CD4 count and rise in viral load [65,66]. Other studies suggest continued immunologic and clinical benefits if the HIV RNA level is maintained <10,000–20,000 copies/ml [67]. Continuing or commencing NRTIs, even in the presence of known resistance may contribute partial ARV activity [55,56]. Hence, if the CD4 cell count is well maintained (>200 cells/ μ L), it may be better to continue the failing regimen and not change treatment until investigational agents are available that can be put together with drugs, which may have only partial activity at best, to increase the likelihood of constructing a virologically suppressive and durable regimen options.

In general, adding a single, fully active ARV to a failing regimen is not recommended because of the risk of rapid development of resistance. However, in patients with a high likelihood of clinical progression (e.g. CD4 cell count <100 cells/mm³) and limited drug options, adding a single drug may reduce the risk of immediate clinical progression, because even transient decreases in HIV RNA and/or transient increases in CD4 cell counts have been associated with clinical benefits [68]. Potential benefits must be balanced with the ongoing risk of accumulating additional resistance mutations and patients should maintain that regimen for the shortest period possible [69,70].

Where feasible, patients should be given the opportunity to enrol in research studies or expanded access programs evaluating investigational new drugs. Some drugs are likely to be available in the near future that might be sequenced in the same class (e.g. dolutegravir) although others with novel sites of action (e.g. maturation inhibitors, CD4 receptor antagonists etc) are still in earlier phases of development and some years off randomised trials. Drugs developed for and used in other settings such as pegylated Interferon that have been incidentally demonstrated to decrease viral load should not be used without discussion with an experienced HIV physician as data is either too limited or contradictory.

Several studies and an early meta-analysis suggested that CCR5 receptor antagonists were associated with significant gains in CD4 cell counts even in the presence of CXCR4 tropic virus. However, a more recent meta-analysis refuted this finding (P=0.22) when comparing with other new drugs [54].

A priority question that the writing committee addressed was whether 3TC/FTC should be used in maintaining an RT mutation at 184 in patients with limited or no therapeutic options.

Although the M184V mutation is associated with resistance to 3TC/FTC, the mutation has a broad influence on the reverse transcriptase enzyme. *In vitro* studies have shown that M184V-possessing enzymes have lower processivity and higher fidelity and replicate more slowly than wild-type enzymes [71]. These observations have led to the hypothesis that maintaining this mutation using 3TC/FTC would provide clinical benefit through the replication deficit provided by the M184V mutation combined with the residual antiviral activity of 3TC/FTC [72,73]. It has been shown that patients harbouring M184V due to 3TC failure who continue on 3TC monotherapy maintain lower viral loads than at baseline and rarely develop new RT or protease mutations [74]. Moreover, ceasing 3TC monotherapy has been demonstrated to result in replication capacity recovery and a reduction in CD4⁺/CD8⁺ ratio driven by the de-selection of the M184V mutation [75]. This strategy is supported by the E-184 study which was a small but randomised, open-label study of 3TC monotherapy versus no therapy in patients failing ART [76]. Monotherapy was associated with significant smaller increases in viral load, smaller declines in CD4⁺ cell counts, and no selection of additional reverse transcriptase mutations.

Finally, the presence of M184V mutation enhances *in vitro* susceptibility to TDF and this translated into a significant HIV RNA response in clinical trials of TDF intensification [77,78].

7.6 References

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8. ART in specific populations

For some patient populations specific considerations need to be taken into account deciding when to start and the choice of ART. The following sections outline specific recommendations and the supporting rationale for defined patient populations. In parallel to guidelines on ART in adults, BHIVA also publishes guidelines on the management and treatment of specific patient populations including co-infection with tuberculosis, co-infection with viral hepatitis B or C, and HIV pregnant women. An outline of the recommendations for when to start and choice of ART, from the BHIVA guidelines for tuberculosis and viral hepatitis is summarised below. The reader should refer to the full published guidelines for these patient populations for more detailed information and guidance at the BHIVA web site (www.bhiva.org/publishedandapproved.aspx) and be aware that BHIVA clinical practice guidelines are periodically updated.

For the BHIVA adult ART 2012 guidelines new guidance on when to start and choice of ART has been developed for HIV related cancers, HIV-associated neurocognitive impairment, chronic kidney disease, cardiovascular disease and women. The guidance only considers specific issues concerning the initiation and choice of ART in these patient populations. Guidance on the management of pregnancy in HIV-positive woman has not been included.

8.1 HIV with tuberculosis co-infection

This guidance provides a brief summary of the key statements and recommendations regarding prescribing ART in HIV-positive patients co-infected with tuberculosis (TB). It is based on the BHIVA 2011 TB/HIV guidelines [1] which should be consulted for further information. The full version of the guidelines is available at:

http://www.bhiva.org/documents/Guidelines/TB/hiv_954_online_final.pdf

8.1.1 When to start ART

8.1.1.1 Recommendations:

- Timing of initiation of antiretroviral therapy during TB therapy.

CD4 count cells/ μ L	When to start HAART
<100	As soon as practical within two weeks after starting TB therapy (1B)
100–350	As soon as practical, but can wait until after completing two months TB treatment, especially when there are difficulties with drug interactions, adherence and toxicities (1B)
>350	At physician's discretion (1B)

Auditable measure

Proportion of patients with TB and CD4 count <100 cells/ μ L started on ART within 2 weeks of starting TB therapy

8.1.1.2 Rationale

Most patients with tuberculosis in the UK present with a low CD4 count, often <100 cells/ μ L. In such patients ART improves survival, but can be complicated by immune reconstitution disease (IRD) and drug toxicity. Data suggests that antiretroviral therapy can be delayed until the first two months of TB therapy has been completed but at CD4 counts <50 cells/ μ L the short-term risk of developing further AIDS-defining events and death is high, and ART should be started as soon as practicable and within two weeks of initiation of TB therapy [2–5]. Starting ART early in severely immunosuppressed HIV-positive patients presenting with TB is associated with decreased mortality and a lowering of the rates of disease progression but rates of IRD are high.

Patients with HIV and a CD4 cell count >350 cells/ μ L have a low risk of HIV disease progression or death during the subsequent six months of TB treatment, depending on age and viral load [6]. They should have their CD4 cell count monitored regularly and antiretroviral therapy can be withheld during the short-course of TB treatment.

One study performed in HIV-associated TB meningitis in the developing world, where 90% were male, the majority drug users, many with advanced disease and the diagnosis being made clinically, showed no difference in mortality starting ART early or late [7].

8.1.2 What to start

8.1.2.1 Recommendations

- We recommend efavirenz in combination with tenofovir and emtricitabine as first-line antiretroviral therapy in TB/HIV co-infection (1B)
- We recommend that when rifampicin is used with efavirenz in patients over 60kg, the efavirenz dose is increased to 800mg daily. Standard doses of efavirenz are recommended if the patient weighs less than 60kg (1C)
- We recommend that rifampicin is not used with nevirapine or ritonavir-boosted protease inhibitors (1C)
- We recommend that where effective ART necessitates the use of ritonavir-boosted protease inhibitors that rifabutin is used instead of rifampicin (1C)

Auditable measure

Proportion of patients with active TB on anti-tuberculosis therapy started on ART containing efavirenz and tenofovir and emtricitabine

8.1.2.2 Rationale

Preferred ART

HIV-related tuberculosis should be treated with a regimen including a rifamycin for the full course of tuberculosis treatment, unless there is rifamycin resistance or intolerance. Rifamycins frequently interact with antiretroviral medications and can lead to similar toxicities, notably rash and hepatitis. We recommend EFV as the preferred therapy for ART because of its confirmed potency when used in TB/HIV co-infection [8–10], and its efficacy in randomized clinical trials. We recommend that EFV be given with TDF and FTC due to the availability of a once daily co-formulation, a reduced risk of rash compared to NVP and improved efficacy at higher HIV viral loads (commonly occurring in this setting). ABC-3TC is an alternative acceptable NRTI backbone in patients with lower HIV viral loads and who are HLAB5701 negative (see Section 4.3 Which NRTI backbone)

There is significant variability in the effect that rifampicin has on EFV concentrations because of liver enzyme induction especially of CYP P450 3A4 [8,11–13]. Sub-therapeutic EFV concentrations may occur among patients who weigh more than 60 kilograms who are taking standard-dose EFV together with rifampicin, and increasing the dose of EFV from 600 mg daily to 800 mg daily may be necessary but there is a risk of increasing adverse effects. A cohort study and a small randomized controlled trial have shown that the standard adult EFV dose (600 mg daily) together with 2 nrtis is well-tolerated and was efficacious in achieving complete viral suppression among adults on concomitant rifampicin-based tuberculosis treatment although the majority of patients were of low body weight [10,14,15].

In summary, we recommend that when EFV is used with rifampicin, and in patients over 60kg, the EFV dose is increased to 800mg daily. Standard doses of EFV are recommended if the patient weighs less than 60kg. We suggest that therapeutic drug monitoring be performed at around week of starting EFV if side effects occur and the dose adjusted accordingly.

Nevirapine

Nevirapine taken with TB treatment is complicated by pharmacokinetic interactions and by overlapping toxicities especially skin rash and hepatitis. One study showed that patients co-infected with HIV and TB who initiated NVP-based ART during TB treatment had a nearly two-fold higher risk of having a detectable HIV viral load after six months compared to those taking NVP who did not have tuberculosis. However, those patients who were established on NVP at the time of initiation of TB treatment did not have a higher risk of HIV virological failure [11]. Using a higher maintenance dose of NVP (300mg bd) to overcome drug interactions has been associated with higher rates of hepatotoxicity [16]. In one randomized trial comparing NVP 200 mg twice daily at initiation to EFV 600 mg once-daily among patients with TB and HIV and CD4 counts below 250 cells/ μ L non inferiority of NVP was not demonstrated compared to EFV [17].

Protease inhibitors

When co-administered with rifampicin, concentrations of standard-dose protease inhibitors are decreased below therapeutic targets and cannot, therefore be recommended [18–20]. Changing the dosing of PI/rs has resulted in unacceptable rates of hepatotoxicity [21–23].

Rifabutin has little effect on the concentrations of PI/rs but rifabutin concentrations are increased when the drug is taken together with protease inhibitors. Current recommendations

are to give rifabutin at a dose of 150 mg thrice-weekly to adults taking PI/rs. Some data suggest that 150 mg od can be given to reduce the theoretical risk of rifampicin resistance due to sub therapeutic rifabutin concentrations but this strategy may be associated with increased side effects [24–31].

Other drugs

There are few clinical data to support the use of newer nrtis, integrase inhibitors and CCR5 receptor antagonists with rifampicin or rifabutin. We recommend that physicians review the PK and other data summarised in the current BHIVA HIV and TB guidelines [1].

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8.2 HIV and viral hepatitis co-infection

8.2.1 Introduction

The following guidance provides a brief summary of the key statements and recommendations regarding prescribing ART in patients with HIV/Hepatitis B and C co-infection. It is based on the BHIVA guidelines for the management of co-infection with HIV-1 and hepatitis B or C virus 2010 [1] which should be consulted for further information and to the BHIVA web site for latest updates (www.bhiva.org/publishedandapproved.aspx).

Where viral hepatitis B or C chronic infection has been diagnosed, individuals should be referred to a dedicated co-infection clinic or hepatologist for appropriate staging of their hepatitis B or C infection. The decision to initiate treatment for either HIV or viral hepatitis infections should ordinarily be made with agreement of the patient's HIV and viral hepatitis physicians.

In patients with cirrhosis (Child-Pugh grade B/C) certain antiretroviral therapy should be used with caution and careful monitoring (including TDM) will be required by physicians experienced in the management of HIV and viral hepatitis co-infection. For further information on use of ART in patients with cirrhosis please refer to the BHIVA HIV and hepatitis B/C co-infection guidelines [1].

Summary of when to start recommendations

CD4 Cells/ μ L	HBV requiring Rx ¹	HBV not requiring Rx	HCV with immediate plan to start HCV Rx ¹	HCV with no immediate plan to start HCV Rx
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>500	Start ART in some patients (2C) (Include tenofovir and emtricitabine)	Defer ART	Defer ART	Defer ART
≤500	Start ART (1B) (Include tenofovir and emtricitabine)	Start ART (1B) (Include tenofovir and emtricitabine)	350–500 Start ART after HCV treatment commenced (1C) <350 Start ART before HCV treatment (1B). Discuss with HIV and viral hepatitis specialist	Start ART (1C)

1. See viral hepatitis Guidelines [1] for indications to treat hepatitis B and C

8.2.2 Hepatitis B

8.2.2.1 When to start ART

Recommendations

- We recommend patients with HIV and hepatitis B virus co-infection who have a CD4 count between 350–500 cells/μL start ART (1C)
- We suggest patients with HIV and hepatitis B virus co-infection who have a CD4 count >500 cells/μL and who require treatment for their hepatitis B start ART (2C)

Auditable measure

Proportion of patients with HIV and hepatitis B virus co-infection with CD4 counts <500 cells/μL on ART

Rationale

Because of the negative effect of immune depletion on HBV disease progression, the availability of single drugs with high level dual hepatitis B and HIV anti-viral activity, and the increased risk of liver-related deaths in patients with CD4 counts below 500 cells/μL, co-infected patients with CD4 counts between 350 and 500 cells/μL should start ART and be treated with drugs active at suppressing both viruses [2]. Consideration can be given to some patients with CD4 counts between 350 and 500 cells/μL and HBV DNA of <2000 IU/L and no evidence of liver

inflammation or fibrosis to close monitoring of their HIV and hepatitis B infections as an acceptable alternative strategy.

Individuals with a CD4 count >500 cells/ μ L who do not require hepatitis B therapy, should be monitored for HIV and hepatitis B disease progression and the need of therapy for either virus infection. Among individuals with a CD4 count >500 cells/ μ L who require treatment for hepatitis B infection there is the option to start ART with drugs active at suppressing both viruses. For indications to start treatment for hepatitis B infection please refer to the BHIVA guidelines on management of co-infection with HIV and hepatitis B or C virus (1).

8.2.2.2 What to start

Recommendations

- We recommend patients with HIV and hepatitis B virus co-infection who start ART include tenofovir and emtricitabine as part of their ART regimen, if there are no contraindications for either drug (1A)

Auditable measure

Proportion of patients with HIV and hepatitis B virus co-infection starting tenofovir and emtricitabine as part of their first ART regimen

Rationale

Tenofovir, FTC and 3TC are agents that have antiviral activity against both HIV and hepatitis B. The efficacy of these drugs against hepatitis B has been assessed in randomized trials extending out to 5 years in mono-infected patients [3]. They are recommended agents in these guidelines for the treatment of HIV-1 infection.

All hepatitis B co-infected individuals who start ART, should commence a regimen containing TDF and FTC. Hepatitis B treatment options for patients declining ART are discussed elsewhere [1].

If an individual becomes intolerant or is unable to commence a TDF containing regimen, TDF should be substituted with either adefovir or entecavir and an alternate antiretroviral agent added to the regimen. No individual co-infected with hepatitis B should receive a regimen containing 3TC or FTC monotherapy as its use may result in the selection of the YMDD mutation [4,5]. HBV resistance to TDF is rare and combination with 3TC and FTC has been demonstrated to be effective at suppressing HBV DNA and may induce hbeag seroconversion and may reduce the risk of HBV breakthrough [6].

In individuals virologically failing hepatitis B therapy a resistance test should be taken and new therapy for HIV and hepatitis B commenced only after close consultation with a specialist virologist or specialists in HIV/viral hepatitis co-infection clinic. Co-infected individuals who need to start a new ART regimen for reasons such as ART virological failure should ensure that effective anti hepatitis B therapy is continued in addition to their new ART regimen. Abrupt withdrawal of effective treatment may lead to a flare in hepatitis B replication with liver damage. This may be particularly severe in patients with cirrhosis.

8.2.3 Hepatitis C

8.2.3.1 When to start ART

Recommendations

- We recommend patients with HIV and hepatitis C virus co-infection be assessed for HCV treatment (GPP)
- We recommend patients with HIV and hepatitis C virus co-infection and CD4 count between 350-500 cells/ μ L start ART: (i) immediately if HCV treatment is deferred, (ii) after initiation of HCV treatment if this is starting immediately.¹ (1C)
- We recommend patients with HIV and hepatitis C virus co-infection and CD4 count <350 cells/ μ L start ART before HCV treatment (1B)

Auditable measure

Proportion of patients with HIV and Hepatitis C virus co-infection and CD4 counts <500 cells/ μ L on ART

Rationale

HCV is believed to have a deleterious effect on HIV disease progression [7,8]. In addition, HIV has an impact on hepatitis C infection. The rate of liver fibrosis progression is faster in HIV/HCV co-infected patients particularly among patients with low CD4 cell counts [9,10,11]. The estimated risk of cirrhosis was two-fold higher in individuals with HIV/HCV co-infection compared with those with HCV mono-infection [12]. Liver mortality rates are reportedly higher in those with a low CD4 count [13] and hepatocellular carcinoma (HCC) is believed to occur at a younger age and within a shorter time period [14]. All patients with chronic hepatitis C should be assessed for their HCV related liver disease as well as for their stage of HIV infection.

Cohort studies examining the effect of ART on the natural history of HCV infection have shown inconsistent results [15,16]. A few studies have concluded that HIV viral load, but not CD4, was directly related to fibrosis progression rate [17], a finding consistent with the role of HIV viral load both as a predictor of AIDS survival and as a predictor of survival in HCV/HIV co-infected individuals [18,19] and also in HCV/ HIV co-infected liver transplant recipients [20]. ART is not associated with serious histological liver disease [21].

For these reasons, patients with HIV and hepatitis C infection with CD4 counts <500 cells/ μ L should start ART. This should be immediate if: (i) CD4 count is <350 cells/ μ L, irrespective of whether HCV treatment is planned or not, (ii) CD4 count is between 350 and 500 cells/ μ L and treatment for HCV has been deferred. For patients with CD4 counts between 350 and 500 cells/ μ L starting HCV treatment immediately, initiation of ART should be delayed until after start of HCV treatment. Individual factors will determine the timing of ART after HCV treatment is commenced.

Individuals with a CD4 count greater than 500 cells/ μ L who defer hepatitis C therapy, should be monitored closely for HIV or hepatitis C disease progression and the need for therapy for either virus.

8.2.3.1 What to start

Recommendations

- We recommend that potential pharmacokinetic interactions between antiretrovirals and anti-hepatitis agents are checked prior to administration (with tools such as: <http://www.hep-druginteractions.org>) (GPP)

Auditable measure

Record in patient's notes of potential pharmacokinetic interactions between antiretrovirals and ant-viral hepatitis C agents

Rationale

Significant pharmacokinetic and pharmacodynamic interactions have been reported between antiretroviral drugs and the newer anti hepatitis agents. Boceprevir and telaprevir undergo extensive hepatic metabolism, boceprevir primarily by way of the aldo-ketoreductase system but also by the cytochrome P450 enzyme system; whereas telaprevir is metabolized only by the cytochrome P450 enzyme system, and the main route of elimination is via the faeces with minimal urinary excretion. Both boceprevir and telaprevir are potent cytochrome P450 inhibitors. Therefore drug–drug interactions (DDI) are likely when used together with antiretroviral drugs. Currently, studies have been completed for TDF, EFV, ATV/r and RAL with telaprevir and for TDF, DRV/r, LPV/r, ATV/r, EFV and RAL for boceprevir [22–27] Other DDI studies are planned and currently information is available at www.hep-druginteractions.org.

Due to the rapidly emerging data on the use of these newer agents and the complexities of the drug interactions, we suggest that the treatment of HCV infection in HCV/HIV co-infected patients should be carried out as part of a clinical trial. If a suitable clinical trial is not available, such treatment should only be carried out by physicians who have experience with the new HCV protease inhibitors and/or directly acting agents. Extreme care should be given to drug–drug interactions in patients who are taking HIV treatment. HIV treatment should be switched to agents where DDI have been studied.

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8.3 HIV-related cancers

Summary auditable measures

Proportion of patients with an AIDS defining malignancy on ART

Proportion of patients with a non-AIDS defining malignancy on ART

Record in patient’s notes of potential pharmacokinetic drug interactions between antiretrovirals and systemic anti-cancer therapy

8.3.1 When to start ART: AIDS-defining malignancies

Kaposi sarcoma, high-grade B-cell non-Hodgkin lymphoma and invasive cervical cancer are all AIDS defining illnesses and are thus indications to commence ART regardless of CD4 cell count or HIV viral load.

8.3.1.1 Kaposi sarcoma (KS)

Recommendation

- We recommend starting ART in HIV positive patients with Kaposi sarcoma (1A)

Rationale

ART has been shown to reduce the incidence of KS in HIV cohort studies [1–4], to prevent KS in patients on ART [5], and in addition increases the time to disease progression in KS [6], improves prognosis in KS and prolongs survival in KS [7-9]. When initiating ART for KS, there appears to be no difference in response or outcome of KS between different HIV treatment regimens [5,10]. Therefore, no recommendation can be made on choice of HIV therapy for patients with KS.

8.3.1.2 Non-Hodgkin lymphoma (NHL)

Recommendation

- We recommend starting ART in HIV positive patients with non-Hodgkin lymphoma (1B)

Rationale

ART has been shown to reduce the incidence of NHL [2,11–20] and to improve the outcome [9,21–24]. Before ART was available, the treatment of NHL with standard doses of chemotherapy produced marked toxicity and a high incidence of opportunistic infections [25]. In an attempt to decrease toxicity, modified dose chemotherapy regimens were used by the AIDS clinical trials group (ACTG). However, the reduced opportunistic infections were offset by the lower response rates [26]. Since the widespread availability of ART, two retrospective studies reported higher tumour response rates and overall survival in HIV seropositive patients with systemic NHL who were treated with CHOP chemotherapy and concomitant ART compared to those who were treated with CHOP alone [21,22]. Similarly, in a separate study of liposomal doxorubicin in combination with cyclophosphamide, vincristine and prednisolone in HIV-associated NHL, improvement in survival was associated with HIV viral control, although complete remission rates were independent of HIV viral load [27].

Further evidence to support the use of ART with chemotherapy in both KS and NHL is the finding from historical comparisons that the fall in CD4 count during chemotherapy is less profound when ART is prescribed concomitantly and that the duration of lymphocyte subset suppression is briefer [28–31].

However, a number of US intergroup studies have either withheld ART during chemotherapy [32,33] or delayed the initiation of ART [34]. The rationale for this approach includes avoiding adverse pharmacokinetic and pharmacodynamic interactions between ART and chemotherapy and the theoretical concern that protease inhibitors may inhibit lymphocyte apoptosis and thus contribute to chemoresistance of lymphomas [35]. Although no new HIV mutations were identified, these studies were small and ART was promptly reinstated after abbreviated chemotherapy. Nevertheless it took 12-18 months after completing the chemotherapy for plasma HIV viraemia to become undetectable in many patients [33]. Importantly, patients with NHL frequently present with CD4 counts <200 cells/ μ L and thus the reduction in CD4 count associated with systemic chemotherapy and structured suspension of ART is not ideal.

8.3.1.3 Cervical cancer

Recommendation

- We suggest starting ART in HIV positive patients with cervical cancer (2C)
- We recommend starting ART in HIV positive patients who are commencing radiotherapy or chemotherapy for cervical cancer (1D)

Rationale

There is less clear evidence to support starting ART in women diagnosed with invasive cervical cancer, despite its status as an AIDS defining illness. Co-registration studies have shown that ART has not reduced the incidence of cervical cancer [36–38], moreover the effects of ART on pre-invasive cervical dysplasia have been variable with some studies suggesting that ART causes regression of cervical intraepithelial neoplasia [39–45] and others showing no beneficial effect of ART [46–49]. The effects of ART on outcomes in HIV positive women with invasive cervical cancer have not been reported but analogies with anal cancer may be drawn as the malignancies share common pathogenesis and treatment modalities. Combined chemoradiotherapy in anal cancer has been shown to cause significant and prolonged CD4 suppression even when ART is administered concomitantly [50–53]. Similarly the toxicity of chemoradiotherapy for HIV-associated anal cancer appears to be less profound amongst patients given ART compared to historical controls [51,52,54–59].

8.3.2 When to start ART: non-AIDS-defining malignancies

Recommendation

- We suggest starting ART in HIV positive patients with non-AIDS defining malignancies (2C)
- We recommend starting ART in HIV positive patients who are commencing immunosuppressiveradiotherapy or chemotherapy for non-AIDS defining malignancies (1C)

Rationale

Whilst ART has little effect on the incidence of non-AIDS defining malignancies (NADMs) [2,60–67] and there is no evidence that ART alone causes regression of NADMs, the immunosuppressive effects of both chemotherapy [28–31] and radiotherapy [50–53] may justify starting ART in HIV positive individuals who are commencing systemic anticancer therapy or radiotherapy.

8.3.3 What to start

Recommendation

- We recommend that potential pharmacokinetic interactions between antiretrovirals and systemic anticancer therapy are checked prior to administration (with tools such as: <http://www.hiv-druginteractions.org>)(GPP)

Rationale

Significant pharmacokinetic and pharmacodynamic interactions have been reported between antiretroviral drugs and systemic anticancer therapies. The mechanisms of the pharmacokinetic interactions include the inhibition and induction by antiretroviral agents of enzymes, especially the cytochrome P450 family and UGT (uridine diphospho-glucuronosyl transferase) isoenzymes, involved in the catabolism and activation of cytotoxic chemotherapy agents. In addition, competition for renal clearance, intracellular phosphorylation and ABC (ATP binding cassette) transporters, has been hypothesised to contribute to these drug interactions [68]. Similarly, pharmacodynamic interactions, in particular overlapping toxicities between antiretrovirals and systemic anticancer therapy suggest that some drug combinations should be avoided in patients with HIV-associated cancers. Much of the guidance on the use of individual antiretroviral agents with systemic anticancer therapy comes from reviews of potential drug interactions rather than from clinical studies [68–70]. The pharmacokinetic interactions between antiretrovirals and systemic anticancer therapy are not confined to cytotoxic chemotherapy agents and extensive interactions with newer targeted therapies such as imatinib, erlotinib, sorafanib, bortezomib and temsirolimus have been described [70].

Recommendation

- We suggest avoiding ritonavir-boosted ART in HIV positive patients who are to receive cytotoxic chemotherapy agents that are metabolised by the CYP450 enzyme system (2C)

Rationale

In general, clinically important pharmacokinetic drug interactions with systemic anticancer therapies are most common with PI/r based ART and most clinicians avoid these combinations where possible. For example, in a cohort study, the rates of severe infections and severe neutropenia following chemotherapy for AIDS related NHL were significantly higher amongst patients receiving concomitant PI (mainly ritonavir boosted) than in those on NNRTI-based ART regimens, although there was no difference in survival between the groups [71]. Furthermore, case reports of clinically significant life-threatening interactions between ritonavir-boosted based ART and docetaxel [72], irinotecan [73], vinblastine [74] have been published.

Recommendation

- We recommend against the use of atazanavir in HIV positive patients who are to receive irinotecan (1C)

Rationale

The camptothecin cytotoxic agent irinotecan is extensively metabolised by UGT1A1 isoenzymes that are inhibited by atazanavir [75]. In patients with Gilbert's syndrome, who have a congenital deficiency of UGT1A1, irinotecan administration has led to life-threatening toxicity [76].

Recommendation

- We suggest avoiding antiretroviral agents in HIV positive patients who are to receive cytotoxic chemotherapy agents that have overlapping toxicities (2C)

Rationale

Both antiretroviral agents and systemic anticancer therapies have substantial toxicity and where these overlap it is likely that the risk of toxicity is greater. For example zidovudine commonly causes myelosuppression and anaemia [77] which are also frequent side effects of cytotoxic chemotherapy and so these should not be co-prescribed where possible. Similarly, dideoxynucleosides cause peripheral neuropathy [78], a common toxicity of taxanes and vinca alkaloids, so co-prescribing should be avoided. Both zidovudine and dideoxynucleosides are no longer recommended for initiation of ART but some treatment-experienced patients may still be receiving these drugs and alternatives should be considered.

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8.4 HIV-associated neurocognitive impairment

8.4.1 Introduction

With the widespread use of effective combination antiretroviral therapy, the incidence of severe HIV-associated cerebral disease has declined dramatically [1], however more subtle forms of brain disease, known as HIV-associated neurocognitive (NC) disorders are reported to remain prevalent [2]. This NC deficit may present with a wide spectrum of clinical symptoms, however typically includes patterns involving ineffective learning and problems with executive function, rather than pure difficulties in formulating new memory (the cortical defect typical of Alzheimer's Disease [3]).

Given the changing picture of this disease, a revised nomenclature system has proposed classifying subjects with abnormal neuropsychological testing results in to three categories based on patient's symptoms, measured via the activities of daily living (ADL) scale [2]. Subjects with abnormal neuropsychiatric testing results, who are otherwise asymptomatic are classified as having HIV-associated asymptomatic neurocognitive impairment (ANI), those who are mildly symptomatic are classified as having HIV-associated mild neurocognitive disorder (MND) and those who are severely symptomatic are classified as having HIV-associated dementia (HAD). The clinical relevance of ANI, namely asymptomatic subjects with abnormal results on neuropsychological testing, remains unclear.

Reports describing rates of NC impairment vary with some groups describing that up to 50% of HIV positive subjects meet the above diagnostic criteria [4]. However such reports should be interpreted with caution as asymptomatic subjects are often included and not all reports correct for effective antiretroviral use. A Swiss cohort has reported 19% of aviraemic HIV positive subjects to meet the classification for MND or above [5].

Risk factors for the development of NC disorders are poorly understood and are likely to be multifactorial including both HIV disease factors [6] and concomitant diseases [7]. Although it is possible the choice of combination antiretroviral therapy a subject receives may influence NC function, this is a controversial area without definitive evidence. The following recommendations apply to patients with symptomatic HIV-associated neurocognitive disorders.

8.4.2 When to start ART

8.4.2.1 Recommendation

- We recommend patients with symptomatic HIV-associated neurocognitive disorders start ART irrespective of CD4+ lymphocyte count (1C)

Auditable measure

Proportion of patients with symptomatic HIV associated neurocognitive disorders on ART

8.4.2.2 Rationale

Current evidence suggests NC function improves after commencing antiretroviral therapy for the first time [8] in both cognitively-symptomatic [9] and –asymptomatic [10] subjects. However these studies have been undertaken in individuals with other indications to commence antiretroviral therapy, in general with CD4+ lymphocyte counts in the designated range where treatment is recommended. For subjects with higher CD4+ lymphocyte counts, the ongoing START study will prospectively assess NC function in HIV positive subjects commencing antiretroviral therapy at an earlier stage of HIV disease.

Therefore, antiretroviral therapy is recommended in NC symptomatic subjects whose CD4+ lymphocyte count itself is an indication to commence therapy.

In the absence of scientific data, in cognitively-symptomatic subjects with higher CD4+ lymphocyte counts in whom antiretroviral therapy would not be otherwise indicated, a recommendation to consider commencing antiretroviral therapy is based firstly on the observed

improvements in cognitive function reported in subjects with lower CD4+ lymphocyte counts commencing therapy [8], and secondly in order to avoid a future decline in CD4+ lymphocyte count in such subjects, given the well described association between low nadir CD4+ lymphocyte count and NC impairment [6].

Sub-optimal adherence to therapy may occur more frequently in subjects with NC impairment, hence adequate support services to optimise adherence are essential.

8.4.3 What to start

8.4.3.1 Recommendation

- We recommend patients with HIV-associated NC disorders start standard combination ART regimens. (1C)

Auditable measure

Proportion of patients with HIV associated NC disorders on ART containing two NRTIs and either a NNRTI or a PI/r or a INI

8.4.3.2 Rationale

Although during the earlier years of antiretroviral therapy, clear benefits on cerebral function of individual antiretroviral drugs such as zidovudine were reported [11] and the benefits of combination therapy overall are well described [8], data are sparse regarding any differences in these benefits between individual agents or combinations. Within cohort studies, the use of the NRTI class within antiretroviral regimens has been associated with a reduced risk of severe HIV-associated dementia [12] compared to the use of other regimens, however the confounders of a cohort study limit the interpretation of these data.

Recent, attempts have been made to establish a relationship between cognitive function and CNS antiretroviral drug delivery based on an antiretroviral scoring system known as the Clinical Penetration Effectiveness (CPE) Score [13]. The CPE score aims to rationally score the cerebral effects of individual antiretroviral agents. However the system is predominantly designed around pharmacokinetic modelling rather than pharmacodynamic endpoints such as data describing changes in NC function. Studies which have assessed the correlation between the CPE scores of antiretroviral regimens with NC function report conflicting findings with some cohorts reporting a positive association [14-15], and others cohorts describing a negative association [16]. Given the potential flaws outlined in the design of the CPE score, a lack of prospective clinical data and discrepancies in findings within cohort studies, the CPE score should not influence therapeutic decisions in subjects with NC impairment commencing antiretroviral therapy.

One small prospective study has assessed the cerebral effects of three different antiretroviral regimens in neurologically asymptomatic subjects reporting greater improvement in NC function in subjects commencing a quadruple nucleoside regimen compared to an EFV or ATV/r containing regimen [17]. However subjects were asymptomatic from a neurological point limiting the relevance of these findings to neurologically symptomatic subjects.

The improvements in NC function observed with zidovudine monotherapy [11] and the greater improvements in NC function observed with a zidovudine containing quadruple nucleoside regimen compared to other ART regimens [17], raise the possibility of selecting a zidovudine containing antiretroviral regimen in subjects with NC impairment. On the converse a lack of comparator data for zidovudine monotherapy and potential toxicities arising from zidovudine use may limit the relevance of these data. Of note, further to peripheral toxicities which are well described with zidovudine use, biomarker data suggest there may also be central nervous system toxicities associated with the use of zidovudine containing regimens [18].

In summary we recommend patients with NC impairment start standard combination ART regimens and the choice should be determined, as with other patients, by different factors including base line viral load, side effects profile, tolerability, drug–drug interactions and patient preference.

8.4.3.3 Novel antiretroviral strategies and NC function

Novel antiretroviral strategies, including protease-inhibitor monotherapy continue to be assessed in clinical trials as cost-beneficial treatment regimens with the potential for reduced long-term toxicities. Concerns have been raised regarding the cerebral effects of PI monotherapy [19], with such concerns based on the hypotheses that PI monotherapy comprises of only one effective antiretroviral agent which may not adequately suppress ongoing HIV replication in sanctuary sites such as the CNS, and on pharmacokinetic modelling which suggests that not all protease-inhibitors have optimal penetration across the blood-brain-barrier [13]. Furthermore, isolated cases describing the evolution of CNS disease in previously stable HIV positive subjects receiving PI monotherapy have been reported [20].

One study was specifically designed to assess the cerebral effects of LPV/r mono-therapy [21], however this study was terminated early due to a lack of efficacy in the plasma compartment. Although cases of CNS disease were reported within this study, such results must be interpreted with caution as virological endpoints in the plasma compartment were not met and therefore such cases may be driven by poor antiretroviral efficacy *per se*, rather than distinct CNS disease itself [22].

In the MONET study assessing DRV/r versus standard therapy, no differences in patient reported cognitive function are observed between the study treatment arms over three years of therapy [23]. Although reassuring, these data represent changes in patient reported observations rather than observations from formal neuropsychological testing. Interestingly, in a small sub-study within MONET, improvements in detailed neuropsychological testing and improvements in cerebral bio-markers measured via imaging techniques, were reported in both treatment arms [24].

In the ongoing UK PIVOT study, detailed neuropsychological testing is being assessed prospectively in subjects on PI monotherapy versus standard therapy, the results of which will be of great interest to this field.

Given the above theoretical concerns regarding the CNS activity of PI monotherapy, and for the majority of HIV positive subjects it may be possible to select other antiretroviral regimens, we suggest this approach is currently avoided in neurologically symptomatic subjects.

8.4.4 Modification of antiretroviral therapy

8.4.4.1 Recommendation

In patients with ongoing or worsening NC impairment despite ART we recommend the following best practice management

- Best practice management should include (GPP):
- Re-assessment for confounding conditions
- Assessment of CSF HIV RNA, CSF HIV genotropism and genotyping of CSF HIV RNA
- In subjects with detectable CSF HIV RNA, modifications to antiretroviral therapy should be based on plasma and CSF genotypic and genotropism results

8.4.4.2 Rationale

Several published randomised controlled studies, assessing both intensification of antiretroviral therapy with a new antiretroviral agent [25] and with adjunctive therapies [26-29] have been published. Unfortunately, none of these studies describe improvements in cognition subsequent to the study interventions. Without evidence based interventions, below outlines a best practice approach based on the current literature.

As HIV-associated NC disorders are a diagnosis of exclusion, re-evaluation of subjects with ongoing NC impairment despite antiretroviral therapy for confounding conditions with expert input from both other clinical specialties such as psychiatry, neurology, and neuropsychology is recommended and where possible input from an HIV-neurology service.

Assessment of CSF HIV RNA, CSF HIV genotropism and genotypic analysis of CSF RNA may be useful tools in the management of subjects with ongoing NC for the following reasons; firstly data from cohorts of untreated HIV positive subjects would suggest CSF HIV RNA to be greater in subjects with HIV-associated dementia and cognitive decline [30,31] and therefore suppression of CSF HIV RNA may be beneficial for cognitive function. Secondly, in subjects with ongoing NC impairment, higher degrees of genetic diversity between HIV viral strains in the CSF and plasma compartment may exist [32], even in subjects with undetectable plasma HIV RNA [33].

Therefore, assessment for CSF HIV resistance may be worthwhile in order to tailor antiretroviral therapy.

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8.5 Chronic kidney disease

8.5.1 When to start ART

8.5.1.1 Recommendation

- We recommend patients with HIV-associated nephropathy (HIVAN) start ART immediately irrespective of CD4 cell count (1C)
- We recommend patients with end-stage kidney disease who are suitable candidates for renal transplantation start ART irrespective of CD4 cell count (1C)

Auditable measure

Proportion of patients with HIV associated nephropathy (HIVAN) started on ART within 2 weeks of diagnosis of CKD

8.5.1.2 Rationale

The use of ART has been associated with a decline in the incidence of HIVAN in HIV cohort studies [1], with renal histological improvement in case reports [2–3], and with delayed progression to end-stage kidney disease in case series [4–5]. In the UK, most HIVAN cases are encountered in patients with advanced immunodeficiency who were not previously known to be HIV positive or who disengaged from care or who declined ART [6]. HIVAN is rare in patients with CD4 cell counts >350 cells/ μ L or with undetectable HIV RNA levels [7]. Patients presenting with higher levels of proteinuria (urine ACR >70mg/mmol or urine PCR >100mg/mmol or urine protein excretion >1g/24h) or proteinuria with haematuria (urine ACR >30mg/mmol or urine PCR >50mg/mmol) or stage 4/5 CKD should be referred for specialist assessment and a renal biopsy considered; those found to have HIVAN should start ART immediately irrespective of CD4 cell count.

For chronic kidney disease (CKD) other than HIVAN, there is limited information on the natural history per se and on whether ART confers renal benefit. Immunodeficiency is a potent risk factor for CKD [8-9]. The majority of patients with CKD have (nadir) CD4 cell counts <350 cells/ μ L and thus qualify for ART as per current treatment guidelines. There are no data to provide guidance on whether HIV-positive patients with (or at risk of developing) CKD benefit from earlier ART initiation. Nonetheless, HIV replication, immune activation and inflammation may play a role in the pathogenesis of kidney diseases or contribute to kidney disease progression in some patients [10]. For this reason ART should be considered in those presenting with chronic kidney disease other than HIVAN.

Renal transplantation is the treatment of choice for those requiring renal replacement therapy. Patients to be considered for renal transplantation are required to have suppressed HIV RNA levels and to have CD4 cell counts >200 cells/ μ L [11], and should start ART, irrespective of CD4 cell count.

8.5.2 What to start

8.5.2.1 Recommendations

- We recommend against the use of antiretroviral drugs that are potentially nephrotoxic, in patients with stages 3–5 CKD if acceptable alternative antiretroviral agents are available. (GPP)
- We recommend dose adjustment of renally cleared antiretroviral drugs in patients with reduced renal function (GPP)

Auditable measure

Number of patients with CKD stages 3-5 on ARVS that are potentially nephrotoxic and record of rationale

Record in patient's notes of calculated dose of renally cleared ARVs in patients with CKD stage 3 or greater.

8.5.2.2 Rationale

There are no data from randomised controlled clinical trials to inform antiretroviral treatment decisions in patients with CKD. The risk of CKD is increased with older age, reduced eGFR, hypertension, diabetes and with cumulative exposure to indinavir, TDF, atazanavir and, to a lesser extent, lopinavir [12,13]. Indinavir use is no longer recommended in view of the high incidence of renal complications: crystalluria and pyuria are reported in 20-67% [14–16] and nephrolithiasis, tubulo-interstitial nephritis and gradual loss of renal function in 4-33% of patients [14,17–20].

Tenofovir (TDF) has been associated with falls in eGFR [12, 21-22], accelerated decline in eGFR [9], acute renal failure [23], tubulo-interstitial nephritis [24], chronic kidney disease [9, 12], renal tubular dysfunction [13, 25] and Fanconi syndrome [26-27]. The incidence of TDF associated renal toxicity is low in clinical trials and cohort studies of the general HIV population [28-29]. Older age, pre-existing renal impairment, co-administration of didanosine or (ritonavir-boosted)

protease inhibitors, advanced HIV infection and low body mass appear to increase the risk of renal complications [9, 13, 25, 27, 30-31].

Atazanavir (ATV) has been associated with reductions in eGFR [32], nephrolithiasis and tubulointerstitial nephritis [13, 24, 33], and chronic kidney disease [12]. The incidence of renal stones with ATV in one cohort was 7.3 per 1000 person-years, with almost half of those who developed renal stones having eGFR <60 at the time of ATV initiation [34].

The nephrotoxic potential of both TDF and ATV is low in patients with normal renal function. However in patients with chronic kidney disease and impaired renal function (eGFR < 75 ml/min/1.73m²), alternative ARVs should be considered.

In patients undergoing renal transplantation, protease inhibitors give rise to challenging drug-drug interactions with calcineurin-inhibitors (<http://www.hiv-druginteractions.org>). Post-transplantation, acute allograft rejection and impaired renal function are common [35]. We suggest TDF and ATV are avoided in patients who are awaiting or who have undergone renal transplantation, and that specialist advice is sought regarding choice and appropriate dose of ARVs.

Non-nucleoside reverse transcriptase inhibitors, integrase inhibitors, ABC and 3TC have not been associated with CKD and can be used in HIV positive patients with CKD. In patients with impaired renal function, specific ARV drugs (all NRTIs except ABC) may need to be dose-adjusted [36]. Impaired survival has been reported with ART prescription errors in patients undergoing dialysis [37]. We recommend dose adjustment of renally cleared ARVs in patients with renal failure but caution against the risk of over-interpreting estimates of renal function for this purpose as true measures of renal function may be substantially higher in patients with mild-moderate renal impairment. Specific ARVs which require dose adjustment in patients with reduced renal function include: 3TC, FTC, TDF, DDI, ZDV and MVC (depending on PI use). For further information and advice the reader should refer to the SPCs for each ARV.

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8.6 Cardiovascular disease

8.6.1 Introduction

Cardiovascular disease (CVD) is a leading cause of non-AIDS morbidity and mortality among HIV positive individuals [1,2] and an increased risk of CVD events has been observed when compared with HIV negative populations [3-8]. This has been attributed to the increased prevalence of surrogate markers of CVD (such as dyslipidaemia) and the pro-inflammatory state associated with HIV infection. However, because ART may not mitigate (or indeed may exacerbate) these effects, caution is required in extrapolating from these markers to effects on overall mortality. The following recommendations apply to patients with or at high risk of CVD.

8.6.2 Definition and assessment of CVD risk

For the purposes of these guidelines, patients with an elevated CVD risk are as defined in the JBS2 guidelines [9] and include:

- People with any form of established atherosclerotic CVD
- Asymptomatic people who have an estimated multifactorial CVD risk >20% over 10 years
- People with diabetes mellitus (type 1 or 2)
- People with elevated blood pressure >160 mm Hg systolic or >100 mm Hg diastolic, or lesser degrees of blood pressure elevation with target organ damage
- People with elevated total cholesterol to high density lipoprotein (HDL) cholesterol ratio >6.0
- People with familial dyslipidaemia

NICE does not recommend a specific CVD risk calculation for the UK population [10]. Cohort data have demonstrated that the observed myocardial infarction (MI) rates in HIV seropositive people in developed countries paralleled those predicted by the Framingham risk equation [11] but the extent to which this can be extrapolated to women and men of non-European ethnicity is unknown. Therefore there is insufficient evidence to recommend a specific CVD risk calculation for the population of HIV positive adults in UK.

The Framingham CVD risk calculator works reasonably well in HIV-positive populations, although it is worth noting that it was not developed for use in non-White groups. Other algorithms may be better suited to these populations. A CVD risk calculator has been developed for use in HIV-positive populations (www.chip.dk/TOOLS) [29], although it should be noted that this provides 5-year risk estimates rather than the usual 10-year estimates. Alternatively, the QRISK calculator (www.qrisk.org) or the QIntervention tool (<http://qintervention.org>), which also provide an estimate of the risk of developing type II diabetes, can be used.

8.6.3 When to start ART

There are insufficient data to inform whether CVD risk should affect the decision to start ART

The SMART trial provides the only randomised data about the effect of ART on CVD risk, but was not powered for a CVD endpoint. Fewer major CVD events were observed in the viral suppression arm but the difference was not statistically significant [12]. In a post hoc analysis, HIV viral load <400 copies/ml was associated with fewer CVD events suggesting that suppression of viraemia may have been protective; CD4 count was not significantly associated with CVD events [13,14].

Several cohort studies have examined changes in rate of cardiovascular events in HIV-positive populations over time since the introduction of ART but no clear protective effect was found [15-18]. In the HOPS cohort baseline CD4 count <350 cells/ μ L was associated with increased CVD risk, but 350-500 cells/ μ L and use of ART were not; in a parallel case control study, cases were more likely to have a current (but not baseline or nadir) CD4 count of 350-500 cells/ μ L [19]. The Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) study found that untreated patients had a lower incidence of MI than those on ART [20] and risk increased with longer exposure to combination therapy [21].

While there is uncertainty as to whether treating HIV infection reduces CVD risk, there is good evidence from RCTs that interventions targeted at modifiable CVD risk factors are of benefit. For this reason all HIV positive adults should be assessed for CVD risk annually and interventions targeted at improving modifiable risk factors.

8.6.4 What to start

8.6.4.1 Recommendations

- We suggest avoiding abacavir (2C), fosamprenavir/ritonavir (2C) and lopinavir/ritonavir (2C) in patients with a high CVD risk, if acceptable alternative antiretroviral drugs are available.

Auditable measure

Number of patients with high CVD risk on either abacavir or fosamprenavir/ritonavir or lopinavir/ritonavir and record of rationale

8.6.4.2 Rationale

Modifiable risk factors should be addressed in all patients with high CVD risk.

No RCTs has been powered to assess the CVD risk associated with the use of individual ARVs and a history of CVD may be an exclusion criteria. A meta-analysis of all RCTs where ABC was assigned randomly found no association with MI, but the event rate in the population was low; the extent to which these findings can be extrapolated to a population with high CVD risk is unknown [22]. Although a post-hoc analysis of the SMART study did find such an association, use of ABC was not randomised [23].

Two cohorts have found a strong association between recent ABC use and MI [24,25] while another, did not [26,27]; all were limited in their ability to adjust for presence of CVD risk factors. An analysis of the manufacturer's trial registry found no association [28], but the trials only enrolled patients with low CVD risk. One case-control study (which did not adjust for

important CVD risk factors) did find an elevated risk of MI associated with ABC use [7] but another did not [29]. Cerebrovascular events were more common in patients exposed to ABC in two cohort studies [8,27] while another found a protective effect [26]. In view of the uncertainty about the safety of ABC in patients with a high CVD risk, we suggest the use of alternative agents where possible.

Early studies of PI exposure and risk of MI gave conflicting results, some reporting an increased risk [5,30] while others did not [3,15,31]. The D:A:D cohort, with longer follow-up, reported an increasing risk of MI with years of PI exposure (independent of measured metabolic effects) [21]. Cumulative exposure to indinavir and LPV/r were associated with increasing risk of MI (adjusted relative risk per year for LPV/r 1.13 (95% CI 1.05-1.21); relative risk at 5 years 1.84) [25]. Case-control studies reported similar associations for LPV/r [7,29] and FPV/r [29] but in one of these important CVD risk factors were not included [7]. A further study found no association between PI exposure and all cerebrovascular events [8]. An updated analysis has recently reported no association between ATV/r use and an increased risk of MI (*add CROI 2012 ref*). Although there has been insufficient data to include DRV/r in these analyses, in patients with a high CVD risk, we suggest the use of alternatives to LPV/r and FPV/r where possible.

In the MOTIVATE studies for treatment-experienced patients, coronary artery disease events were only reported in the MVC arm (11 in 609 patient years), while there were none in the placebo arm (0 in 111 patient years); those affected generally had pre-existing CVD risk. No such signal was found in the MERIT study for treatment-naïve patients. Maraviroc has also been associated with postural hypotension when used at higher than recommended doses in healthy volunteers; patients with a history of postural hypotension, renal impairment or taking antihypertensive agents may be at increased risk [32]. In view of the limited data available, special caution should be exercised in the use of MVC in patients with a high CVD risk and use of alternative agents where possible considered.

8.6.5 References

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8.7 Women

8.7.1 Introduction

The following guidance considers issues concerning the initiation and choice of ART for HIV positive women who are not currently pregnant. For guidance on the management of pregnancy in HIV-positive woman please refer to the BHIVA pregnancy guidelines [1].

There are few specific data on ART treatment in women other than in pregnancy. Data available are largely from a meta-analysis, post hoc analyses or derived from cohort studies. The majority of the randomised clinical trial data on ART comes from studies that have enrolled mostly male subjects. If RCTs do enrol women the numbers are often too small to draw significant gender based conclusions.

Approximately one third of people diagnosed with and accessing care for HIV in the UK are women [2]. A majority are of child bearing age but the age range is increasing, adding the complexity of menopause and its sequelae to the management of HIV positive women. Many HIV positive women in the UK are of African heritage and face overlapping challenges to their health and wellbeing [3].

Women's experience of HIV reflects multiple social and cultural influences, which when combined with sex specific biological factors influences individual responses to HIV.

8.7.2 When to start

8.7.2.1 Recommendations

- We recommend therapy naïve HIV positive women who are not pregnant start ART according to the same indicators as in men (see Section 4: When to start) (1A)

Auditable measure

Proportion of HIV positive women with CD4 cell count <350 cells/ μ L not on ART

8.7.2.2 Rationale

Gender differences in HIV viral load and CD4 count at different stages of infection have been observed [4] but have not been consistently associated with long term clinical outcomes for HIV positive women. Based on current data the indications for starting ART do not differ between women who are not pregnant and men.

Gender-specific socio economic and cultural factors may impact on women's ability to access care and manage their medication, compromising their ability to initiate and adhere to therapy, and require support from the multidisciplinary team.

8.7.3 What to start

8.7.3.1 Recommendations

- We recommend therapy naïve HIV positive women start ART containing two NRTIs and either a ritonavir-boosted protease inhibitor, or a NNRTI or an integrase inhibitor (1A), as per therapy naïve HIV positive men.
- We recommend therapy naïve HIV positive women start ART with preferred or alternative NRTI backbone and third agent as per therapy naïve HIV positive men (See Section 5.1: What to start: summary recommendations) (1A). Factors such as potential side effects, co-morbidities, drug interactions, patient preference and dosing convenience need to be considered in selecting ART in individual women.
- We recommend both HIV positive women of child bearing potential and health care professionals who prescribe ART are conversant with the benefits and risks of ARV agents for both the health of the HIV positive women and for that of an unborn child (GPP)
- We recommend that potential pharmacokinetic interactions between antiretrovirals, hormonal contraceptive agents and hormone replacement therapy are checked prior to administration (with tools such as: <http://www.hiv-druginteractions.org>) (GPP)

8.7.3.2 Rationale

Efficacy

There are few data to guide prescribing of initial ART specifically for women, as no RCT in patients starting ART has been powered to detect sex differences in efficacy. From the limited data available, virological outcomes within clinical trial settings generally appear to be no different between men and women.

A meta-analysis of FDA registrational RCTs analysed data from 22,411 HIV positive patients participating in 43 trials for 16 ARVs. Overall 20% of study participants were women. No significant differences in treatment response at week 48 were reported between men and women. Rates of ART discontinuation for virological failure were higher in men (8.15%) than in women (4.25%) [5].

A RCT comparing ATV/r and LPV/r in ART naïve patients of whom 31% were women, a subanalysis showed comparable virological efficacy at week 96 between the two treatment arms in women [6] although virological response rates were lower in women when compared to men.

In a study comparing ATV/r and EFV in 1857 ART naïve patients of whom 17% were women, female sex was associated with increased virological failure on ATV/r compared to EFV [7]. No difference was seen with EFV between men and women.

The efficacy and tolerability of RAL were shown not to be different between men and women at 48 weeks in one study of a diverse cohort of both treatment naïve and experienced patients [8]. RPV in ART naïve men and women showed no difference in rates of virological suppression at 48

and 96 weeks between men and women, but the number of women included was low and the study was not designed to investigate sex differences [9,10].

Cohort studies in the UK have reported similar virological outcomes during the first year of treatment in heterosexual men and women [11]. An Italian cohort study reported no significant effect of gender on clinical progression or the risk of developing a clinical event [12]. Data from Spain in which both naive and ARV experienced women patients showed similar virological responses to men [13].

HIV positive women starting ART should use ARVs from the list of preferred and alternative drugs outlined in Section 5.1 (What to start: summary recommendations). Factors including potential for side effects, drug interactions, patient preference, co-morbidities and dosing convenience need to be taken into consideration when selecting ART regimens in individual women.

Toxicity, discontinuation and adherence

Adverse events and treatment discontinuations within ART clinical trials and cohort studies published between 2002 and 2007 have been systematically reviewed. The overall event rate is often the same but the adverse event profile may be different. Women were reported to be more likely than men to experience ART related lipodystrophy, rash, and nausea and also to discontinue therapy [4].

Data from the USA have shown that women are more likely than men to discontinue ART for poor adherence, dermatologic symptoms, neurological reasons, constitutional symptoms and concurrent medical conditions [14]. UK cohort data found 88.6% of men compared to 80.7% of women spent 100% of the first year after starting HAART actually on therapy [11].

Comparison of ATV/r with LPV/r found poorer virological outcomes in treatment naive women compared to men. Gender differences in efficacy were due to higher discontinuation rates in women than men in both treatment arms [6]. Central nervous system side effects of varying severity can occur with EFV, particularly at the initiation of therapy. This may be partly explained by the greater EFV exposure associated with a CYP2B6 variant, more commonly found in Africans and African Americans [15]. In the UK population this is of particular relevance to women a majority of whom are of African ethnicity. NVP associated rash occurs more frequently in women than men [16]. Hepatotoxicity associated with NVP is more common in women with a CD4 count above 250 cells/ μ L, restricting women's use of the drug [17].

A systematic review of studies on gender and ART adherence published between 2000 and 2011 in the resource rich world concluded that overall reported adherence is lower in women than men [18]. However of over 1000 studies initially identified for review only 44 had adequate data on gender to allow any comparisons to be made. The authors identified the particular factors for lower adherence in women were depression, lack of supportive interpersonal relationships, young age, drug and alcohol use, black ethnicity ART of six or more pills per day, higher numbers of children, self perception of abdominal fat gain, sleep disturbances and increased levels of distress.

Fetal safety

Concerns about potential fetal toxicity of ARVs have influenced prescribing practice in HIV positive women. Of note, other than ZDV in the third trimester, no ARV drug has a licence for use in pregnancy.

Pregnancy in women living with HIV who are already on effective therapy is increasing; 70% of HIV positive pregnant women in the UK in 2010 were diagnosed prior to the current pregnancy, of whom 60% were already on ART at conception [19]. Where newer drugs are available, women are conceiving on these agents, with ZDV now rarely used as first line therapy for adults. European cohort data comparing pregnancies that were managed with ZDV-containing regimens versus those without ZDV found no difference in risk of detectable viral load at delivery, vertical transmission, or congenital abnormality when comparing ZDV-sparing with ZDV-containing ART [20].

The most robust data on teratogenicity and first trimester antiretroviral therapy exposure are from the Antiretroviral Pregnancy Registry (APR) [21]. This international prospective reporting system records rates of congenital birth defects in babies born to women with exposure to antiretroviral therapy at any stage of pregnancy. 200 or more reports need to be received for a particular compound before data are reported for that compound by the APR. There are now over 200 prospective reports in the APR of first trimester exposure for ABC, ATV, EFV, FTC, 3TC, LPV, NVP, ritonavir, TDF and ZDV. No signal of increased risk of congenital abnormality has been demonstrated, and a greater than 2 fold higher rate than in the general population has been excluded. There are so far fewer than 200 prospective reports for DRV, RAL and RPV within the APR and hence no reports on these agents are yet available.

Despite previous concerns over the safety of EFV based on preclinical animal studies and retrospective case reports in human subjects, the current data do not provide evidence of excess teratogenicity above the expected baseline for infants exposed to EFV in the first trimester. Sufficient numbers of first trimester exposures of EFV have been monitored to detect at least a two-fold increase in risk of overall birth defects within the APR and no such increases have been detected to date [21].

Data from Cote d'Ivoire found no significant increased risk of unfavourable pregnancy outcome in women with first trimester exposure to EFV compared with NVP [22]. A systematic review and meta-analysis of observational cohorts carried out in 2010 [23] and further updated in 2011 [24] reported birth outcomes among women exposed to EFV during the first trimester. No increased risk of overall birth defects amongst the babies of women exposed to EFV during first trimester compared with exposure to other antiretroviral drugs was found. The prevalence of overall birth defects with first trimester EFV exposure was similar to the ranges reported in the general population.

A review of live births to women with HIV in a large unselected UK population between 1990 and 2007 found no increased risk of abnormalities in infants exposed to EFV in the first trimester, providing further reassurance that ART in utero does not pose a major risk of fetal anomaly [25]. Mathematical modelling using North American cohort data has demonstrated a theoretical loss of life expectancy in women who delay EFV at initiation of ARV [26].

Based on current evidence, EFV can be initiated in women of child bearing potential, can be continued in women who conceive on the drug and commenced in pregnancy but the data should be discussed in detail with the individual woman when deciding on her preferred treatment regimen. Given that no antiretroviral drug is licensed for use in pregnancy apart from ZDV in the third trimester, a discussion regarding the potential unknown long and short term effects on an unborn child should be had with any woman of childbearing potential who commences any antiretroviral drug regimen. Further details can be found in the BHIVA pregnancy guidelines [1].

Hormone interactions

Significant pharmacokinetic and pharmacodynamic interactions have been reported between antiretroviral drugs and hormonal agents. Inducers of hepatic enzymes by ARVs may result in increased breakdown of ethinyl oestradiol and progestogens that can compromise contraceptive and HRT efficacy. Additional contraceptive measures or different antiretroviral regimens may be required in these circumstances. Potential drug-drug interactions should be checked using various resources including specialist HIV pharmacists, web based tools such as the University of Liverpool website on HIV drug interactions and medical information departments in pharmaceutical companies. There is no significant interaction between ETV and the combined OCP, and no interaction is anticipated with RAL. Hormonal contraceptive agents which have been shown not to have a significant interaction or where there is no anticipated interaction include depot medroxyprogesterone acetate, and the levonorgestrel IUS (Mirena coil)

8.7.4 HIV positive women experiencing virological failure

There is very little evidence to guide prescribing ART in HIV positive women experiencing virological failure on ART, with most studies recruiting approximately 10% of women. One study investigating DRV/r in ART experienced patients recruited a large proportion of women and was powered to show a difference in virological efficacy between men and women; this and showed a higher discontinuation rates were among women than men, with nausea being cited as a particular problem but overall there was no difference in virological efficacy [27]. A further study has reported similar efficacy and tolerability of Raltegravir in ART experienced HIV positive women [8].

In HIV positive women experiencing virological failure on ART the same principals of management and recommendations apply as per HIV positive men experiencing virological failure (see Section 7: Management of virological failure)

8.7.5 References

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9. Acknowledgements

The Writing Group thanks the BHIVA Secretariat for administrative help, Alison Richards for conducting the systematic literature search and Jacoby Patterson for work on critical appraisal, evidence profiles and construction of GRADE tables.

The writing group also thanks Professor Francois Raffi and Professor Jose Arribas for their peer review of the guidelines and Dr Annemiek de Ruiter and Dr Fiona Lyons for their peer review of the section on women.

9.1 Conflicts of interest statements

Dr Ian Williams has received grant support from Gilead Sciences and Janssen-Cilag and his department has received grant support from Boehringer Ingelheim, Gilead Sciences and Janssen-Cilag.

Dr Duncan Churchill has no conflicts of interest to declare.

Professor Jane Anderson has received lecture fees from Abbott, Gilead and ViiV and consultancy fees from Abbott, Bristol-Myers Squibb and Gilead. Her department has received a research grant from Gilead.

Professor Jose Arribas has a financial interest/relationship or affiliation: Tibotec, Janssen, Abbott, BMS, Gilead Sciences, MSD, ViiV Healthcare

Dr Marta Boffito has received consultancy fees and grant support from Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharp and Dohme, Pfizer, Roche and Tibotec/Janssen.

Professor Mark Bower has no conflicts of interest to declare.

Mr Gus Cairns has no conflicts of interest to declare.

Dr Kate Cwynarski has received lecture and consultancy fees from Pfizer and Roche.

Dr Annemiek de Ruiter has received lecture and consultancy fees from Bristol-Myers Squibb and Gilead.

Dr Simon Edwards has received lecture fees from ViiV and Janssen, and consultancy fees from Boehringer Ingelheim, Merck Sharp and Dohme and ViiV.

Dr S Fidler has no conflicts of interest to declare.

Dr Martin Fisher has received lecture fees from Abbott, Astellis, Bristol-Myers Squibb, Gilead and ViiV and he has received consultancy fees from Abbott, Bristol-Myers Squibb, Gilead, Janssen, Merck Sharp and Dohme and ViiV.

Dr Andrew Freedman has received lecture and consultancy fees from Abbott, Bristol-Myers Squibb, Gilead and Tibotec/Janssen.

Professor Anna Maria Geretti has received consultancy fees from Gilead and her department has received research grants from Janssen, Merck Sharp and Dohme and ViiV.

Dr Yvonne Gilleece has no conflicts of interest to declare.

Professor Rob Horne has no conflicts of interest to declare.

Professor Margaret Johnson has received lecture and consultancy fees from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Janssen and Merck Sharp and Dohme.

Professor Saye Khoo has received lecture and consultancy fees from Abbott, Gilead and ViiV.

Professor Clifford Leen has received consultancy fees from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Janssen and Merck Sharp and Dohme. His department has received research awards from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Janssen and ViiV.

Dr Fiona Lyons has no conflicts of interest to declare

Mr Neal Marshall has received lecture and consultancy fees from Abbott, Bristol-Myers Squibb, Janssen and ViiV.

Dr Mark Nelson has received lecture fees from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Merck Sharp and Dohme, Tibotec and ViiV and consultancy fees from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Idenix, Merck Sharp and Dohme, Pfizer, Tibotec, and ViiV. His department has received research grants from Abbott, Aspen Pharmaceuticals, Bristol-Myers Squibb, Gilead, Merck Sharp and Dohme, Tibotec and ViiV.

Dr Chloe Orkin has received lecture fees from Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead, GSK, Janssen, Merck Sharp and Dohme, Pfizer, Tibotec and ViiV. She has received consultancy fees from Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead, GSK, Janssen, Merck Sharp and Dohme, Pfizer, Tibotec and ViiV. Her department has received research grants from Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead, GSK, Janssen, Merck Sharp and Dohme, Pfizer, Tibotec and ViiV.

Dr Nicholas Paton's department has received research grants from Abbott and Merck Sharp and Dohme.

Professor Andrew Phillips has received consultancy fees from Bristol-Myers Squibb, Gilead, GSK Bio, Johnson and Johnson, Merck Sharp and Dohme and ViiV and his department has received research grants from Bristol-Myers Squibb.

Dr Frank Post has received lecture fees from Bristol-Myers Squibb, Gilead, Merck Sharp and Dohme, Tibotec/Janssen and ViiV/GSK and his department has received research grants from Gilead and ViiV.

Dr Anton Pozniak has received lecture and consultancy fees from Boehringer Ingelheim and Bristol-Myers Squibb, Gilead, Janssen, Merck Sharp and Dohme and ViiV and conference support from Bristol-Myers Squibb and Merck Sharp and Dohme.

Professor Francois Raffi received research funding or honoraria from, or consulted for, Bristol-Myers Squibb, Gilead Sciences and Roche.

Professor Caroline Sabin has received lecture and consultancy fees from Abbott, Bristol-Myers Squibb, Gilead, and Janssen.

Mr Roy Trelvelion has no conflict of interests to declare.

Dr Andy Ustianowski has received lecture and consultancy fees from Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Merck Sharp and Dohme, Janssen and ViiV and his department has received research grants from Abbott.

Dr Laura Waters has received lecture and consultancy fees from Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Janssen, Merck Sharp and Dohme and ViiV.

Dr John Walsh has no conflict of interests to declare.

Dr Ed Wilkins has received lecture and consultancy fees from Abbott, Bristol-Myers Squibb, Gilead, Janssen, Merck Sharp and Dohme and Pfizer.

Dr Alan Winston has received lecture fees from Janssen and his department has received research grants from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen, Pfizer, Roche and ViiV.

Dr Mike Youle has received lecture and consultancy fees from Abbott and Gilead.

9. List of abbreviations

3TC	2',3'-dideoxy-3'-thiacytidine, Lamivudine
ABC	Abacavir
ACTG	AIDS Clinical Trials Group
ADL	Activities of daily living
AE	Adverse event
AIDS	Acquired immune deficiency syndrome
ALT	Alanine transaminase
ANI	Asymptomatic neurocognitive impairment
ART	Antiretroviral therapy
ARV	Antiretroviral
AST	Aspartate transaminase
ATV	Atazanavir
ATV/r	Atazanavir/ritonavir
BHIVA	British HIV Association
BPS	British Psychological Society
CCR5	C-C chemokine receptor type 5
CD4	Cluster of differentiation 4
CD8	Cluster of differentiation 8
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisolone chemotherapy regimen
CI	Confidence interval
CKD	Chronic kidney disease
C _{min}	Minimum concentration
CNS	Central nervous system
CPE	Clinical penetration effectiveness
CSF	Cerebrospinal fluid
CVD	Cardiovascular disease
CYP450	Cytochrome P450
CXCR4	C-X-C chemokine receptor type 4
DDI	Drug–drug interaction
DRV	Darunavir
DRV/r	Darunavir/ritonavir
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EFV	Efavirenz
eGFR	Estimated glomerular filtration rate
ELV	Elvitegravir
ETV	Etravirine
FDC	Fixed-dose combination
FPV	Fosamprenavir
FPV/r	Fosamprenavir/ritonavir
FTC	Emtricitabine
GPP	Good practice point
GRADE	Grading of recommendations assessment, development and evaluation
GSS	Genotypic sensitivity score
HAD	HIV-associated dementia

HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
HIVAN	HIV-associated nephropathy
HLA	Human leukocyte antigen
HOPS	HIV Outpatients Study
INI	Integrase inhibitor
IQR	Interquartile range
IRD	Immune reconstitution disorder
KS	Kaposi's sarcoma
LDL	Low density lipoprotein
LPV	Lopinavir
LPV/r	Lopinavir/ritonavir
MVC	Maraviroc
MDT	Multidisciplinary team
MI	Myocardial infarction
MND	Mild neurocognitive disorder
MSM	Men who have sex with men
NADM	non AIDS-defining malignancy
NC	Neurocognitive
NHL	Non-Hodgkin's lymphoma
NICE	National Institute for Clinical Excellence
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleos(t)ide reverse transcriptase inhibitor
NVP	Nevirapine
OBT	Optimised background therapy
OI	Opportunistic infection
PCP	Pneumocystis pneumonia
PHI	Primary HIV infection
PI	Protease inhibitor
PI/r	Ritonavir-boosted protease inhibitor
PK	Pharmacokinetic
RAL	Raltegravir
RAM	Resistance associated mutation
RCT	Randomised clinical trial
RPV	Rilpivirine
RT	Reverse transcriptase
RR	Relative risk
SPC	Summary of product characteristics
SQV/r	Saquinavir/ritonavir
STI	Sexually transmitted infection
TB	Tuberculosis
TDF	Tenofovir disoproxil fumarate
TDM	Therapeutic drug monitoring
TPV	Tipranavir
TPV/r	Tipranavir/ritonavir
UGT	Uridine diphosphoglucuronosyl transferase
UK CAB	UK Community Advisory Board
VL	Viral load
WT	Wild type
ZDV	Zidovudine

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Appendix 1

Summary of the modified GRADE system

BHIVA revised and updated the association's guideline development manual in 2011 [1]. BHIVA has adopted the modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for the assessment, evaluation and grading of evidence and the development of recommendations [2,3].

1A

Strong recommendation.

High-quality evidence.

Benefits clearly outweigh risk and burdens, or vice versa.

Consistent evidence from well performed randomised, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk.

Strong recommendations, can apply to most patients in most circumstances without reservation.

Clinicians should follow a strong recommendation unless there is a clear rationale for an alternative approach.

1B

Strong recommendation.

Moderate-quality evidence.

Benefits clearly outweigh risk and burdens, or vice versa

Evidence from randomised, controlled trials with important limitations (inconsistent

results, methods flaws, indirect or imprecise), or very strong evidence of some other research design. Further research may impact on our confidence in the estimate of benefit and risk.

Strong recommendation and applies to most patients.

Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.

1C

Strong recommendation.

Low-quality evidence.

Benefits appear to outweigh risk and burdens, or vice versa

Evidence from observational studies, unsystematic clinical experience, or from randomised, controlled trials with serious flaws. Any estimate of effect is uncertain.

Strong recommendation, and applies to most patients. Some of the evidence base supporting the recommendation is, however, of low quality.

1D

Strong recommendation.

Very low-quality evidence.

Benefits appear to outweigh risk and burdens, or vice versa.

Evidence limited to case studies. Strong recommendation based mainly on case studies and expert judgment.

2A

Weak recommendation.

High-quality evidence.

Benefits closely balanced with risks and burdens

Consistent evidence from well performed randomised, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk.

Weak recommendation, best action may differ depending on circumstances or patients“ or societal values.

2B

Weak recommendation.

Moderate-quality evidence.

Benefits closely balanced with risks and burdens, some uncertainly in the estimates of benefits, risks and burdens.

Evidence from randomised, controlled trials with important limitations (inconsistent results, methods flaws, indirect or imprecise). Further research may change the estimate of benefit and risk.

Weak recommendation, alternative approaches likely to be better for some patients under some circumstances.

2C

Weak recommendation.

Low-quality evidence.

Uncertainty in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens.

Evidence from observational studies, unsystematic clinical experience, or from randomised, controlled trials with serious flaws. Any estimate of effect is uncertain.

Weak recommendation; other alternatives may be reasonable.

2D

Weak recommendation.

Very low-quality evidence.

Uncertainty in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens.

Evidence limited to case studies and expert judgment.

Very weak recommendation; other alternatives may be equally reasonable.

References

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Appendix 2**Systematic literature search****2.1 Questions and PICO criteria**

Data bases: Medline, Embase, Cochrane Library,

Conference Abstracts:

- IAS Conference on HIV pathogenesis and treatment
- International AIDS conference
- Conference on retroviruses and opportunistic infections
- European conference on clinical aspects and treatment of HIV infection
- Interscience conference on antimicrobial agents and chemotherapy

- International congress on drug therapy in HIV infection
- British HIV Association annual conference

Date parameters:

- data bases: 2008 –September 2011
- conference abstracts: 2009-September 2011

When to start:

Study design: Systematic reviews (SRs), randomised control trials (RCTs), Observational, risk, economic

Chronic HIV Infection:

Population: HIV infected naïve to Antiretroviral(ART) therapy

Intervention: starting ART early: i) at CD4 count >350 cells/μL, ii) at CD4 count >500 cells/μL, iii) immediate at time of diagnosis

Comparator: Starting ART CD4 count <350 cells/μL

Outcomes: Death, AIDS, non-AIDS co-morbidities, drug adverse events, drug resistance, HIV transmission/incidence

Questions:

1. Is there improved or greater long term clinical benefit starting patients with chronic HIV infection earlier at CD4 counts >350 cells/μL compared to starting when CD4 count is 350 cells/μL or lower?
2. Does early ART prevent Non AIDS co-morbidities (cirrhosis, end stage renal failure, myocardial infarction, cardiovascular disease, cancer, all cause mortality)?
3. What is the cost (financial, toxicity, resistance) vs. benefit (decreased AIDS, death, non-AIDS endpoints and transmission) of early vs. later ART?

Primary HIV infection:

Population: Acute/primary HIV infection

Intervention: immediate ART therapy (short course or continued)

Comparator: no therapy, starting ART as per chronic infection

Outcomes: time to CD4 count <350cells/μL, death, AIDS, HIV transmission/incidence

Question

4. Is there benefit in starting patients diagnosed with primary/acute HIV infection immediately on ART compared to waiting till CD4 count <350 or <500 cells/μL? What is the magnitude of this benefit?

Advanced HIV disease

Population: HIV infection, advanced disease,

Intervention: immediate ART

Comparator: deferred ART

Outcomes: Death, new AIDS diagnosis, immune reconstitution disorders.

Question

5. Should patients presenting with severe AIDS defining opportunistic infections start ART immediately, or defer until after treatment of OI?

.

ART to prevent transmission

Population: HIV infected with HIV negative partner, sero-discordance

Intervention: Immediate ART

Comparator: starting ART at CD4 count <350 cells/ μ L

Outcome: HIV transmission to negative partner

Question

6. What is the cost (financial, toxicity, resistance) vs. benefit (reduced AIDS, death, non-AIDS endpoints and reduced transmission) of starting treatment earlier [similar question to 3 above]

What to start with

Study design: SRs, RCTs,

Preferred regimen/ choice of third agent

Population: HIV infected naïve to ART and i) VL >100,000, ii) VL <100,000 copies/ml

Intervention: Darunavir or Atazanavir or Raltegravir, Maraviroc, Etravirine or Rilpivirine containing combination ART

Comparator: Efavirenz containing combination ART

Outcome: virological suppression (VL <50 copies/ml), virological failure, discontinuing regimen secondary to AEs, grade 3/4 AEs, HIV drug resistance

Question

7. How does each third drug compare to efavirenz in terms of efficacy and safety?

Preferred regimen/Choice of NRTI backbone

Population: HIV infected naïve to ART

Intervention: Abacavir/lamivudine containing combination ART

Comparator: Tenofovir/Emtricitabine containing combination ART

Outcomes: virological suppression (VL <50 copies/ml), virological failure, discontinuing regimen secondary to AEs, grade 3/4 AEs, HIV drug resistance

Question

8. What are the advantages and disadvantages of using tenofovir/emtricitabine (Truvada) vs. abacavir/lamivudine (Kivexa)?

Novel treatment strategies

Population: HIV infected naïve to ART

Intervention: i) PI mono-therapy ii) NRTI sparing and PI based dual regimens (Raltegravir + either Darunavir/r or Atazanavir/r or Kaletra; Maraviroc + either Darunavir/r or Atazanavir/r)

Comparator: standard triple combination ART

Outcome: virological suppression (VL <50 copies/ml), virological failure, discontinuing regimen secondary to AEs, grade 3/4 AEs, HIV drug resistance

Question

9. What are the advantages and disadvantages of each of these strategies compared to standard triple combination ART?

Supporting patients on ART

Switching Therapy (simplification)

Study design: SRs, RCTs

Population: Antiretroviral therapy experienced, treatment experienced, virologically suppressed, viral load <50 copies/ml

Intervention: protease inhibitor monotherapy, switch third agent, switch NRTI backbone

Comparator; continuing current therapy

Outcome; virological suppression, virological failure, discontinuing regimen, grade3/4 AEs, HIV drug resistance

Questions

10. What are the benefits and disadvantages of simplifying from conventional ART to protease inhibitor monotherapy?

11. In patients on conventional ART (2 NRTIs + EFV or boosted PI), what are the relative advantages and disadvantages of switching to alternative third agents or NRTI backbone (e.g PI/r → NNRTI, Integrase inhibitor, ; NNRTI → PI/r)?

Stopping therapy

Study design: SRs, RCTs, observational

Population: Antiretroviral therapy experienced, treatment experienced

Intervention: Stopping ART, treatment/ART interruption

Comparator: continuing ART

Outcome: HIV drug resistance, PK parameters

Question

12. Which is the least harmful (risk of resistance and/or failure to re-suppress on re-starting ART) way to stop treatment containing an NNRTI (simultaneous/staggered or switched stopping)?

Managing Virological failure

Low level viraemia and recurrent viral load blips

Virological failure with treatment options

Virological failure with limited treatment options

Study designs: SRs, RCTs, observational

Population: ART experienced, virological failure, dual and triple class HIV drug resistance, viral load blips

Intervention: switching ART, continuing lamivudine(3TC) or Emtricitabine (FTC), salvage therapy, etravirine, Raltegravir, maraviroc, tipranavir, Darunavir

Outcomes: virological suppression, virological failure, discontinuing regimen secondary to AEs, Grade3/4 AEs, CD4 count, HIV drug resistance

Questions

13. What is the risk of virological failure with resistance in patients with recurrent (2 or more) viral load blips above different thresholds?

14. Should FTC/3TC be included in second-line regimens in patients who had developed M184V at time of virological failure of first-line therapy?

15. What is the best management of patients with virological resistance to 2/3 drug classes – how many fully/partially active drugs are necessary for full efficacy of the optimal treatment regimen?

ART in special populations

Study design: SRs, RCTs, observational

HIV associated neurocognitive disorders

Population: HIV associated neurocognitive impairment/disorders, HIV associated dementia

Intervention: Antiretroviral therapy (list all ART drugs)

Outcomes: progressive HIV neurocognitive disorders.

Question

16: Does the choice of specific drugs or regimens with high CSF penetration lead to improved neurocognitive outcomes in any specific circumstances?

Non-AIDS co-morbidities: chronic kidney disease, cardiovascular disease

Population: chronic kidney disease, estimated Glomerular filtration rate <60 mls/min/1.73sqm, cardiovascular disease, myocardial infection

Intervention: ART, Tenofovir, Abacavir, protease inhibitors (Lopinavir/r, Darunavir/r, Atazanavir/r)

Outcomes: progressive CKD, Kidney disease clinical events, CVD clinical events

Question

17. Are there patients with evidence of renal or cardiovascular disease in whom treatment with tenofovir, abacavir or PI/rs respectively should be avoided?

2.2 Search protocols (main databases search)

Search 1: When to Initiate ART

Questions 1-6

Component	Description
Review area	Timing of ART initiation
Objectives	To assess the benefits and risks of earlier rather than later initiation of ART
Populations	Chronic HIV Infection, Primary HIV infection, Advanced HIV disease, HIV infected with HIV negative partner
Interventions	Antiretroviral therapy (all drugs)
Comparisons/ aspects covered by search	Initiation : at diagnosis: at CD4 count >350 cells/ μ L: at CD4 count >500 cells/ μ L
Outcomes	To be decided by writing groups
Study designs	SRs, RCTs, observational studies, risk, economic
Exclusions	Animal studies, letters, editorials, comments, case reports, Non English studies.
How the information was searched	Databases: Medline, Embase, Cochrane Library Language: restrict to English only date parameters : 2008-current
Search terms and date searched	HIV + ARVS + early/late starting See attached Medline strategy document for details: searched 15/9/11
Search results	Medline= 529 Embase= 595 Cochrane = 108 Total deduplicated/sifted = 525
Key papers	SMART study J Infect Dis 2008,197:1133-1144; Sterne JA et al Lancet 2009,373:1352-1363; HIVCAUSAL Collab Annals of internal medicine 2011, 154(8):509-151; Fidler, S (conf Ab); Grant PM Plosone 2010 Jul1, 5(7) e11416 ; Cohen M S New Engl Jnl 2011, 365(6): 493-505

Search 2: ART first line regimens

Questions 7-9

Component	Description
Review area	Preferred initial ART regimens
Objectives	Safety and efficacy of various different first line regimens in ART naïve patients
Populations	HIV infected, naïve to ART Adults – all questions
Interventions	Q7: third agents rilpivirine darunavir, atazanavir, raltegravir, maraviroc, etravirine, nevirapine, lopinavir/r Q8: Kivexa (abacavir/ lamivudine) Q9: PI monotherapy or NRTI sparing regimens (raltegravir, darunavir, atazanavir ,lopinavir/r, maraviroc)
Comparisons/ aspects covered by search	Q7: third agent efavirenz Q8: Truvada (tenofovir/ emtricitabine) Q9: conventional triple combination HAART
Outcomes	To be decided by writing groups
Study designs	SRs, RCTs,
Exclusions	Animal studies, letters, editorials, comments, case reports Non English studies.
How the information was searched	Databases: Medline, Embase, Cochrane Library Language: restrict to English only date parameters : 2008-current
Search terms and date searched	HIV + ARVS (selected terms) + naïve/ first line See attached strategy document for details: searched 15/9/2011
Search results	Medline=460 Embase= 510 Cochrane = 259 Total deduplicated/sifted = 556
Key papers	McComsey et al Clin Infect Dis 2011; 53 (2):185-96, Daar, ES Ann Inter med 2011;154(7):445-56, Lennox, JL JAIDS 2010; 55(1): 39-48, Taiwo, B AIDS epub Aug 2011 (not yet on Medline or Embase), Ghosn, J HIV Med 2010; 11(2:) 137-42

Search 3 : Switching/ simplification of ART regimens and /or stopping therapy

Questions 10-12

Component	Description
Review area	ART simplification/ switching/ stopping options
Objectives	Safety and efficacy of switching drug therapy, simplifying drug regimens or stopping ART therapy
Populations	HIV infected on ART Adults – all questions
Interventions	Q10: PI monotherapy Q11: alternative third agents, NRTI backbone Q12: treatment cessation
Comparisons/ aspects covered by search	Standard combination triple ART
Outcomes	To be decided by writing groups
Study designs	SRs, RCTs
Exclusions	Animal studies, letters, editorials, comments, case reports, Non English studies.
How the information was searched	Databases: Medline, Embase, Cochrane Library Language: restrict to English only date parameters : 2008-current
Search terms and date searched	HIV + ARVS + switching/ simplification/ treatment cessation See attached strategy document for details : searched 16/9/11
Search results	Medline= 375 Embase= 465 Cochrane = 168 Total deduplicated/sifted = 489
Key papers	MONET trial J Antimicrob Therap; 2011 66(8) :1878-85, Katlama C AIDS 2010 24(15:) 2365-74 , Waters L AIDS2011 25(1): 65-71, Squires KE AIDS 2010 24(13:) 2019-27, Martinez E JAIDS 2009 51 (3) :290-7

Search 4: Virological failure

Questions 13-15

Component	Description
Review area	Managing Virological failure/drug resistance
Objectives	Risk of and management of patient with virological failure/ resistance
Populations	HIV infected on ART with or at risk of virological failure/ resistance Adults – all questions
Interventions	resistance or virological risk stratification Alternative ARVs/ strategies
Comparisons/ aspects covered by search	Standard combination triple ART
Outcomes	To be decided by writing groups
Study designs	SRs, RCTs, observational, risk
Exclusions	Animal studies, letters, editorials, comments, case reports, Non English studies.
How the information was searched	Databases: Medline, Embase, Cochrane Library Language: restrict to English only date parameters : 2008-current
Search terms and date searched	HIV + ARVS + resistance/ virological (treatment) failure See attached strategy document for details: searched 16/9/11
Search results	Medline= 831 Embase= 855 Cochrane = 206 Total deduplicated/sifted = 1104
Key papers	OPTIMA PlosOne2011 6(3):e14764 , Katlama C Antivir Ther 2010 15(7): 1045-52, Garcia-Gasco P J antimicrob Chemo 2008 61 (3): 699-704

Search 6 : ART in HIV patients with CKD and / or CVD

Questions 17

Component	Description
Review area	ART use in HIV patients with CKD and / or CVD
Objectives	To establish whether PIs, tenofovir and abacavir should be avoided in patients with CKD/CVD
Populations	HIV infected on ART Adults – all questions
Interventions	Tenofovir, abacavir, lopinavir/r, darunavir/r, atazanavir/r, NNRTIs, maraviroc
Comparisons/ aspects covered by search	Risk of each/ all drugs
Outcomes	To be decided by writing groups
Study designs	SRs, RCTs, observational, risk
Exclusions	Animal studies, letters, editorials, comments, case reports, Non English studies.
How the information was searched	Databases: Medline, Embase, Cochrane Library Language: restrict to English only date parameters : 2008-current
Search terms and date searched	HIV + ARVS + CVD/Renal See attached strategy document for details: date searched 16/9/11
Search results	Medline= 188 Embase= 397 Cochrane = 26 Total deduplicated/sifted = 432
Key papers	Cruciani M AIDS 2011 epub (not yet on databases), Choi AI AIDS 2011 25 (10) :1289-98, Lang S Arch inter med 2010 170(14):1228-38, Worm SW J infect Dis 2010 201(3:) 318-30, Mocroft A AIDS 2010 24(11) :1667-78

Appendix 3: GRADE tables

3.1 What to Start: Which NRTI backbone:

Design: RCTs, Systematic reviews

Population: ART naive

Intervention: which NRTI backbone (TDF/FTC or ABC/3TC)

Outcomes: Viral load, CD4 count, HIV resistance, adverse events, clinical events

The table below outlines key outcomes and an importance rating (based on GRADE) for each.

OUTCOME	IMPORTANCE
Viral suppression (<50) at week 48	9: critical
Viral suppression at week 96	8: critical
Proportion of all randomised subjects with protocol-defined virological failure at week 48 +/- week 96	9: critical
Proportion of all randomised subjects who develop drug resistance	8: critical
Quality of life	8: critical
Proportion discontinuing for adverse events	7: critical
Proportion with grade 3/4 adverse events (overall)	7: critical
Proportion with grade 3/4 rash	7: critical
Proportion with grade 3/4 ALT/AST elevation	7: critical
Proportion with grade 3/4 CNS events	5: important
Proportion with grade 3/4 diarrhoea	5: important
10% or more limb fat loss	5: important
% change in limb fat	5: important
% change in trunk fat	5: important
% change in visceral adipose tissue	5: important
Change in visceral:total adipose tissue ratio	5: important
Renal impairment	4: important
Proportion with grade 3/4 total cholesterol events	3: not important
Proportion with grade 3/4 LDL cholesterol	3: not important

Proportion with grade 3/4 triglycerides	3: not important
Total hip BMD decrease 6% or more	3: not important
Total spine BMD decrease 6% or more	3: not important
Change in lumbar spine BMD	3: not important
Change in hip BMD	3: not important
Bone fractures	3: not important

Three randomised trials were found comparing these two NRTI backbones:

- ACTG5202:
 - Sax *et al.* Abacavir–Lamivudine versus Tenofovir–Emtricitabine for Initial HIV-1 Therapy. *New Engl J Med* 2009; 361(23): 2230-40 (ClinicalTrials.gov number, NCT00118898).
 - Sax *et al.* Abacavir/ Lamivudine Versus Tenofovir DF/Emtricitabine as Part of Combination Regimens for Initial Treatment of HIV: Final Results. *J Infect Dis* 2011; 204: 1191–201.
 - Daar ES *et al.* Atazanavir Plus Ritonavir or Efavirenz as Part of a 3-Drug Regimen for Initial Treatment of HIV-1 A Randomized Trial. *Ann Intern Med.* 2011; 154: 445-456.
 - McComsey GA *et al.* Bone Mineral Density and Fractures in Antiretroviral-Naive Persons Randomized to Receive Abacavir-Lamivudine or Tenofovir Disoproxil Fumarate-Emtricitabine Along With Efavirenz or Atazanavir-Ritonavir: AIDS Clinical Trials Group A5224s, a Substudy of ACTG A5202. *J Infect Dis* 2011; 203: 1791-801.
 - McComsey GA *et al.* Peripheral and Central Fat Changes in Subjects Randomized to Abacavir-Lamivudine or Tenofovir-Emtricitabine With Atazanavir-Ritonavir or Efavirenz: ACTG Study A5224s. *Clinical Infectious Diseases* 2011; 53(2): 185–196.

- ASSERT
 - Post *et al.* Randomized Comparison of Renal Effects, Efficacy, and Safety With Once-Daily Abacavir/ Lamivudine Versus Tenofovir/ Emtricitabine, Administered With Efavirenz, in Antiretroviral-Naive, HIV-1–Infected Adults: 48-Week Results From the ASSERT Study. *J Acquir Immune Defic Syndr* 2010; 55(1): 49-57.
 - Stellbrink HJ *et al.* Comparison of Changes in Bone Density and Turnover with Abacavir-Lamivudine versus Tenofovir-Emtricitabine in HIV-Infected Adults: 48-Week Results from the ASSERT Study. *Clin Infect Dis* 2010; 51: 963-72.
 - Moyle, G. J., H. J. Stellbrink, *et al.* (2010). "Comparison of bone and renal toxicities in the ASSERT study: Final 96 week results from a prospective randomized safety trial." *Antiviral Therapy* 15: A19.

- HEAT
 - Smith *et al.* Randomized, double-blind, placebo-matched, multicenter trial of abacavir/ lamivudine or tenofovir/ emtricitabine with lopinavir/ ritonavir for initial HIV treatment. *AIDS* 2009; 23(12): 1547-56.

Also, one meta-analysis was identified. This reviewed 12 trials (3399 subjects on TDF/FTC, 1769 ABC/3TC, with a boosted PI [Hill A, Sawyer W. Effects of nucleoside reverse transcriptase inhibitor backbone on the efficacy of first-line boosted highly active antiretroviral therapy based on protease inhibitors: metaregression analysis of 12 clinical trials in 5168 patients. *HIV Med* 2009;10(9):527-35]). It included prospective clinical trials of HAART regimens containing RTV-boosted HIV PIs in antiretroviral-naïve, HIV-infected individuals published between 1 January 2000 and 1 March 2008; trials had to involve at least 50 chronically infected treatment-naïve, HIV-infected individuals aged 16 years or above at any stage of HIV infection; the minimum duration of follow-up reported for these trials at the moment of inclusion in the systematic review had to be 48 weeks; efficacy data had to be reported for the 48-week timepoint using the FDA-endorsed TLOVR algorithm for the virological response (% of patients with a plasma viral load <50 copies/mL); they had to evaluate, in at least one treatment arm, HAART regimens comprising an RTV-boosted PI (a PI co-administered with ≤200 mg/day of RTV) and a fixed combination of two NRTIs: either ABC or TDF in combination with 3TC or FTC. The included studies were not all head-to-head comparisons of TDF vs ABC – the only included study that was a head-to-head trial was HEAT (included above). The authors stated that “The interpretation of all results should be made with the caveat that there was a wide range of baseline patient characteristics and all trials not were conducted identically. While statistical models to account for baseline variables and the usage of the ITT TLOVR endpoint may help to reduce the impact of any baseline imbalance, this is not guaranteed.” They also state that “There may be other differences between the trials – in country selection, adherence, patient management – that could explain the difference in efficacy between the NRTIs, but could not be adjusted for in the multivariate analysis.” There is likely to be so much heterogeneity between trial methodologies that combining them in this way is difficult. In addition, the authors have combined means and medians, which may not be valid if the underlying population distributions are skewed. The information from this analysis could not be used further.

Evidence tables

Reference	Study type and methodological quality	No. pts	Patient characteristics	Intervention	Comparison	Length follow-up	Outcome measures	Funding
ACTG5202: Sax <i>et al.</i> Abacavir–Lamivudine versus Tenofovir–Emtricitabine for Initial HIV-1 Therapy. <i>New Engl J Med</i> 2009 ;	RCT Allocation to treatment Random Method of randomisation: Allocation used a	Total N: 1858 First analysis includes data from the 797 patients	INCLUSION CRITERIA HIV-1–infected patients who were at least 16 years of age, who had received at most 7 days of antiretroviral	Drug(s): 300mg tenofovir DF plus 200mg emtricitabine	Drug(s): 600mg abacavir plus 300 mg lamivudine (plus 600mg	Treatment duration: planned and actual study	Primary endpoint: time from randomization to virologic failure (defined as a confirmed HIV-1 RNA level > or = 1000 copies/ ml at or after	Abbott Pharmaceuticals, Bristol-Myers Squibb,

<p>361(23): 2230-40 (ClinicalTrials.gov number NCT00118898).</p> <p>Sax et al. Abacavir/ Lamivudine Versus Tenofovir DF/ Emtricitabine as Part of Combination Regimens for Initial Treatment of HIV: Final Results. <i>J Infect Dis</i> 2011; 204: 1191–201.</p> <p>Daar ES et al. Atazanavir Plus Ritonavir or Efavirenz as Part of a 3-Drug Regimen for Initial Treatment of HIV-1 A Randomized Trial. <i>Ann Intern Med</i> 2011; 154: 445-456.</p> <p>McComsey GA et al. Bone Mineral Density and Fractures in</p>	<p>centralized computer system. Randomization was stratified according to the screening HIV-1 RNA level obtained before study entry ($\geq 100,000$ vs. $<100,000$ copies per milliliter), with the use of a permuted-block design with dynamic balancing according to the main institution</p> <p>Concealment: adequate</p> <p>Blinding double blinded with regard to NRTIs</p> <p>Sample size calculation Regimens were considered equivalent if the two-sided 95% confidence interval for the hazard ratio was between 0.71 and 1.40. A planned sample size of 1800 subjects (450 per group) would provide an 89.8% probability of declaring</p>	<p>with a screening HIV-1 RNA level of 100,000 copies per milliliter or more. 718 patients (90%) remained in the study. Follow-up was discontinued in 41 patients assigned to abacavir–lamivudine and in 38 patients assigned to tenofovir DF–emtricitabine, with no significant difference in the distributions of time to</p>	<p>therapy previously, and who had acceptable laboratory values.</p> <p>EXCLUSION CRITERIA pregnant or breastfeeding; were using immunomodulators; had any known allergies to the study drugs; abused substances that would interfere with the study; had a serious illness; had an important cardiac conduction disorder; required prohibited medications; showed evidence of major resistance mutations; were incarcerated; or, as of July 2006, had hepatitis B. Resistance testing was required for recently infected patients.</p> <p>Baseline</p>	<p>(Truvada) (plus 600mg efavirenz or 300mg atazanavir plus 100mg ritonavir)</p> <p>n=399 in first subgroup analysis (HIV-1 RNA levels of 100 000 copies/mL or more at screening)</p> <p>n=530 in second subgroup analysis</p>	<p>efavirenz or 300mg atazanavir plus 100mg ritonavir)</p> <p>n=398 in first subgroup analysis (HIV-1 RNA levels of 100 000 copies/mL or more at screening)</p> <p>n=530 in second subgroup analysis (HIV-1 RNA levels < 100 000 copies/mL at screening)</p>	<p>duration 96 weeks after enrollment of last patient</p> <p>Assessments at: before entry, at weeks 4, 8, 16, and 24, and every 12 weeks thereafter</p> <p>Follow-up after end of treatment: none</p> <p>Median follow-up first analysis</p>	<p>16 weeks and before 24 weeks, or ≥ 200 copies /ml at or after 24 weeks)</p> <p>Other endpoints: Time from the initiation of treatment to the first grade 3 or 4 sign, symptom, or laboratory abnormality that was at least one grade higher than that at baseline, excluding isolated unconjugated hyper-bilirubinemia and elevations in the creatine kinase level, while the patient was receiving the randomly assigned treatment. Adverse events</p> <p>Copriary objectives of A5224s were to compare effects of starting ABC-3TC with those of TDF/FTC on spine and hip BMD and on body fat. A5224s 2ry objectives</p>	<p>Gilead Sciences, and GlaxoSmithKline provided the study medications and had input into the protocol development and review of the manuscript.</p>
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<p>Antiretroviral-Naive Persons Randomized to Receive Abacavir-Lamivudine or Tenofovir Disoproxil Fumarate-Emtricitabine Along With Efavirenz or Atazanavir-Ritonavir: AIDS Clinical Trials Group A5224s, a Substudy of ACTG A5202. J Infect Dis 2011; 203: 1791-801.</p> <p>McComsey GA et al. Peripheral and Central Fat Changes in Subjects Randomized to Abacavir Lamivudine or Tenofovir-Emtricitabine With Atazanavir-Ritonavir or Efavirenz: ACTG Study A5224s. Clinical Infectious</p>	<p>equivalence if two regimens were the same, assuming uniform accrual, exponential virologic failure, and lost-to-follow-up time distributions among the four groups, with event probabilities of 17.46% and 10.00%, respectively, at 48 weeks. Study conduct and safety data were reviewed yearly by the data and safety monitoring board. Efficacy data were reviewed annually starting with the second review of study data. Early stopping guidelines for inferiority were prespecified, with a regimen considered to be inferior if the 99.95% two-sided confidence interval for the hazard ratio for virologic failure did not include 1.0.</p> <p>ITT analysis</p>	<p>discontinuation (P = 0.91).</p> <p>Second analysis: low screening HIV RNA stratum (n=1060)</p>	<p>comparability between groups: yes</p> <p>Age: median 38 years (IQR 31-45) Gender: 83% male Severity of disease: median CD4 cell count 229.5cells/ml (IQR 89.5-333.8)</p> <p>Specific A5224s exclusion criteria were uncontrolled thyroid disease or hypogonadism; endocrine diseases, including Cushing’s syndrome, diabetes mellitus, and the use of growth hormone, anabolic steroids, glucocorticoids, or osteoporosis medications; or the intent to start bone-related treatment.</p>	<p>(HIV-1 RNA levels < 100 000 copies/mL at screening)</p> <p>A5224s was a substudy of AIDS Clinical Trials Group (ACTG) A5202: for n in each group see results section</p>	<p>)</p> <p>A5224s was a substudy of AIDS Clinical Trials Group (ACTG) A5202: for n in each group see results section</p>	<p>: 60 weeks (range 0-112 weeks); full analysis : 136 weeks</p> <p>Median (25th, 75th percentile) final (Daar 2011) follow-up was 138 weeks (106 weeks, 169 weeks)</p>	<p>were to compare BMD changes between EFV and ATV/r arms, to compare TDF-FTC with ABC-3TC and EFV with ATV/r on BMD changes at week 48, and to compare % with bone fractures. Substudy evaluations included whole-body dual-energy X-ray absorptiometry (DEXA) scans at baseline and weeks 24, 48, 96, 144, and 192 and a single-slice abdomen CT scan at the L4-L5 level at baseline and week 96. Fat distribution was measured by DEXA in antero-posterior view (with use of Hologic or Lunar scanners). Technicians were instructed to use the same machine on the same subject throughout the study. CT was used to</p>
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Diseases 2011 ; 53(2): 185–196.	Yes Setting: Outpatients						quantify visceral adipose tissue (VAT) and total adipose tissue (TAT).
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Patient disposition (data from both Sax publications)

Total (n=1857)							
High HIV RNA stratum (n=797)				Low HIV RNA stratum (n=1060)			
TDF/FTC (n=399)		ABC/3TC (n=398)		TDF/FTC (n=530)		ABC/3TC (n=530)	
with EFV (n=199)	with ATV (n=200)	with EFV (n=199)	with ATV (n=199)	with EFV (n=265)	with ATV (n=265)	with EFV (n=266)	with ATV (n=264)
VF*: 11/199 (6%)	15/200 (8%)	25/199 (13%)	32/199 (16%)	33/265 (12%)	29/265 (11%)	39/266 (15%)	35/264 (13%)
26/399		57/398		62/530		74/530	

*VF=virological failure

Combining high and low strata: TDF/FTC

All (n=1857)			
TDF/FTC (n=929)		ABC/3TC (n=928)	
with EFV (n=464)	with ATV (n=465)	with EFV (n=465)	with ATV (n=463)
VF: 44/464	44/465	64/465	67/463
88/929		131/928	

The data and safety monitoring board (DSMB) met on January 29, 2008, for the first efficacy review. Protocol prespecified time-to-event distributions were presented overall and within each screening HIV-1 RNA stratum. The DSMB noted excess virologic failures in both groups of patients who received regimens containing abacavir–lamivudine; additional requested analyses showed that these excess failures associated with abacavir–lamivudine occurred within the higher screening HIV-1 RNA stratum. When data in the four groups were combined and analyzed as two groups (i.e., the group receiving regimens with abacavir–lamivudine and the group receiving regimens without abacavir–lamivudine), the difference between these two groups was determined to be highly statistically significant. The DSMB found the strength and validity of these findings sufficient to warrant stopping the further study of abacavir–lamivudine among participants with a screening HIV-1 RNA level of at least 100,000 copies per milliliter. The board specified that the remainder of the study should continue without change. On release of these findings from the DSMB, the study team completed additional analyses based on a previous analysis plan. Treatment-effect modification was assessed for six prespecified baseline covariates:

sex, race or ethnic group, age, HIV-1 RNA level, CD4 cell count, and available or unavailable test results for HIV-1 genotype at screening.

First analysis includes data from the 797 patients with a screening HIV-1 RNA level of 100,000 copies per milliliter or more (high stratum).

High stratum	tenofovir DF–emtricitabine group (n=399)	abacavir–lamivudine group (n=398)	hazard ratio (HR), confidence interval (CI), p value
Protocol-defined virologic failure	26 patients	57 patients	
Time to virologic failure			HR 2.33; 99.95% CI 1.01 to 5.36; 95% CI, 1.46 to 3.72; P<0.001
Estimated probability of remaining free of virologic failure beyond 48 weeks	0.93 (95% CI 0.90 to 0.96)	0.84 (95% CI 0.79 to 0.88)	HR 2.08 (95% CI 1.28 to 3.37)

The relative hazard of virologic failure between the NRTI groups according to the six baseline covariates (univariate analysis) showed significant treatment interactions with sex (P = 0.04), available/unavailable genotype information at screening (P = 0.02), and baseline CD4 cell count (P = 0.007). Tenofovir DF–emtricitabine treatment was associated with a lower rate of virologic failure than abacavir–lamivudine among men, pts with a screening genotype result, and pts with a lower baseline CD4 cell count. When a multivariable model was fitted with these baseline factors, the differences in the hazard ratios for failure remained significant for male sex (P = 0.05), available genotype information (P = 0.03), and lower CD4 cell count (P = 0.01).

Other outcomes:

CD4 cell count distributions and the change from baseline were similar in the two groups. At week 48, the median increase from baseline was 194 cells/mm³ (interquartile range, 126 to 305) in the 248 patients assigned to abacavir–lamivudine and 199 cells/mm³ (IQR, 129 to 302) in the 248 patients assigned to tenofovir DF–emtricitabine (P = 0.78).

High HIV RNA stratum	tenofovir DF–emtricitabine (n=399)	abacavir–lamivudine (n=398)	hazard ratio, CI, p value
at least one grade 3 or 4 sign, symptom, or laboratory abnormality that was at least one grade higher than the baseline value, while receiving their initial regimen	78	130	
grade 4 event	13	24	
time to the safety end point			1.89; 95% CI, 1.43 to 2.50; P<0.001
week 48 median change in total cholesterol level	26mg/dl	34mg/dl	P<0.001
week 48 median change in HDL cholesterol level	7mg/dl	9mg/dl	P=0.05

week 48 median change in triglyceride level	3mg/dl	25mg/dl	P = 0.001
median change in total: HDL cholesterol ratio	-0.2	-0.2	P = 0.50
Suspected study drug-related hypersensitivity	27 (7%)	27 (7%); 1 died	
Subsequent virologic failure among patients with suspected drug hypersensitivity	3	4	
AIDS events	17 (4%)	26 (7%)	
HIV-related cancers	4	8	
Bone fractures	10	7	
Myocardial infarctions	0	0	
Renal failure	2	2	
median change from baseline in creatinine clearance	2ml/min (IQR -11 to 16); n=241	4ml/min(IQR -7 to 16); n=212	P = 0.10

Among the 81 patients with resistance data that could be evaluated, major reverse-transcriptase or protease resistance mutations at baseline were detected in 5 pts randomly assigned to abacavir-lamivudine and 4 to tenofovir DF-emtricitabine. Emergence of major drug-resistance mutations was noted in 25 patients in the abacavir-lamivudine group (6% of those randomly assigned to the group and 45% of group members with virologic failure) and in 10 patients in the tenofovir DF-emtricitabine group (3% and 38%, respectively). Among the 35 patients with the emergence of new major resistance mutations at the time of virologic failure, 3 in each group had other major mutations at baseline.

Main (final results) publication:

	TDF/FTC	ABC/3TC	Comparisons between TDF and ABC groups: Hazard ratio, CI, p value or difference	p value for difference between ATV and EFV
NRTI comparison combined across ATV/r and EFV regimens (factorial analysis) for all patients (high and low HIV RNA stratum): virologic failure	88/929	131/928	HR 1.70 (95% CI 1.23, 2.35)	
combining high and low HIV RNA strata (with ATV/r)	44/465	67/463	HR 1.48 (95% CI, 0.95, 2.31)	p=0.38
combining high and low HIV RNA strata (with EFV)	44/465	64/465	HR 1.98 (95% CI 1.22, 3.20)	
high HIV RNA stratum: virologic failure (with ATV/r)	15/200	32/199	HR 2.22 (95% CI, 1.19, 4.14)	p=0.82
high HIV RNA stratum: virologic failure (with EFV)	11/199	25/199	HR 2.46 (95% CI, 1.20, 5.05)	
low HIV RNA stratum: virologic failure (with ATV/r)	29/265 (11%)	35/264 (13%)	HR 1.25 (95% CI 0.76, 2.05)	

low HIV RNA stratum: virologic failure (with EFV)	33/265 (12%)	39/266 (15%)	HR 1.23 (95% CI, 0.77, 1.96)	
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CD41 Cell Count Changes in the Low HIV RNA Stratum

Among those randomized to ATV/r, there was no significant difference in distribution of change from baseline CD41 cells/mm³ between ABC/3TC and TDF/FTC at week 48 (week 96); median 170 ABC/3TC and 157 TDF/FTC (240 ABC/3TC and 241 TDF/FTC), P > 0.6 for both time points. Among those randomized to EFV, ABC/3TC recipients experienced significantly greater CD41 cells/mm³ increases compared with TDF/FTC at weeks 48 and 96 (median 175 vs 147, P = .035; and 227 vs 200, P = .035, respectively).

Tolerability Endpoints in the Low HIV RNA Stratum

Low HIV RNA stratum	tenofovir DF– emtricitabine (n=530)	abacavir– lamivudine (n=530)	hazard ratio, CI, p value
time to first antiretroviral drug modification			ATV/r: HR 1.43 (95% CI, 1.06, 1.92, P = .018); EFV: HR 1.48 (95% CI, 1.12, 1.95, P = .005).
time to first modification of the NRTIs			ATV/r: HR 1.57 (95% CI 1.14, 2.16, P = .006); ETV: HR 1.84 (95% CI 1.36, 2.51, P < .0001)
unblinding of NRTIs for suspected drug hypersensitivity			
ATV/r	11 (4 renal)	23	
EFV	8 (5 renal)	32	
severe hypersensitivity reaction when rechallenged	1	0	
Safety event			
Time to first safety event with ATV/r			HR 1.13; 95% CI 0.83 to 1.54 P=.44
Time to first safety event with EFV			HR 1.38; 95% CI, 1.03, 1.85, P = .03
Death			
with ATV	0	4 (non-Hodgkin's lymphoma, MI, car accident, drug overdose/ suicide)	
with EFV	3 (bacterial pneumonia, stroke, Mycobacterium)	3 (bladder carcinoma, hepatic)	

	avium complex)	carcinoma, unknown)	
Cardiovascular events with ATV/r with EFV	34 15/265 (6%) 19/265 (7%)	29 15/264 (6%) 14/266 (5%)	
Bone fractures with ATV/r with EFV	10/265 (4%) 13/265 (5%)	7/264 (3%) 15/266 (6%)	
Site-reported incidence of renal disease with ATV/r with EFV	7/265 (3%) 5/265 (2%)	10/264 (4%) 10/266 (4%)	

Data on change from baseline in calculated creatinine clearance to weeks 48 and 96 were available for the 75% and 66% of pts who started study regimen, respectively. Statistically significant improvements from baseline to weeks 48 and 96 was found in all treatment arms (all P = .018) at both time points, except for ATV/r with TDF/FTC at week 96 (P = .14). With ATV/r, there were significant differences in the distribution of change from baseline calculated creatinine clearance between ABC/3TC and TDF/FTC at both week 48 (median +3.3 vs -3.1 mL/min, P < .001) and week 96 (median +5.2 mL/min vs -3.1 mL/min, P < .001). For EFV with ABC/3TC vs TDF/FTC, there was no significant difference in the change from baseline in calculated creatinine clearance at week 48 (median +2.6 mL/min vs +3.3 mL/min, P = .83) or week 96 (+7.0 mL/min vs +4.5 mL/min, P = .15). For pts on a randomized treatment regimen with fasting samples (range 154–188 patients per treatment arm), changes from baseline in lipids levels were generally greater with ABC/ 3TC than TDF/FTC. With ATV/r, median changes for ABC/3TC vs TDF/FTC at week 48 respectively were total cholesterol, 30 vs 8 mg/dL (P < .001); low-density lipoprotein (LDL) cholesterol, 14 vs 0 mg/dL (P < .001); high-density lipoprotein (HDL) cholesterol, 7 vs 4 mg/dL (P < .001); and triglycerides, 27 vs 14 mg/dL (P = .004). With EFV, changes in total cholesterol were 34 vs 19 mg/dL (P < .001); LDL cholesterol, 17 vs 6 mg/dL (P < .001); HDL cholesterol, 12 vs. 9 mg/dL (P = .006); and triglycerides, 12 vs 13 mg/dL (P = .49), respectively. There was no significant difference between NRTIs in the change in the total:HDL cholesterol ratio. Results were similar at week 96.

Selected Events That Triggered a Safety Endpoint While Receiving Randomized Antiretroviral Drugs in Low Screening HIV RNA Stratum

	ABC (n = 263)	TDF (n = 265)	ABC (n = 264)	TDF (n = 263)	All subjects (n = 1055) who started medication
	ATV/r		EFV		
Overall, n (%)	80 (30)	98 (37)	78 (29)	83 (32)	339 (32)
Metabolic, n (%)	22 (8)	19 (7)	24 (9)	13 (5)	78 (7)
Total cholesterol (fasting), n	4	1	9	4	

LDL (fasting), n	7	7	15	8	
Triglycerides (fasting), n	8	3	5	0	
Glucose (nonfasting)	2	5	0	1	
Gastrointestinal, n (%)	21 (8)	16 (6)	12 (5)	12 (5)	61 (6)
Diarrhoea/loose stool, n.	2	4	8	2	
ALT, n	7	1	1	6	
Nausea and/or vomiting, n	6	3	3	1	
Neuropsychological, n (%)	8 (3)	1 (<1)	16 (6)	14 (5)	39 (4)
Depression, n.	3	0	3	7	
General body, n (%)	29 (11)	30 (11)	42 (16)	30 (11)	131 (12)
Ache/pain/discomfort, n	20	11	12	17	
Fever, n	6	7	6	1	
Asthenia/fatigue, n	3	3	7	3	
Rash/allergic reaction, n	2	2	5	2	
Headache, n	3	3	6	1	
Hematologic, n (%)	1 (<1)	7 (3)	4 (2)	7 (3)	19 (2)
Neutrophil count, n	1	6	4	7	

In the low HIV RNA stratum, 136 pts had virologic failure, with resistance data available at baseline and failure in all but 2 pts. Baseline major resistance was present in 13 (10%) pts with virologic failure. Among 122 virologic failures with no major resistance at baseline, there was no significant difference in the occurrence of major resistance mutations between ABC/3TC and TDF/FTC when given with either ATV/r or EFV. Resistance data for pts in the high HIV RNA stratum with virologic failure at the time of the DSMB review showed that when given with ATV/r, the emergence of major NRTI resistance mutations was not significantly different with ABC/3TC (6 of 29) or TDF/FTC (3 of 14, P = 1.0 of failures and P = .34 of randomized). With EFV, major NRTI resistance emerged in 15 of 23 and 2 of 8 randomized to ABC/3TC and TDF/FTC, respectively (P=.10 of failures and P=.002 of randomized).

Daar 2011 Publication:

Summary of Primary End Points at Baseline, 96 Weeks, and Full Follow-up, With Efavirenz as the Reference in All Comparisons

Variable	Abacavir–Lamivudine		Tenofovir DF–Emtricitabine	
	Efavirenz	Atazanavir Ritonavir	Efavirenz	Atazanavir Ritonavir

Time to virologic failure				
Baseline Persons at risk, n	465	463	464	465
96 wk Events/persons at risk (Kaplan–Meier estimate), n/n (%)	63/331 (14.7)	72/338 (16.6)	44/367 (10.2)	48/364 (11.0)
Difference in 96-wk Kaplan–Meier estimate (95% CI), %	1.9 (2.9 to 6.8)		0.8 (3.3 to 4.9)	
Full follow-up Events/total person-years at risk, n/n	72/1011.7	83/1017.1	57/1095.6	57/1086.4
Estimated HR (95% CI)	1.13 (0.82 to 1.56) NB no difference by viral load stratum (p=0.147)		1.01 (0.70 to 1.46) NB no difference by viral load stratum (p=0.37)	
Time to primary safety end point (1st grade-3 or -4 sign, symptom, or lab abnormality while receiving originally assigned 3rd drug (atazanavir/ritonavir or efavirenz) that was ≥1 grade higher than baseline, excluding isolated unconjugated hyperbilirubinemia and creatine kinase)				
Baseline persons at risk, n	461	462	461	464
96 wk Events/persons at risk (Kaplan–Meier estimate), n/n (%)	175/176 (41.7)	152/229 (35.5)	126/248 (30.2)	119/268 (27.7)
Difference in 96-wk Kaplan–Meier estimate (95% CI), percentage points; P value	6.2 (12.9 to 0.4); 0.066		2.5 (8.6 to 3.7); 0.43	
Full follow-up Events/total person-years at risk, n/n	187/631.2	170/762.5	147/814.3	141/868.9
Estimated HR (95% CI); P value	0.81 (0.66 to 1.00); 0.048 no difference in effect by viral load stratum (P=0.71)		0.91 (0.72 to 1.15); 0.44 no difference in effect by viral load stratum (P=0.85)	
Time to AIDS or death	HR, 0.93 [CI, 0.56 to 1.54]; P = 0.77		HR, 1.23 [CI, 0.70 to 2.39]; P = 0.42	
Time to primary tolerability end point (1st change in therapy, ignoring NRTIs)				
Baseline Persons at risk, n	461	462	461	464
96 wk Events/persons at risk (Kaplan–Meier estimate), n/n (%)	155/290 (33.7)	110/334 (23.9)	114/328 (24.8)	97/347 (21.0)
Difference in 96-wk Kaplan–Meier estimate (95% CI),	9.8 (15.6 to 4.0); 0.001		3.8 (9.2 to 1.6); 0.170	

percentage points; P value				
Full follow-up Events/total person-years at risk, n/n	186/943.7	142/1052.6	142/1032.1	126/1088.5
Estimated HR (95% CI); P value	0.69 (0.56 to 0.86); <0.001 no difference by viral load stratum (<i>P</i> = 0.63)		0.84 (0.66 to 1.07); 0.166 no difference by viral load stratum (<i>P</i> = 0.90).	

A prespecified comparison of atazanavir plus ritonavir and efavirenz with NRTIs combined (factorial analysis) was done because there was no evidence that the treatment effect differed by NRTIs (*P* = 0.65). For atazanavir plus ritonavir versus efavirenz, the HR for time to virologic failure was 1.08 (CI, 0.85 to 1.38), with CIs within the prespecified equivalence boundaries. However, for this comparison, there was a significant interaction with screening viral load (*P* = 0.080), in which the HRs were 1.35 (CI, 0.96 to 1.92) and 0.88 (CI, 0.62 to 1.23) for the high and low viral load stratum, respectively.

	abacavir–lamivudine			tenofovir DF–emtricitabine		
	ATZ/r	efavirenz	difference	ATZ/r	efavirenz	difference
Pts with HIV-1 RNA levels <50 copies/mL (regardless of previous virologic failure or regimen change) of the 1642 (88%) and 1498 (81%) of patients with HIV-1 RNA results available at week 48 and week 96, respectively*	n not stated	n not stated		n not stated	n not stated	
Week 48**	78%	87%	8 percentage points [CI, 13 to 3]; <i>P</i> = 0.03	84%	90%	6 percentage points [CI, 11 to 1]; <i>P</i> = 0.012
Week 96**	85%	91%	6 percentage points [CI, 11 to 1]; <i>P</i> = 0.012	90%	91%	difference, 1 percentage point [CI, 5 to 3]; <i>P</i> = 0.58
Time to 1st confirmed virologic failure or discontinuation of assigned PI or NNRTI			HR, 0.87 [CI, 0.71 to 1.08]			HR, 0.93 [CI, 0.74 to 1.17]

*Data were missing primarily because of premature discontinuation of the study (e.g. pt moved, was incarcerated, was deported) or the pt lost to follow-up. Pts with missing data were more likely than those with results to be younger, to be a non-Hispanic black person, to report previous intravenous drug use, and to have hepatitis B or C infection.

**In a prespecified, worst-case sensitivity analysis, in which patients with missing data were assigned to the group with HIV-1 RNA levels of 50 copies/mL or more, 48-week results were similar to primary analyses, and at 96 weeks, abacavir–lamivudine no longer favored efavirenz.

Change in CD4 cell counts from baseline to weeks 48 and 96 was examined in 1645 (89%) and 1493 (80%) of patients with results available, respectively. Reasons for missing CD4 values were similar to reasons noted for HIV-1 RNA. Change in CD4 cell counts did not differ between persons given atazanavir plus ritonavir or efavirenz with abacavir–lamivudine, with a median change of 0.178 vs 0.188 x 10⁹ cells/L (*P* = 0.94) and 0.250 vs 0.251 x 10⁹ cells/L (*P* = 0.89), respectively. Change in CD4 cell count was greater in persons given atazanavir plus ritonavir than those given efavirenz with tenofovir DF–emtricitabine at weeks 48 and 96, with a median change of 0.175 vs 0.163 x 10⁹ cells/L (*P* = 0.040) and 0.252 vs 0.221 x 10⁹ cells/L (*P* = 0.002), respectively. n not stated

Safety events

	Abacavir–Lamivudine		Tenofovir DF–emtricitabine	
	Efavirenz (n = 461)	Atazanavir/ Ritonavir (n = 462)	Efavirenz (n = 461)	Atazanavir/ Ritonavir (n = 464)
Death, n (of the 1857 randomly assigned patients)	11	8	6	6
Selected primary safety end point event, n (%): overall	187 (41)	170 (37)	147 (32)	141 (30)
Fasting total cholesterol level	21	11	7	2
Fasting LDL cholesterol level	29	14	15	7
Fasting triglycerides level	17	16	5	7
Blood glucose level	4	7	2	4
Gastrointestinal	23 (5)	38 (8)	22 (5)	25 (5)
AST	6	14	6	6
ALT	5	13	9	5
Diarrhoea or loose stools	11	7	6	6
Nausea, vomiting, or both	5	8	2	3
Neuropsychological	28 (6)	14 (3)	28 (6)	10 (2)
Depression	6	4	13	5
Dizzy or lightheaded	6	0	2	2
Insomnia, dreams, or sleep	6	0	5	0
General	71 (15)	64 (14)	46 (10)	59 (13)
Ache, pain, or discomfort	25	35	23	21
Fever	10	16	4	12

Asthenia, fatigue, or malaise	8	5	7	8
Headache	10	7	3	6
Rash or allergic rash	9	3	4	6
Vascular events (coronary artery disease, infarction, ischemia, angina, CVA, TIA or peripheral vascular disease)	2 (<1%)	2 (<1%)	6 (1%)	1 (<1%)
Renal diagnoses of the Fanconi syndrome, toxic nephropathy, proteinuria, or renal failure	5 (1%)	4 (1%)	3 (1%)	6 (1%)
bone fractures	22 (5%)	16 (3%)	21 (5%)	21 (5%)
suspected hypersensitivity reaction	53 (11%)	34 (7%)	25 (5%)	27 (6%)

Of the 269 pts with protocol-defined virologic failure, 265 had resistance data available at failure and baseline; of these, 25 had major mutations at baseline. Among pts with virologic failure, emergent resistance mutations were less frequent in those assigned to received atazanavir plus ritonavir than in those assigned to receive efavirenz, combined with either NRTI ($P < 0.001$ for both). There was also a lower frequency of NRTI-associated mutations among pts on ATZ/r than on efavirenz with abacavir–lamivudine ($P < 0.001$) or tenofovir DF–emtricitabine ($P = 0.046$).

	Abacavir–Lamivudine		Tenofovir DF–emtricitabine	
	Efavirenz (n = 461)	Atazanavir/ Ritonavir (n = 462)	Efavirenz (n = 461)	Atazanavir/ Ritonavir (n = 464)
Virologic failure Events, n (%)	72 (15)	83 (18)	57 (12)	57 (12)
Genotype available at failure	71	83	55	57
Major mutations at baseline	8	7	7	3
Without mutations at baseline	63	76	48	54
Mutations , n (%) [%] *				
Any major mutation	41 (9) [65]	12 (3) [16]	27 (6) [56]	5 (1) [9]
NRTI-associated	25 (5) [40]	11 (2) [14]	11 (2) [23]	5 (1) [9]
NNRTI-associated	41 (9) [65]	1 (<1) [1]	27 (6) [56]	0 (0) [0]
NRTI + NNRTI-associated	25 (5) [40]	0 (0) [0]	11 (2) [23]	0 (0) [0]
Protease-associated (N88N/S)	0 (0) [0]	1 (<1) [1]	0 (0) [0]	0 (0) [0]

*Excludes patients with major resistance mutations present at baseline but includes 1 person who had resistance data available at virologic failure but

not at baseline. Total may not add up to 100% because some patients had >1 mutation. Values are total number (% of pts randomly assigned) [% of pts with a genotype and without baseline resistance]

A5224s substudy of AIDS Clinical Trials Group (ACTG) A5202 (McComsey bone paper)

	Efavirenz + TDF (n =69)	Efavirenz + ABC (n = 70)	ATZ/R + TDF (n = 65)	ATZ/R + ABC (n = 65)
Median age (IQR)	40 (33-44)	39 (31-46)	38 (30-44)	37 (29-43)
Male	58 (84%)	56 (80%)	56 (86%)	59 (91%)
Median (IQR) CD4 cells/ μ L	250 (132-334)	213 (106-350)	247 (114-319)	222 (75-332)
Median (IQR) lumbar spine BMD (g/cm^2)	1.12 (1.00-1.23)	1.08 (.97-1.23)	1.13 (1.03-1.24)	1.13 (1.04-1.23)
Median (IQR) hip BMD (g/cm^2)	0.99 (.92-1.07)	1.02 (.93-1.11)	1.05 (.98-1.18)	1.02 (.97-1.13)
Mean (SD) change lumbar spine BMD (%), week 0-96	-2.52 (4.08), n=54, p<0.001	-0.78 (5.20), n=53, p=0.28	-4.38 (4.95), n=43, p<0.001	-1.99 (4.69), n=48, p=0.005
Mean (SD) change in hip BMD (%), week 0-96	-3.69 (3.81), n=54, p<0.001	-2.54 (4.40), n=51, p<0.001	-4.31 (5.17), n=42, p<0.001	-2.68 (3.30), n=48, p<0.001

The estimated mean % change in spine BMD for all pts was 23.0% at week 48 and 22.3% at week 96. The comparison of ABC-3TC (n = 135) and TDF-FTC (n = 134) with EFV and ATV/r combined (factorial analysis) was performed, because there was no significant evidence that the treatment effect between these drugs differed at 96 weeks by the NNRTI-PI component (P = .63). Similarly, the comparison of EFV (n = 139) and ATV/r (n = 130) with ABC-3TC and TDF-FTC combined was performed.

Changes by NRTI Components: Primary Analysis.

By ITT at week 96, there was a significant decrease in mean % change in spine BMD for all arms except ABC-3TC plus EFV, but significantly less for ABC-3TC (estimated mean of -1.3%) than for TDF-FTC (-3.3%; difference [Δ] = 2.0%; 95% confidence interval [CI], 0.7%–3.3%; P = .004).

At week 96, among pts assigned to EFV, there was a trend toward a greater decrease in mean % change in spine BMD when combined with TDF-FTC than when combined with ABC-3TC (Δ , 1.7%; 95% CI, .04%–3.5%; P = .056). In ATV/r-treated arms, there was a significantly greater decrease in mean percentage change in spine BMD when combined with TDF-FTC than when combined with ABC/3TC (Δ , 2.4%; 95% CI, .4%–4.4%; P = .020, by ITT).

Changes by NNRTI-PI Component: Secondary Analysis.

At week 96, by ITT analysis, the mean % change in spine BMD was significantly greater in those assigned to ATV/r (-3.1%) than in those in the EFV arm (-1.7%; Δ , -1.5%; 95% CI, 22.8% to 2.1%; P = .035).

Changes by NRTI Components: Primary Analysis.

At week 96, ITT analysis showed that the ABC-3TC arms had a significantly smaller decrease in mean % change in hip BMD, compared with the TDF-FTC

arms (-2.6% vs -4.0%; Δ , 1.4%; 95% CI, .2%–2.5%; $P = .024$). For pts on EFV, at 96 weeks, the mean % change in hip BMD was not statistically significantly different between the NRTI components, compared with those assigned to receive ABC-3TC; the estimated mean change was -2.5%, compared with -3.7% for those given TDF-FTC (Δ , 1.2%; 95% CI, 2.4% to 2.7%; $P = .15$). There was a trend toward a smaller decrease in mean % change in hip BMD for persons given ATV/r with ABC-3TC (-2.7%), compared with those given TDF-FTC (-4.3%; Δ , 1.6%; 95% CI, .2%–3.4%; $P = .075$).

Changes by NNRTI-PI Component: Secondary Analysis.

At week 96 and by ITT analysis, the mean % change in hip BMD was not statistically significantly different between EFV and ATV/r (Δ , -.3%; 95% CI, -1.5% to .9%; $P = .61$).

The ITT analyses of mean % change from entry to week 96 of spine and hip BMD were adjusted for the following prespecified baseline covariates that could affect BMD, first individually and then jointly, with use of linear regression: NNRTI-PI (or NRTI components for the NNRTI-PI analyses), spine BMD (or hip BMD for corresponding analysis), sex, age, race/ethnicity, \log_{10} HIV-1 RNA load, CD4 cell count, and BMI. For analyses of the NRTI component effect or the NNRTI-PI component effect, all of the adjusted models led to results similar to those of the unadjusted analyses. In the 96-week % change in lumbar spine BMD, multivariable analysis, ABC-3TC (vs TDF-FTC) $p=0.003$ and ATV/r (vs EFV) $p=0.039$ were significant and in the 96-week % change in hip BMD, multivariable analysis, ABC-3TC (vs TDF-FTC) was significant $p=0.033$.

Bone fractures: EFV: 10; ATZ: 5. No significant difference between the NRTIs ($P = 1.00$) or the NNRTI and PI study arms ($P = .29$). Similarly, no statistically significant difference in time to first bone fracture between NRTI ($P = .76$) or NNRTI/PI study arms ($P = .27$). In the parent study-A5202, 80 participants (4.3%) reported at least one bone fracture on study (ABC-3TC plus EFV, 4.7%; ABC-3TC plus ATV/r, 3.5%; TDF-FTC plus EFV, 4.5%; and TDF-FTC plus ATV/r, 4.5%). Among these, 10 (12.7%) were atraumatic. The bone fractures were balanced across the study arms, with no statistically significant differences between the NRTI ($P = .73$) or the NNRTI and PI components ($P = .57$). No statistically significant difference in time to first bone fracture was seen between the NRTIs ($P=.71$) or the NNRTI and PI components ($P = .49$). Similarly, incidence rates were similar across arms (ABC-3TC plus EFV, 1.9/100 pt-years; ABC-3TC plus ATV/r, 1.4/100 pt-years; TDF-FTC plus EFV, 1.8/100 pt-years; and TDF-FTC plus ATV/r, 1.8/100 pt-years).

Overall, 66 (25%) of the A5224s participants prematurely discontinued the substudy, and 4 (1%) died. In addition, 31 participants (12%) discontinued, because their sites were defunded during the study. There was no significant difference in time to premature study discontinuation between NRTI components ($P = .13$, site closure and death censored) or NNRTI-PI components ($P = .86$). The median time from randomization to the last clinic visit was 165 weeks.

McComsey lipodystrophy paper

Variable	EFV/ TDF-FTC (n = 56)	EFV /ABC-3TC (n = 53)	ATV-r/ TDF-FTC (n = 45)	ATV-r / ABC-3TC (n = 49)
No. pts with $\geq 10\%$ limb fat loss	8	10	7	8
Prevalence of $\geq 10\%$ limb fat loss	14.3 (6.4–26.2)	18.9 (9.4–32.0)	15.6 (6.5–29.5)	16.3 (7.3–29.7)

(primary analysis), % (95% CI)				
No. pts with $\geq 20\%$ limb fat loss	5	2	0	3
Prevalence of $\geq 20\%$ limb fat loss (post hoc analysis), % (95% CI)	8.9 (3.0–19.6)	3.8 (0.5–13.0)	0.0 (0.0–7.9)	6.1 (1.3–16.9)
Mean (SD) change in limb fat (%) wk 0–96	15.3 (36.7) n=56, p=0.003	17.7 (30.7) n=53, p<0.001	27.8 (36.4) n=45, p<0.001	32.7 (48.0) n=49, p<0.001
Mean (SD) change in trunk fat (%) wk 0–96	20.1 (44.1) n=56, p=0.001	22.2 (44.6) n=53, p=0.001	35.9 (50.7) n=45, p<0.001	37.0 (58.3) n=49, p<0.001
Mean (SD) change in VAT (%) wk 0–96	14.8 (48.7) n=54, p=0.03	9.9 (45.1) n=51, p=0.12	29.5 (88.4) n=45, p=0.031	23.7 (41.4) n=45, p<0.001
Mean (SD) change in VAT:TAT ratio (%) wk 0–96	-0.2 (19.7) n=54, p=0.95	-1.9 (20.9) n=51, p=0.52	-2.2 (19.1) n=45, p=0.44	-2.3 (21.4) n=45, p=0.48

	combining the ATVr and EFV groups, within the ABC-3TC arms	combining the ATVr and EFV groups, within the TDF-FTC arms	difference, p value
prevalence (upper bound of 1-sided 95% confidence interval [CI]) of lipoatrophy	17.6% (25.0%)	14.9% (21.5%)	p=0.70
mean absolute and percentage changes in limb fat	1.66 kg and 24.9%	1.11 kg and 20.9%	difference (Δ) 0.55 kg (95%CI, -0.14 to 1.24; P = .12) and 4% (95% CI, -6.7% to 14.7%; P = .46)
mean absolute and percentage changes in trunk fat			Δ = 0.37 kg (95% CI, -0.58 to 1.32; P = .45) and 2.2% (95% CI, -11.6% to 15.9%; P = .76)
absolute and percentage changes in VAT and VAT:TAT ratio			-2.8 cm ² (95% CI, -12.9 to 7.3; P = .58), -5.1% (95% CI, -21.5% to 11.4%; P = .55), and 0.00 (95% CI, -0.02 to 0.02; P=.94)
gains in mean BMI (post hoc endpoint)			Δ = 0.63 kg/m ² ; 95% CI, -0.12 to 1.38; P = .099

In multivariable analysis, ABC vs. TDF (p=0.013), ATV vs. EFV (p=0.32) and number of copies of HIV RNA/mL (p<0.001) were significant for limb fat.

	combining ABC-3TC and TDF-FTC, within the ATV-r arms	combining ABC-3TC and TDF-FTC, within the EFV arms	difference, p value
mean absolute and percentage changes in limb fat	1.88 kg and 30.4%	0.96 kg and 16.5%	difference (Δ) 0.93 kg (95% CI, 0.24–1.61; P = .008) and 13.9% (95% CI, 3.3%–24.5%; P = .010)
mean absolute and percentage changes in trunk fat	2.42 kg; 36.5%	1.33 kg; 21.1 %	Δ = 1.09 kg (95% CI, 0.15–2.03; P = .023) and 15.4% (95% CI, 1.7%–29.0%; P = .028).
absolute and percentage changes from baseline in VAT and VAT:TAT ratio			Δ = 7.6 cm ² (95% CI, -2.4 to 17.7; P = .14), 14.2% (95% CI, -2.2% to 30.6%; P = .090) and 0.00 (95% CI, -0.02 to 0.02; P = .92).
gains in mean BMI (post hoc endpoint)			Δ =0.88 kg/m ² ; 95% CI, 0.13–1.62; P 5 .022

Authors' conclusion

This large comparative clinical trial of ABC/3TC and TDF/FTC combined with either ATV/r or EFV found little difference in virologic efficacy between the 2 NRTI strategies when the screening HIV RNA was <10⁵ copies/mL. By contrast, in the high RNA stratum, the time to virologic failure was faster with ABC/3TC than TDF/FTC with either ATV/r or EFV; furthermore, safety and tolerability generally favored TDF/FTC over ABC/3TC. Overall, these results support recent treatment guidelines that TDF/FTC be the preferred initial NRTI combination in treatment-naïve patients, with ABC/3TC being an effective alternative choice. Several factors should be considered when selecting the optimal initial NRTI combination for an individual patient, including baseline HIV RNA level, HLA-B*5701 status, coinfection with hepatitis B, renal function, and lipid parameters.

At week 96, TDF-FTC, both in the spine and hip, and ATV/r in the spine produced significantly more bone loss than did ABC-3TC– or EFV-based regimens.

ABC-3TC– and TDF-FTC–based regimens increased limb and visceral fat at week 96, with a similar prevalence of lipoatrophy. Compared to the EFV group, subjects assigned to ATV-r had a trend towards higher mean percentage increase in VAT.

Reference	Study type/ methodologic quality	No. pts	Patient characteristics	Interven tion	Comparis on	Length follow-up	Outcome measures	Fundin g
<p>ASSERT Post <i>et al.</i> Randomized Comparison of Renal Effects, Efficacy, and Safety With Once- Daily Abacavir/ Lamivudine Versus Tenofovir/ Emtricitabine, Administered With Efavirenz, in Antiretroviral-Naive, HIV-1–Infected Adults: 48-Week Results From the ASSERT Study. J Acquir Immune Defic Syndr 2010; 55(1): 49-57.</p> <p>Stellbrink HJ et al. Comparison of Changes in Bone Density and Turnover with Abacavir-Lamivudine versus Tenofovir-</p>	<p>RCT</p> <p>Allocation to treatment Random Method of randomisation : unclear Concealment: unclear Blinding not blinded Sample size calculation stated ITT analysis Yes Setting: Outpatients</p>	<p>Total N: 392 randomise d; 385 received treatment. At the week 48 data cut- off, 107 subjects (28%) had withdrawn prematurel y, 63 subjects (33%) receiving abacavir/ lamivudine, and 44 subjects (23%) receiving tenofovir/ emtricitabi ne.</p>	<p>INCLUSION CRITERIA HIV; antiretroviral-naive (no previous therapy with any nucleoside reverse transcriptase inhibitor and ≤14 days of prior therapy with any other antiretroviral), HLA- B*5701-negative adults (≥18 years of age) with a plasma HIV-1 RNA ≥1000 copies per milliliter at screening. EXCLUSION CRITERIA estimated creatinine clearance <50 mL per minute (Cockcroft-Gault method) during the screening period; subjects with an active, AIDS- defining illness at baseline; subjects positive for hepatitis B; subjects were assessed for transmitted resistance to the antiretrovirals in the study using the Virco TYPE HIV-1 assay:</p>	<p>n=197 randomi sed; 193 exposed</p> <p>Drug(s): tenofovi r/emtric itabine</p>	<p>n=195 randomis ed; 192 exposed</p> <p>Drug(s): abacavir/ lamivudin e</p>	<p>Treatmen t duration: 96 weeks</p> <p>Assessme nts at: week 4, week 12, and thereafter every 12 weeks. Follow-up after end of treatmen t: 2–4 weeks after the completio n of treatment for any subject with an ongoing adverse</p>	<p>Primary endpoint: change from baseline in eGFR (MDRD), at week 48</p> <p>Other endpoints: change from baseline in eGFR (Cockcroft- Gault), proportion of subjects with decline from baseline in eGFR, and proportion of subjects with National Kidney Foundation chronic kidney disease, adverse events. Week 24 and 48 proportion of subjects with HIV-1 RNA <50 copies/mL, proportion of subjects with HIV-1 RNA <400 copies/mL, absolute values and change</p>	<p>GlaxoS mithKli ne</p>

<p>Emtricitabine in HIV-Infected Adults: 48-Week Results from the ASSERT Study. Clin Infect Dis 2010; 51: 963-72.</p> <p>Moyle, G. J., H. J. Stellbrink, et al. (2010). "Comparison of bone and renal toxicities in the ASSERT study: Final 96 week results from a prospective randomized safety trial." Antiviral Therapy 15: A19.</p>			<p>subjects with evidence of resistance at screening or prior documented evidence of genotypic and/or phenotypic resistance were excluded.</p> <p>Baseline comparability between groups: yes</p> <p>Age: median 37.0 (range 18–70) years</p> <p>Gender: 81% male</p> <p>Severity of disease: median CD4 cell count 240 (range 10–610) cells/ml</p>		event	<p>from baseline in HIV-1 RNA and CD4+ cell count, CD4+ and CD8+ lymphocyte counts, and HIV-1–associated conditions.</p> <p>Virologic failure (defined as failure to achieve a 1-log reduction in HIV-1 RNA by wk 4, or a confirmed rebound to ≥ 400 copies/mL after confirmed reduction to < 400 copies/mL by wk 24, or confirmed HIV-1 RNA ≥ 400 copies/mL after wk 24.</p>	
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Main outcomes:
 At week 48, the adjusted mean change from baseline in eGFR by MDRD was +0.22 mL/min/1.73 m² and +1.18 mL/min/1.73 m² for the abacavir/lamivudine and tenofovir/emtricitabine arms, respectively. The adjusted mean difference between arms was 0.953 mL/min/1.73 m² [95% confidence interval (CI): -1.445 to +3.351, P = 0.435]. No differences were observed between treatment arms in the proportion of subjects with a decline from baseline in eGFR of ≥ 10 mL/min, > 20 mL/min, 10%, or 20% when estimated by either MDRD or Cockcroft-Gault or the proportion of subjects with renal failure using the National Kidney Foundation chronic kidney disease stage categories.

Other outcomes:

	tenofovir/emtricitabine	abacavir/lamivudine	difference between groups
Prematurely withdrawn	44/193 (23%)	63/192 (33%)	
Withdrawn for adverse events	20/193 (10%)	25/192 (13%)	
At week 48 achieved HIV-1 RNA < 400 copies/mL	148 of 193 (77%)	129 of 192 (67%)	difference 9.5%, 95% CI: 0.6 to 18.4*

At week 48 achieved HIV-1 RNA <50 copies/mL low viral load subgroup (<100,000 copies/mL) high viral load subgroup (≥100,000 copies/mL)	137 of 193 (71%) 75% (62 of 83) 68% (75 of 110)	114 of 192 (59%) 64% (61 of 95) 55% (53 of 97)	difference 11.6%, 95% CI: 2.2 to 21.1*
Protocol-defined virologic failures at week 48	2	6	
Median CD4+ cell count increases at week 48	+150 cells/mm ³ ; n = 156	+150 cells/mm ³ ; n = 136	
HIV-1 disease progression to Centers for Disease Control and Prevention Class C or death.	5/193 (3%)	3/192 (2%)	

* Difference between treatment arms driven by investigator reported lack of efficacy and early withdrawals (occurring before virologic suppression), specifically from AEs. Administrative discontinuations (e.g. lost to follow-up, protocol violation, subject decision) in the study were unusually high and higher in the abacavir/lamivudine arm. Despite HLA B*5701 testing, differences in the rate of withdrawals due to AEs between the arms was driven by drug hypersensitivity events.

Three pts (all on abacavir/lamivudine) developed efavirenz-associated mutations (K103N, V106M, and G190A/G) and 1 of these also developed K65R, D67N mutations. 3 wks before the wk 36 virologic failure time point, this pt started the prohibited medication St Johns Wort (contraindicated with efavirenz); it potentially decreases efavirenz levels, leading to increased viral load and possible resistance to efavirenz or cross-resistance to other anti-HIV drugs.

	tenofovir/emtricitabine	abacavir/lamivudine
withdrawals due to AEs	<1%	6%
drug-related (investigator opinion) AEs drug-related grade 2–4 AEs (dizziness, abnormal dreams, and drug hypersensitivity were the most common AEs and occurred in both arms)	91/193 (47%) 20%	98/192 (51%) 29%
Drug hypersensitivity, including abacavir HSR clinically suspected abacavir HSRs (no reports of abacavir rechallenge/death)	1/193 (<1%) -	12/192 (6%) 6 (3%)
cardiac AE by week 48	4/193 (2%) included 1 MI	5/192 (3%) included 1 intracardiac thrombus: this subject had suffered an MI before participating in the trial
increases from baseline in median TC	0.66 mg/dL	1.36 mg/dL
increases from baseline in median triglycerides	0.05 mg/dL	0.23 mg/dL
increases from baseline in median low-density lipoprotein cholesterol	0.39 mg/dL	0.81 mg/dL
increases from baseline in median HDL-cholesterol	0.28 mg/dL	0.38 mg/dL
reduction in mean TC/HDL cholesterol ratio	-0.934	-0.599

Authors' conclusion

No differences in eGFR were observed between the arms, although increases in markers of tubular dysfunction were observed in the tenofovir/emtricitabine arm. The long-term clinical significance of these results are unclear, and ASSERT continues through to 96 weeks to study this further.

Stellbrink 2010:

Variable	TDF-FTC (n = 193)		ABC-3TC (n = 192)	
	No. pts	No. (%) pts with ↓ in BMD ≥6%	No. pts	No. (%) pts with ↓ in BMD ≥6%
Total hip, actual relative time				
Week 24	160	6 (4%)	137	1 (<1%)
Week 48	143	18 (13%)	120	3 (3%)
Lumbar spine, actual relative time				
Week 24	165	17 (10%)	142	10 (7%)
Week 48	143	15 (10%)	126	6 (5%)

The adjusted mean % change from baseline in total hip BMD was -1.9% in the abacavir-lamivudine group and -3.6% in the tenofovir-emtricitabine group (treatment difference -1.7% (95% CI, -2.26 to -1.10; p<0.001). The adjusted mean % change from baseline in lumbar spine BMD was -1.6% in the abacavir-lamivudine group and -2.4% in the tenofovir-emtricitabine group (treatment difference, -0.8%; 95% CI, -1.61% to -0.06%; P=.036).

For those with Z score measurements at wk 48, both arms showed a small decrease in mean (+/-standard deviation [SD]) Z-score from baseline: -0.11+/-0.16 and -0.11+/-0.26 in the abacavir-lamivudine group for total hip and lumbar spine, respectively, and -0.24+/-0.18 and -0.22+/-0.33 in the tenofovir-emtricitabine group for total hip and lumbar spine, respectively.

Moyle abstract describes an analysis that explores changes in bone mineral density (BMD) measured by dual energy X-ray absorptiometry (DXA) and bone turnover using biomarkers over 96 weeks. Changes in renal function were also examined.

Over 96 wks there was a continued ↓ from baseline in hip BMD, and the difference between the arms remained significant (ABC/3TC -2.2%, TDF/FTC -3.5%; P<0.001). The BMD at the spine decreased initially and then increased between weeks 24 and 96 with the difference between the arms remaining significant to wk 48 but not to wk 96 (ABC/3TC -0.9%, TDF/FTC -1.7%; P=0.112). Bone turnover markers increased from baseline in both treatment arms over the first 24–48 weeks and subsequently decreased or stabilised. At week 96 there were significantly greater bone biomarker increases in the TDF/FTC arm compared with the ABC/3TC arm. No significant difference in change of eGFR from baseline was observed between the

arms (ABC/3TC +1.48ml/ min/1.73m², TDF/FTC -1.15ml/min/1.73m²; P=0.06). Changes in glomerular function markers did not differ between arms.

Despite a high subject discontinuation rate (37% in ABC/3TC versus 33% in TDF/FTC), the overall virological failure rate was low for both treatment arms; a lower proportion of subjects achieved HIV RNA<50 copies/ml in the ABC/3TC arm (51%) compared with the TDF/FTC arm (59%). The adverse event rate was similar between arms with no new safety signal identified.

Reference	Study type/ methodologic quality	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
HEAT Smith <i>et al.</i> Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavir for initial HIV treatment. AIDS 2009; 23(12):	RCT Allocation to treatment Random Method of randomisation : unclear Concealment: unclear Blinding double blind Sample size calculation stated ITT analysis Yes Setting: Outpatients	Total N: 694 randomised and 688 received treatment ; 66% (455/688) complete 96 weeks of study	INCLUSION CRITERIA ART-naive, HIV-1-infected patients, at least 18 years old with plasma HIV-1 RNA \geq 1000 copies/ml (c/ml) and any CD4+ cell count. EXCLUSION CRITERIA medical conditions compromising patient safety, use of prohibited medications, protocol-specified abnormal laboratory values, and estimated Cockcroft–Gault creatinine clearance below 50 ml/min. Baseline comparability between groups: yes Age: median 38 years	n=345 Drug(s): TDF/FTC (300 mg/200 mg, Truvada) with open-label LPV/r (800mg/200mg, Kaletra)	n=343 Drug(s): ABC/3TC (600 mg/300mg, Epzicom) or Kivexa) with open-label LPV/r (800mg/200mg, Kaletra)	Treatment duration: 96 wks Assessments at: screening, baseline (day 1), and at wks 2, 6, 12, 18, 24, 32, 40, 48, 60, 72, 84, and 96, or withdrawal Follow-up after end of treatment: none	Primary endpoint: proportion of pts with HIV-1 RNA <50 c/ml at 48 wks (missing = failure, M=F) and the primary safety endpoint was the incidence of adverse events over 96 wks. Secondary endpoints: proportion with HIV-1 RNA < 400 c/ml, change in HIV-1 RNA and CD4+ cell counts, time to virologic failure, time to loss of virologic response (TLOVR), development of genotypic and phenotypic resistance at virologic failure, rate of blinded NRTI discontinuation due to suspected ABC HSR or PRTD, fasting lipid measures. Virologic failure was defined as either failure to achieve HIV-1RNA below 200 c/ml or confirmed	GlaxoSmithKline

1547-56.			Gender: 82% male Severity of disease: median CD4+ cell count was 202 cells/ml.				rebound to ≥ 200 c/ml after reduction to below 50 c/ml by wk 24. After wk 24, virologic failure was defined as a confirmed HIV-1 RNA rebound to ≥ 200 c/ml.
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Main outcomes:

Summary HIV RNA < 50 copies/ml at week 48

	tenofovir/emtricitabine	abacavir/lamivudine	95% CI for treatment difference
achieved an HIV-1 RNA < 50 c/ml at wk 48	231/345 (67%)	232/343 (68%)	-6.63 to +7.40 (non-inferiority)
wk 96	200/345 (58%)	205/343 (60%)	
TLOVR	61%	63%	
MD is equal to F	62%	64%	
observed analyses of the ITT-E population	87%	84%	
patients with baseline HIV-1 RNA $\geq 100\,000$ c/ml:			
HIV-1 RNA < 50 c/ml at week 48	65%	63%	
maintained this endpoint at week 96	58%	56%	
patients with baseline HIV-1 RNA < 100,000 c/ml			
< 50 c/ml at week 48	69%	71%	
and at week 96.	58%	63%	
protocol-defined virologic failure	48 (14%)	49 (14%)	

Other outcomes:

At week 96, median CD4+ cell count increased by 250 cells/ml from baseline in the ABC/3TC group [IQR 148–358] and by 247 cells/ml in the TDF/FTC group (IQR 149–359). Median CD4+ cell counts at week 96 in the ABC/3TC and TDF/FTC groups were 466 and 445 cells/ml, respectively.

Drug-associated resistance as defined by the IAS-USA resistance guidelines was assessed for the 97 pts (14%) with protocol-defined virologic failure (ABC/3TC, 49; TDF/FTC, 48). 86 of these pts had paired baseline and on-treatment samples for genotypic and phenotypic analysis; 40/86 (47%) pts had virus with treatment-emergent mutations. 28/86 (33%) pts had virus with acquired NRTI associated mutations (ABC/3TC, 11; TDF/FTC, 17); the most common substitution occurred at codon 184 (ABC/3TC, 11; TDF/FTC, 17). 18/86 (21%) pts acquired minor protease inhibitor-associated mutations (ABC/3TC, 11; TDF/FTC, 7). One pt receiving ABC/3TC acquired primary protease inhibitor resistance. This pt had a documented re-exposure to HIV from a partner who was heavily ART experienced, prior to the virologic failure timepoint. Phenotypic results confirmed these genotypic findings.

	tenofovir/emtricitabine (n=345)	abacavir/lamivudine (n=343)
The proportion of grade 2–4 adverse events over 96 weeks	80%	80%
drug related grade 2–4 adverse events over 96 weeks	157 (46%)	171 (50%)
drug-related grade 2–4 diarrhoea	19%	19%
drug-related grade 2–4 nausea	6%	8%
drug-related grade 2–4 increased triglycerides	6%	6%
drug-related grade 2–4 increased cholesterol	4%	7%
drug-related grade 2–4 decreased GFR	5%	5%
grade 3–4 adverse events through week 96	97/345 (28%)	103/343 (30%)
considered drug related	52/345 (15%)	50/343 (15%)
grade 3-4 drug-related diarrhoea	1%	2%
grade 3-4 drug-related nausea	<1%	0%
grade 3-4 drug-related increased triglycerides	10 (3%)	7 (2%)
grade 3-4 drug-related increased cholesterol	3 (1%)	3 (1%)
grade 3-4 drug-related decreased GFR	2%	2%
SAEs (exclusive of ABC HSR) through 96 weeks	41/345 (12%)	31/343 (9%)
Drug-related SAEs	10 (3%)	18/343 (5%)
suspected ABC HSR	3 (<1%)	14 (4%)
Immune reconstitution syndrome	0	2 (<1%)
Anemia	1 (<1%)	1 (<1%)
Renal failure	2 (<1%)	0
Hepatotoxicity	0	1 (<1%) Pt also had hep B
Sepsis	1 (<1%)	0
Decreased creatinine renal clearance	1 (<1%)	0
Pulmonary embolism	2 (<1%); 1 also had DVT	1 (<1%)
Changed LPV/r dosing from once daily to bd due to gastrointestinal intolerability	51 (15%)	59 (17%)
Study withdrawals due to an adverse event	22 (6%)	19 (6%)
suspected ABC HSR	0	2 (<1%)
renal failure	2 (<1%)	0
diarrhoea	2 (<1%)	1 (<1%)

vomiting	2 (<1%)	1 (<1%)
nausea	2 (<1%)	0
hyperlipidemia	1 (<1%)	2 (<1%)
increased triglycerides	2 (<1%)	3 (<1%)
increased aspartate aminotransferase	1 (<1%)	2 (<1%)
mycobacterium–avium complex infection	2 (<1%)	0
Suspected ABC HSR	3 (<1%)	14 (4%)
grade 3	1	4
grade 4	0	0
Drug-related death	0	0
Death	7 (pneumonia, GI haemorrhage, cardiopulmonary failure after larynx surgery, disseminated mycobacterium infection, exacerbation of COPD and respiratory failure, progressive multifocal leukoencephalopathy, and AIDS in a patient with heavy ethanol use and depression)	1 (head trauma following a fall)
Progression to a more advanced CKD stage	49/328 (15%)	31/324 (10%)
progressed to stage 3 CKD (eGFR <60 ml/min/ 1.73m ²)	11	4
progressed to stage 4 CKD (eGFR <30 ml/min/1.73m ²)	0	0
proximal renal tubule dysfunction (PRTD; defined as a confirmed rise in serum creatinine of at least 0.5 mg/dl from baseline and serum phosphate below 2 mg/dl or either of the above accompanied by any two of the following: proteinuria (≥100 mg/dl), glycosuria (≥250 g/dl), low serum potassium (<3 mEq/l), or low serum bicarbonate (<19 mEq/l).	5 (1%): 4 men (two whites, one African–American, and one Other race) and 1 Japanese female patient; 2 pts had confounding risk factors at baseline; one was receiving trimethoprim–sulfamethoxazole concurrently and one was coinfecting with hepatitis C. 2 switched to another nucleoside backbone, 4 recovered from the event, but recovery status was unknown for one who discontinued study prematurely	0
Grade 3/4 ALT elevations	4/339	8/340
patients without coinfection with hepatitis B or C	2/306	3/295
patients coinfecting with hepatitis B, C, or both	2/33	5/45
Cardiovascular event	4 (cardiac arrest following a cocaine overdose, severe aggravated heart failure with congestive heart failure precipitated by worsening renal insufficiency, CVA in	2 (chest pain in a pt with history of angina and hypertension and

considered related to study drug	a patient with history of smoking, and TIA in a patient with history of hypertension and hypertriglyceridemia) 0	TIA in another pt with a history of hypertension and hypertriglyceridemia) 0
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Median (range) laboratory parameters at baseline and 96 weeks

Median (mg/dl)	ABC				TDF			
	No. tested (baseline, wk 96)	Baseline	Week 96	Median change	No. tested (baseline, wk 96)	Baseline	Week 96	Median change
Total cholesterol:HDL ratio	278, 204	4.41 (1.70–40)	4.07 (1.72–18.25)	-0.27	286, 187	4.45 (1.81–89)	4 (2.04–12.13)	-0.44
Total cholesterol	279, 205	158 (71–264)	202 (106–334)	36	286, 188	159 (59–297)	186 (97–297)	28
HDL-cholesterol	278, 204	36 (3–80)	47 (8–137)	10	286, 189	35 (2–93)	47 (8–96)	12
LDL-cholesterol	261, 186	93 (4–197)	107 (10–222)	9	270, 172	92 (0–221)	94 (42–201)	8
Triglycerides	279, 205	122 (34–1153)	187 (54–1209)	54	286, 188	134 (40–968)	180 (53–1191)	42
Non-HDL-cholesterol	278, 204	123 (37–227)	150 (63–297)	25	286, 188	123 (39–239)	140 (71–258)	18
Glucose	343, 236	90 (46–286)	90 (28–383)	-1	344, 219	89 (61–576)	89 (47–266)	1
Insulin (mIU/ml)	323, 228	10 (1–158)	8 (1–438)	-1	330, 213	10 (1–95)	7 (1–204)	-2
MDRD GFR (ml/min/1.73)	339, 325	88 (36–208)	93 (36–180)	0	340, 333	87 (44–177)	88 (30–176)	0
C-G GFR (ml/min)	339, 325	103 (35–281)	112 (46–292)	7	340, 333	100 (45–211)	103 (35–282)	4

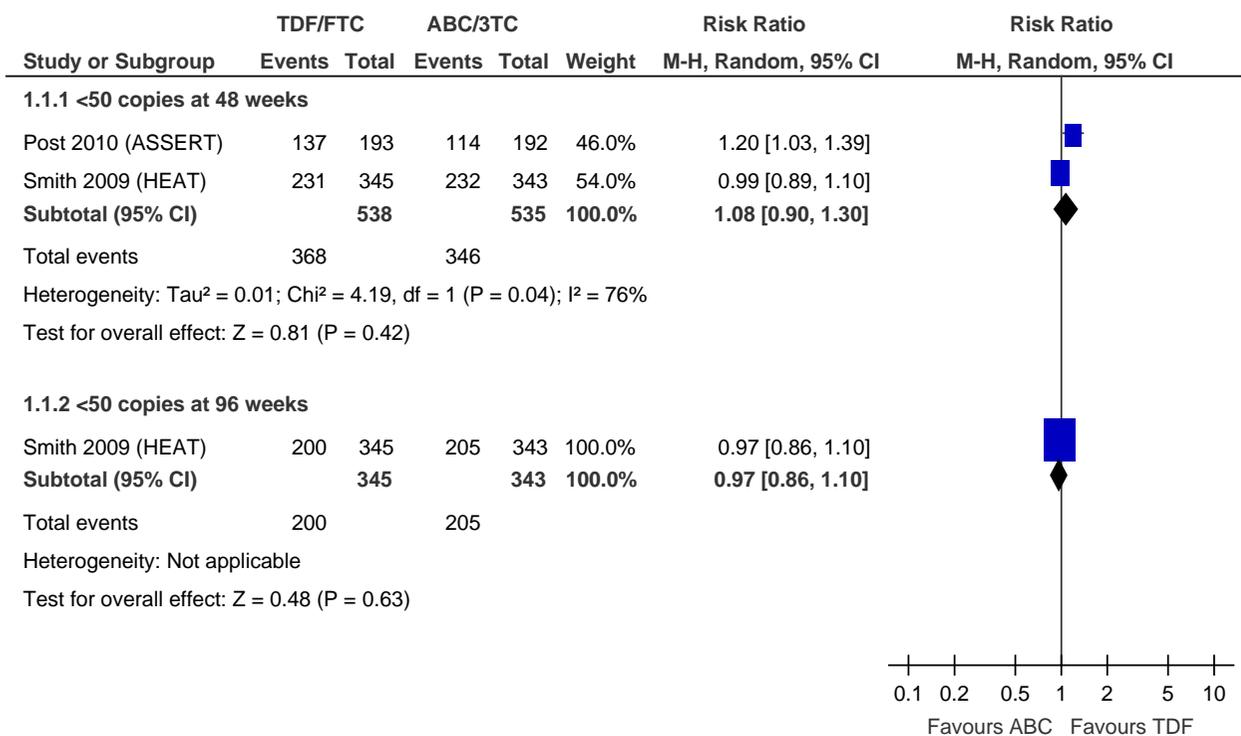
Authors' conclusion

ABC/3TCandTDF/FTC, each in combination with LPV/r, are highly effective initial regimens regardless of baseline viral load or CD4+ cell count. Long-

term virologic, immunologic, safety, tolerability, and antiretroviral resistance for ABC/3TC were similar to those with TDF/FTC over 96 wks. In this study, both ABC/3TC and TDF/FTC proved to be effective and well tolerated backbones for initial ART.

Forest plots

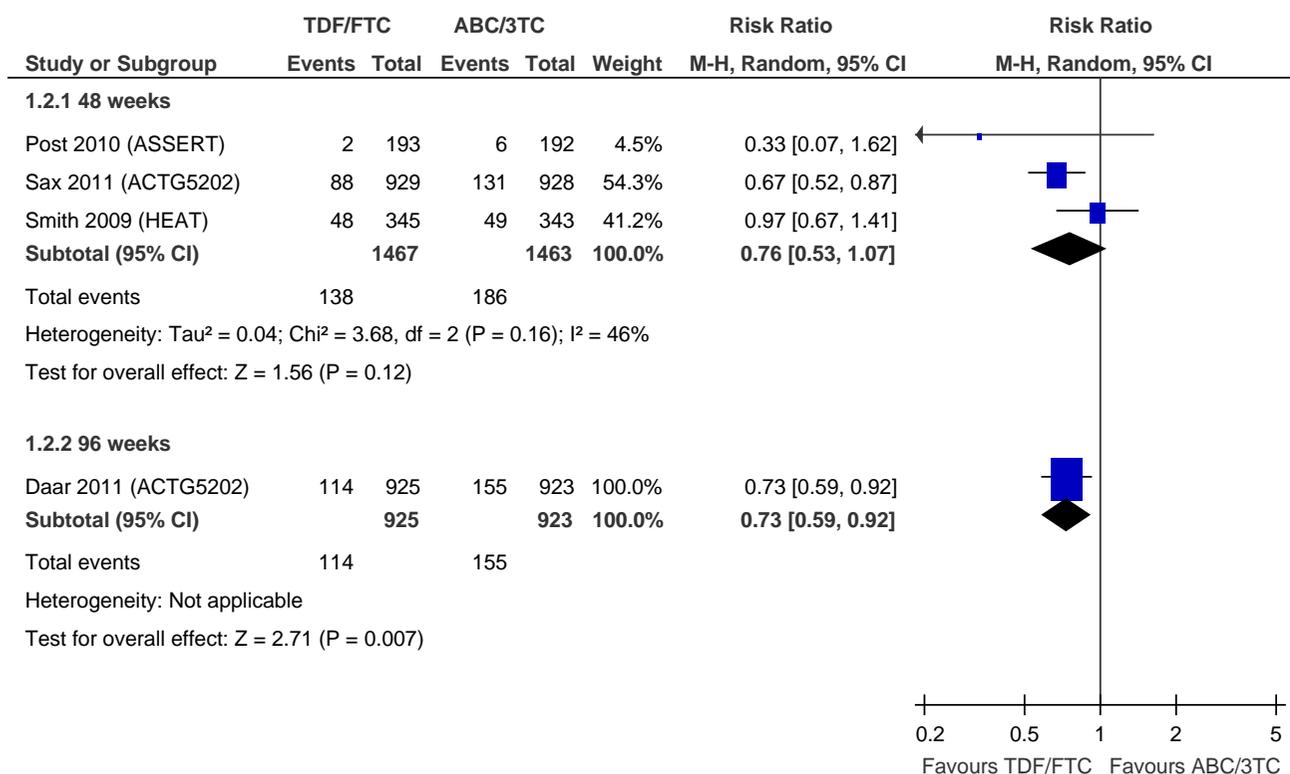
Viral suppression (<50) at week 48/week 96



No clear evidence of a difference between the treatment arms.

NB The authors of the ASSERT trial state that the difference between the treatment arms was driven by investigator reported lack of efficacy and early withdrawals (occurring before virologic suppression), specifically from AEs. Therefore the virological failure outcome (assuming comparable definitions between trials, see below) is probably a fairer comparison than the suppression outcome.

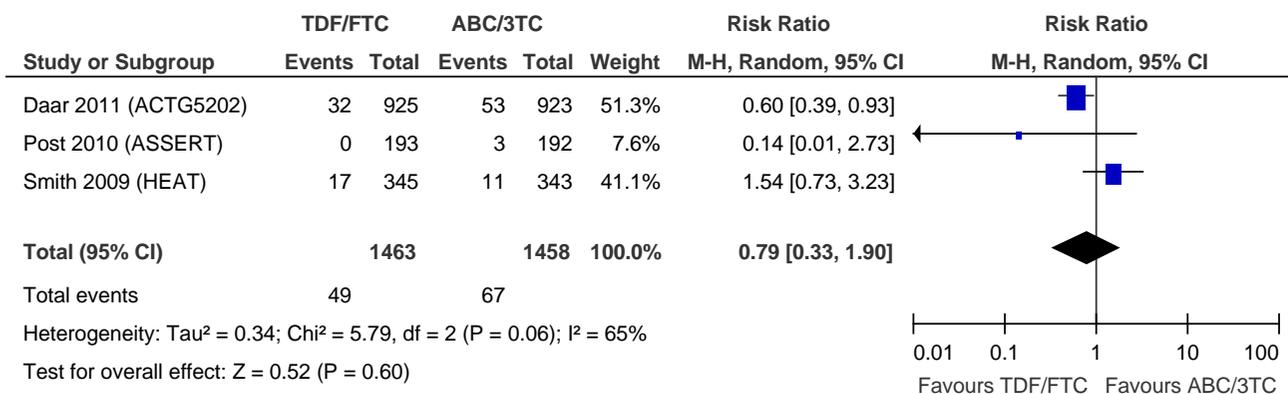
Proportion of all randomised subjects with protocol-defined virological failure at week 48 +/- week 96



There is statistical heterogeneity between these studies (I² = 46%) and also clinical heterogeneity in terms of the outcome definitions:

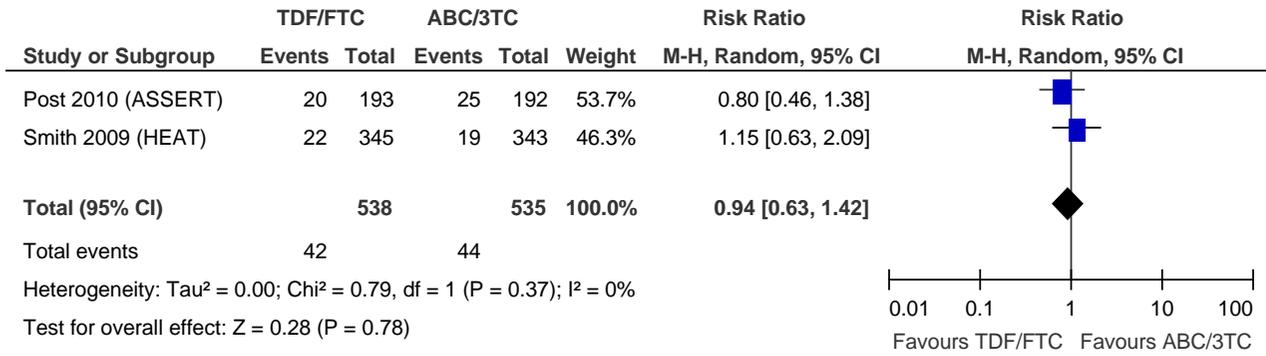
- In the ASSERT trial, virologic failure was defined in the protocol as failure to achieve a 1-log reduction in HIV-1 RNA by wk 4, or a confirmed rebound to ≥ 400 copies/mL after confirmed reduction to < 400 copies/mL by wk 24, or confirmed HIV-1 RNA ≥ 400 copies/mL after wk 24.
- In the ACTG 5202 trial, the primary efficacy endpoint was HIV RNA levels > 1000 copies/mL at wks 16–24, or HIV RNA > 200 copies/mL after wk 24.
- In the HEAT trial, virologic failure was defined as either failure to achieve HIV-1RNA < 200 c/ml or confirmed rebound to ≥ 200 c/ml after reduction to below 50 c/ml by wk 24; after wk 24, virologic failure was defined as a confirmed HIV-1 RNA rebound to ≥ 200 c/ml.

Proportion of all randomised subjects who develop drug resistance



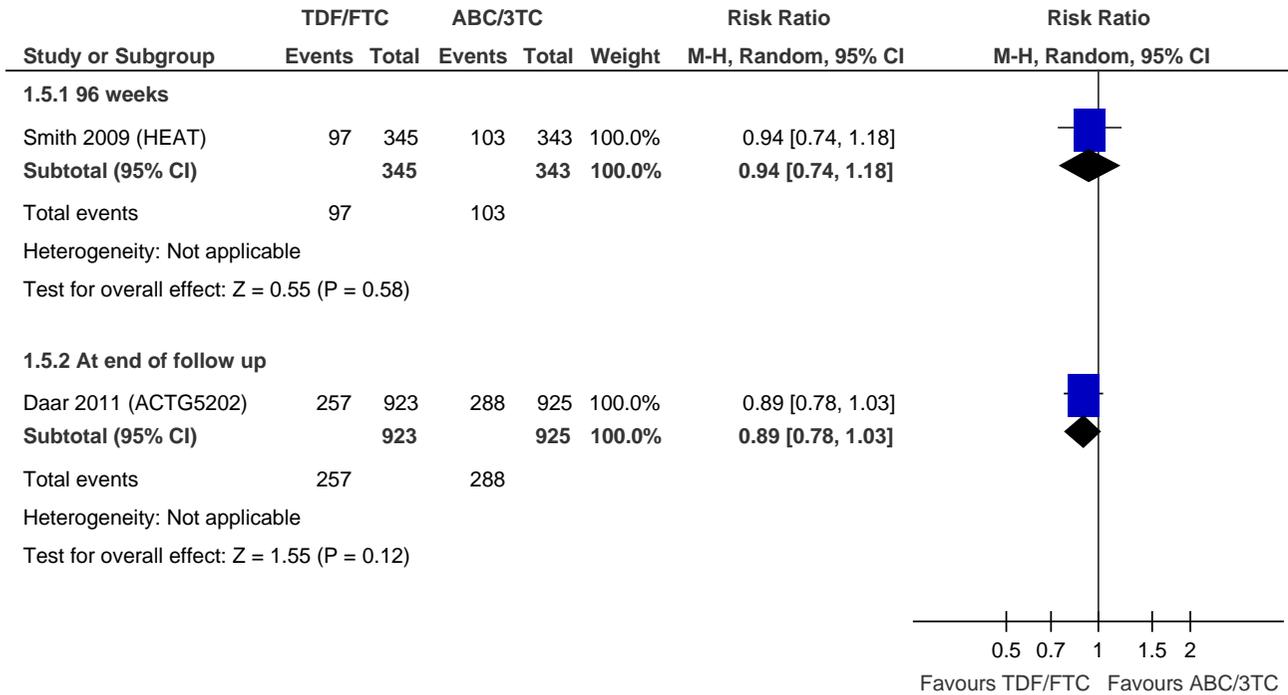
NB heterogeneity

Proportion discontinuing for adverse events



No clear evidence of a difference between the treatment arms.

Proportion with any grade 3/4 adverse events

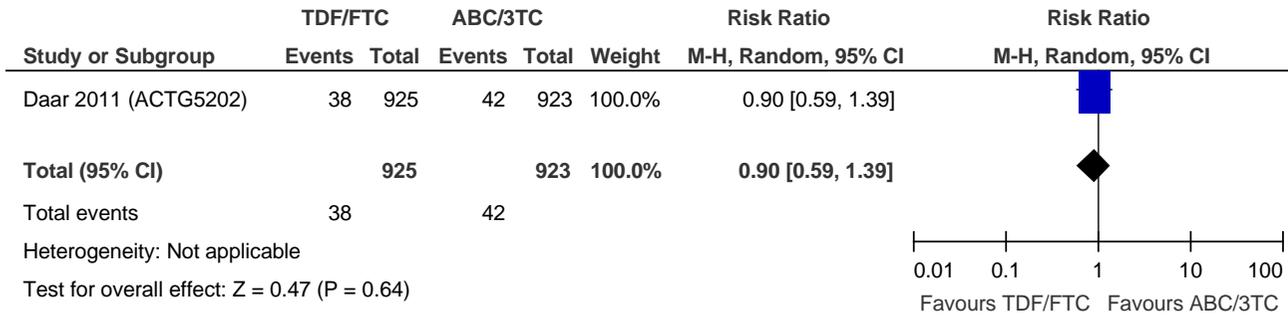


No clear evidence of a difference between the treatment arms.

Proportion with grade 3/4 clinical events; proportion with grade 3/4 laboratory events; quality of life

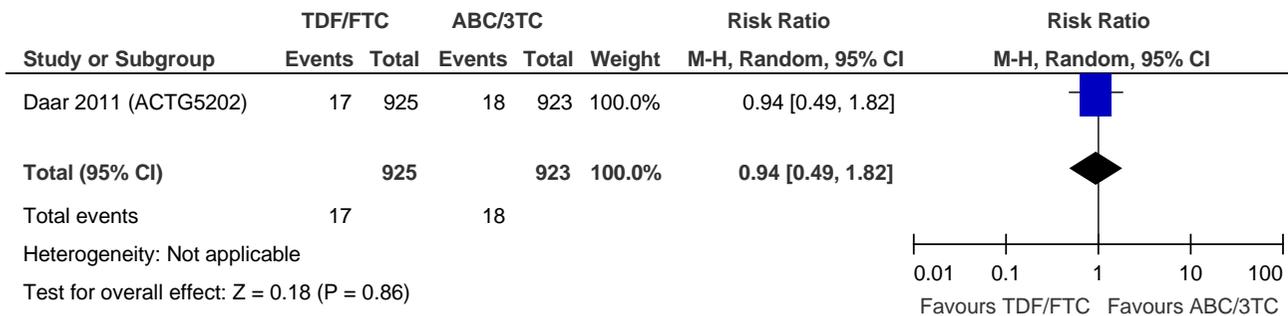
No data from these studies to address these outcomes.

Proportion with grade 3/4 neurological events



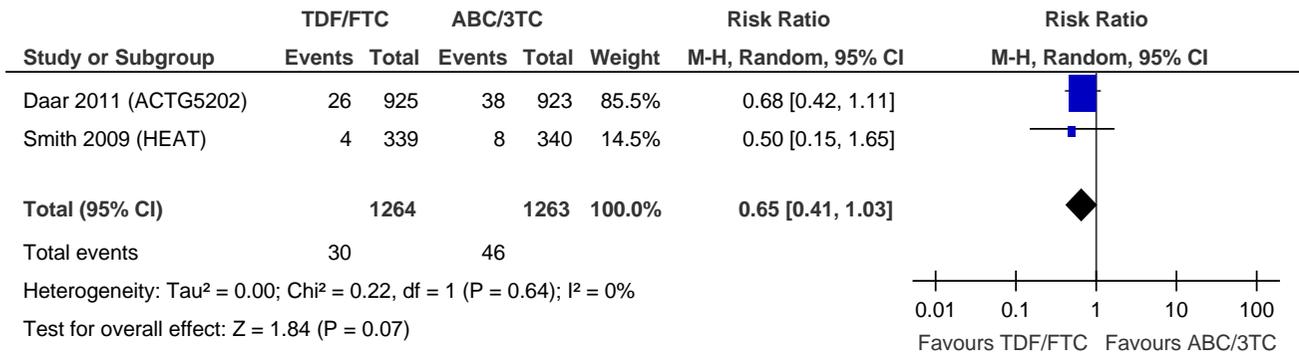
No clear evidence of a difference between the treatment arms.

Proportion with grade 3/4 diarrhoea



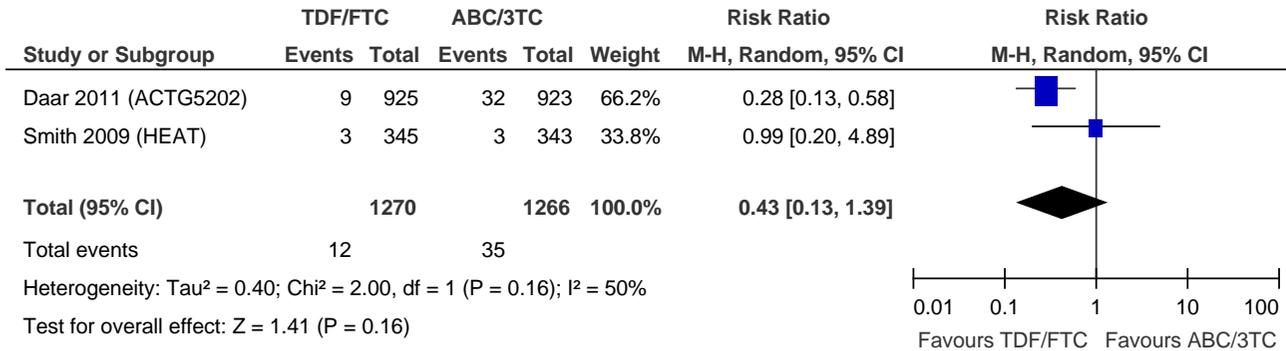
No clear evidence of a difference between the treatment arms.

Proportion with grade 3/4 ALT/AST elevation



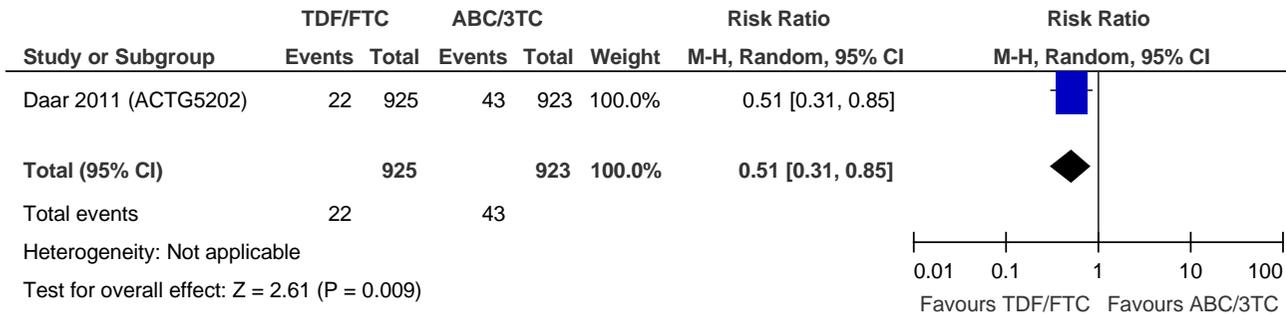
No clear evidence of a difference between the treatment arms.

Proportion with grade 3/4 total cholesterol



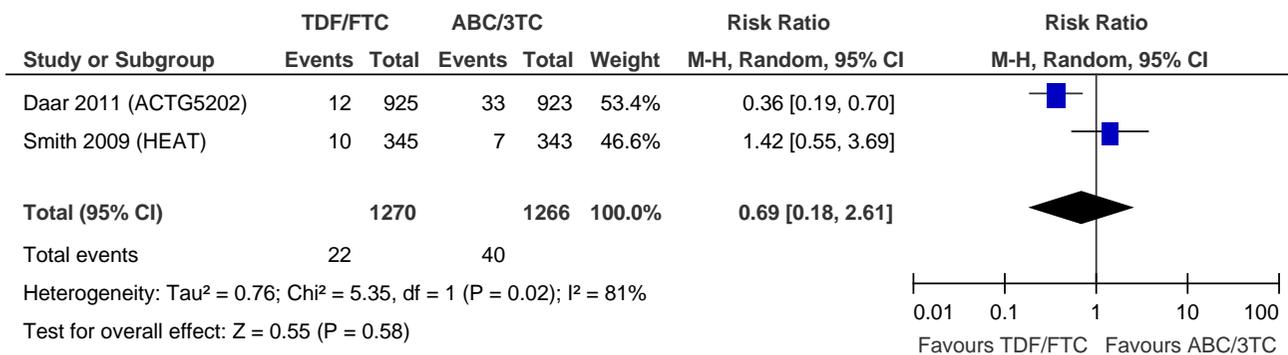
No clear evidence of a difference between the treatment arms.

Proportion with grade 3/4 LDL cholesterol



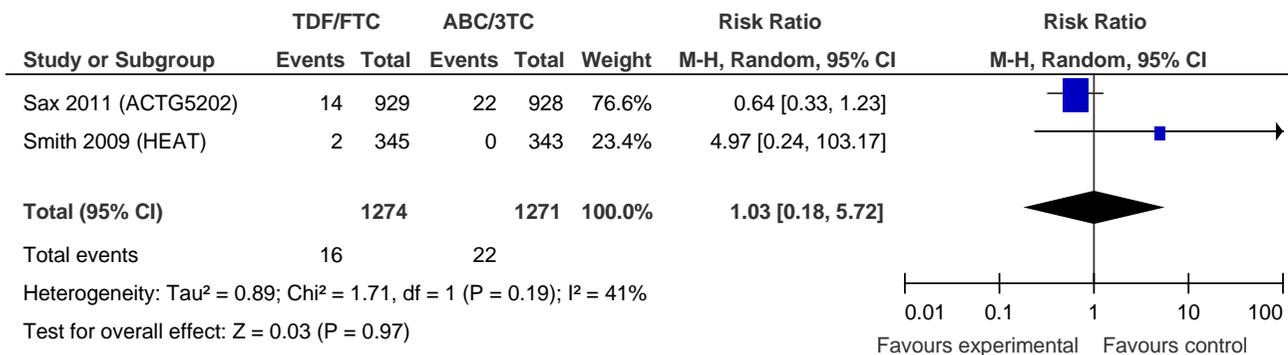
Favours TDF/FTC.

Proportion with grade 3/4 triglycerides



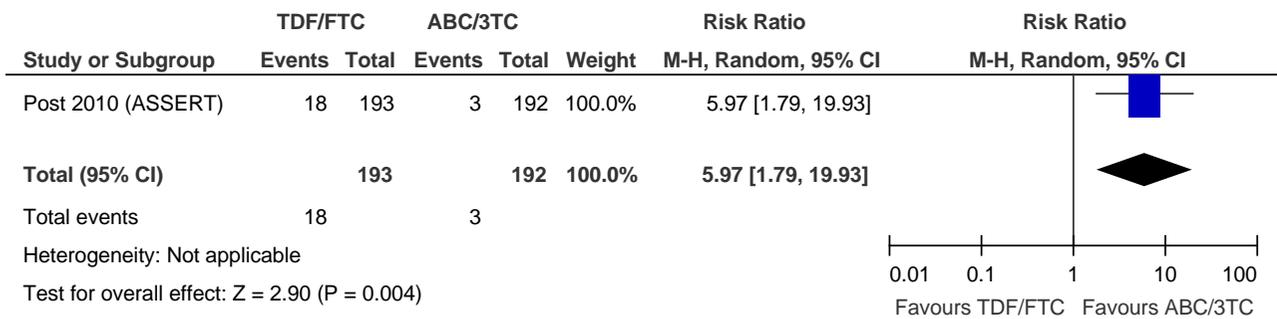
No clear evidence of a difference between the treatment arms.

Renal failure

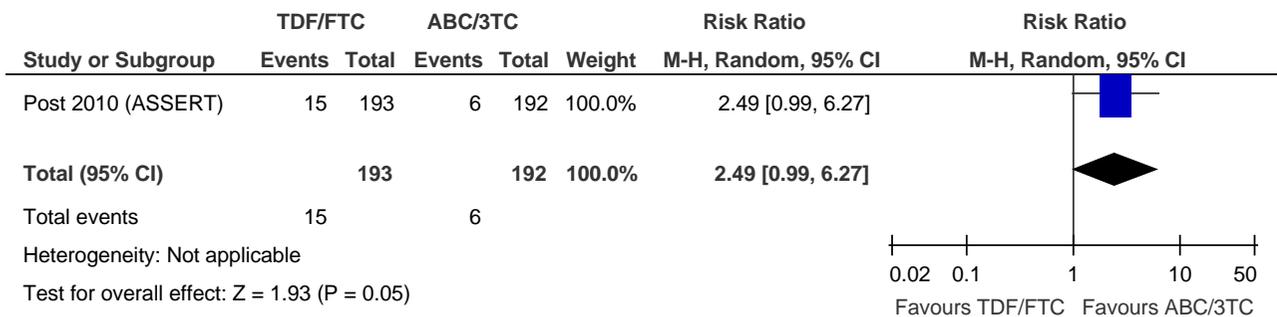


No clear evidence of a difference between the treatment arms.

Chronic toxicities (bone): % with total hip BMD decrease 6% or more at week 48.

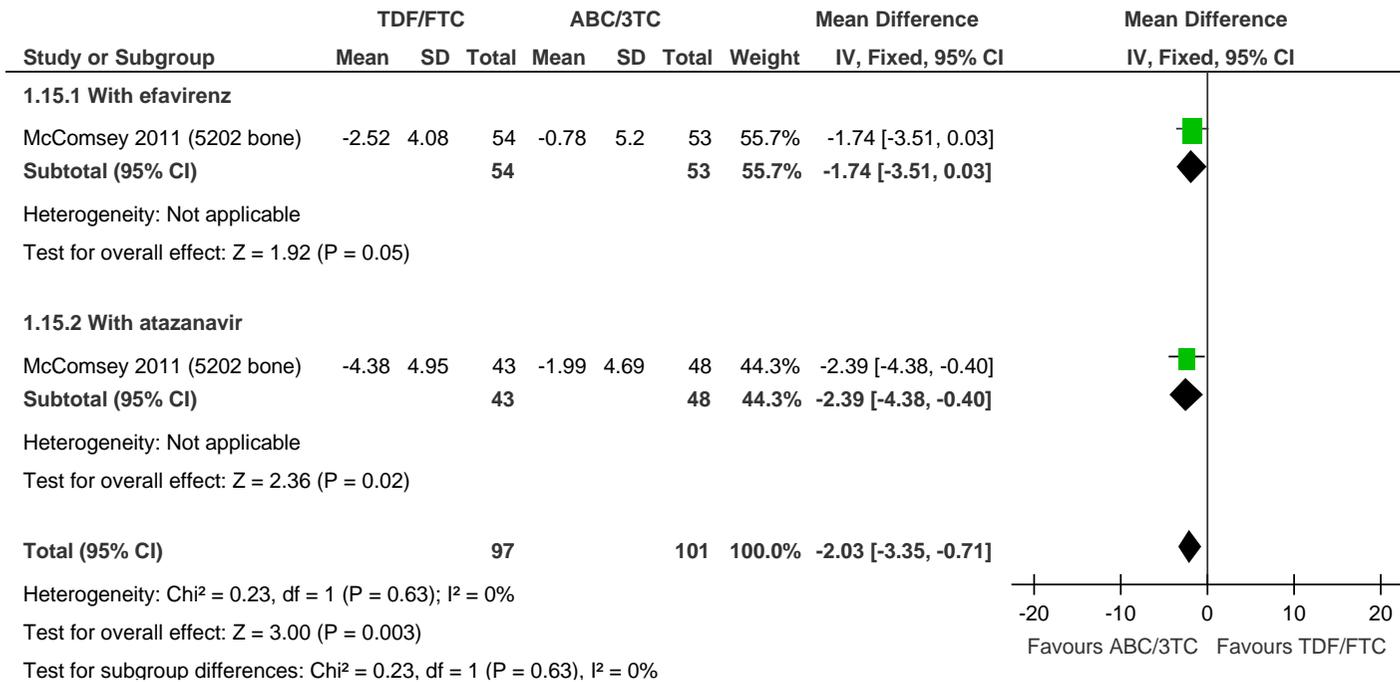


% with total spine BMD decrease 6% or more at week 48.

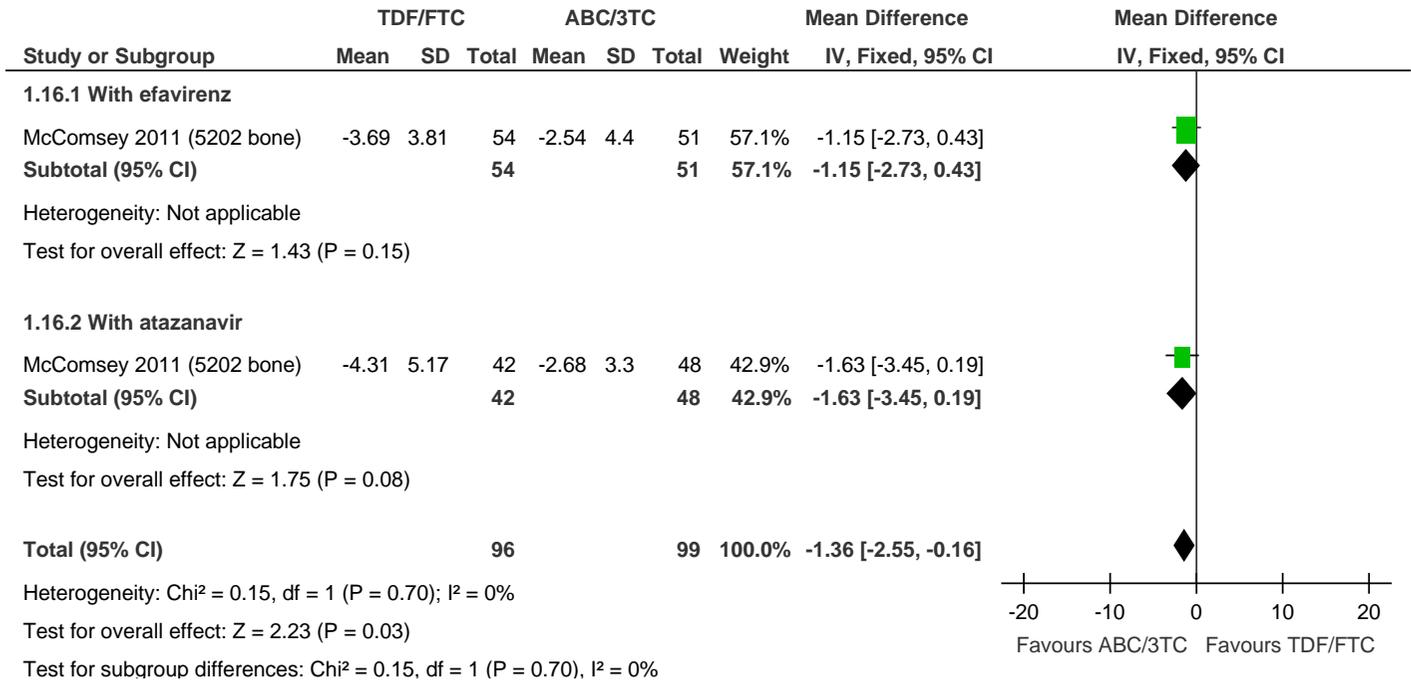


These both suggest that there is less bone loss with ABC/3TC, but is the decrease of 6% a) a recognised cut-off point? b) clinically significant?

Change in lumbar spine BMD (%), week 96).

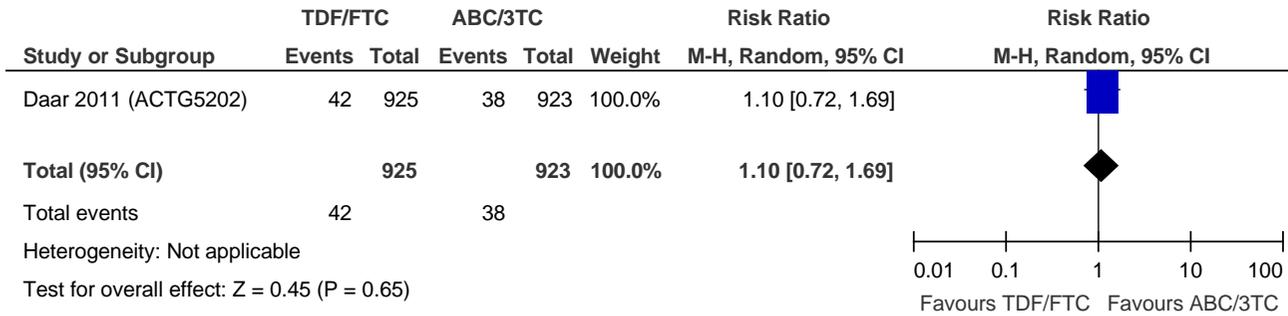


Change in hip BMD (% , week 96).



Equally, is a difference of 1-2% in the change in BMD significant?

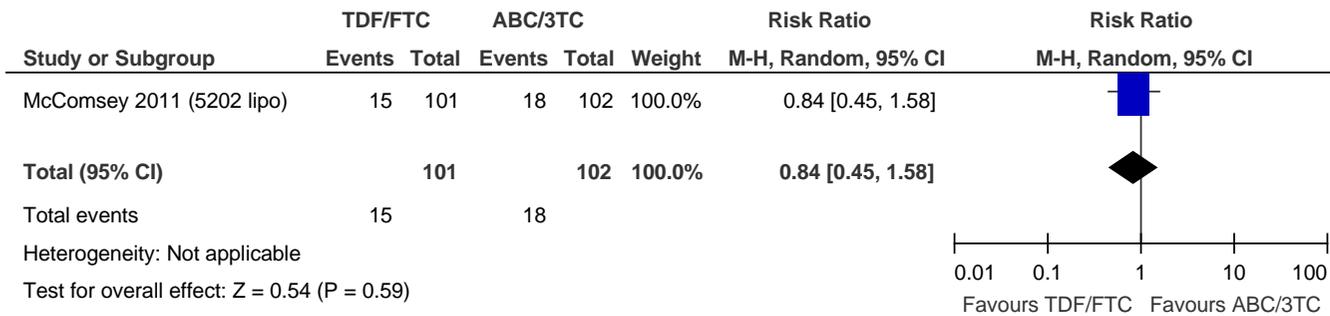
Bone fractures



Suggests no difference between groups.

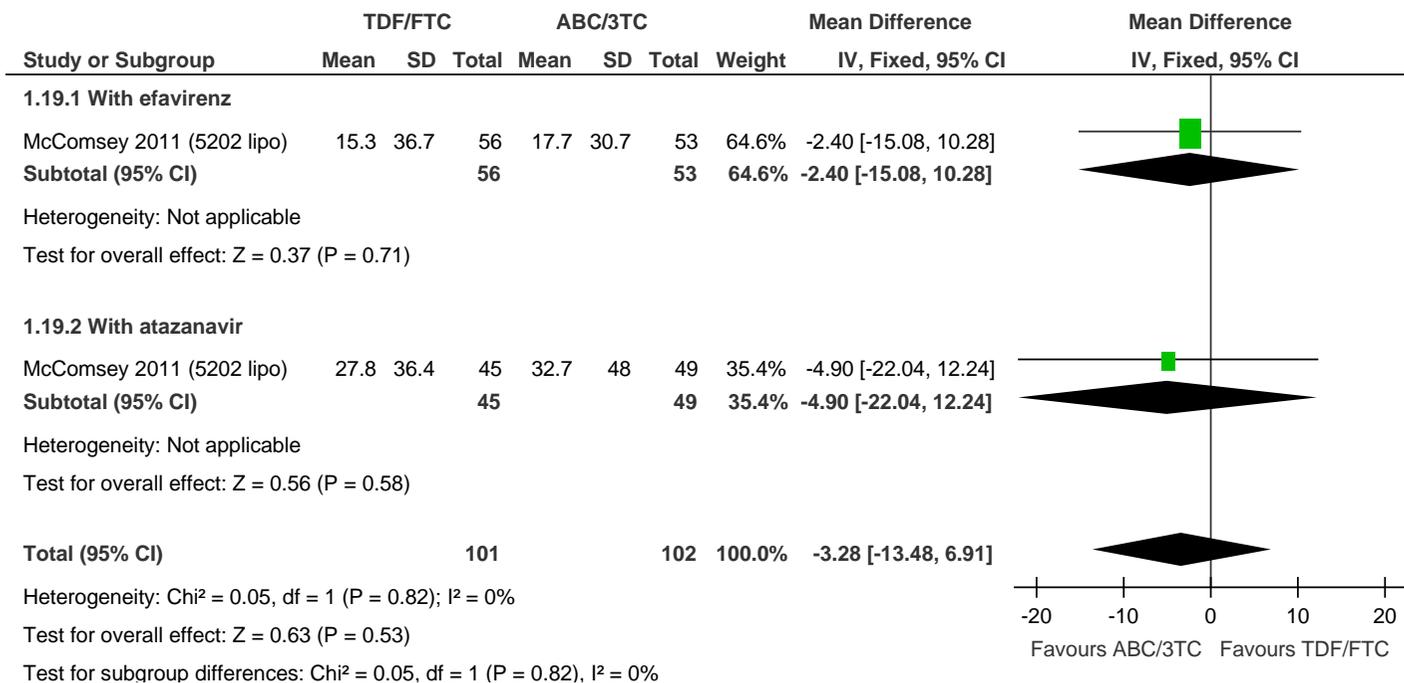
Lipodystrophy outcomes

Patients with 10% or more limb fat loss (week 96).



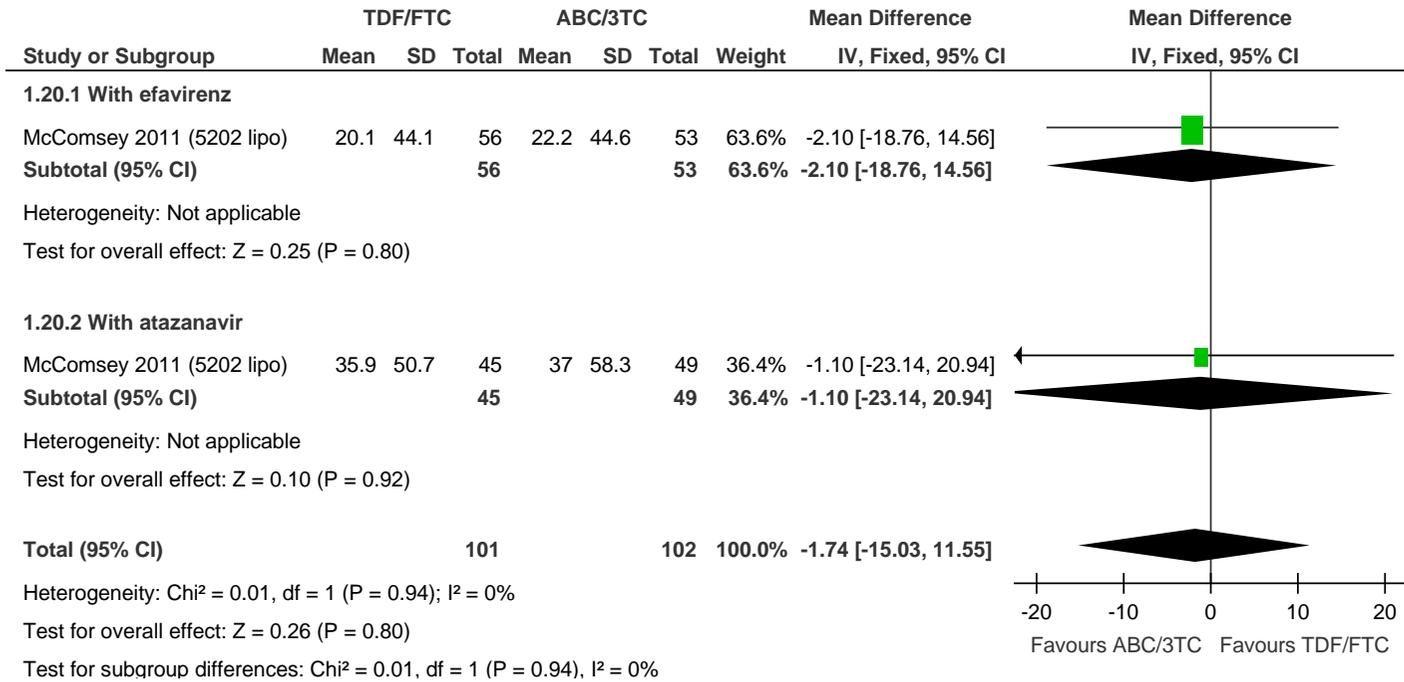
Suggests no difference between groups.

Change in limb fat (% , week 96).



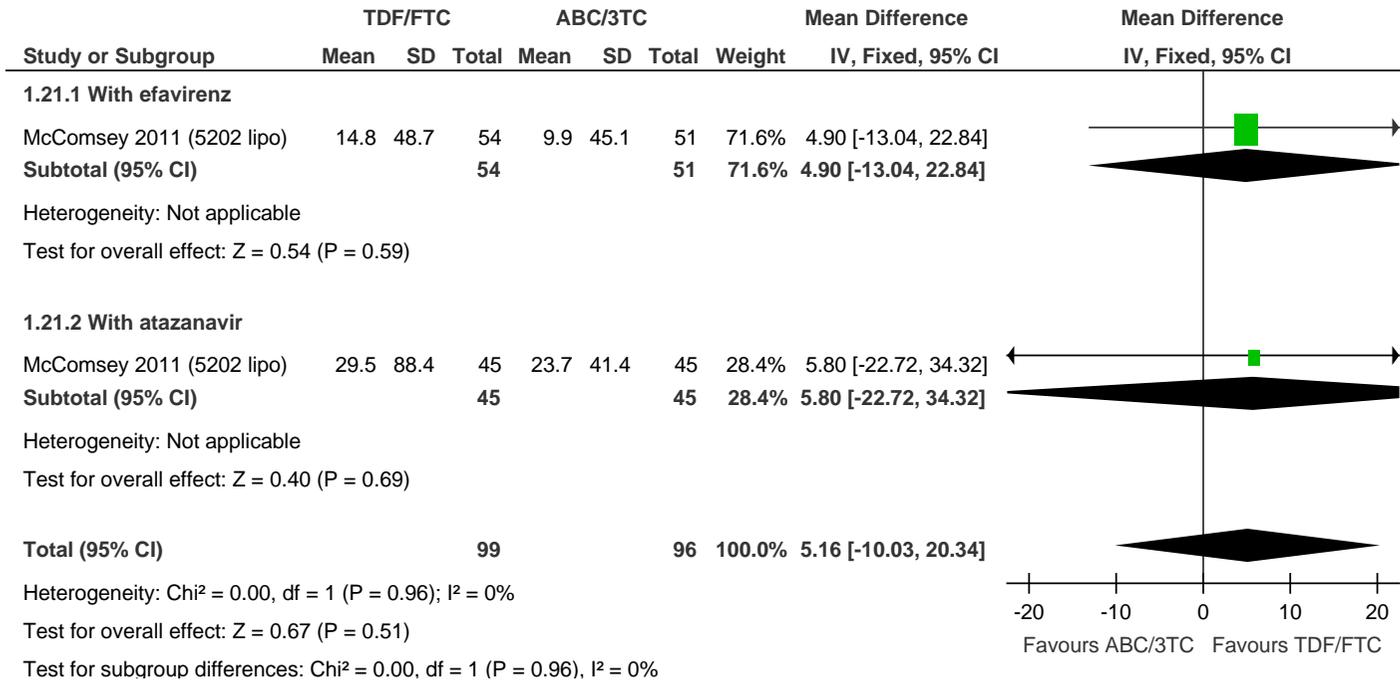
Suggests no difference between groups.

Change in trunk fat (% , week 96).



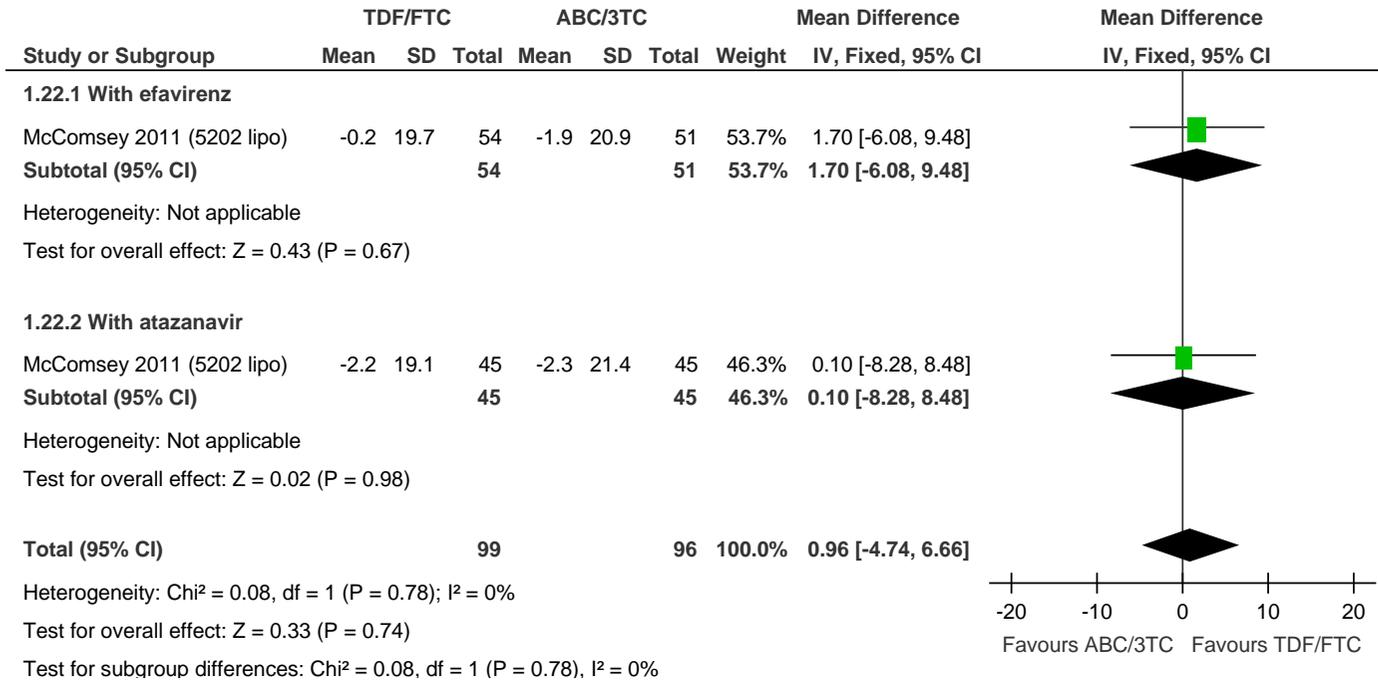
Suggests no difference between groups.

Change in visceral adipose tissue (VAT; %, week 96).



Suggests no difference between groups.

Change in visceral:total adipose tissue (VAT:TAT; %, week 96).



Suggests no difference between groups.

GRADE table:

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	TDF/FTC versus ABC/3TC	control	Relative (95% CI)	Absolute		
Virological suppression - <50 copies at 48 weeks (follow-up 48 weeks)												
2	randomised trials	very serious ^{1,2}	serious ³	no serious indirectness	no serious imprecision	none	368/538 (68.4%)	346/535 (64.7%) 63.5%	RR 1.08 (0.9 to 1.3)	52 more per 1000 (from 65 fewer to 194 more) 51 more per 1000 (from 64 fewer to 190 more)	⊕○○○ VERY LOW	CRITICAL
Virological suppression - <50 copies at 96 weeks (follow-up 96 weeks)												
1	randomised trials	very serious ^{1,2}	no serious inconsistency	no serious indirectness	no serious imprecision	none	200/345 (58%)	205/343 (59.8%) 59.8%	RR 0.97 (0.86 to 1.1)	18 fewer per 1000 (from 84 fewer to 60 more) 18 fewer per 1000 (from 84 fewer to 60 more)	⊕⊕○○ LOW	CRITICAL
Virological failure (all pts) - 48 weeks (follow-up 48 weeks)												
3	randomised trials	very serious ^{1,2}	serious ³	no serious indirectness	no serious imprecision	none	138/1467 (9.4%)	186/1463 (12.7%) 14.1%	RR 0.76 (0.53 to 1.07)	31 fewer per 1000 (from 60 fewer to 9 more) 34 fewer per 1000 (from 66 fewer to 10 more)	⊕○○○ VERY LOW	CRITICAL
Virological failure (all pts) - 96 weeks (follow-up 96 weeks)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	114/925 (12.3%)	155/923 (16.8%)	RR 0.73 (0.59 to 0.92)	45 fewer per 1000 (from 13 fewer to 69 fewer)	⊕⊕⊕⊕	CRITICAL

								16.8%		45 fewer per 1000 (from 13 fewer to 69 fewer)	HIGH	
Drug resistance (follow-up 96 weeks)												
3	randomised trials	very serious ^{1,2}	serious ³	no serious indirectness	no serious imprecision	none	49/1463 (3.3%)	67/1458 (4.6%)	RR 0.79 (0.33 to 1.9)	10 fewer per 1000 (from 31 fewer to 41 more)	⊕○○○ VERY LOW	CRITICAL
								3.2%		7 fewer per 1000 (from 21 fewer to 29 more)		
Patients discontinuing for adverse events (follow-up 96 weeks)												
2	randomised trials	very serious ^{1,2}	no serious inconsistency	no serious indirectness	no serious imprecision	none	42/538 (7.8%)	44/535 (8.2%)	RR 0.94 (0.63 to 1.42)	5 fewer per 1000 (from 30 fewer to 35 more)	⊕⊕○○ LOW	CRITICAL
								9.3%		6 fewer per 1000 (from 34 fewer to 39 more)		
Grade 3-4 adverse events (any) - 96 weeks (follow-up 96 weeks)												
1	randomised trials	very serious ^{1,2}	no serious inconsistency	no serious indirectness	no serious imprecision	none	97/345 (28.1%)	103/343 (30%)	RR 0.94 (0.74 to 1.18)	18 fewer per 1000 (from 78 fewer to 54 more)	⊕⊕○○ LOW	CRITICAL
								30%		18 fewer per 1000 (from 78 fewer to 54 more)		
Grade 3-4 adverse events (any) - At end of follow up												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	257/923 (27.8%)	288/925 (31.1%)	RR 0.89 (0.78 to 1.03)	34 fewer per 1000 (from 68 fewer to 9 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								31.1%		34 fewer per 1000 (from 68 fewer to 9 more)		
Grade 3-4 neurological event (follow-up 96 weeks)												
1	randomised	no serious	no serious	no serious	no serious	none	38/925 (4.1%)	42/923	RR 0.9 (0.59 to	5 fewer per 1000 (from 19	⊕⊕⊕⊕	IMPORTANT

	trials	limitations	inconsistency	indirectness	imprecision			(4.6%)	1.39)	fewer to 18 more)	HIGH	
								4.6%		5 fewer per 1000 (from 19 fewer to 18 more)		
Grade 3-4 diarrhoea (follow-up 96 weeks)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	17/925 (1.8%)	18/923 (2%)	RR 0.94 (0.49 to 1.82)	1 fewer per 1000 (from 10 fewer to 16 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
								2%		1 fewer per 1000 (from 10 fewer to 16 more)		
Grade 3-4 ALT/AST elevation (follow-up 96 weeks)												
2	randomised trials	very serious ^{1,2}	no serious inconsistency	no serious indirectness	no serious imprecision	none	30/1264 (2.4%)	46/1263 (3.6%)	RR 0.65 (0.41 to 1.03)	13 fewer per 1000 (from 21 fewer to 1 more)	⊕⊕○○ LOW	CRITICAL
								3.2%		11 fewer per 1000 (from 19 fewer to 1 more)		
Grade 3-4 increased total cholesterol (follow-up 96 weeks)												
2	randomised trials	very serious ^{1,2}	serious ³	no serious indirectness	no serious imprecision	none	12/1270 (0.9%)	35/1266 (2.8%)	RR 0.43 (0.13 to 1.39)	16 fewer per 1000 (from 24 fewer to 11 more)	⊕○○○ VERY LOW	NOT IMPORTANT
								2.2%		13 fewer per 1000 (from 19 fewer to 9 more)		
Grade 3-4 LDL cholesterol (follow-up 96 weeks)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	22/925 (2.4%)	43/923 (4.7%)	RR 0.51 (0.31 to 0.85)	23 fewer per 1000 (from 7 fewer to 32 fewer)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
								4.7%		23 fewer per 1000 (from 7 fewer to 32 fewer)		
Grade 3-4 increased triglycerides (follow-up 96 weeks)												

2	randomised trials	very serious ^{1,2}	serious ³	no serious indirectness	no serious imprecision	none	22/1270 (1.7%)	40/1266 (3.2%)	RR 0.69 (0.18 to 2.61)	10 fewer per 1000 (from 26 fewer to 51 more)	⊕○○○ VERY LOW	NOT IMPORTANT
								2.8%		9 fewer per 1000 (from 23 fewer to 45 more)		
Renal failure (follow-up 96 weeks)												
2	randomised trials	very serious ^{1,2}	serious ³	no serious indirectness	no serious imprecision	none	16/1274 (1.3%)	22/1271 (1.7%)	RR 1.03 (0.18 to 5.72)	1 more per 1000 (from 14 fewer to 82 more)	⊕○○○ VERY LOW	IMPORTANT
								1.2%		0 more per 1000 (from 10 fewer to 57 more)		
% with total hip BMD decrease 6% or more at week 48 (follow-up 48 weeks)												
1	randomised trials	very serious ^{1,2}	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/193 (9.3%)	3/192 (1.6%)	RR 5.97 (1.79 to 19.93)	78 more per 1000 (from 12 more to 296 more)	⊕⊕○○ LOW	NOT IMPORTANT
								1.6%		80 more per 1000 (from 13 more to 303 more)		
% with total spine BMD decrease 6% or more at week 48 (follow-up 48 weeks)												
1	randomised trials	very serious ^{1,2}	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/193 (7.8%)	6/192 (3.1%)	RR 2.49 (0.99 to 6.27)	47 more per 1000 (from 0 fewer to 165 more)	⊕⊕○○ LOW	NOT IMPORTANT
								3.1%		46 more per 1000 (from 0 fewer to 163 more)		
Change in lumbar spine BMD (% , week 96) (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	97	101	-	MD 2.03 lower (3.35 to 0.71 lower)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
Change in lumbar spine BMD (% , week 96) - With efavirenz (follow-up 96 weeks; Better indicated by higher values)												
1	randomised	no serious	no serious	no serious	no serious	none	54	53	-	MD 1.74 lower (3.51	⊕⊕⊕⊕	NOT

	trials	limitations	inconsistency	indirectness	imprecision						lower to 0.03 higher)	HIGH	IMPORTANT
Change in lumbar spine BMD (% , week 96) - With atazanavir (follow-up 96 weeks; Better indicated by higher values)													
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	43	48	-		MD 2.39 lower (4.38 to 0.4 lower)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
Change in hip BMD (% , week 96) (follow-up 96 weeks; Better indicated by higher values)													
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	96	99	-		MD 1.36 lower (2.55 to 0.16 lower)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
Change in hip BMD (% , week 96) - With efavirenz (follow-up 96 weeks; Better indicated by higher values)													
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	54	51	-		MD 1.15 lower (2.73 lower to 0.43 higher)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
Change in hip BMD (% , week 96) - With atazanavir (follow-up 96 weeks; Better indicated by higher values)													
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	42	48	-		MD 1.63 lower (3.45 lower to 0.19 higher)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
Bone fractures (follow-up 96 weeks)													
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	42/925 (4.5%)	38/923 (4.1%)	RR 1.1 (0.72 to 1.69)		4 more per 1000 (from 12 fewer to 28 more)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
								4.1%			4 more per 1000 (from 11 fewer to 28 more)		
Patients with 10% or more limb fat loss (week 96) (follow-up 96 weeks)													
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/101 (14.9%)	18/102 (17.6%)	RR 0.84 (0.45 to 1.58)		28 fewer per 1000 (from 97 fewer to 102 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
								17.7%			28 fewer per 1000 (from 97 fewer to 103 more)		

Change in limb fat (% , week 96) (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁴	none	101	102	-	MD 3.28 lower (13.48 lower to 6.91 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
Change in limb fat (% , week 96) - With efavirenz (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁴	none	56	53	-	MD 2.4 lower (15.08 lower to 10.28 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
Change in limb fat (% , week 96) - With atazanavir (Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁴	none	45	49	-	MD 4.9 lower (22.04 lower to 12.24 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
Change in trunk fat (% , week 96) (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁴	none	101	102	-	MD 1.74 lower (15.03 lower to 11.55 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
Change in trunk fat (% , week 96) - With efavirenz (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁴	none	56	53	-	MD 2.1 lower (18.76 lower to 14.56 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
Change in trunk fat (% , week 96) - With atazanavir (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁴	none	45	49	-	MD 1.1 lower (23.14 lower to 20.94 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
Change in visceral adipose tissue (VAT; % , week 96) (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁴	none	99	96	-	MD 5.16 higher (10.03 lower to 20.34 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
Change in visceral adipose tissue (VAT; % , week 96) - With efavirenz (follow-up 96 weeks; Better indicated by higher values)												

1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁴	none	54	51	-	MD 4.9 higher (13.04 lower to 22.84 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
Change in visceral adipose tissue (VAT; %, week 96) - With atazanavir (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁴	none	45	45	-	MD 5.8 higher (22.72 lower to 34.32 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
Change in visceral:total adipose tissue (VAT:TAT; %, week 96) (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁴	none	99	96	-	MD 0.96 higher (4.74 lower to 6.66 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
Change in visceral:total adipose tissue (VAT:TAT; %, week 96) - With efavirenz (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁴	none	54	51	-	MD 1.7 higher (6.08 lower to 9.48 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
Change in visceral:total adipose tissue (VAT:TAT; %, week 96) - With atazanavir (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ⁴	none	45	45	-	MD 0.1 higher (8.28 lower to 8.48 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
Drug-related adverse events grades 2-4 (follow-up 96 weeks)												
2	randomised trials	very serious ^{1,2}	no serious inconsistency	no serious indirectness	no serious imprecision	none	42/538 (7.8%)	44/535 (8.2%)	RR 0.94 (0.63 to 1.42)	5 fewer per 1000 (from 30 fewer to 35 more)	⊕⊕○○ LOW	CRITICAL
								9.3%		6 fewer per 1000 (from 34 fewer to 39 more)		

¹ Randomisation method and allocation concealment unclear

² High drop out

³ Heterogeneity between studies

⁴ Wide confidence intervals

Appendix 3: Grade tables

3.2. What to Start: Which third agent

Design: RCTs, Systematic reviews

Population: ART naive

Intervention: which third agent (Efavirenz, Raltegravir, Darunavir/ritonavir, Atazanavir/ritonavir)

Outcomes: Viral load, CD4 count, HIV resistance, adverse events, clinical events

The table below outlines key outcomes and an importance rating (based on GRADE) for each.

OUTCOME	IMPORTANCE
Viral suppression (<50) at week 48	9: critical
Viral suppression at week 96	8: critical
Proportion of all randomised subjects with protocol-defined virological failure at week 48 +/- week 96	9: critical
Proportion of all randomised subjects who develop drug resistance	8: critical
Proportion discontinuing for adverse events	7: critical
Proportion with grade 3/4 adverse events (overall)	7: critical
Proportion with grade 3/4 adverse events (clinical)	7: critical
Proportion with grade 3/4 adverse events (laboratory)	6: important
Proportion with grade 3/4 CNS events	5: important
Proportion with grade 3/4 diarrhoea	5: important
Proportion with grade 3/4 ALT/AST elevation	7: critical
Proportion with grade 3/4 total cholesterol events	3: not important
Proportion with grade 3/4 LDL cholesterol	3: not important
Proportion with grade 3/4 triglycerides	3: not important
Renal impairment	4: important
Total hip BMD decrease 6% or more	3: not important
Total spine BMD decrease 6% or more	3: not important
Change in lumbar spine BMD	3: not important
Change in hip BMD	3: not important
Bone fractures	3: not important

10% or more limb fat loss	5: important
% change in limb fat	5: important
% change in trunk fat	5: important
% change in visceral adipose tissue	5: important
Change in visceral:total adipose tissue ratio	5: important

A **Atazanavir/r versus Efavirenz**

Two randomised trials were found comparing etavirenz versus atazanavir:

- ALTAIR study:
 - Puls, R. L., P. Srasuebku, et al. (2010). "Efavirenz versus boosted atazanavir or zidovudine and abacavir in antiretroviral treatment-naive, HIV-infected subjects: week 48 data from the Altair study." *Clinical Infectious Diseases* 51(7): 855-864.
 - Winston A et al. Does Choice of Combination Antiretroviral Therapy (cART) Alter Changes in Cerebral Function Testing after 48 Weeks in Treatment-Naive, HIV-1–Infected Individuals Commencing cART? A Randomized, Controlled Study. *Clinical Infectious Diseases* 2010; 50:920–929
- ACTG5202:
 - Sax *et al.* Abacavir–Lamivudine versus Tenofovir–Emtricitabine for Initial HIV-1 Therapy. *New Engl J Med* 2009; 361(23): 2230-40 (ClinicalTrials.gov number, NCT00118898).
 - Sax *et al.* Abacavir/ Lamivudine Versus Tenofovir DF/Emtricitabine as Part of Combination Regimens for Initial Treatment of HIV: Final Results. *J Infect Dis* 2011; 204: 1191–201.
 - Daar ES et al. Atazanavir Plus Ritonavir or Efavirenz as Part of a 3-Drug Regimen for Initial Treatment of HIV-1 A Randomized Trial. *Ann Intern Med.* 2011;154:445-456.
 - McComsey GA *et al.* Bone Mineral Density and Fractures in Antiretroviral-Naive Persons Randomized to Receive Abacavir-Lamivudine or Tenofovir Disoproxil Fumarate-Emtricitabine Along With Efavirenz or Atazanavir-Ritonavir: AIDS Clinical Trials Group A5224s, a Substudy of ACTG A5202. *J Infect Dis* 2011; 203: 1791-801.
 - McComsey GA *et al.* Peripheral and Central Fat Changes in Subjects Randomized to Abacavir-Lamivudine or Tenofovir-Emtricitabine With Atazanavir-Ritonavir or Efavirenz: ACTG Study A5224s. *Clinical Infectious Diseases* 2011;53(2):185–196.

Reference	Study type and methodological quality	No. pts	Patient characteristics	Intervention	Comparison	Follow-up	Outcome measures	Funding
<p>Puls, R. L., P. Srasuebku, et al. (2010). "Efavirenz versus boosted atazanavir or zidovudine and abacavir in antiretroviral treatment-naive, HIV-infected subjects: week 48 data from the Altair study." Clinical Infectious Diseases 51(7): 855-864.</p> <p>Winston A et al. Does Choice of Combination Antiretroviral Therapy</p>	<p>RCT</p> <p>Allocation to treatment Random Method of randomisation: Randomization was stratified for clinical site and plasma HIV-RNA <100,000 or ≥100,000 copies/mL at baseline. Concealment: unclear Blinding not blinded Sample size calculation yes ITT analysis Yes Setting: Outpatients</p>	<p>Total N: 329</p> <p>Winston substudy n=30 (9, 9, and 12 subjects in arms 1, 2, and 3, respectively)</p>	<p>INCLUSION CRITERIA healthy, ART-naive, adult HIV-infected pts with CD4+ cell counts 150 cells/mL and plasma HIV-1 RNA 12000 copies/mL. Pts were required to have laboratory parameters within protocol specified ranges, creatinine clearance of ≥70 mL/min (Cockcroft-Gault), and no evidence of HIV-drug resistance</p> <p>EXCLUSION CRITERIA HLA-B*5701–positive, were pregnant and/or breast-feeding, used prohibited substances, had serious infection or illness requiring intervention, or had known renal insufficiency, obstructive liver disease, intractable diarrhoea, cardiomyopathy, or substantial cardiovascular disease</p> <p>Baseline comparability between groups: yes</p> <p>Age: mean 36.6 SD 9.2 years Gender: 76% male Severity of disease: mean CD4</p>	<p>Drug(s): 600 mg once daily EFV (Arm I) combined with TDF-FTC (fixed dose combination, i.e. Truvada)</p> <p>Arm I n=114</p>	<p>Drug(s): r/ATV (Arm II) or 250 mg or 300 mg twice daily ZDV plus 600 mg once daily ABC (Arm III), combined with TDF-FTC (fixed dose combination, i.e. Truvada)</p> <p>Arm II n=105; Arm III n=103</p>	<p>Treatment duration: 96 weeks</p> <p>Assessments: weeks 0, 4, 12, 24, 36, and 48</p> <p>Follow-up after end of treatment: none</p>	<p>Primary endpoint: time-weighted area under the curve (TWAUC) mean change from baseline plasma HIV-RNA to wk 48 by treatment arm. Proportions of pts with plasma HIV-RNA <50 copies/mL, <200 copies/mL (principal measure), and <400 copies/mL)</p> <p>Other endpoints: physical examination, adverse events, clinical biochemistry, haematology, T cell subsets, quality of life (SF-12 questionnaire); assessment of stress, anxiety, and depression (DASS-21 questionnaire); and timed gait tests; 10-year Framingham risk</p> <p>Winston substudy: changes in cerebral function testing:</p>	<p>The Australian Government Department of Health and Ageing; Gilead Sciences</p>

<p>(cART) Alter Changes in Cerebral Function Testing after 48 Weeks in Treatment-Naive, HIV-Infected Individuals Commencing cART? A Randomized, Controlled Study. Clinical Infectious Diseases 2010; 50:920-929</p>		<p>cell count 229 SD 115 cells/ml</p> <p>Winston substudy: Specific exclusion criteria were: current or recent use of antidepressant or antipsychotic therapies, current or recent history of alcohol or recreational drug dependence, recent significant head injury, established dementia, active opportunistic infections, untreated early syphilis, hepatitis C infection (i.e. positive for hepatitis C antibody), and/or evidence of established chronic liver disease, cirrhosis, or hepatic encephalopathy (in the previous 12 weeks); in the 48-h period prior to study investigations being performed, consumption of alcohol or caffeine was not permitted.</p>		<p>neurocognitive function testing at baseline and week 48 (Cognitive testing: A computerized cognitive test battery [CogState] that has been validated for HIV-1-infected subjects; domains were detection, identification, learning [matching learning and associate learning], monitoring, working memory and executive function] and measurement of cerebral metabolite ratios using magnetic resonance spectroscopy (MRS) at baseline and week 48 (performed at 3 voxel locations: right frontal white matter, mid-frontal grey matter, and the right basal ganglia).</p>	
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Main outcomes:

	Arm I (n=114)	Arm II (n=105)	Arm III (n=103)
Death	2 (accidental electrocution and autoimmune haemolytic anaemia)	0	0
Loss to follow up/withdrew consent	1	1	9
Remained in follow-up	111	104	94
Cessation and/or modifications of ART	rash (n=3) and neurological	jaundice (n=5)	gastrointestinal disorders (n=17) and anemia

	symptoms (<i>n</i> =3)		(<i>n</i> =7)
discontinuations attributed to TDF-FTC	0	0	0
mean reductions in TWAUC (ITT pop'n)	2.59 logs	2.67 logs	2.39 logs

Other outcomes:

	Arm I vs. Arm II	Arm I vs. Arm III	Arm II vs. Arm III
Mean difference in TWAUC (ITT population)	0.08 (95% CI -0.08 to +0.23), p=0.323	-0.20 (95% CI -0.39 to -0.01), p=0.038	-0.28 (95% CI, -0.46 to -0.10), P=0.003
Mean difference in TWAUC (PP population)	0.02 (95% CI -0.16 to +0.19), p=0.829	-0.25 (95% CI -0.45 to -0.05), p=0.014	-0.27 (95% CI, -0.46 to -0.08), P=0.007

Week 48:

HIV-1 RNA threshold	Arm I (EFV/TDF)	Arm II (ATV/TDF)	Arm III (ZDV/ABC/TDF)	p value Arm I vs. Arm II	p value Arm I vs. Arm III
<50 copies/mL ITT*	97/108 (90%)	93/101 (92%)	75/98 (76%)	0.446	0.017
<50 copies/mL PP	82/88 (93%)	81/87 (93%)	60/64 (94%)	0.755	0.367
<200 copies/mL ITT	108/114 (95%)	101/105 (96%)	85/103 (82%)	0.750	0.005
<200 copies/mL PP	93/93 (100%)	89/91 (98%)	64/67 (96%)	0.243	0.077
<400 copies/mL ITT	109/114 (95%)	102/105 (97%)	85/103 (82%)	0.723	0.002
<400 copies/mL PP	93/100 (93%)	89/91 (98%)	64/67 (96%)	0.243	0.072

*14 patients at one site excluded due to lower limit of detection of HIV-RNA viral load assay 80 copies/mL

There were no differences in time to plasma HIV-RNA <200 copies/mL for either Arm II (*n*=105) or Arm III (*n*=97), compared with Arm I (*n*=111) (Arm I vs Arm II HR, 0.86; 95% CI, 0.66–1.13; and Arm I vs Arm III HR, 0.95; 95% CI, 0.72–1.24).

In the ITT population with confirmed HIV-RNA <200 copies/mL, 17 pts in Arm III rebounded to >200 copies/mL. This occurred at a significantly greater rate in Arm III, compared with the rate in Arm I (*n*=6) (HR, 3.30; 95% CI, 1.03–8.37; *P*=.012), although the rate in Arm II (*n*=5) was not significantly different from the rate in Arm I (HR, 0.88; 95% CI, 0.27–2.89; *P*=.840). Results were consistent for other HIV RNA thresholds and the PP population.

Variable	Arm I EFV/TDF-FTC (<i>n</i> =114)	Arm II r/ATV/TDF-FTC (<i>n</i> =105)	Arm III ZDV/ABC/TDF-FTC (<i>n</i> =103)
No. of adverse events (48 weeks)	495	409	485
No. of pts with adverse event	99	95	91
No. of adverse events ≥grade 3	25	35	32

No. of serious adverse events	15	15 (Arm I vs Arm II, $P=0.922$)	30 (Arm I vs Arm III, $P=0.062$)
No. of pts with ≥ 1 SAE	14	8	12
immune reconstitution inflammatory syndrome (IRIS)	14	17	21
mean change from baseline CD4+ cell count	187 cells/mL	192 cells/mL (Arm I vs Arm II, $P=0.814$)	163 cells/mL (Arm I vs Arm III, $P=0.217$)
Virologic failure	4	4	11
No. with resistance data available:	3	3	7
RT inhibitor mutations	2	1	2
Protease inhibitor mutations	1	0	4

There were no significant differences between treatment arms in quality of life; stress, anxiety, and depression score; or timed gait test result from week 0 to week 48 in both ITT and PP populations (data not shown).

Winston substudy

	Arm 1 (EFV/TDF)			Arm 2 (ATV/TDF)			Arm 2 vs arm 1	Arm 3 (ZDV/ABC/TDF)			Arm 3 vs arm 1
	No.	Mean	SD	No.	Mean	SD	Change ^a (95% CI), p	No.	Mean	SD	Change ^a (95% CI), p
Detection ^b log ₁₀ ms											
Baseline	9	2.51	0.13	8	2.56	0.16	-.513 [-1.501 to 0.475] .30	11	2.57	0.11	-0.717 (-1.631 to 0.197) .12
Week 48	9	2.55	0.18	8	2.55	0.10		12	2.54	0.13	
Identification ^b log ₁₀ ms											
Baseline	9	2.72	0.12	8	2.76	0.08	-0.681 (-1.635 to 0.273) 0.15	11	2.75	0.07	-0.908 (-1.791 to -0.026) 0.04
Week 48	9	2.75	0.14	8	2.73	0.06		12	2.70	0.05	
Monitoring ^b log ₁₀ ms											
Baseline	9	2.58	0.10	8	2.66	0.10	-0.809 (-1.793 to 0.175) 0.10	11	2.60	0.10	-0.288 (-1.198 to 0.623) 0.51
Week 48	9	2.57	0.11	8	2.60	0.11		12	2.58	0.07	
Learning (matched) ^b log ₁₀ ms											
Baseline	9	2.82	0.09	8	2.83	0.04	-0.290 (-1.288 to 0.708) 0.56	11	2.83	0.05	-0.652 (-1.576 to 0.271) 0.27
Week 48	9	2.83	0.15	8	2.83	0.05		12	2.80	0.06	
One card learning ^c arcsine											

Baseline	9	2.58	0.10	8	2.66	0.10	-0.046 (-1.060 to 0.969)	0.93	11	2.60	0.10	0.383 (-0.538 to 1.304)	0.40
Week 48	9	2.57	0.11	8	2.60	0.11			12	2.58	0.07		
Working memory ^c arcsine													
Baseline	9	1.08	0.36	8	1.17	0.21	-0.057 (-1.094 to 0.981)	0.91	11	1.09	0.44	0.105 (-0.854 to 1.065)	0.82
Week 48	9	1.18	0.30	8	1.25	0.15			12	1.22	0.14		
Associate learning ^c arcsine													
Baseline	9	0.82	0.26	8	0.99	0.17	0.240 (-0.793 to 1.274)	0.64	11	0.86	0.16	0.229 (-0.727 to 1.185)	0.63
Week 48	9	0.81	0.24	8	1.03	0.13			12	0.89	0.23		
Executive function ^d total no. of errors													
Baseline	9	43.44	27.86	8	47.38	18.55	-0.259 (-1.652 to 1.134)	0.71	11	56.36	27.69	-1.539 (-2.828 to -0.251)	0.02
Week 48	9	48.44	21.83	8	48.63	18.28			11	39.09	22.61		
Composite speed score, log10 ms													
Baseline	9	2.66	0.10	8	2.70	0.08	-0.785 (-1.729 to 0.158)	0.10	11	2.69	0.07	-0.939 (-1.812 to -0.066)	0.04
Week 48	9	2.68	0.08	8	2.68	0.07			12	2.65	0.06		
Composite accuracy score, arcsine													
Baseline	9	0.88	0.23	8	1.02	0.15	0.055 (-0.974 to 1.084)	0.91	11	0.91	0.24	0.362 (-0.635 to 1.268)	0.50
Week 48	9	0.92	0.18	8	1.06	0.15			12	0.99	0.12		

a Changes assessed using the methodology recommended by CogState. In brief, changes in standardized scores were weighted by the pooled standard deviation (SD) and entered into a linear regression model with the arm as a categorical covariate. Coefficient of change represents the mean difference for each treatment group compared to arm 1, and P values are the pairwise comparative significance tests.

b Used to determine speed; a lower score represents an improved response.

c Used to determine correct responses (i.e. accuracy of response); a higher score represents an improved response.

d A lower score represents an improved response.

	Arm 1			Arm 2			Arm 2 vs arm 1	Arm 3			Arm 3 vs arm 1		
Voxel:	No.	Mean	SD	No.	Mean	SD	Change ^a (95% CI), p	No.	Mean	SD	Change ^a (95% CI), p		
Front white matter: NAA/Cr ratio													
Baseline	7	1.860	0.280	9	1.834	0.269	-0.777 (-1.519 to -0.036)	0.041	12	1.924	0.436	-0.686 (-1.385 to 0.014)	0.054
Week 48	7	2.481	1.115	9	1.677	0.174			12	1.859	0.646		
Front white matter: Cho/Cr ratio													

Baseline	7	1.107	0.168	9	1.159	0.283	-0.116 (-0.450 to 0.219) 0.483	12	1.243	0.400	-0.103 (-0.419 to 0.213) 0.508
Week 48	7	1.168	0.183	9	1.105	0.133		12	1.201	0.195	
Front white matter: MI/Cr ratio											
Baseline	7	3.854	1.761	9	3.803	1.092	1.065 (-0.842 to 2.972) 0.261	12	3.881	1.994	1.513 (-0.297 to 3.322) 0.097
Week 48	6	2.595	1.581	9	3.729	0.770		12	4.255	1.596	
Frontal grey matter: NAA/Cr ratio											
Baseline	8	1.561	0.286	9	1.539	0.166	-0.120 (-0.758 to 0.517) 0.701	12	1.637	0.286	-0.295 (-0.894 to 0.303) 0.320
Week 48	9	1.919	0.357	9	1.814	0.953		12	1.737	0.312	
Frontal grey matter: Cho/Cr ratio											
Baseline	8	0.714	0.146	9	0.705	0.179	0.047 (-0.130 to 0.225) 0.587	12	0.657	0.137	0.045 (-0.121 to 0.212) 0.580
Week 48	9	0.688	0.161	9	0.724	0.171		12	0.674	0.149	
Frontal grey matter: MI/Cr ratio											
Baseline	6	3.268	1.804	9	3.247	0.857	-0.253 (-1.754 to 1.249) 0.731	12	2.774	1.017	-0.160 (-1.606 to 1.285) 0.821
Week 48	8	2.997	1.662	9	2.970	1.422		11	2.646	1.400	
Right basal ganglia: NAA/Cr ratio											
Baseline	7	1.908	0.431	8	2.274	0.976	-0.427 (-1.893 to 1.038) 0.552	12	1.921	0.340	-0.150 (-1.467 to 1.167) 0.815
Week 48	8	2.723	1.477	7	2.782	0.824		12	2.612	1.032	
Right basal ganglia: Cho/Cr ratio											
Baseline	7	0.974	0.183	8	1.225	1.121	-0.347 (-1.121 to 0.427) 0.363	12	0.893	0.186	0.139 (-0.557 to 0.835) 0.683
Week 48	8	0.910	0.235	7	0.875	0.188		12	0.976	0.381	
Right basal ganglia: MI/Cr ratio											
Baseline	6	3.268	1.804	9	3.247	0.857	-0.016 (-1.446 to 1.414) 0.982	12	2.774	1.017	0.099 (-1.218 to 1.416) 0.877
Week 48	7	3.219	1.452	7	3.001	0.907		11	2.604	0.708	

No statistically significant differences between changes in neurocognitive testing results and study treatment arms I versus II were observed, and none of the associations described differed when excluding subjects with a detectable plasma HIV-1 RNA level at week 48 or correcting for age in a sensitivity analysis. In a multivariate model, absolute change in the NAA/Cr ratio over 48 weeks was statistically significantly greater in arm 1 versus arm 2 (coefficient -0.789 (95% CI -1.516 to -0.063), $P=.03$). No other factors, including ethnicity, age, or detectable plasma HIV-1 RNA level, at week 48 were associated with these changes ($P > .15$ for all comparisons). Finally, no significant associations were observed between changes in cerebral metabolite ratios and neurocognitive testing results.

Authors' conclusion

A novel quadruple nucleo(t)side combination demonstrated significantly less suppression of HIV replication, compared with the suppression demonstrated by standard antiretroviral therapy regimens and safety performance. Efavirenz and ritonavir-boosted atazanavir arms were equivalent in viral suppression and safety.

In the Winston substudy, greater improvements in neuronal recovery (NAA/Cr ratio) were observed for recipients of tenofovir-emtricitabine plus efavirenz (arm 1), and greater improvements in neurocognitive function testing were observed for recipients of tenofovir-emtricitabine plus zidovudine-abacavir (arm 3).

Reference	Study type and methodological quality	No. pts	Patient characteristics	Intervention	Comparison	Follow-up	Outcome measures	Funding
<p>ACTG5202: Sax <i>et al.</i> Abacavir–Lamivudine versus Tenofovir–Emtricitabine for Initial HIV-1 Therapy. <i>New Engl J Med</i> 2009; 361(23): 2230-40 (ClinicalTrials.gov number, NCT00118898).</p> <p>Sax <i>et al.</i> Abacavir/ Lamivudine Versus Tenofovir DF/ Emtricitabine as Part of Combination Regimens for Initial</p>	<p>RCT</p> <p>Allocation to treatment</p> <p>Random Method of randomisation: Allocation used a centralized computer system. Randomization was stratified according to the screening HIV-1 RNA level obtained before study entry ($\geq 100,000$ vs. $<100,000$ copies per milliliter), with the use of a permuted-block design with dynamic balancing according to</p>	<p>Total N: 1858</p> <p>First analysis includes data from the 797 patients with a screening HIV-1 RNA level of 100,000 copies per milliliter or more. 718 patients (90%) remained in the study.</p>	<p>INCLUSION CRITERIA HIV-1–infected pts who were at least 16 years of age, who had received at most 7 days of antiretroviral therapy previously, and who had acceptable laboratory values.</p> <p>EXCLUSION CRITERIA pregnant or breastfeeding; were using immune-modulators; had any known allergies to the study drugs; abused substances</p>	<p>Drug(s): 300mg tenofovir DF plus 200mg emtricitabine (Truvada) (plus 600mg efavirenz or 300mg atazanavir plus 100mg ritonavir)</p> <p>n=399 in first sub-group analysis</p>	<p>Drug(s): 600mg abacavir plus 300mg lamivudine (plus 600mg efavirenz or 300mg atazanavir plus 100mg ritonavir)</p> <p>n=398 in first sub-group analysis (HIV-1 RNA</p>	<p>Treatment duration: planned and actual study duration 96 weeks</p> <p>Assessments at: before entry, at entry, at weeks 4, 8, 16, and 24, and</p>	<p>Primary endpoint: time from randomization to virologic failure (a confirmed HIV-1 RNA level ≥ 1000 copies/ml at or after 16 wks and before 24 wks, or ≥ 200 copies/ml at or after 24 wks)</p> <p>Other endpoints: Time from initiation of treatment to 1st grade 3 or 4 sign, symptom, or lab abnormality that was at least one grade higher than that at baseline, excluding isolated</p>	<p>Abbott Pharmaceuticals, Bristol-Myers Squibb, Gilead Sciences, and GlaxoSmithKline provided the study medications and</p>

<p>Treatment of HIV: Final Results. J Infect Dis 2011; 204: 1191–201.</p> <p>Daar ES et al. Atazanavir Plus Ritonavir or Efavirenz as Part of a 3-Drug Regimen for Initial Treatment of HIV-1 A Randomized Trial. Ann Intern Med 2011; 154: 445-456.</p> <p>McComsey GA et al. Bone Mineral Density and Fractures in Antiretroviral-Naive Persons Randomized to Receive Abacavir-Lamivudine or Tenofovir Disoproxil Fumarate-Emtricitabine Along With Efavirenz or Atazanavir-Ritonavir: AIDS</p>	<p>the main institution Concealment: adequate Blinding double blinded with regard to NRTIs Sample size calculation Regimens were considered equivalent if the two-sided 95% confidence interval for the hazard ratio was between 0.71 and 1.40. A planned sample size of 1800 subjects (450 per group) would provide an 89.8% probability of declaring equivalence if two regimens were the same, assuming uniform accrual, exponential virologic failure, and lost-to-follow-up time distributions among the four groups, with event probabilities of 17.46% and 10.00%, respectively, at 48 weeks. Study conduct</p>	<p>Follow-up was discontinued in 41 patients assigned to abacavir–lamivudine and in 38 patients assigned to tenofovir DF–emtricitabine, with no significant difference in the distributions of time to discontinuation (P = 0.91).</p> <p>Second analysis: low screening HIV RNA stratum (n=1060)</p>	<p>that would interfere with the study; had a serious illness; had an important cardiac conduction disorder; required prohibited medications; showed evidence of major resistance mutations; were incarcerated; or, as of July 2006, had hepatitis B. Resistance testing was required for recently infected pts.</p> <p>Baseline comparability between groups: yes</p> <p>Age: median 38 years (IQR 31-45) Gender: 83% male Severity of disease: median CD4 cell count 229.5cells/ml (IQR 89.5-333.8)</p>	<p>(HIV-1 RNA levels of 100 000 copies/mL or more at screening) n=530 in second sub-group analysis (HIV-1 RNA levels < 100 000 copies/mL at screening)</p> <p>A5224s was a substudy of AIDS Clinical Trials Group (ACTG) A5202: A5202:</p>	<p>levels of 100 000 copies/mL or more at screening) n=530 in second sub-group analysis (HIV-1 RNA levels < 100 000 copies/mL at screening)</p> <p>A5224s was a substudy of AIDS Clinical Trials Group (ACTG) A5202: for n in each</p>	<p>every 12 weeks thereafter</p> <p>Follow-up after end of treatment: none</p> <p>Median follow-up first analysis: 60 weeks (range 0-112 weeks); full analysis: 136 weeks</p> <p>Median (25th, 75th percentile) final (Daar 2011) follow-</p>	<p>unconjugated hyperbilirubinemia and elevations in the creatine kinase level, while the pt was receiving the randomly assigned treatment. Adverse events</p> <p>Coprimary objectives of A5224s were to compare effects of starting ABC-3TC with those of TDF/FTC on spine and hip BMD and on body fat. A5224s 2ry objectives were to compare BMD changes between EFV and ATV/r arms, to compare TDF-FTC with ABC-3TC and EFV with ATV/r on BMD changes at wk 48, and to compare % with bone fractures. Substudy evaluations included whole-body dual-energy X-ray absorptiometry (DEXA) scans at</p>	<p>had input into the protocol development and review of the manuscript.</p>
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<p>Clinical Trials Group A5224s, a Substudy of ACTG A5202. J Infect Dis 2011; 203: 1791-801.</p> <p>McComsey GA et al. Peripheral and Central Fat Changes in Subjects Randomized to Abacavir Lamivudine or Tenofovir-Emtricitabine With Atazanavir-Ritonavir or Efavirenz: ACTG Study A5224s. Clinical Infectious Diseases 2011; 53(2): 185–196.</p>	<p>and safety data were reviewed yearly by the data and safety monitoring board. Efficacy data were reviewed annually starting with the second review of study data. Early stopping guidelines for inferiority were prespecified, with a regimen considered to be inferior if the 99.95% two-sided confidence interval for the hazard ratio for virologic failure did not include 1.0.</p> <p>ITT analysis Yes Setting: Outpatients</p>		<p>Specific A5224s exclusion criteria were uncontrolled thyroid disease or hypogonadism; endocrine diseases, including Cushing’s syndrome, diabetes mellitus, and the use of growth hormone, anabolic steroids, glucocorticoids, or osteoporosis medications; or the intent to start bone-related treatment.</p>	<p>for n in each group see results section</p>	<p>group see results section</p>	<p>up was 138 weeks (106 weeks, 169 weeks)</p>	<p>baseline and weeks 24, 48, 96, 144, and 192 and a single-slice abdomen CT scan at the L4-L5 level at baseline and week 96. Fat distribution was measured by DEXA in antero-posterior view (with use of Hologic or Lunar scanners). Technicians were instructed to use the same machine on the same subject throughout the study. CT was used to quantify visceral adipose tissue (VAT) and total adipose tissue (TAT).</p>	
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Patient disposition (data from both Sax publications)

Total (n=1857)							
High HIV RNA stratum (n=797)				Low HIV RNA stratum (n=1060)			
TDF/FTC (n=399)		ABC/3TC (n=398)		TDF/FTC (n=530)		ABC/3TC (n=530)	
with EFV (n=199)	with ATV (n=200)	with EFV (n=199)	with ATV (n=199)	with EFV (n=265)	with ATV (n=265)	with EFV (n=266)	with ATV (n=264)
VF*: 11/199 (6%)	15/200 (8%)	25/199 (13%)	32/199 (16%)	33/265 (12%)	29/265 (11%)	39/266 (15%)	35/264 (13%)
26/399		57/398		62/530		74/530	

*VF=virological failure

Combining high and low strata: TDF/FTC

All (n=1857)			
EFV (n=929)		ATV (n=928)	
with TDF (n=464)	with ABC (n=465)	with TDF (n=465)	with ABC (n=463)
VF: 44/464	64/465	44/465	67/463
108/929		111/928	

The data and safety monitoring board (DSMB) met on January 29, 2008, for the first efficacy review. Protocol prespecified time-to-event distributions were presented overall and within each screening HIV-1 RNA stratum. The DSMB noted excess virologic failures in both groups of pts who received regimens containing abacavir–lamivudine; additional requested analyses showed that these excess failures associated with abacavir–lamivudine occurred within the higher screening HIV-1 RNA stratum. When data in the four groups were combined and analyzed as two groups (i.e., the group receiving regimens with abacavir–lamivudine and the group receiving regimens without abacavir–lamivudine), the difference between these two groups was determined to be highly statistically significant. The DSMB found the strength and validity of these findings sufficient to warrant stopping the further study of abacavir–lamivudine among participants with a screening HIV-1 RNA level of at least 100,000 copies/mL. The board specified that the remainder of the study should continue without change.

On release of these findings from the DSMB, the study team completed additional analyses based on a previous analysis plan. Treatment-effect modification was assessed for six prespecified baseline covariates: sex, race or ethnic group, age, HIV-1 RNA level, CD4 cell count, and available or unavailable test results for HIV-1 genotype at screening.

First analysis includes data from the 797 patients with a screening HIV-1 RNA level of 100,000 copies/mL or more (high stratum).

High stratum	tenofovir DF–emtricitabine group (n=399)	abacavir–lamivudine group (n=398)	hazard ratio (HR), confidence interval (CI), p value
Protocol-defined virologic failure	26 patients	57 patients	
Time to virologic failure			HR 2.33; 99.95% CI 1.01 to 5.36; 95% CI, 1.46 to 3.72; P<0.001
Estimated probability of remaining free of virologic failure beyond 48 weeks	0.93 (95% CI 0.90 to 0.96)	0.84 (95% CI 0.79 to 0.88)	HR 2.08 (95% CI 1.28 to 3.37)

The relative hazard of virologic failure between the NRTI groups according to the six baseline covariates (univariate analysis) showed significant

treatment interactions with sex (P = 0.04), available or unavailable genotype information at screening (P = 0.02), and baseline CD4 cell count (P = 0.007). Tenofovir DF–emtricitabine treatment was associated with a lower rate of virologic failure than abacavir–lamivudine among men, pts with a screening genotype result, and pts with a lower baseline CD4 cell count. When a multivariable model was fitted with these baseline factors, the differences in the hazard ratios for failure remained significant for male sex (P = 0.05), available genotype information (P = 0.03), and lower CD4 cell count (P = 0.01).

Other outcomes:

CD4 cell count distributions and the change from baseline were similar in the two groups. At week 48, the median increase from baseline was 194 cells/mm³ (interquartile range, 126 to 305) in the 248 pts assigned to abacavir–lamivudine and 199 cells/mm³ (IQR 129 to 302) in the 248 pts assigned to tenofovir DF–emtricitabine (P = 0.78).

High HIV RNA stratum	tenofovir DF–emtricitabine (n=399)	abacavir–lamivudine (n=398)	hazard ratio, CI, p value
at least one grade 3 or 4 sign, symptom, or laboratory abnormality that was at least one grade higher than the baseline value, while receiving their initial regimen	78	130	
grade 4 event	13	24	
time to the safety end point			1.89; 95% CI, 1.43 to 2.50; P<0.001
week 48 median change in total cholesterol level	26mg/dl	34mg/dl	P<0.001
week 48 median change in HDL cholesterol level	7mg/dl	9mg/dl	P=0.05
week 48 median change in triglyceride level	3mg/dl	25mg/dl	P = 0.001
median change in total: HDL cholesterol ratio	-0.2	-0.2	P = 0.50
Suspected study drug–related hypersensitivity	27 (7%)	27 (7%); 1 died	
Subsequent virologic failure among patients with suspected drug hypersensitivity	3	4	
AIDS events	17 (4%)	26 (7%)	
HIV-related cancers	4	8	
Bone fractures	10	7	
Myocardial infarctions	0	0	
Renal failure	2	2	
median change from baseline in calculated creatinine	2ml/min (IQR -11 to	4ml/min (IQR -7 to	P = 0.10

clearance	16); n=241	16); n=212	
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Among the 81 patients with resistance data that could be evaluated, major reverse-transcriptase or protease resistance mutations at baseline were detected in 5 patients randomly assigned to abacavir–lamivudine and 4 randomly assigned to tenofovir DF–emtricitabine. Emergence of major drug-resistance mutations was noted in 25 patients in the abacavir–lamivudine group (6% of those randomly assigned to the group and 45% of group members with virologic failure) and in 10 patients in the tenofovir DF–emtricitabine group (3% and 38%, respectively). Among the 35 patients with the emergence of new major resistance mutations at the time of virologic failure, 3 in each group had other major mutations at baseline.

Main (final results Sax 2011) publication:

	TDF/FTC	ABC/3TC	Comparisons between TDF and ABC groups: Hazard ratio, CI, p value or difference	p value for difference between ATV and EFV
NRTI comparison combined across ATV/r and EFV regimens (factorial analysis) for all patients (high and low HIV RNA stratum): virologic failure	88/929	131/928	HR 1.70 (95% CI 1.23, 2.35)	
combining high and low HIV RNA strata (with ATV/r)	44/465	67/463	HR 1.48 (95% CI, 0.95, 2.31)	p=0.38
combining high and low HIV RNA strata (with EFV)	44/465	64/465	HR 1.98 (95% CI 1.22, 3.20)	
high HIV RNA stratum: virologic failure (with ATV/r)	15/200	32/199	HR 2.22 (95% CI, 1.19, 4.14)	p=0.82
high HIV RNA stratum: virologic failure (with EFV)	11/199	25/199	HR 2.46 (95% CI, 1.20, 5.05)	
low HIV RNA stratum: virologic failure (with ATV/r)	29/265 (11%)	35/264 (13%)	HR 1.25 (95% CI 0.76, 2.05)	
low HIV RNA stratum: virologic failure (with EFV)	33/265 (12%)	39/266 (15%)	HR 1.23 (95% CI, 0.77, 1.96)	

CD41 Cell Count Changes in the Low HIV RNA Stratum

Among those on ATV/r, there was no significant difference in distribution of change from baseline CD41 cells/mm³ between ABC/3TC and TDF/FTC at week 48 (week 96); median 170 ABC/3TC and 157 TDF/FTC (240 ABC/3TC and 241 TDF/FTC), P > 0.6 for both time points. Among those on EFV, ABC/3TC recipients experienced significantly greater CD41 cells/mm³ increases compared with TDF/FTC at weeks 48 and 96 (median 175 vs 147, P = .035; and 227 vs 200, P = .035, respectively).

Tolerability Endpoints in the Low HIV RNA Stratum

Low HIV RNA stratum	tenofovir DF–emtricitabine (n=530)	abacavir–lamivudine (n=530)	hazard ratio, CI, p value
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time to first antiretroviral drug modification			ATV/r: HR 1.43 (95% CI, 1.06, 1.92, P = .018); EFV: HR 1.48 (95% CI, 1.12, 1.95, P = .005).
time to first modification of the NRTIs			ATV/r: HR 1.57 (95% CI 1.14, 2.16, P = .006); ETV: HR 1.84 (95% CI 1.36, 2.51, P < .0001)
unblinding of NRTIs for suspected drug hypersensitivity ATV/r EFV severe hypersensitivity reaction when rechallenged	11 (4 renal) 8 (5 renal) 1	23 32 0	
Safety event Time to first safety event with ATV/r Time to first safety event with EFV			HR 1.13; 95% CI 0.83 to 1.54 P=.44 HR 1.38; 95% CI, 1.03, 1.85, P = .03
Death with ATV with EFV	0 3 (bacterial pneumonia, stroke, Mycobacterium avium complex)	4 (non-Hodgkin's lymphoma, MI, car accident, drug overdose/ suicide) 3 (bladder carcinoma, hepatic carcinoma, unknown)	
Cardiovascular events with ATV/r with EFV	34 15/265 (6%) 19/265 (7%)	29 15/264 (6%) 14/266 (5%)	
Bone fractures with ATV/r with EFV	10/265 (4%) 13/265 (5%)	7/264 (3%) 15/266 (6%)	
Site-reported incidence of renal disease with ATV/r with EFV	7/265 (3%) 5/265 (2%)	10/264 (4%) 10/266 (4%)	

Data on change from baseline in calculated creatinine clearance to weeks 48 and 96 were available for the 75% and 66% of patients who started study regimen, respectively. Statistically significant improvements from baseline to weeks 48 and 96 was found within all treatment arms (all P = .018) at both time points, except for ATV/r with TDF/FTC group at week 96 (P = .14). With ATV/r, there were significant differences in the distribution of change from baseline calculated creatinine clearance between ABC/3TC and TDF/FTC at both week 48 (median +3.3 vs -3.1 mL/min, P < .001) and week 96 (median +5.2 mL/min vs -3.1 mL/min, P < .001). For EFV with ABC/3TC vs TDF/FTC, there was no significant difference in the change from baseline in calculated creatinine clearance at week 48 (median +2.6 mL/min vs +3.3 mL/min, P = .83) or week 96 (+7.0 mL/min vs +4.5 mL/min, P = .15). For patients on a randomized treatment regimen with fasting samples (range 154–188 patients per treatment arm), changes from baseline in lipids levels were generally greater with ABC/ 3TC than TDF/FTC. With ATV/r, median changes for ABC/3TC vs TDF/FTC at week 48 respectively were total cholesterol, 30 vs 8 mg/dL (P < .001); low-density lipoprotein (LDL) cholesterol, 14 vs 0 mg/dL (P < .001); high-density lipoprotein (HDL) cholesterol, 7 vs 4 mg/dL (P < .001); and triglycerides, 27 vs 14 mg/dL (P = .004). With EFV, changes in total cholesterol were 34 vs 19 mg/dL (P < .001); LDL cholesterol, 17 vs 6 mg/dL (P < .001); HDL cholesterol, 12 vs. 9 mg/dL (P = .006); and triglycerides, 12 vs 13 mg/dL (P = .49), respectively. There was no significant difference between NRTIs in the change in the total:HDL cholesterol ratio. Results were similar at week 96.

Selected Events That Triggered a Safety Endpoint While Receiving Randomized Antiretroviral Drugs in Low Screening HIV RNA Stratum

	ABC (n = 263)	TDF (n = 265)	ABC (n = 264)	TDF (n = 263)	All subjects (n = 1055) who started medication
	ATV/r		EFV		
Overall, n (%)	80 (30)	98 (37)	78 (29)	83 (32)	339 (32)
Metabolic, n (%)	22 (8)	19 (7)	24 (9)	13 (5)	78 (7)
Total cholesterol (fasting), n	4	1	9	4	
LDL (fasting), n	7	7	15	8	
Triglycerides (fasting), n	8	3	5	0	
Glucose (nonfasting)	2	5	0	1	
Gastrointestinal, n (%)	21 (8)	16 (6)	12 (5)	12 (5)	61 (6)
Diarrhoea/loose stool, n.	2	4	8	2	
ALT, n	7	1	1	6	
Nausea and/or vomiting, n	6	3	3	1	
Neuropsychological, n (%)	8 (3)	1 (<1)	16 (6)	14 (5)	39 (4)
Depression, n.	3	0	3	7	
General body, n (%)	29 (11)	30 (11)	42 (16)	30 (11)	131 (12)
Ache/pain/discomfort, n	20	11	12	17	

Fever, n	6	7	6	1	
Asthenia/fatigue, n	3	3	7	3	
Rash/allergic reaction, n	2	2	5	2	
Headache, n	3	3	6	1	
Hematologic, n (%)	1 (<1)	7 (3)	4 (2)	7 (3)	19 (2)
Neutrophil count, n	1	6	4	7	

In the low HIV RNA stratum, 136 pts had virologic failure, with resistance data available at baseline and failure in all but 2 pts. Baseline major resistance was present in 13 (10%) pts with virologic failure. Among 122 virologic failures with no major resistance at baseline, there was no significant difference in the occurrence of major resistance mutations between ABC/3TC and TDF/FTC when given with either ATV/r or EFV. Resistance data for pts in the high HIV RNA stratum with virologic failure at the time of the DSMB review showed that when given with ATV/r, the emergence of major NRTI resistance mutations was not significantly different with ABC/3TC (6 of 29) or TDF/FTC (3 of 14, P=1.0 of failures and P=.34 of randomized). With EFV, major NRTI resistance emerged in 15/23 and 2/8 randomized to ABC/3TC and TDF/FTC, respectively (P = .10 of failures and P = .002 of randomized).

Daar 2011 Publication:

Summary of Primary End Points at Baseline, 96 Weeks, and Full Follow-up, With Efavirenz as the Reference in All Comparisons

Variable	Abacavir–Lamivudine		Tenofovir DF–Emtricitabine	
	Efavirenz	Atazanavir Ritonavir	Efavirenz	Atazanavir Ritonavir
Time to virologic failure				
Baseline Persons at risk, n	465	463	464	465
96 wk Events/persons at risk (Kaplan–Meier estimate), n/n (%)	63/331 (14.7)	72/338 (16.6)	44/367 (10.2)	48/364 (11.0)
Difference in 96-wk Kaplan–Meier estimate (95% CI), percentage points	1.9 (2.9 to 6.8)		0.8 (3.3 to 4.9)	
Full follow-up Events/total person-years at risk, n/n	72/1011.7	83/1017.1	57/1095.6	57/1086.4
Estimated HR (95% CI)	1.13 (0.82 to 1.56) NB no difference by viral load stratum (p=0.147)		1.01 (0.70 to 1.46) NB no difference by viral load stratum (p=0.37)	
Time to primary safety end point (First grade-3 or -4 sign,				

symptom, or laboratory abnormality while receiving the originally assigned third drug (atazanavir/ritonavir or efavirenz) that was ≥ 1 grade higher than baseline, excluding isolated unconjugated hyperbilirubinemia and creatine kinase)				
Baseline Persons at risk, n	461	462	461	464
96 wk Events/persons at risk (Kaplan–Meier estimate), n/n (%)	175/176 (41.7)	152/229 (35.5)	126/248 (30.2)	119/268 (27.7)
Difference in 96-wk Kaplan–Meier estimate (95% CI), percentage points; P value	6.2 (12.9 to 0.4); 0.066		2.5 (8.6 to 3.7); 0.43	
Full follow-up Events/total person-years at risk, n/n	187/631.2	170/762.5	147/814.3	141/868.9
Estimated HR (95% CI); P value	0.81 (0.66 to 1.00); 0.048 no difference in effect by viral load stratum ($P = 0.71$)		0.91 (0.72 to 1.15); 0.44 no difference in effect by viral load stratum ($P = 0.85$)	
Time to AIDS or death	HR, 0.93 [CI, 0.56 to 1.54]; $P = 0.77$		HR, 1.23 [CI, 0.70 to 2.39]; $P = 0.42$	
Time to primary tolerability end point (First change in therapy, ignoring nucleoside reverse transcriptase inhibitors)				
Baseline Persons at risk, n	461	462	461	464
96 wk Events/persons at risk (Kaplan–Meier estimate), n/n (%)	155/290 (33.7)	110/334 (23.9)	114/328 (24.8)	97/347 (21.0)
Difference in 96-wk Kaplan–Meier estimate (95% CI), percentage points; P value	9.8 (15.6 to 4.0); 0.001		3.8 (9.2 to 1.6); 0.170	
Full follow-up Events/total person-years at risk, n/n	186/943.7	142/1052.6	142/1032.1	126/1088.5
Estimated HR (95% CI); P value	0.69 (0.56 to 0.86); <0.001 no difference by viral load stratum ($P = 0.63$)		0.84 (0.66 to 1.07); 0.166 no difference by viral load stratum ($P = 0.90$).	

A prespecified comparison of atazanavir plus ritonavir and efavirenz with NRTIs combined (factorial analysis) was done because there was no evidence that the treatment effect differed by NRTIs ($P = 0.65$). For atazanavir plus ritonavir versus efavirenz, the HR for time to virologic failure was 1.08 (CI, 0.85 to 1.38), with CIs within the prespecified equivalence boundaries. However, for this comparison, there was a significant interaction with screening viral load ($P = 0.080$), in which the HRs were 1.35 (CI, 0.96 to 1.92) and 0.88 (CI, 0.62 to 1.23) for the high and low viral load stratum, respectively.

	abacavir–lamivudine			tenofovir DF–emtricitabine		
	ATZ/r	efavirenz	difference	ATZ/r	efavirenz	difference
Pts with HIV-1 RNA levels <50 copies/mL (regardless of previous virologic failure or regimen change) of the 1642 (88%) and 1498 (81%) of patients with HIV-1 RNA results available at week 48 and week 96, respectively*	n not stated	n not stated		n not stated	n not stated	
Week 48**	78%	87%	8 percentage points [CI, 13 to 3]; P = 0.03	84%	90%	6 percentage points [CI, 11 to 1]; P = 0.012
Week 96**	85%	91%	6 percentage points [CI, 11 to 1]; P = 0.012	90%	91%	difference, 1 percentage point [CI, 5 to 3]; P = 0.58
Time to 1st confirmed virologic failure or discontinuation of assigned PI or NNRTI			HR, 0.87 [CI, 0.71 to 1.08]			HR, 0.93 [CI, 0.74 to 1.17]

*Data were missing primarily because of premature discontinuation of the study (e.g. pt moved, was incarcerated, was deported) or the pt was lost to follow-up. Patients with missing data were more likely than persons with results to be younger, to be a non-Hispanic black person, to report previous intravenous drug use, and to have hepatitis B or C infection.

**In a prespecified, worst-case sensitivity analysis, in which patients with missing data were assigned to the group with HIV-1 RNA levels of 50 copies/mL or more, 48-week results were similar to primary analyses, and at 96 weeks, abacavir–lamivudine no longer favored efavirenz.

Change in CD4 cell counts from baseline to weeks 48 and 96 was examined in 1645 (89%) and 1493 (80%) of patients with results available, respectively. Reasons for missing CD4 values were similar to reasons noted for HIV-1 RNA. Change in CD4 cell counts did not differ between persons given atazanavir plus ritonavir or efavirenz with abacavir–lamivudine, with a median change of 0.178 versus 0.188 x 10⁹ cells/L (P = 0.94) and 0.250 versus 0.251 x 10⁹ cells/L (P = 0.89), respectively. Change in CD4 cell count was greater in persons given atazanavir plus ritonavir than those given efavirenz with tenofovir DF–emtricitabine at weeks 48 and 96, with a median change of 0.175 versus 0.163 x 10⁹ cells/L (P = 0.040) and 0.252 versus 0.221 x 10⁹ cells/L (P = 0.002), respectively. n not stated

Safety events

	Abacavir–Lamivudine	Tenofovir DF–emtricitabine

	Efavirenz (n = 461)	Atazanavir/ Ritonavir (n = 462)	Efavirenz (n = 461)	Atazanavir/ Ritonavir (n = 464)
Death, n (Of the 1857 randomly assigned patients)	11	8	6	6
Selected primary safety end point event, n (%): overall	187 (41)	170 (37)	147 (32)	141 (30)
Fasting total cholesterol level	21	11	7	2
Fasting LDL cholesterol level	29	14	15	7
Fasting triglycerides level	17	16	5	7
Blood glucose level	4	7	2	4
Gastrointestinal	23 (5)	38 (8)	22 (5)	25 (5)
AST	6	14	6	6
ALT	5	13	9	5
Diarrhoea or loose stools	11	7	6	6
Nausea, vomiting, or both	5	8	2	3
Neuropsychological	28 (6)	14 (3)	28 (6)	10 (2)
Depression	6	4	13	5
Dizzy or lightheaded	6	0	2	2
Insomnia, dreams, or sleep	6	0	5	0
General	71 (15)	64 (14)	46 (10)	59 (13)
Ache, pain, or discomfort	25	35	23	21
Fever	10	16	4	12
Asthenia, fatigue, or malaise	8	5	7	8
Headache	10	7	3	6
Rash or allergic rash	9	3	4	6
Vascular events (coronary artery disease, infarction, ischemia, angina, CVA, TIA or peripheral vascular disease)	2 (<1%)	2 (<1%)	6 (1%)	1 (<1%)
Renal diagnoses of the Fanconi syndrome, toxic nephropathy, proteinuria, or renal failure	5 (1%)	4 (1%)	3 (1%)	6 (1%)
bone fractures	22 (5%)	16 (3%)	21 (5%)	21 (5%)
suspected hypersensitivity reaction	53 (11%)	34 (7%)	25 (5%)	27 (6%)

Of the 269 patients with protocol-defined virologic failure, 265 had resistance data available at failure and baseline; of these, 25 had major mutations at baseline. Among patients with virologic failure, emergent resistance mutations were less frequent in those assigned to received atazanavir plus

ritonavir than in those assigned to receive efavirenz, combined with either NRTI ($P < 0.001$ for both). There was also a lower frequency of NRTI-associated mutations among persons assigned to receive atazanavir plus ritonavir than those assigned to receive efavirenz with abacavir–lamivudine ($P < 0.001$) or tenofovir DF–emtricitabine ($P = 0.046$).

	Abacavir–Lamivudine		Tenofovir DF–emtricitabine	
	Efavirenz (n = 461)	Atazanavir/ Ritonavir (n = 462)	Efavirenz (n = 461)	Atazanavir/ Ritonavir (n = 464)
Virologic failure Events, n (%)	72 (15)	83 (18)	57 (12)	57 (12)
Genotype available at failure	71	83	55	57
Major mutations at baseline	8	7	7	3
Without mutations at baseline	63	76	48	54
Mutations, n (%) [%] *				
Any major mutation	41 (9) [65]	12 (3) [16]	27 (6) [56]	5 (1) [9]
NRTI-associated	25 (5) [40]	11 (2) [14]	11 (2) [23]	5 (1) [9]
NNRTI-associated	41 (9) [65]	1 (<1) [1]	27 (6) [56]	0 (0) [0]
NRTI + NNRTI-associated	25 (5) [40]	0 (0) [0]	11 (2) [23]	0 (0) [0]
Protease-associated (N88N/S)	0 (0) [0]	1 (<1) [1]	0 (0) [0]	0 (0) [0]

*Excludes patients with major resistance mutations present at baseline but includes 1 person who had resistance data available at virologic failure but not at baseline. Total may not add up to 100% because some patients had >1 mutation. Values are total number (percentage of persons randomly assigned) [percentage of persons with a genotype and without baseline resistance]

A5224s substudy of AIDS Clinical Trials Group (ACTG) A5202 (McComsey bone paper)

	Efavirenz + TDF (n =69)	Efavirenz + ABC (n = 70)	Atazanavir/ Ritonavir + TDF (n = 65)	Atazanavir/ Ritonavir + ABC (n = 65)
Median age (IQR)	40 (33-44)	39 (31-46)	38 (30-44)	37 (29-43)
Male	58 (84%)	56 (80%)	56 (86%)	59 (91%)
Median (IQR) CD4 cells/ μ L	250 (132-334)	213 (106-350)	247 (114-319)	222 (75-332)
Median (IQR) lumbar spine BMD (g/cm ²)	1.12 (1.00-1.23)	1.08 (.97-1.23)	1.13 (1.03-1.24)	1.13 (1.04-1.23)
Median (IQR) hip BMD (g/cm ²)	0.99 (.92-1.07)	1.02 (.93-1.11)	1.05 (.98-1.18)	1.02 (.97-1.13)

Mean (SD) change in lumbar spine BMD (%), week 0-96	-2.52 (4.08), n=54, p<0.001	-0.78 (5.20), n=53, p=0.28	-4.38 (4.95), n=43, p<0.001	-1.99 (4.69), n=48, p=0.005
Mean (SD) change in hip spine BMD (%), week 0-96	-3.69 (3.81), n=54, p<0.001	-2.54 (4.40), n=51, p<0.001	-4.31 (5.17), n=42, p<0.001	-2.68 (3.30), n=48, p<0.001

The estimated mean % change in spine BMD for all participants was 23.0% at week 48 and 22.3% at week 96. The comparison of ABC-3TC (n = 135) and TDF-FTC (n = 134) with EFV and ATV/r combined (factorial analysis) was performed, because there was no significant evidence that the treatment effect between these drugs differed at 96 weeks by the NNRTI-PI component (P = .63). Similarly, the comparison of EFV (n = 139) and ATV/r (n = 130) with ABC-3TC and TDF-FTC combined was performed.

Changes by NRTI Components: Primary Analysis.

By ITT at week 96, there was a significant decrease in mean % change in spine BMD for all arms except ABC-3TC plus EFV, but significantly less for ABC-3TC (estimated mean of -1.3%) than for TDF-FTC (-3.3%; difference [Δ] = 2.0%; 95% confidence interval [CI], 0.7%–3.3%; P = .004).

At wk 96, among pts assigned to receive EFV, there was a trend toward a greater decrease in mean % change in spine BMD when combined with TDF-FTC than when combined with ABC-3TC (Δ, 1.7%; 95% CI, .04%–3.5%; P = .056). In ATV/r-treated arms, there was a significantly greater decrease in mean % change in spine BMD when combined with TDF-FTC than when combined with ABC/3TC (Δ, 2.4%; 95% CI, .4%–4.4%; P = .020, by ITT).

Changes by NNRTI-PI Component: Secondary Analysis.

At week 96, by ITT analysis, the mean % change in spine BMD was significantly greater in those assigned to ATV/r (-3.1%) than in those in the EFV arm (-1.7%; Δ, -1.5%; 95% CI, 22.8% to 2.1%; P = .035).

Changes by NRTI Components: Primary Analysis.

At wk 96, ITT analysis showed that the ABC-3TC arms had a significantly smaller decrease in mean % change in hip BMD, compared with the TDF-FTC arms (-2.6% vs -4.0%; Δ, 1.4%; 95% CI, .2%–2.5%; P = .024). For persons assigned to receive EFV, at 96 wks, the mean % change in hip BMD was not significantly different between the NRTI components, compared with those assigned to receive ABC-3TC; the estimated mean change was -2.5%, compared with -3.7% for those given TDF-FTC (Δ, 1.2%; 95% CI, 2.4% to 2.7%; P = .15). There was a trend toward a smaller decrease in mean % change in hip BMD for persons given ATV/r with ABC-3TC (-2.7%), compared with those given TDF-FTC (-4.3%; Δ, 1.6%; 95% CI, .2%–3.4%; P = .075).

Changes by NNRTI-PI Component: Secondary Analysis.

At week 96 and by ITT analysis, the mean % change in hip BMD was not statistically significantly different between EFV and ATV/r (Δ, -.3%; 95% CI, -1.5% to .9%; P = .61).

The ITT analyses of mean % change from entry to wk 96 of spine and hip BMD were adjusted for the following prespecified baseline covariates that could affect BMD, first individually and then jointly, with use of linear regression: NNRTI-PI (or NRTI components for the NNRTI-PI analyses), spine BMD (or hip BMD for corresponding analysis), sex, age, race/ethnicity, log₁₀ HIV-1 RNA load, CD4 cell count, and BMI. For analyses of the NRTI component effect or the NNRTI-PI component effect, all of the adjusted models led to results similar to those of the unadjusted analyses. In the 96-week

percentage change in lumbar spine BMD, multivariable analysis, ABC-3TC (vs TDF-FTC) $p=0.003$ and ATV/r (vs EFV) $p=0.039$ were significant and in the 96-week percentage change in hip BMD, multivariable analysis, ABC-3TC (vs TDF-FTC) was significant $p=0.033$.

Bone fractures: EFV: 10; ATZ: 5. No significant difference between the NRTIs ($P = 1.00$) or the NNRTI and PI study arms ($P = .29$). Similarly, there was no statistically significant difference in time to first bone fracture between NRTI ($P = .76$) or NNRTI/PI study arms ($P = .27$). In the parent study-A5202, 80 participants (4.3%) reported at least one bone fracture on study (ABC-3TC plus EFV, 4.7%; ABC-3TC plus ATV/r, 3.5%; TDF-FTC plus EFV, 4.5%; and TDF-FTC plus ATV/r, 4.5%). Among these, 10 (12.7%) were atraumatic. The bone fractures were balanced across the study arms, with no statistically significant differences between the NRTI ($P = .73$) or the NNRTI and PI components ($P = .57$). No statistically significant difference in time to first bone fracture was seen between the NRTIs ($P=.71$) or the NNRTI and PI components ($P = .49$). Similarly, incidence rates were similar across arms (ABC-3TC plus EFV, 1.9/100 pt-years; ABC-3TC plus ATV/r, 1.4/100 pt-years; TDF-FTC plus EFV, 1.8/100 pt-years; and TDF-FTC plus ATV/r, 1.8/100 pt-years).

Overall, 66 (25%) of the A5224s pts prematurely discontinued the substudy, and 4 (1%) died. In addition, 31 pts (12%) discontinued because their sites were defunded during the study. There was no significant difference in time to premature study discontinuation between NRTI components ($P = .13$, site closure and death censored) or NNRTI-PI components ($P = .86$). The median time from randomization to the last clinic visit was 165 weeks.

McComsey lipodystrophy paper

Variable	EFV/ TDF-FTC (n = 56)	EFV /ABC-3TC (n = 53)	ATV-r/ TDF-FTC (n = 45)	ATV-r / ABC-3TC (n = 49)
No. pts with $\geq 10\%$ limb fat loss	8	10	7	8
Prevalence of $\geq 10\%$ limb fat loss (primary analysis), % (95% CI)	14.3 (6.4–26.2)	18.9 (9.4–32.0)	15.6 (6.5–29.5)	16.3 (7.3–29.7)
No. pts with $\geq 20\%$ limb fat loss	5	2	0	3
Prevalence of $\geq 20\%$ limb fat loss (post hoc analysis), % (95% CI)	8.9 (3.0–19.6)	3.8 (0.5–13.0)	0.0 (0.0–7.9)	6.1 (1.3–16.9)
Mean (SD) change in limb fat (%) week 0–96	15.3 (36.7), n=56, $p=0.003$	17.7 (30.7), n=53, $p<0.001$	27.8 (36.4), n=45, $p<0.001$	32.7 (48.0), n=49, $p<0.001$
Mean (SD) change in trunk fat (%) week 0–96	20.1 (44.1), n=56, $p=0.001$	22.2 (44.6), n=53, $p=0.001$	35.9 (50.7), n=45, $p<0.001$	37.0 (58.3), n=49, $p<0.001$
Mean (SD) change in VAT (%) week 0–96	14.8 (48.7), n=54, $p=0.03$	9.9 (45.1), n=51, $p=0.12$	29.5 (88.4), n=45, $p=0.031$	23.7 (41.4), n=45, $p<0.001$
Mean (SD) change in VAT:TAT ratio (%) week 0–96	-0.2 (19.7), n=54, $p=0.95$	-1.9 (20.9), n=51, $p=0.52$	-2.2 (19.1), n=45, $p=0.44$	-2.3 (21.4), n=45, $p=0.48$

	combining the ATVr and EFV groups, within the ABC-3TC arms	combining the ATVr and EFV groups, within the TDF-FTC arms	difference, p value
prevalence (upper bound of 1-sided 95% confidence interval [CI]) of lipoatrophy	17.6% (25.0%)	14.9% (21.5%)	p=0.70
mean absolute and percentage changes in limb fat	1.66 kg and 24.9%	1.11 kg and 20.9%	difference (Δ) 0.55 kg (95%CI, -0.14 to 1.24; P = .12) and 4% (95% CI, -6.7% to 14.7%; P = .46)
mean absolute and percentage changes in trunk fat			Δ = 0.37 kg (95% CI, -0.58 to 1.32; P = .45) and 2.2% (95% CI, -11.6% to 15.9%; P = .76)
absolute and percentage changes in VAT and VAT:TAT ratio			-2.8 cm ² (95% CI, -12.9 to 7.3; P = .58), -5.1% (95% CI, -21.5% to 11.4%; P = .55), and 0.00 (95% CI, -0.02 to 0.02; P=.94)
gains in mean BMI (post hoc endpoint)			Δ = 0.63 kg/m ² ; 95% CI, -0.12 to 1.38; P = .099

In multivariable analysis, ABC vs. TDF (p=0.013), ATV vs. EFV (p=0.32) and number of copies of HIV RNA/mL (p<0.001) were significant for limb fat.

	combining ABC-3TC and TDF-FTC, within the ATV-r arms	combining ABC-3TC and TDF-FTC, within the EFV arms	difference, p value
mean absolute and percentage changes in limb fat	1.88 kg and 30.4%	0.96 kg and 16.5%	difference (Δ) 0.93 kg (95% CI, 0.24–1.61; P = .008) and 13.9% (95% CI, 3.3%–24.5%; P = .010)
mean absolute and percentage changes in trunk fat	2.42 kg; 36.5%	1.33 kg; 21.1 %	Δ = 1.09 kg (95% CI, 0.15–2.03; P = .023) and 15.4% (95% CI, 1.7%–29.0%; P = .028).
absolute and percentage changes from baseline in VAT and VAT:TAT ratio			Δ = 7.6 cm ² (95% CI, -2.4 to 17.7; P = .14), 14.2% (95% CI, -2.2% to 30.6%; P = .090) and 0.00 (95% CI, -0.02 to 0.02; P = .92).

gains in mean BMI (post hoc endpoint)			$\Delta=0.88 \text{ kg/m}^2$; 95% CI, 0.13–1.62; P 5 .022
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Authors' conclusion

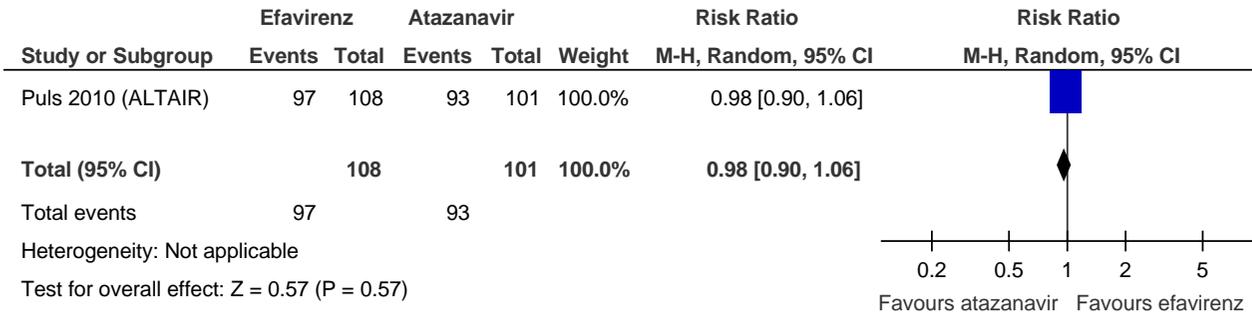
This large comparative clinical trial of ABC/3TC and TDF/FTC combined with either ATV/r or EFV found little difference in virologic efficacy between the 2 NRTI strategies when the screening HIV RNA was $<10^5$ copies/mL. By contrast, in the high RNA stratum, the time to virologic failure was faster with ABC/3TC than TDF/FTC with either ATV/r or EFV; furthermore, safety and tolerability generally favored TDF/FTC over ABC/3TC. Overall, these results support recent treatment guidelines that TDF/FTC be the preferred initial NRTI combination in treatment-naive patients, with ABC/3TC being an effective alternative choice. Several factors should be considered when selecting the optimal initial NRTI combination for an individual patient, including baseline HIV RNA level, HLA-B*5701 status, coinfection with hepatitis B, renal function, and lipid parameters.

At week 96, TDF-FTC, both in the spine and hip, and ATV/r in the spine produced significantly more bone loss than did ABC-3TC– or EFV-based regimens.

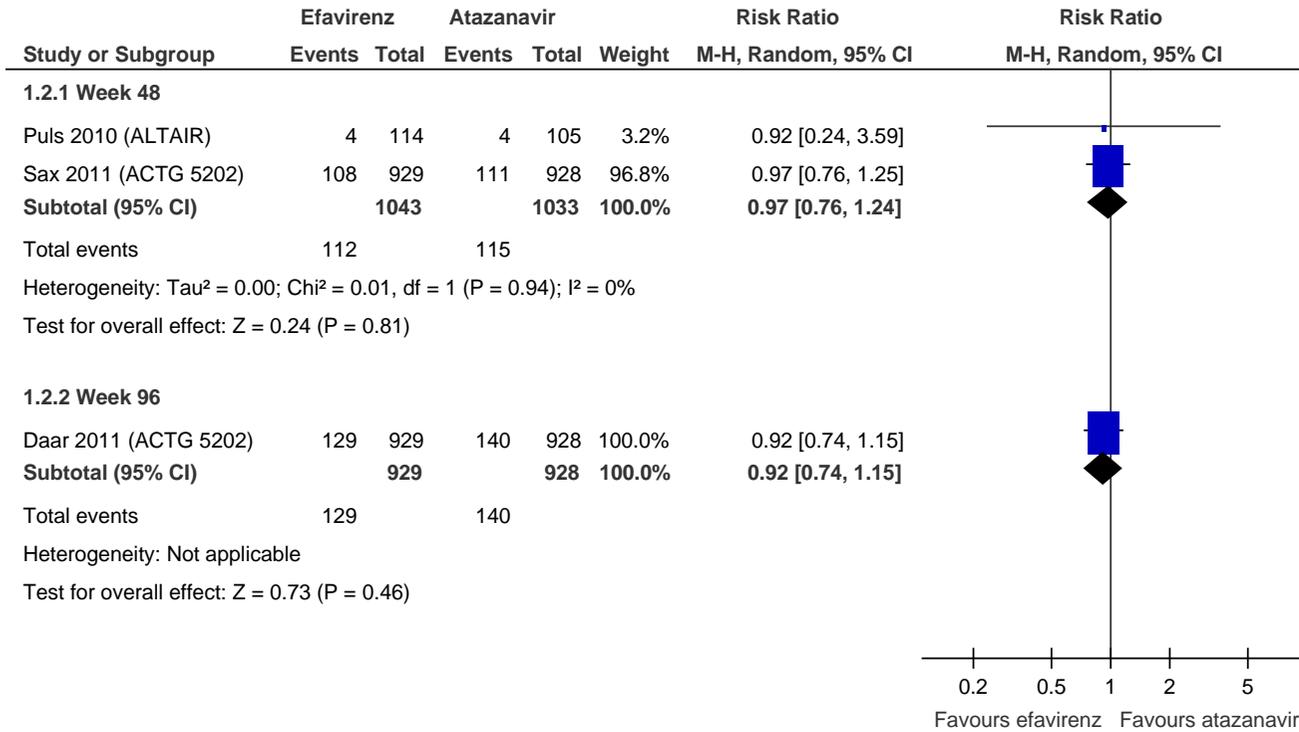
ABC-3TC– and TDF-FTC–based regimens increased limb and visceral fat at week 96, with a similar prevalence of lipoatrophy. Compared to the EFV group, subjects assigned to ATV-r had a trend towards higher mean percentage increase in VAT.

Forest plots

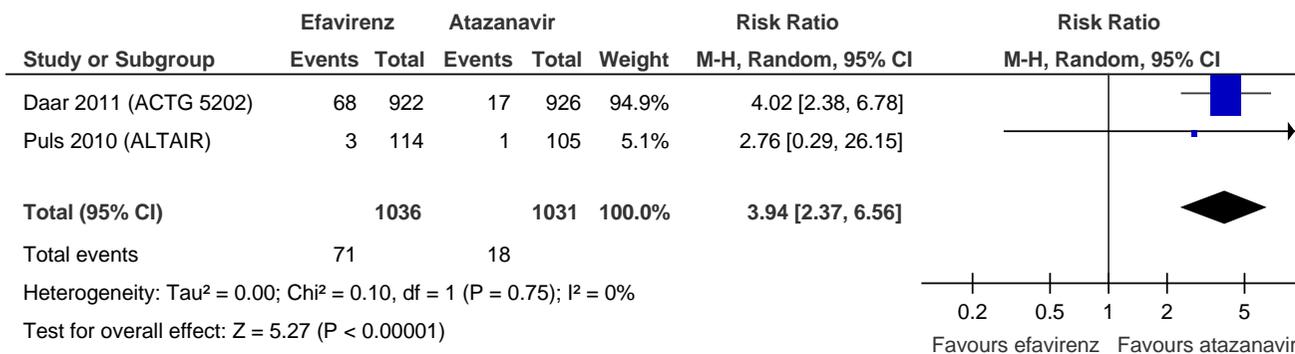
Forest plot of comparison: 1 Efavirenz versus atazanavir, outcome: 1.1 Viral suppression <50 copies week 48.



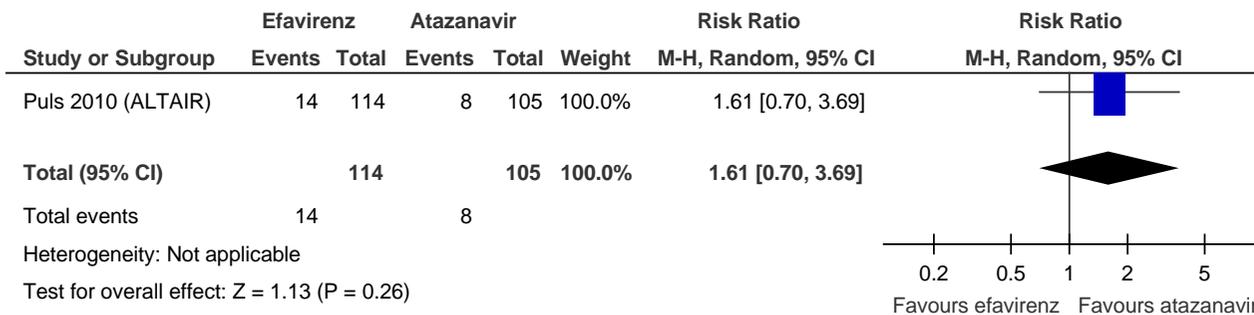
Forest plot of comparison: 1 Efavirenz versus atazanavir, outcome: 1.2 Virological failure.



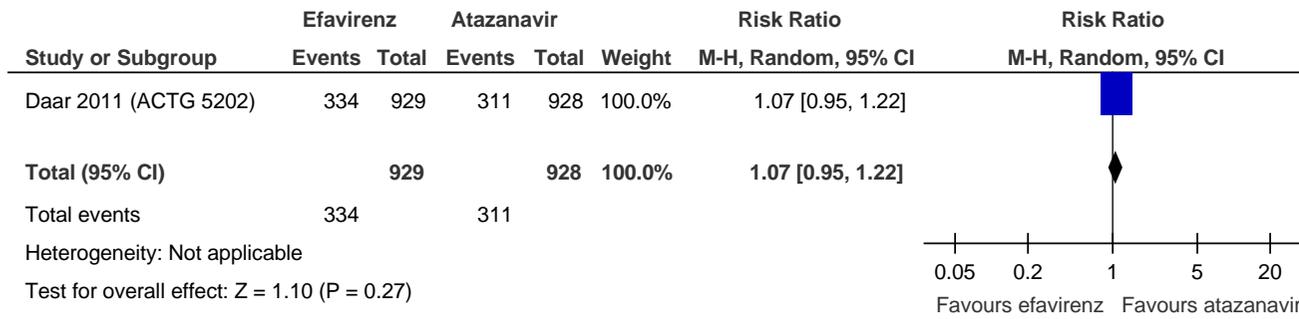
Forest plot of comparison: 1 Efavirenz versus atazanavir, outcome: 1.3 Drug resistance.



Forest plot of comparison: 1 Efavirenz versus atazanavir, outcome: 1.4 Serious adverse event.



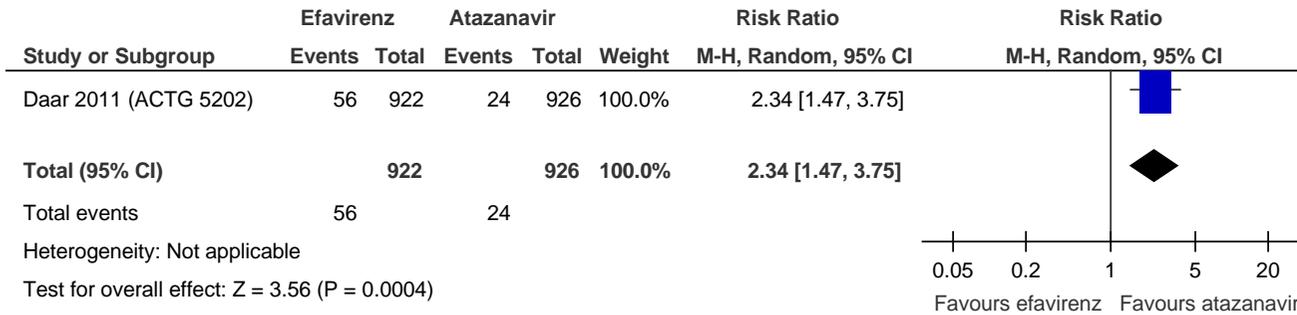
Proportion with grade 3/4 adverse events



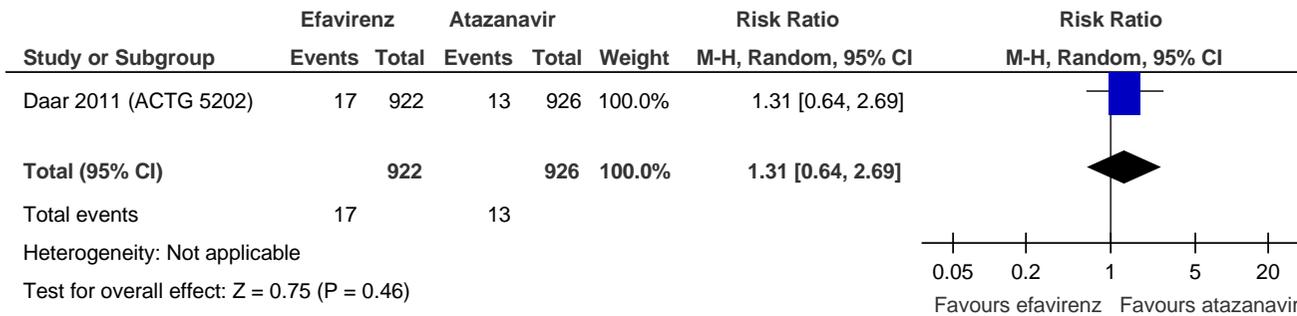
Quality of life

No data from these studies to address these outcomes.

Proportion with grade 3/4 neurological events

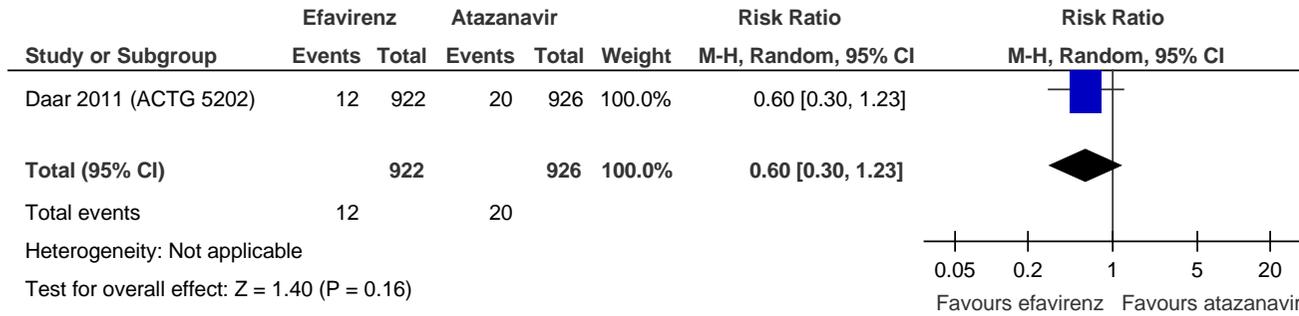


Proportion with grade 3/4 diarrhoea



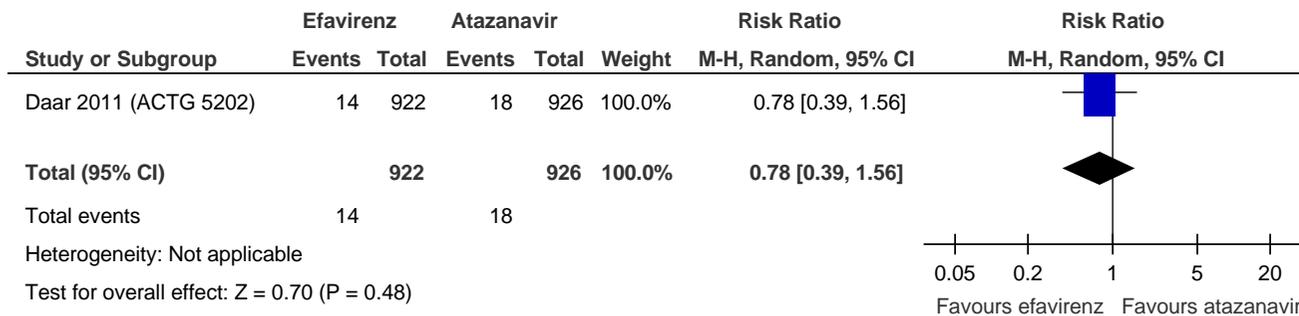
No clear evidence of a difference between the treatment arms.

Proportion with grade 3/4 AST elevation

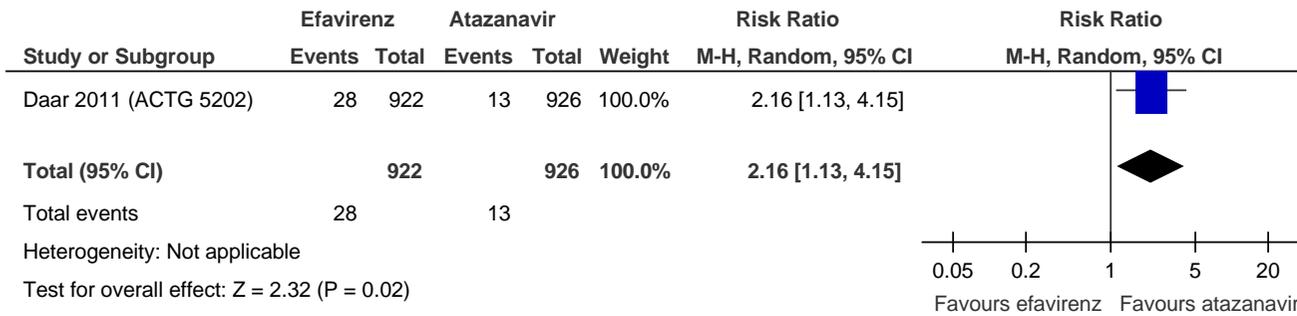


No clear evidence of a difference between the treatment arms.

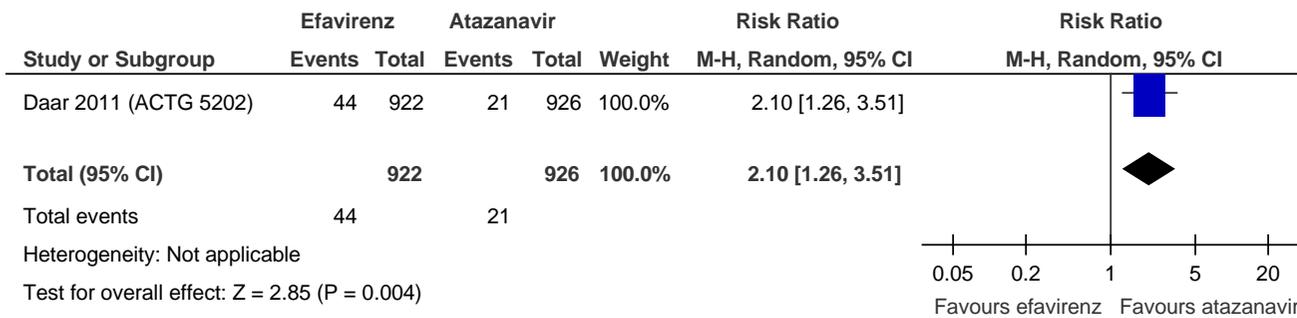
Proportion with grade 3/4 ALT elevation



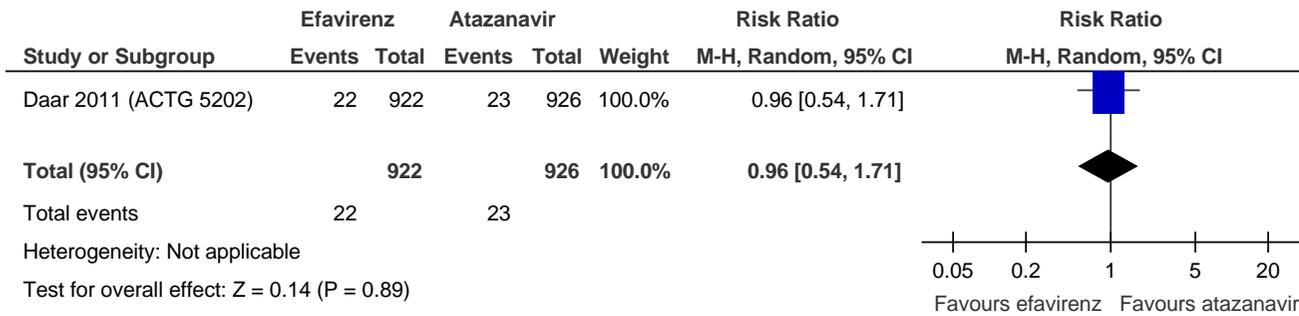
Proportion with grade 3/4 total cholesterol



Proportion with grade 3/4 LDL cholesterol

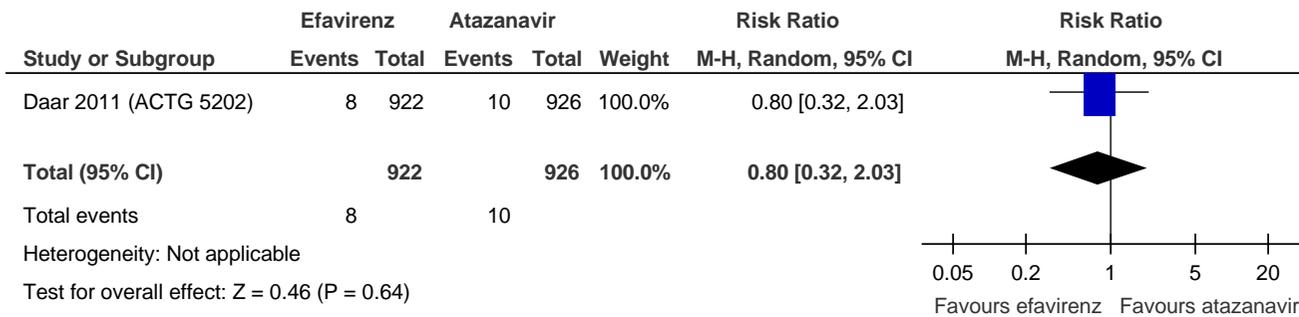


Proportion with grade 3/4 triglycerides



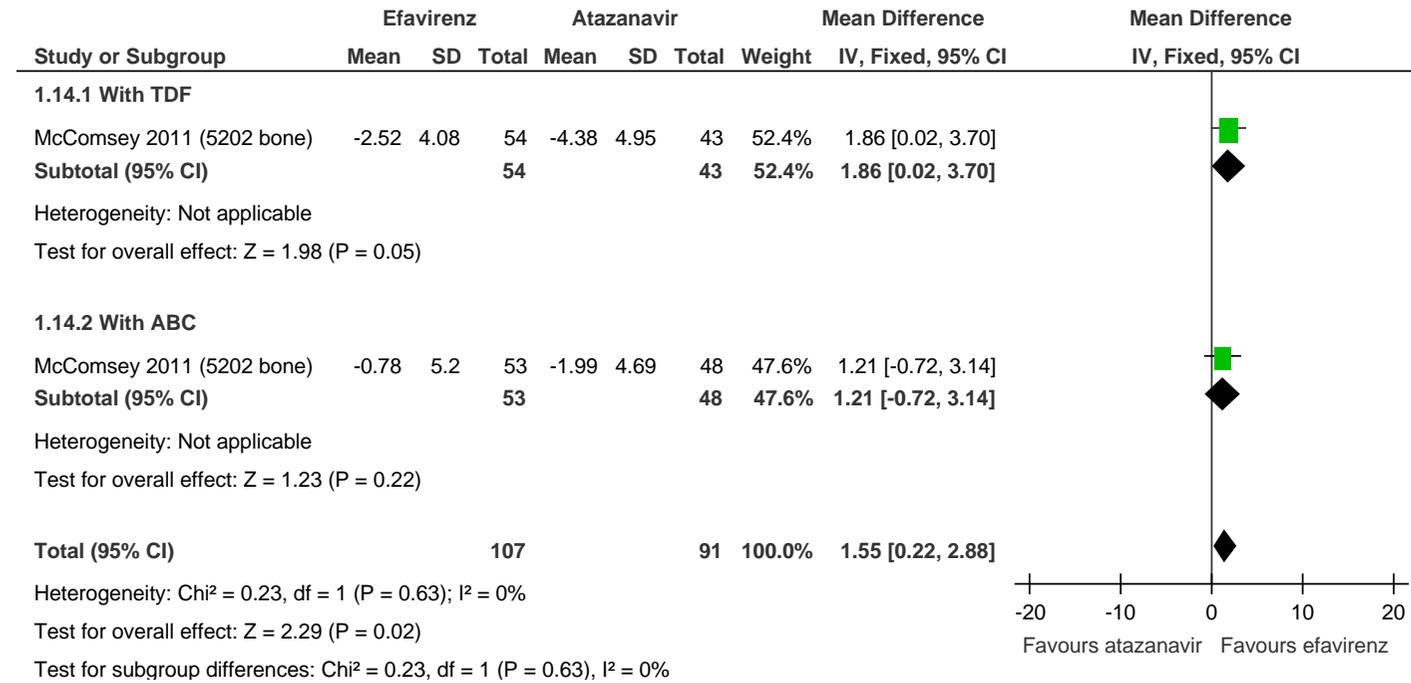
No clear evidence of a difference between the treatment arms.

Renal failure

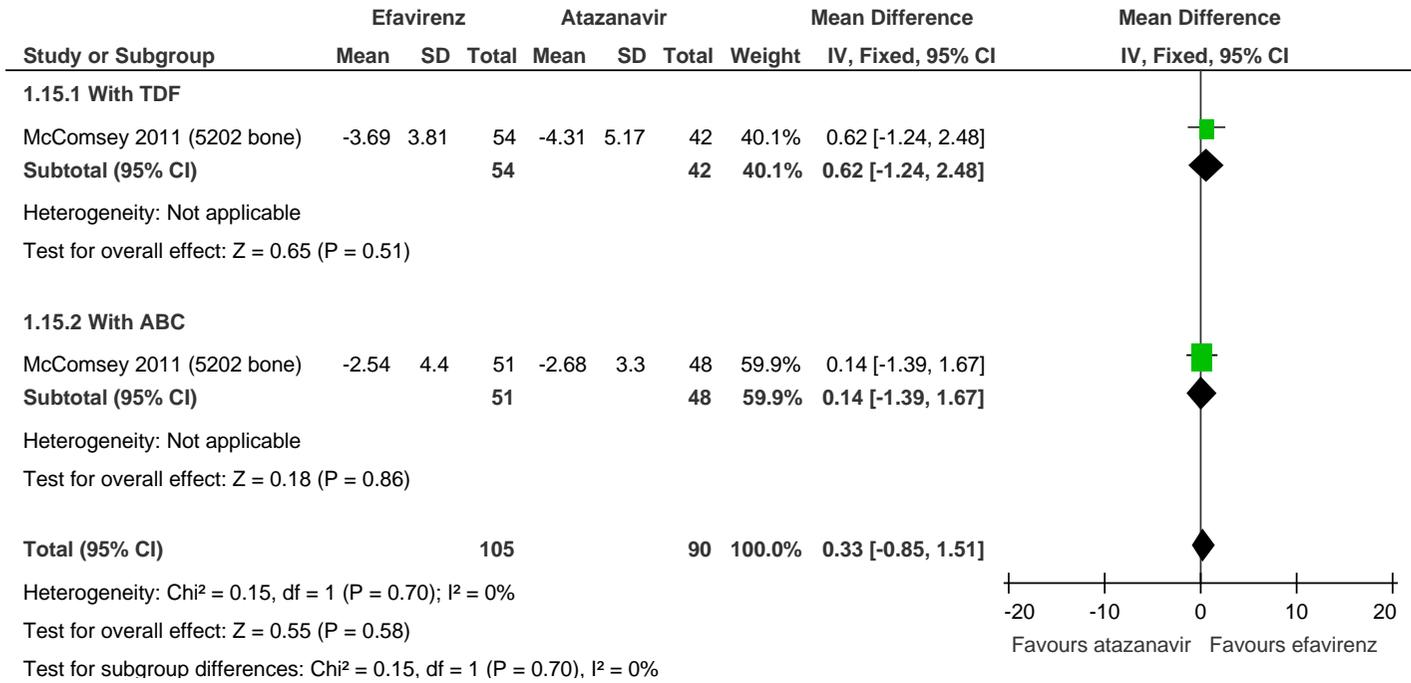


No clear evidence of a difference between the treatment arms.

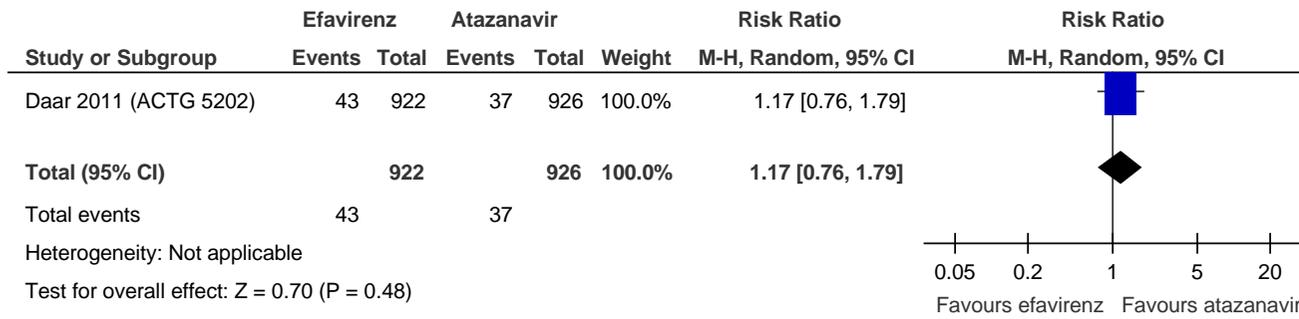
Chronic toxicities (bone): Change in lumbar spine BMD (% , week 96).



Change in hip BMD (% , week 96).



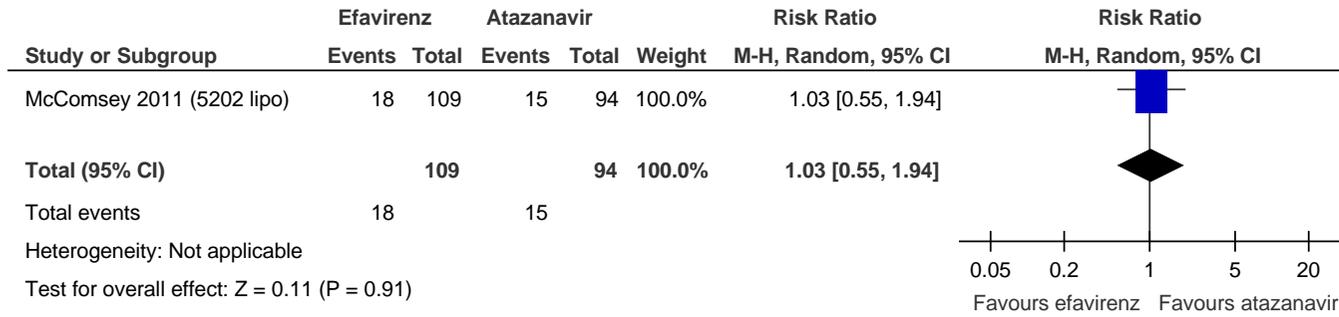
Bone fractures



No clear evidence of a difference between the treatment arms.

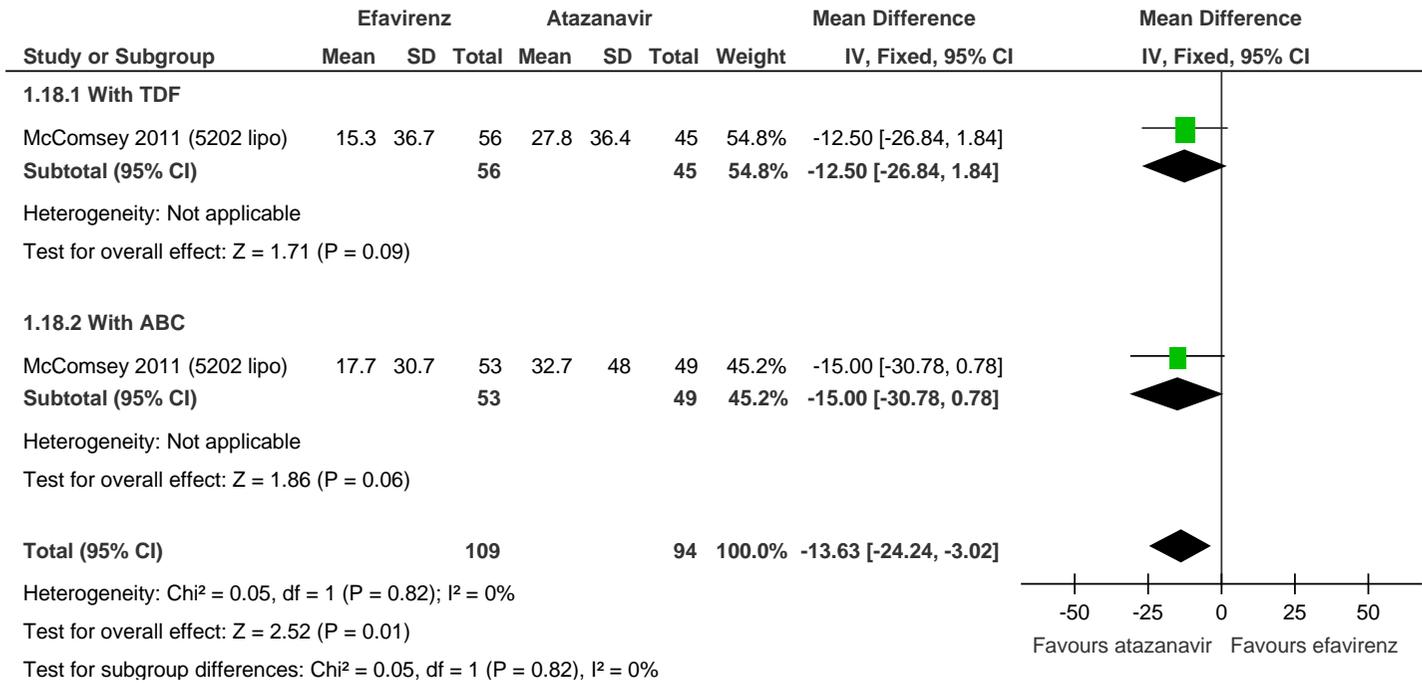
Lipodystrophy outcomes

Patients with 10% or more limb fat loss (week 96).

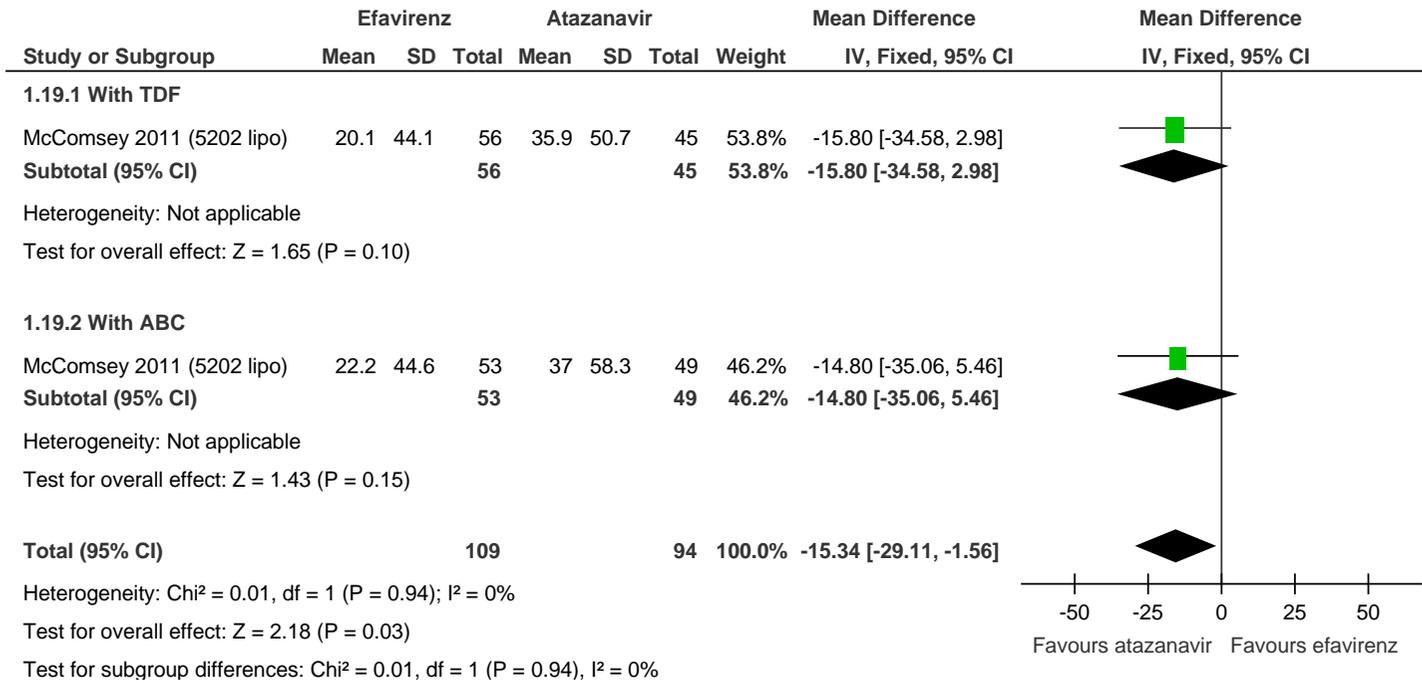


Suggests no difference between groups.

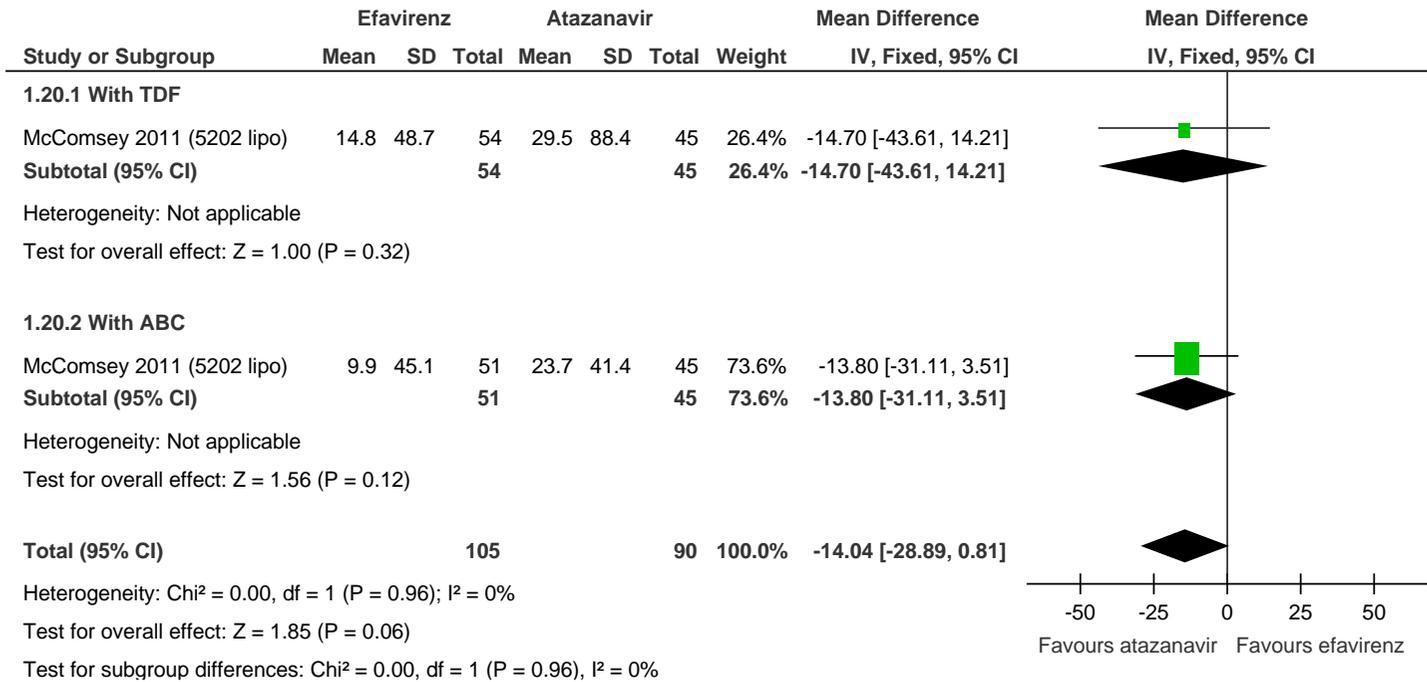
Change in limb fat (% , week 96).



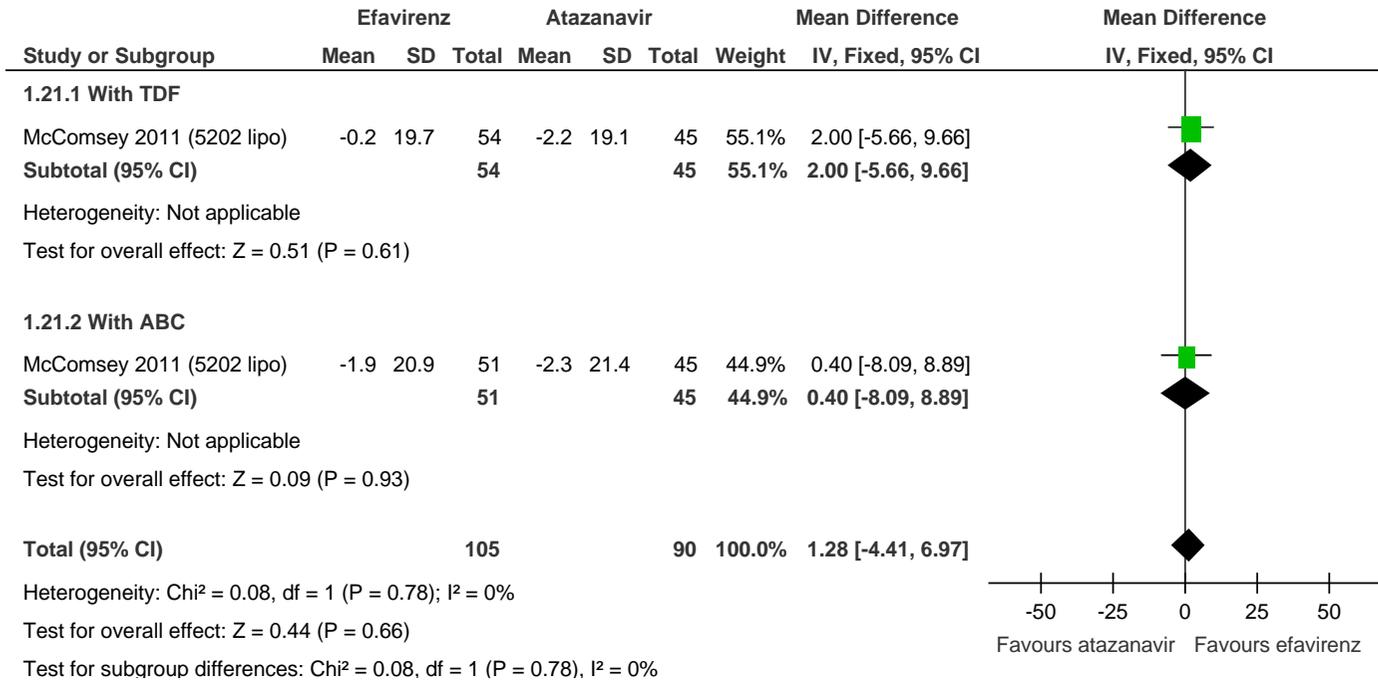
Change in trunk fat (% , week 96).



Change in visceral adipose tissue (VAT; %, week 96).

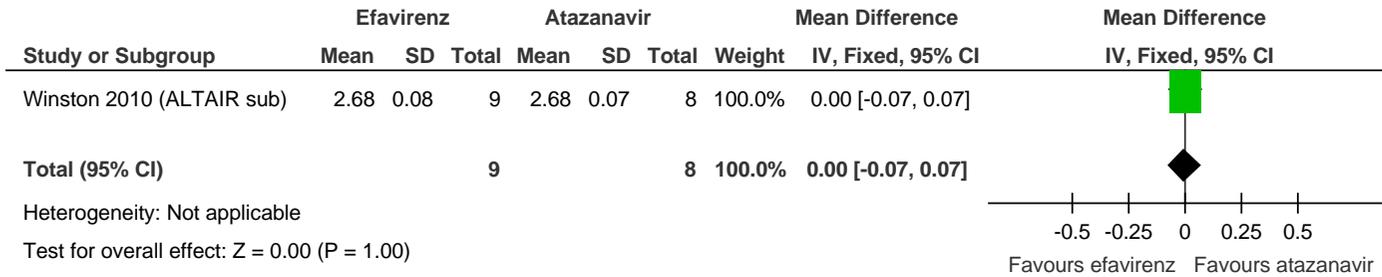


Change in visceral: total adipose tissue (VAT:TAT; %, week 96).

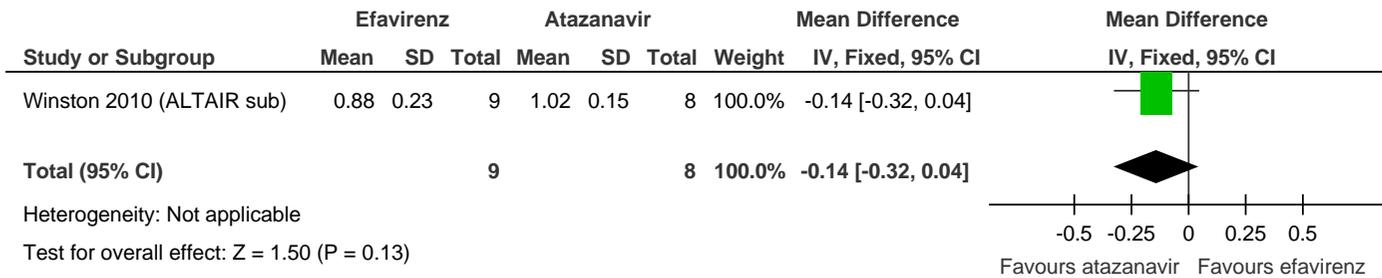


Cognitive outcomes

Cognitive speed score (lower = better).



Cognitive accuracy score (higher = better).



NNT/NNH table for Efavirenz versus atazanavir

Efavirenz and atazanavir were **equally effective** (outcomes of viral suppression, virological failure).

The only significant differences between the drugs were for the following *safety* outcomes:

	Efavirenz better	Atazanavir better	ARR	NNT
Drug resistance	no	yes	51/1000	20
grade 3/4 neurological events	no	yes	35/1000	
grade 3/4 total cholesterol	no	yes	16/1000	
grade 3/4 LDL cholesterol	no	yes	25/1000	

20 people would need to be treated with atazanavir rather than efavirenz to avoid 1 case of drug resistance.

B Rilpivirine versus efavirenz

Two randomised trials were found comparing rilpivirine versus efavirenz:

- ECHO:
 - Molina JM et al. Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naive adults infected with HIV-1 (ECHO): a phase 3 randomised double-blind active-controlled trial. Lancet 2011; 378: 238–46.
- THRIVE:
 - Cohen CJ et al. Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected with HIV-1 (THRIVE): a phase 3, randomised, non-inferiority trial. Lancet 2011; 378: 229–37.

Reference	Study type/ methodological quality	No. pts	Patient characteristics	Intervention	Comparison	Length of follow -up	Outcome measures	Funding
Molina, J.-M., P. Cahn, et al. (2011). "Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naive adults infected with HIV-1 (ECHO): a phase 3	RCT: Efficacy Comparison in Treatment-naive, HIV-infected Subjects of TMC278 and Efavirenz (ECHO) Allocation to treatment Random Method of randomisation: computer-	Total N: 694; 50/346 rilpivirine discontinued (14.4%) and 56/344 efavi	INCLUSION CRITERIA pts aged 18 years or older, who had not been previously treated with antiretroviral drugs, a plasma viral load at screening of ≥ 5000 copies/mL, and viral sensitivity to tenofovir-disoproxil-fumarate and emtricitabine (assessed with the resistance genotype virco TYPE HIV-1 assay; Virco BVBA, Beerse, Belgium). EXCLUSION CRITERIA infection with HIV-2, documented evidence of at least one NNRTI resistance-associated mutation (RAM) from a list of 39 (A98G, L100I, K101E/P/Q,	Drug(s): rilpivirine 25mg daily + tenofovir-disoproxil-fumarate 300mg and emtricitabine 200mg n=346	Drug(s): efavirenz 600mg daily + tenofovir-disoproxil-fumarate 300mg and emtricitabine 200mg n=348 (of whom 4 not	Treatment duration: 96 weeks Assessments wks 2 and 4, every 4 wks until wk 16,	Primary endpoint: % of pts with confirmed response (according to the intention-to-treat time-to-loss-of virological-response [ITT-TLOVR] algorithm) at 48 wks (non-inferiority at a margin of 12%) Other endpoints: non-inferiority at a 10% margin, superiority (if non-inferiority was shown), durability of	Tibotec

<p>randomised double-blind active-controlled trial." <u>Lancet</u> 378(9787): 238-246</p>	<p>generated interactive web response system Concealment: adequate Blinding double blinded Sample size calculation yes ITT analysis Yes Setting: Outpatients</p>	<p>renz (16.3 %)</p>	<p>K103H/N/S/T, V106A/M, V108I, E138A/G/K/Q/R, V179D/E, Y181C/I/V, Y188C/H/L, G190A/C/E/Q/S/T, P225H, F227C, M230I/L, P236L, K238N/T, and Y318F), any active clinically significant disease (e.g. pancreatitis, cardiac dysfunction, active and significant psychiatric disorder, adrenal insufficiency, hepatic impairment), renal impairment (estimated glomerular filtration rate based on creatinine <50 mL/min), and, for women, pregnancy or breastfeeding.</p> <p>Disallowed drugs included those which could reduce exposure to rilpivirine (i.e. potent cytochrome 3A4-inducers and proton-pump inhibitors); drugs disallowed for efavirenz or tenofovir-disoproxil-fumarate and emtricitabine, as per the package inserts; any anti-HIV treatment other than drugs used in our trial; and all investigational drugs.</p> <p>Baseline comparability between groups: yes</p> <p>Age: median 36 (range 18-78) yr on rilpivirine and 36 (19-67) yr on efavirenz</p> <p>Gender: 78 (23%) female on rilpivirine</p>		<p>treated)</p>	<p>and then every 8 wks</p> <p>Follow-up after end of treatment: 4 weeks</p>	<p>antiviral activity, changes from baseline in CD4 cell count, safety, tolerability, HIV genotypic and phenotypic characteristics (in virological failures), adherence (measured with the Modified Medication Adherence Self-Report Inventory [M-MASRI]), pharmacokinetics, and pharmacokinetic and pharmacodynamic relations</p>	
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			and 69 (20%) on efavirenz Severity of disease: median CD4 cell count 240 (range 1-888) on rilpivirine and 257 (1-757) cells/ml on efavirenz					
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Main outcomes:

Week 48	Rilpivirine	Efavirenz	% difference (95% CI)
ITT-TLOVR outcome	N=346	N=344	
Viral load < 50 copies per mL	287 (83%)	285 (83%)	0.1 (-5.5 to 5.7)
VF _{eff} = virological failure for the efficacy (ITT-TLOVR) endpoint: never suppressed [no confirmed response before week 48]	38 (11%) 22 (6%)	15 (4%) 7 (2%)	
rebounders [confirmed response before wk 48 with confirmed rebound ≤ wk 48]	16 (5%)	8 (2%)	
Discontinuation due to adverse events	6 (2%)	25 (7%)	
Discontinuation due to reason other than an adverse event (lost to follow-up, non-compliance, withdrew consent, ineligible to continue, or sponsor's decision)	15 (4%)	19 (6%)	
Model-predicted response (logistic regression (ITT-TLOVR outcome <50 copies per mL) adjusted for baseline viral load)	83%	84%	-0.4 (-5.9 to 5.2)
Per-protocol-TLOVR outcome: number of assessable pts in each treatment group	335	330	
Viral load < 50 copies per mL	282 (84%)	275 (83%)	0.8 (-4.8 to 6.5)

Other outcomes:

At week 48, mean change in absolute CD4 cell count from baseline was 196 cells per μ L (95% CI 179-212) for rilpivirine and 182 cells per μ L (165-198) for efavirenz (p=0.13).

Week 48	Rilpivirine (n=346)	Efavirenz (n=344)
VF _{res} =virological failure established with the resistance analysis defined as any pt in the ITT population experiencing treatment failure irrespective of time of failure, treatment status, or reason for discontinuation providing the following criteria were met: never achieved two consecutive viral-load values of < 50 copies per mL and had an increase in viral load of 0.5 log ₁₀ copies per mL or greater above the nadir (never suppressed), or first achieved two consecutive viral-load values of < 50 copies per mL with two subsequent consecutive (or single, when last available) viral load values of ≥50 copies per mL (rebounder).	45 (13%)	19 (6%)

VFres with resistance data at time of failure	40	13
VFres with any treatment-emergent NNRTI RAM	26/40 (65%)	8/13 (62%)
VFres with any treatment-emergent IAS-USA N(t)RTI RAM	28/40 (70%)	4/13 (31%)
VFres with any treatment-emergent NNRTI or IAS-USA N(t)RTI RAM	29/40 (73%)	8/13 (62%)
NNRTI RAM incidence in patients who failed with NNRTI mutations (1 pt on efavirenz had V108I (8%), as did one pt on rilpivirine (3%))	n=26	n=8
E138K 18	(69%)	0
K101E 5	(19%)	0
Y181C 5	(19%)	0
V90I 4	(15%)	0
H221Y	4 (15%)	0
V189I	3 (12%)	0
E138Q	2 (8%)	0
K103N	0	7 (88%)
IAS-USA N(t)RTI RAM incidence in pts who failed with N(t)RTI mutations (K70E was reported in 1 pt in the rilpivirine group versus 0 pts in the efavirenz group)	n=28	n=4
M184I, V, or both	26 (93%)	4 (100%)
M184I only	20 (71%)	1 (25%)
M184V only	4 (14%)	2 (50%)
M184I/V mixtures	2 (7%)	1 (25%)
K65R	3 (11%)	0
K219E	3 (11%)	0
Y115F	2 (7%)	0

Adverse events

	Rilpivirine N=346	Efavirenz N=344	p value
Median treatment duration (weeks; range)	56 (0-87)	56 (1-88)	
Any adverse event	303 (88%)	317 (92%)	
Any treatment-related adverse event of grade 2 or greater	55 (16%)	108 (31%)	<0.0001
Adverse event leading to permanent discontinuation	8 (2%)	27 (8%)	
Any serious adverse event (including death)	23 (7%)	31 (9%)	

Death	0	1 (0%)	
Most common treatment-related adverse event of grade 2 or greater in ≥2% of pts in either group (excluding laboratory abnormalities reported as an adverse event)			
Dizziness	4 (1%)	23 (7%)	
Abnormal dreams or nightmares	5 (1%)	18 (5%)	
Insomnia	5 (1%)	10 (3%)	
Nausea	3 (1%)	8 (2%)	
Rash (rash, macular/maculopapular/papular/pustular/scaly rash, erythema, allergic dermatitis, urticaria, drug eruption, exanthem, toxic skin eruption, urticaria papular)	6 (2%)	26 (8%)	0.0002
Treatment-emergent grade 3 or 4 laboratory abnormalities in ≥2% of pts in either gp	N=345	N=340	
Any grade 3 or 4 laboratory abnormality	34 (10%)	55 (16%)	
Increased pancreatic amylase	11 (3%)	16 (5%)	
Increased aspartate aminotransferase	8 (2%)	12/339 (4%)	
Hypophosphataemia	6 (2%)	4/339 (1%)	
Increased alanine aminotransferase	4 (1%)	12 (4%)	
Increased LDL-C	3 (1%)	8/339 (2%)	
Increased triglycerides	1 (0%)	5/339 (2%)	
Increased total cholesterol	1 (0%)	6/339 (2%)	
Mean (95% CI) change in total cholesterol (mmol/L)	0.03 (-0.06 to 0.11)	0.63 (0.53 to 0.73)	<0.0001
Mean (95% CI) change in HDL-C (mmol/L)	0.07 (0.04 to 0.10)	0.24 (0.21 to 0.27)	<0.0001
Mean (95% CI) change in total cholesterol/HDL-C	-0.14 (-0.33 to 0.05)	-0.24 (-0.40 to -0.09)	0.25
Mean (95% CI) change in LDL-C (mmol/L)	-0.04 (-0.10 to 0.03)	0.31 (0.23-0.39)	<0.0001
Mean (95% CI) change in triglycerides (mmol/L)	-0.10 (-0.19 to -0.01)	0.16 (-0.07 to 0.38)	0.01
Grade 3 rash	1	2	
Grade 4 rash	0	0	
Grade 3 or 4 abnormalities in creatinine	0	0	
Discontinuation for renal adverse events	0	0	
Mean change from baseline in QT interval corrected according to Fridericia's formula	10.9 ms (9.0-12.8)	12.0 ms (10.1-13.7)	

Authors' conclusion

These data suggest that once-daily rilpivirine, perhaps as a single tablet regimen in combination with tenofovir-disoproxil fumarate and emtricitabine, is expected to be a valuable treatment option for patients infected with HIV who have not been previously treated with antiretroviral drugs.

Reference	Study type/ quality	No. pts	Patient characteristics	Intervention	Comparison	Follow-up	Outcome measures	Funding
Cohen, C. J., J. Andrade-Villanueva, et al. (2011). "Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected with HIV-1 (THRIVE): a phase 3, randomised, non-inferiority trial." <u>Lancet</u> 378 (9787):	<p>RCT: NCT00543725; TMC278 against HIV, in a once-daily regimen versus efavirenz (THRIVE)</p> <p>Allocation to treatment Random Method of randomisation: computer generated interactive web-response system Concealment: adequate Blinding double blinded Sample size calculation yes ITT analysis Yes Setting: Outpatients</p>	Total N: 680	<p>INCLUSION CRITERIA adults (≥ 18 years) naive to antiretroviral therapy, with a screening plasma viral load of ≥ 5000 copies/mL and viral sensitivity to the background N(t)RTIs, as assessed with the vircoTYPE HIV-1 assay</p> <p>EXCLUSION CRITERIA HIV-2 infection, presence of at least one of 39 NNRTI resistance-associated mutations (RAMs) active clinically significant disease (e.g. pancreatitis, cardiac dysfunction, active and significant psychiatric disorder, adrenal insufficiency, or hepatic impairment), renal impairment, pregnancy or breastfeeding.</p> <p>Disallowed drugs were all investigational drugs, drugs that could reduce rilpivirine exposure (e.g. those with a potent cytochrome 3A4-inducing effect or proton-pump inhibitors), drugs disallowed for efavirenz or the background regimen (as per the package inserts) and any anti-HIV therapy other than those used in the trial.</p>	Drug(s): rilpivirine (TMC278) 25mg once daily + N(t)RTI regimen, which included tenofovir-disoproxil-fumarate plus emtricitabine (60%), zidovudine plus lamivudine (30%), or abacavir plus lamivudine (10%).	Drug(s): efavirenz 600mg once daily + N(t)RTI regimen, which included tenofovir-disoproxil plus emtricitabine (60%), zidovudine plus lamivudine (30%), or abacavir plus lamivudine (10%). n=340 (2 not treated)	Treatment duration: 96 weeks Assessments at: wks 2, 4, 8, 12 and 16, and every 8 wks thereafter. Follow-up after end of treatment: 4 weeks	Primary endpoint: non-inferiority of rilpivirine to efavirenz in terms of % of all pts who received at least one dose of rilpivirine or efavirenz who had a confirmed virological response (defined by the intent-to-treat TLOVR algorithm) at 48 wks with a non-inferiority margin of 12%. Other endpoints: non-inferiority with a 10% margin and superiority (if non-inferiority was shown), antiviral activity in time, changes from baseline in CD4 cell count, safety, tolerability, HIV genotypic and phenotypic characteristics (in virological failures), adherence (assessed by the Modified Medication Adherence	Tibotec

229-237.			Baseline comparability between groups: Age: median (range) 36 (19-62) years on rilpivirine and 36 (19-69) on efavirenz Gender: 90 (26%) female on rilpivirine and 94 (28%) on efavirenz Severity of disease: median (range) CD4 cell count 263 (2-744) cells/ml on rilpivirine and 263 (1-1137) on efavirenz	n=340			Self-Report Inventory), pharmacokinetics, and pharmacokinetic and pharmacodynamic relations
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Main outcomes:

	Rilpivirine N=340	Efavirenz N=338	difference (95% CI)
Patients who received at least one drug dose			
Viral load <50 copies per mL	291 (86%)	276 (82%)	3.9% (-1.6 to 9.5)
Virological failure (efficacy endpoint)	24 (7%)	18 (5%)	
Rebounders (confirmed response before wk 48 with confirmed rebound ≤week 48)	8 (2%)	7 (2%)	
Never suppressed (no confirmed response before week 48)	16 (5%)	11 (3%)	
Discontinuation due to adverse event or death	9 (3%)	24 (7%)	
Other discontinuation (lost to follow-up, non-compliance, withdrew consent, ineligible to continue, or sponsor's decision)	16 (5%)	20 (6%)	
Predicted response (%) Primary analysis adjusted for baseline viral load and background nucleoside or nucleotide reverse transcriptase inhibitors.	87%	83%	3.5% (-1.7 to 8.8)
Per-protocol population			
Viral load <50 copies per mL	287/334 (86%)	273/332 (82%)	3.7% (-1.9 to 9.3)

Other outcomes:

At wk 48, the mean change from baseline in CD4 cell count was 189 cells per μ L (95% CI 174-203) with rilpivirine and 171 cells per μ L (155-187) with efavirenz (p=0.09).

	Rilpivirine N=340	Efavirenz N=338	
Virological failure (resistance analysis): any pt who received at least one dose of drug who had a treatment failure irrespective of time of failure, treatment status, or reason for discontinuation, providing the following criteria were met: never achieved two consecutive viral load values of <50 copies per mL and had an increase in viral load of 0.5 log ₁₀ copies per mL or more above the nadir (never suppressed) or first achieved two consecutive viral load values of < 50 copies per mL followed by two consecutive (or single, when last available) viral load values ≥50 copies per mL (rebounder)	27 (8%)	20 (6%)	
Virological failure (resistance analysis) with resistance data at time of failure: With any treatment-emergent NNRTI and/or IAS–USA N(t)RTI RAM	15/22 (68%)	8/15 (53%)	
NNRTI RAM incidence in patients who failed with NNRTI mutations			
E138K	10/13 (77%)	0/7	
K101E	3/13 (23%)	1/7 (14%)	
V189I	2/13 (15%)	0/7	
H221Y	2/13 (15%)	0/7	
K103N	0/13	4/7 (57%)	
V106M	0/13	2/7 (29%)	
Y188C	0/13	2/7 (29%)	
IAS–USA N(t)RTI RAM incidence in patients who failed with N(t)RTI mutations			
M184I and/or V	12/14 (86%)	3/5 (60%)	
M184V only	5/14 (36%)	3/5 (60%)	
M184I only	4/14 (29%)	0/5	
M184I/V mixtures	3/14 (21%)	0/5	
K65R	0	2/5 (40%)	
48 weeks	Rilpivirine N=340	Efavirenz N=344	p value
Median treatment duration (weeks; range)	55 (2-83)	55 (0-84)	
Any adverse event	313 (92%)	312 (92%)	
Any treatment-related adverse event of grade 2 or greater	54 (16%)	104 (31%)	<0.0001
Adverse event leading to permanent discontinuation	15 (4%)	25 (7%)	
Any serious adverse event (including death)	22 (7%)	24 (7%)	
Death	1 (<1%)	3 (1%)	
Most common treatment-related adverse event of grade 2 or greater in ≥2% of pts in			

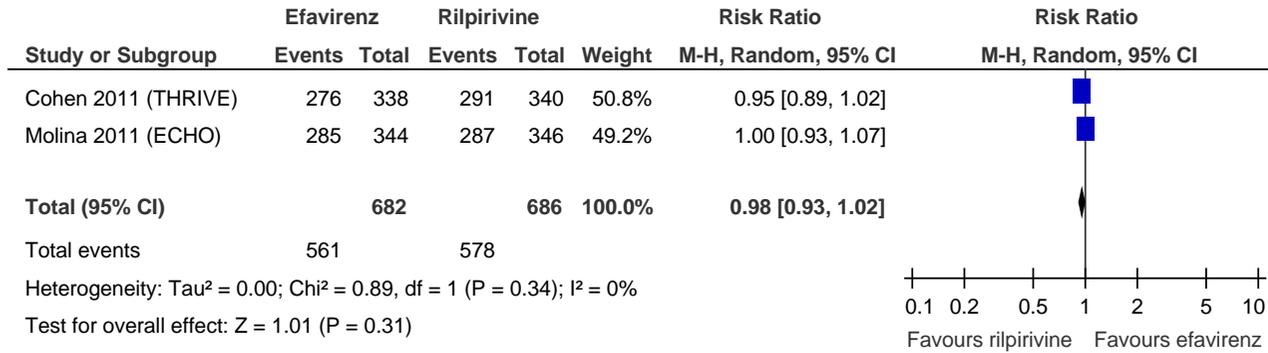
either group (excluding laboratory abnormalities reported as an adverse event)			
Insomnia	7 (2%)	6 (2%)	
Headache	5 (1%)	9 (3%)	
Nausea	2 (1%)	9 (3%)	
Dizziness	0	20 (6%)	
Rash (rash, macular/maculopapular/papular/pustular/scaly rash, erythema, allergic dermatitis, urticaria, drug eruption, exanthem, toxic skin eruption, urticaria papular)	1 (<1%)	30 (9%)	<0.0001
Treatment-emergent grade 3 or 4 laboratory abnormalities in ≥2% of pts in either gp			
Any grade 3 or 4 laboratory abnormality	41/340 (12%)	63/330 (19%)	
Increased pancreatic amylase	9/340 (3%)	11/330 (3%)	
Increased aspartate aminotransferase	6/340 (2%)	7/330 (2%)	
Increased alanine aminotransferase	6/340 (2%)	11/330 (3%)	
Reduced white blood cell count	7/340 (2%)	5/329 (2%)	
Increased LDL-C	2/340 (1%)	19/327 (6%)	
Increased triglycerides	1/340 (<1%)	10/329 (3%)	
Increased total cholesterol	0/340	11/329 (3%)	
Increased lipase (fasting)	2/340 (1%)	5/330 (2%)	
Mean (95% CI) change in total cholesterol (mmol/L)	0.08 (-0.01 to 0.16)	0.79 (0.69 to 0.90)	<0.0001
Mean (95% CI) change in HDL-C (mmol/L)	0.11 (0.08 to 0.13)	0.27(0.24 to 0.30)	<0.0001
Mean (95% CI) change in total cholesterol/HDL-C	-0.36 (-0.48 to -0.25)	-0.28 (-0.38 to -0.17)	0.25
Mean (95% CI) change in LDL-C (mmol/L)	-0.02 (-0.09 to 0.05)	0.44 (0.34 to 0.53)	<0.0001
Mean (95% CI) change in triglycerides (mmol/L)	-0.07 (-0.17 to 0.04)	0.14 (0.01 to 0.26)	<0.0001
Grade 3 rash	0	1/338	
Grade 4 rash	0	0	
Grade 3 or 4 abnormalities in creatinine	0	0	
Discontinuation for renal adverse events	0	0	
Mean change from baseline in QT interval corrected according to Fridericia's formula	12.0 ms (10.1-13.8)	14.1 ms (12.3-16.0)	

Authors' conclusion

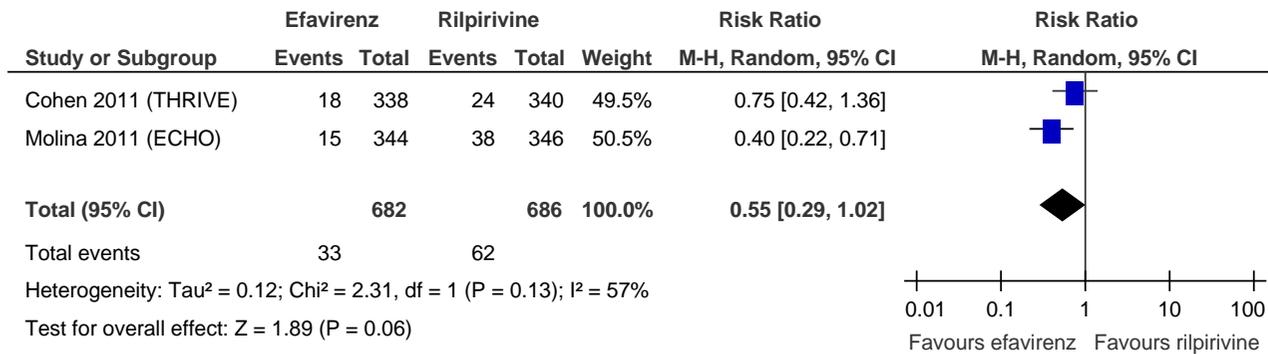
Rilpivirine is expected to be a valuable treatment option for antiretroviral-naive patients infected with HIV-1.

Forest plots for Rilpivirine versus efavirenz:

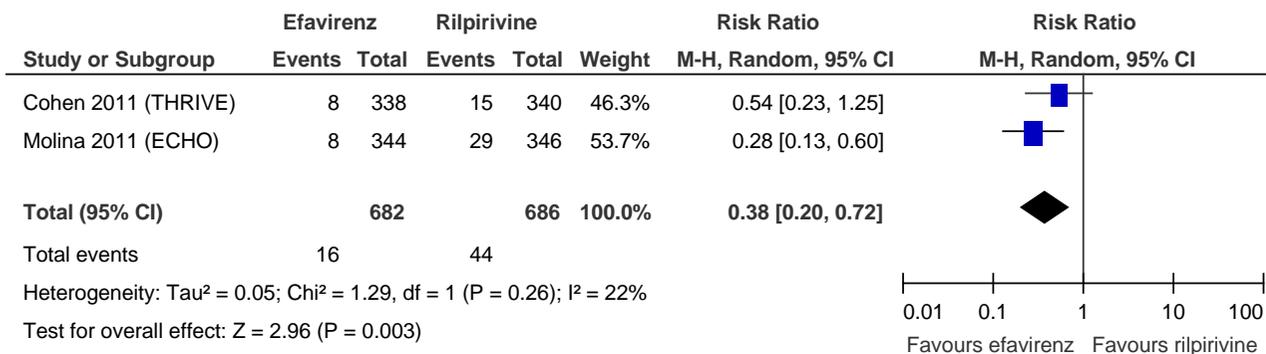
Viral suppression <50 copies/mL.



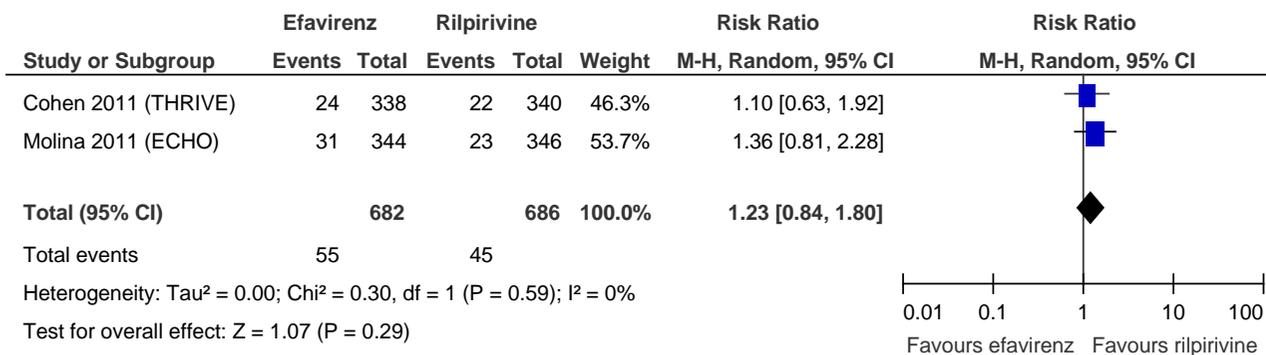
Virological failure.



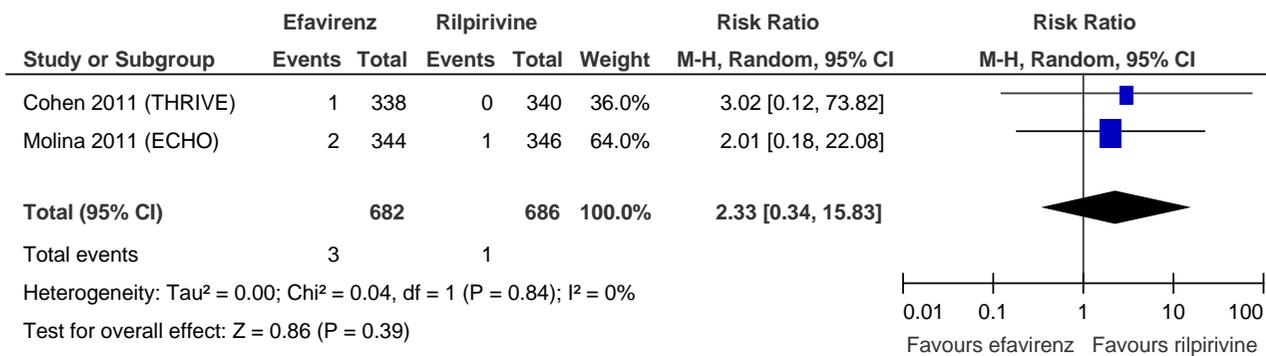
Drug resistance.



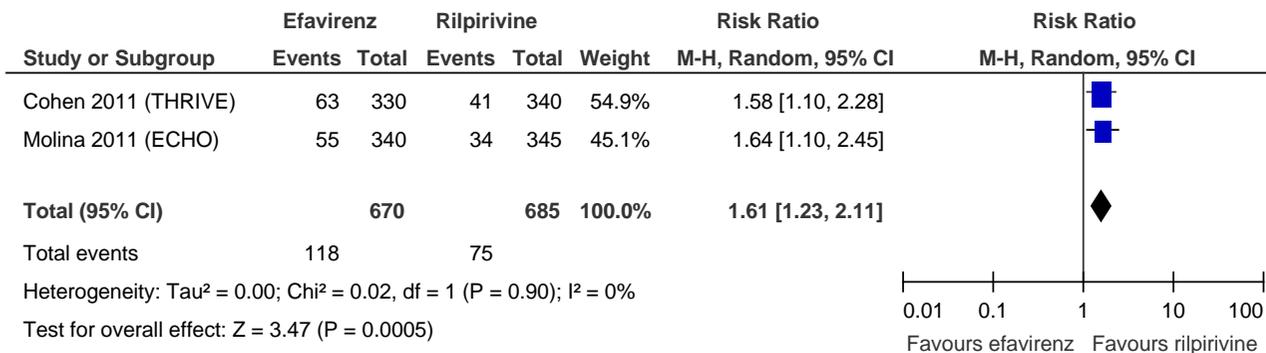
Serious adverse event.



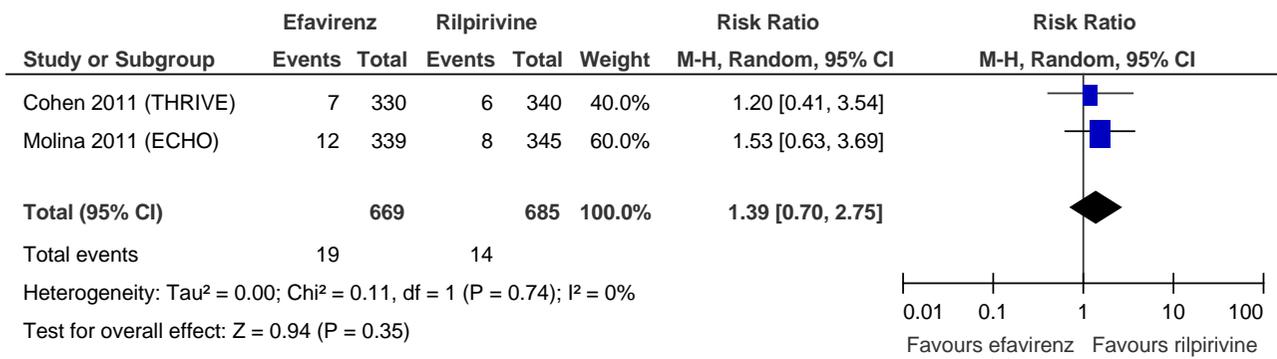
Grade 3 or 4 rash.



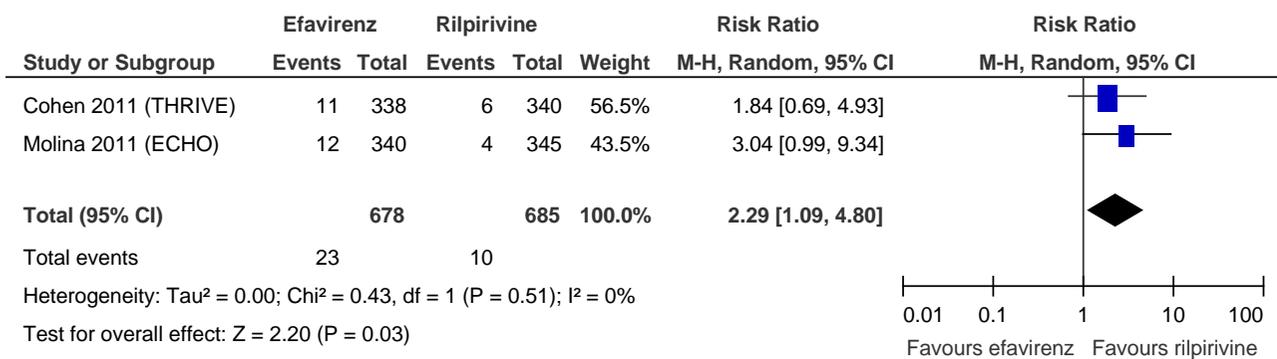
Grade 3 or 4 laboratory adverse event.



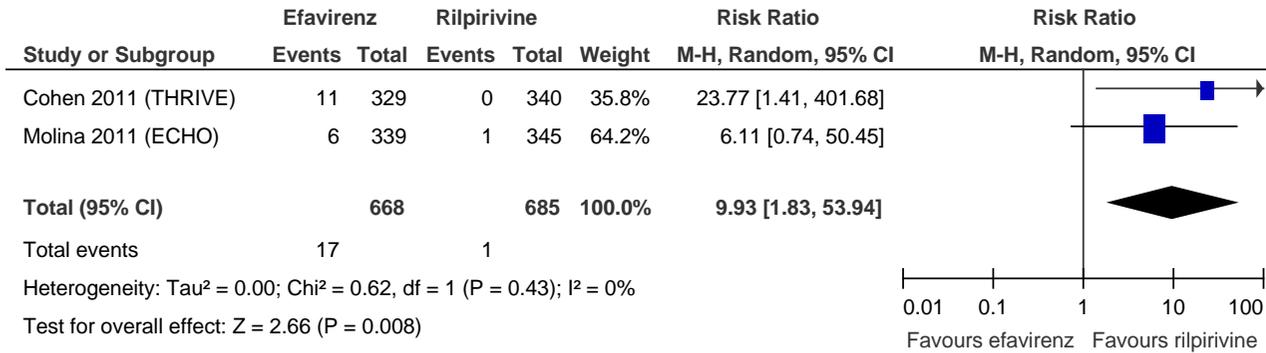
Grade 3 or 4 AST.



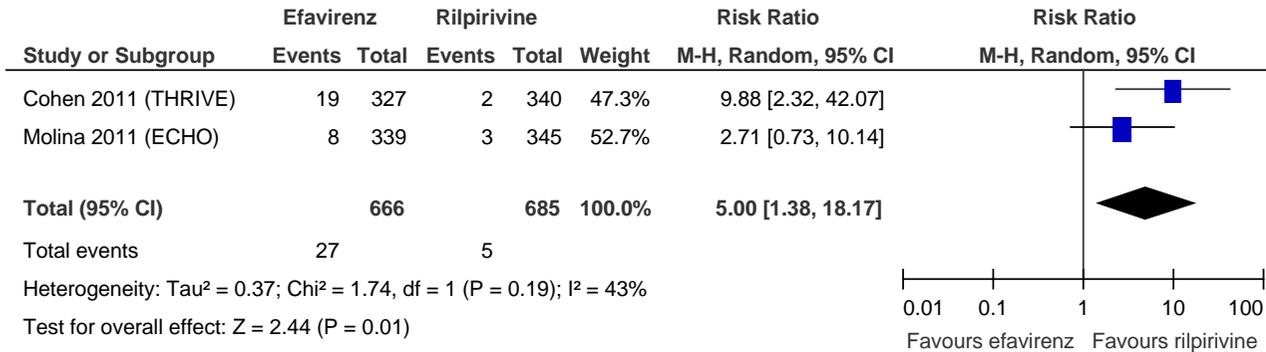
Grade 3 or 4 ALT.



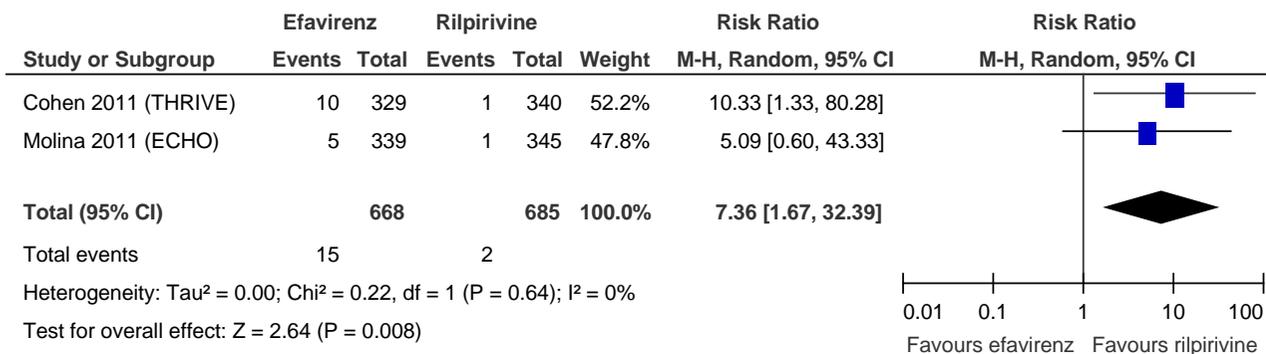
Grade 3 or 4 total cholesterol.



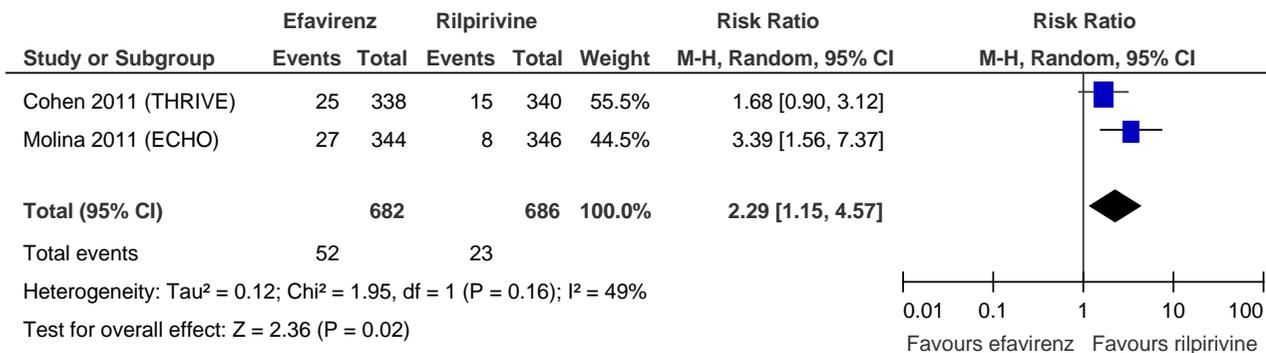
Grade 3 or 4 LDL cholesterol.



Grade 3 or 4 triglycerides.



Discontinuation due to adverse event.



NNT/NNH table for rilpivirine versus efavirenz

Efavirenz and rilpivirine were **equally effective** (outcomes of viral suppression, virological failure).

The only significant differences between the drugs were for the following *safety* outcomes:

	Efavirenz better	Rilpivirine better	ARR	NNT
Drug resistance	yes	no	40/1000	25
Grade 3 or 4 laboratory adverse event	no	yes	67/1000	
Grade 3 or 4 ALT	no	yes	19/1000	
Grade 3/4 total cholesterol	no	yes	13/1000	
Grade 3/4 LDL cholesterol	no	yes	29/1000	
Grade 3 or 4 triglycerides	no	yes	19/1000	
Discontinuation due to adverse event	no	yes	43/1000	

25 people would need to be treated with efavirenz rather than rilpivirine to avoid 1 case of drug resistance. But this is at the expense of more laboratory adverse events and discontinuations due to adverse events.

If 1000 people were treated with efavirenz rather than rilpivirine, there would be 40 fewer cases of drug resistance, but 67 more grade 3 or 4 laboratory adverse events and 43 more discontinuations due to adverse events.

C Raltegravir versus efavirenz

Two randomised trials were found comparing raltegravir versus efavirenz:

- STARTMRK
 - Lennox, J. L., E. DeJesus, et al. (2009). "Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial." *Lancet***374**(9692): 796-806.
 - Lennox, J. L., E. DeJesus, et al. (2010). "Raltegravir versus Efavirenz regimens in treatment-naive HIV-1-infected patients: 96-week efficacy, durability, subgroup, safety, and metabolic analyses." *Journal of Acquired Immune Deficiency Syndromes: JAIDS***55**(1): 39-48.
- Protocol 004
 - Markowitz, M., B.-Y. Nguyen, et al. (2009). "Sustained antiretroviral effect of raltegravir after 96 weeks of combination therapy in treatment-naive patients with HIV-1 infection." *Journal of Acquired Immune Deficiency Syndromes: JAIDS***52**(3): 350-356

Reference	Study type/ quality	No. pts	Patient characteristics	Intervention	Comparison	Follow-up	Outcome measures	Funding
Lennox, J. L., E. DeJesus, et al. (2009). "Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial." <i>Lancet</i> 374 (9692): 796-806.	RCT: STARTMRK (MK-0518 Protocol 021) Allocation to treatment Random Method of randomisation : central interactive voice response system according to a computer-generated	Total N: 563 36 pts (13%) in the raltegravir gp and 50 pts (18%) in the efavirenz gp discontinued the	INCLUSION CRITERIA treatment-naive HIV-infected patients ≥18 years of age with vRNA levels >5000 copies/mL without genotypic resistance to tenofovir, emtricitabine, and/or efavirenz EXCLUSION CRITERIA renal insufficiency or acute or decompensated chronic hepatitis or any medical disorder that could possibly affect the undertaking or interpretation of the study Baseline comparability	Drug(s): raltegravir 400mg + coformulated tenofovir and emtricitabine (Truvada) n=281	Drug(s): efavirenz 600mg + coformulated tenofovir and emtricitabine (Truvada) n=282	Treatment duration: 96 weeks Assessments at: 48 and 96 weeks; clinical status was assessed at regularly scheduled visits	Primary endpoint: noninferior antiretroviral activity determined by the proportion of pts achieving vRNA levels <50 copies/mL at 48 wks Other endpoints: vRNA levels <50 copies/mL at 96 weeks, changes from baseline CD4 cell counts, pre-specified subgroup analyses based on	Merk and Co, Inc

Lennox, J. L., E. Dejesus, et al. (2010). "Raltegravir versus Efavirenz regimens in treatment-naive HIV-1-infected patients: 96-week efficacy, durability, subgroup, safety, and metabolic analyses." <i>JAIDS</i> 55(1): 39-48.	randomized allocation schedule Concealment: adequate Blinding double blinded Sample size calculation yes ITT analysis Yes Setting: Outpatients	study before week 96.	between groups: yes Age: median (range) 37 (19–67) on raltegravir and 36 (19–71) years on efavirenz Gender: 227 (81%) male on raltegravir and 231 (82%) on efavirenz Severity of disease: median (range) CD4 cell count 212 (1–620) cells/ml on raltegravir and 204 (4–807) on efavirenz			and as needed Follow-up after end of treatment: none	demographic and prognostic factors at baseline, time to virologic response, time to loss of virologic response, adverse events, lipid levels, glucose levels and body composition measurements by DEXA	
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Main outcomes:

	%* Patients (95% CI) With HIV RNA <50 copies/mL		Change‡ From Baseline CD4 cells/mm ³ (95% CI)	
	48-Week	96-Week	48-Week	96-Week
Raltegravir	241/280; 86% (82 to 90)	81% (76 to 86), n=281 [228]	189 (174 to 204), n=280	240 (220 to 259), n=281
Efavirenz	230/281; 82% (77 to 86)	79% (74 to 83), n=282 [223]	163 (148 to 178), n=281	225 (206 to 244), n=282
Difference between treatment groups	4.2 (-1.9 to 10.3), p for non-inferiority <0.001	2 (-4 to 9), p for non-inferiority <0.001	26 (4 to 47), p=0.0184	15 (-13 to 42)

*Missing data were handled by counting non-completers as failures

‡Missing data were handled by the observed-failure approach with baseline values carried forward for virologic failures.

Resistance: Week 96	Raltegravir (n=281)	Efavirenz (n=282)
Virological failure	39	45
Had both vRNA levels >400 copies/mL and available genotyping results	16/39	11/45
Resistant viruses	Raltegravir-resistant virus: 4/12 pts in the raltegravir group in which the integrase gene was amplified (1 case each showing Q148H + G140S, Q148R + G140S, Y143H + L74L/M + E92Q + T97A, Y143R); in the 3 cases	The reverse transcriptase gene could not be amplified in 2/11 pts in the efavirenz arm. 5/9 evaluable patients had efavirenz-resistant virus (1 case each showing K103N, K103N + V108I, K103K/N

with data on the reverse transcriptase gene, the viruses were sensitive to tenofovir and resistant to emtricitabine. In the 4 remaining cases where the integrase gene could not be amplified, there were 2 patients who developed resistance to emtricitabine.

+ V106V/M, K103N, K103N + V108I + P225H); the efavirenz resistant virus was emtricitabine resistant but sensitive to tenofovir in 2 cases and susceptible to both emtricitabine and tenofovir in the other 3 cases.

Other outcomes:

Time to confirmed virologic response was significantly shorter for raltegravir recipients than efavirenz recipients (P < 0.001). Time to loss of confirmed virologic response did not significantly differ by treatment arm (P = 0.276).

Adverse events

48 weeks	Clinical Adverse Events				Laboratory Adverse Events			
	Raltegravir N=281 n (%)	Efavirenz N=282 n (%)	Difference Δ (95% CI)	p	Raltegravir N=281 n (%)	Efavirenz N=282 n (%)	Difference Δ (95% CI)	p
With ≥ 1 AE	253 (90.0%)	272 (96.5%)	-6.4% (-10.9 to -2.4)	0.002	27 (9.6%)	41 (14.5%)	-4.9% (-10.4 to 0.5)	0.092
With drug-related AE [§]	124 (44.1%)	217 (77.0%)	-32.8% (-40.2 to -25.0)	<0.0001	14 (5.0%)	24 (8.5%)	-3.5% (-7.9 to 0.7)	0.130
With serious AE	28 (10.0%)	27 (9.6%)	0.4% (-4.6 to 5.4)	0.888	0	1 (0.4%)	-0.4% (-2.0 to 1.0)	1.000
With serious drug-related AE [§]	4 (1.4%)	5 (1.8%)	-0.4% (-2.8 to 2.1)	1.000	0	0	0.0% (-1.4 to 1.4)	ND
Discontinued study medications due to AE	9 (3.2%)	17 (6.0%)	-2.8% (-6.6 to 0.7)	0.159	0	1 (0.4%)	-0.4% (-2.0 to 1.0)	1.000
Discontinued due to drug-related AE [§]	3 (1.1%)	11 (3.9%)	-2.8% (-5.9 to -0.3)	ND	0	1 (0.4%)	-0.4% (-2.0 to 1.0)	ND
Discontinued due to serious AE	7 (2.5%)	4 (1.4%)	1.1% (-1.4 to 3.8)	ND	0	0	0.0% (-1.4 to 1.4)	ND
Discontinued due to serious drug-related AE [§]	1 (0.4%)	2 (0.7%)	-0.4% (-2.2 to 1.3)	ND	0	0	0.0% (-1.4 to 1.4)	ND

96 weeks	Clinical Adverse Events				Laboratory Adverse Events			
	Raltegravir N=281 n (%)	Efavirenz N=282 n (%)	Difference Δ (95% CI)	p	Raltegravir N=281 n (%)	Efavirenz N=282 n (%)	Difference Δ (95% CI)	p
With ≥ 1 AE	266 (95)	275 (98)	-3 (-6 to 0.4)	0.086	36 (13)	59 (21)	-8 (-14 to -1.9)	0.013
With drug-related AE [§]	132 (47)	220 (78)	-31 (-38 to -23)	<0.001	19 (7)	35 (12)	-6 (-11 to -1)	0.031
With serious AE	40 (14)	34 (12)	2 (-4 to 8)	0.457	0 (0)	2 (1)	-1 (-3 to 1)	0.499
With serious drug-related AE [§]	6 (2)	5 (2)	0.4 (-2 to 3)	0.772	0 (0)	12 (0.4)	-0.4 (-2 to 1)	1.000
Discontinued study medications due to AE	11 (4)	17 (6)	-2 (-6 to 2)	0.333	0 (0)	3 (1)	-1 (-3 to 0.3)	0.249
Discontinued due to drug- related AE [§]	3 (1)	12 (4)	-3 (-6 to -1)	ND	0 (0)	2 (7)	-0.7 (-3 to 0.7)	ND
Discontinued due to serious AE	9 (3)	5 (2)	1 (-1 to 4)	ND	0 (0)	1 (0.4)	-0.4 (-2 to 1)	ND
Discontinued due to serious drug-related AE [§]	1 (0.4)	2 (0.7)	-0.4 (-2.2 to 1.3)	ND	0 (0)	1 (0.4)	-0.4 (-2 to 1)	ND
Nervous system side effects	29%	61%	-32% (-39 to - 24)	<0.001				
Depression	21 (8%)	25 (9%)						
Depression SAE	2	2						

[§]Determined by investigator to be possibly, probably, or definitely drug-related to any drug in the study regimen.

ND = not done (because the test was not prespecified in the data analysis plan).

96 weeks	Raltegravir N=281 n (%)	Efavirenz N=282 n (%)
Serious musculoskeletal AE	1 (myopathy)	0
Immune reconstitution syndromes as AE	19 (7%)	13 (5%)
New or recurrent cancers	3 (1%): Kaposi sarcoma, basal cell carcinoma, and metastatic lung cancer	11 (4%): Kaposi sarcoma (6); basal cell carcinoma (2); bone cancer, B-cell lymphoma, squamous cell carcinoma of the anus (1 each)
Death (not drug-related)	3: Kaposi sarcoma, cerebral haemorrhage, and metastatic lung cancer	0
Death (drug-related)	0	0

Most common specific drug-related (determined by investigator to be possibly, probably, or definitely related to any drug in the study regimen) clinical adverse events of moderate to severe intensity present in ≥2% of either treatment group:

	Raltegravir N=281 n (%)		Efavirenz N=282 n (%)	
	Week 48	Week 96	Week 48	Week 96
Rash: includes the MedDRA terms for unspecified, generalized, macular, and/or papular rashes (but not for allergic dermatitis, drug eruption, eczema, and skin lesion) under the category of “Skin and Subcutaneous Tissue Disorders”		0 (0.0)		19 (6.7)
Headache	11 (4%)	11 (3.9)	13 (5%)	13 (4.6)
Dizziness	4 (1%)	4 (1.4)	18 (6%)	18 (6.4)
Insomnia	10 (4%)	10 (3.6)	9 (3%)	9 (3.2)
Nausea	8 (3%)	8 (2.8)	10 (4%)	10 (3.5)
Fatigue	4 (1%)	5 (1.8)	8 (3%)	8 (2.8)
Diarrhoea	3 (1%)	3 (1.1)	8 (3%)	8 (2.8)

Grade 3/4* Laboratory Abnormalities

	Raltegravir N=281 n (%)		Efavirenz N=282 n (%)	
	Week 48	Week 96	Week 48	Week 96
Absolute neutrophil count <750 cells/mL	5 (2%)	7/281 (2.5)	3 (1%)	3/278 (1.1)
Haemoglobin <7.5 gm/dL	2 (1%)	2/281 (0.7)	2 (1%)	2/278 (0.7)
Platelet count <50,000/mL		0/276 (0.0)		1/276 (0.4)
Fasting total cholesterol >300 mg/dL		0/276 (0.0)		11/267 (4.1)
Fasting LDL-cholesterol ≥190 mg/dL	3 (1%)	3/271 (1.1)	10/280 (4%)	17/262 (6.5)
Fasting triglycerides >750 mg/dL	1 (<1%)	1/276 (0.4)	3 (1%)	4/267 (1.5)
Fasting glucose >250 mg/dL		3/274 (1.1)		0/266 (0.0)
Total bilirubin >2.5 x ULN		2/281 (0.7)		0/279 (.0)
Alkaline phosphatase >5 x ULN		0/281 (0.0)		2/279 (0.7)
Aspartate aminotransferase >5 x ULN	6 (2%)	9/281 (3.2)	5 (2%)	8/279 (2.9)
Alanine aminotransferase >5 x ULN	5 (2%)	5/281 (1.8)	6 (2%)	7/279 (2.5)

Lipoatrophy (loss of ≥20% appendicular fat)		3/37 (8%)		2/38 (5%)		
	Raltegravir N=281 n (%)	Efavirenz N=282 n (%)	p value	Raltegravir N=281 n (%)	Efavirenz N=282 n (%)	p value
	Week 48: mean (SD)			Week 96: mean (no SDs given)		
Mean change (mg/dL) in total cholesterol	0.55 (1.62)	1.82 (1.87)	<0.0001	10	38	≤0.001
Mean change (mg/dL) in HDL cholesterol	0.23 (0.47)	0.56 (0.61)	<0.0001	3	10	≤0.001
Mean change (mg/dL) in LDL cholesterol	0.33 (1.37)	0.89 (1.61)	0.0002	7	21	≤0.001
Mean change (mg/dL) in triglycerides	-0.16 (4.52)	2.08 (7.16)	<0.0001	-4	40	≤0.00
Mean change in the total cholesterol:HDL-cholesterol ratio	-0.02 (0.06)	-0.01 (0.08)	0.2924	-0.18	0.04	0.192
Mean change (mg/dL) from baseline glucose levels				2	6	0.025

Authors' conclusion

Raltegravir had noninferior antiretroviral efficacy relative to efavirenz through 96 weeks of therapy. Although raltegravir was associated with significantly fewer drug-related clinical adverse events of any intensity than efavirenz, the rates of serious clinical adverse events and discontinuations due to clinical adverse events were similar in each treatment arm. Metabolic perturbations were modest in both treatment groups. Raltegravir provides another potent and durable therapeutic option for the initial treatment of HIV-1-infected patients.

Reference	Study type/ quality	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Funding
Markowitz, M., B.-Y. Nguyen, et al. (2009). "Sustained antiretroviral effect of raltegravir after 96 weeks of combination	RCT: Protocol 004 Allocation to treatment Random Method of randomisation: not stated Concealment: not stated Blinding	Total N: 185	INCLUSION CRITERIA treatment-naive HIV-1-infected pts with plasma HIV-1 RNA levels ≥5000 copies/mL and CD4+ T-cell counts ≥100 cells/mm ³ at screening. Part I consisted of 10 days of raltegravir monotherapy in 35 pts. Part II examined the safety, tolerability, and efficacy of raltegravir dosed 100, 200, 400, or 600 mg twice daily vs efavirenz	Drug(s): raltegravir 100, 200, 400 or 600mg twice daily + tenofovir 300mg and lamivudine 300mg daily. It was previously reported that	Drug(s): efavirenz 600 mg per day + tenofovir 300mg per day and lamivudine	Treatment duration: 96 weeks Assessments at: wks 60, 72, 84 and 96	Primary endpoint: proportion of pts achieving plasma HIV-1 RNA <400 copies/ml Other endpoints: proportion of pts achieving plasma HIV-1 RNA <50	Merk & Co

<p>therapy in treatment-naive patients with HIV-1 infection." <u>JAIDS 52(3):</u> 350-356</p>	<p>double blinded</p> <p>Sample size calculation This was an estimation study only and was not powered for formal efficacy comparisons between raltegravir and efavirenz.</p> <p>ITT analysis Yes</p> <p>Setting: Outpatients</p>		<p>600 mg per day, each with tenofovir 300 mg per day and lamivudine 300 mg per day, for up to 48 weeks in 30 pts from part I (cohort I) plus 171 pts randomized into part II (cohort II). Pts who reached week 48 of the original study were given the option to continue in a double-blind extension. Pts who received any dose of raltegravir in the original study received raltegravir 400 mg twice a day in the extension phase. Pts who received efavirenz in the original study continued on efavirenz in the extension. Both open-label drugs, tenofovir and lamivudine, continued unchanged in the extension.</p> <p>EXCLUSION CRITERIA not stated</p> <p>Baseline comparability between groups: yes</p> <p>Age, gender: not stated Severity of disease: mean CD4 cell count ranged between the groups from 271 to 338 cells/ml</p>	<p>all doses of raltegravir showed generally similar efficacy and safety at wk 48 in this study; after wk 48, all pts on raltegravir received 400 mg bd so the efficacy data beyond week 48 are displayed in this current analysis as a single raltegravir gp that combines all original dose gps.</p> <p>n=150; 148 entered extension phase</p>	<p>300mg per day</p> <p>n=35; all entered extension phase</p>	<p>Follow-up after end of treatment: none</p>	<p>copies/mL change from baseline in HIV-1 RNA (log₁₀ copies/mL), and the change from baseline in CD4+ T-cell count.</p>	
<p>Main outcomes:</p>								
			<p>Raltegravir 400 mg twice a day (N =</p>	<p>Efavirenz 600 mg every day (N = 38)</p>	<p>Difference (95% CI)</p>			

	160) n (%)		n (%)		
	n/N	% (95% CI)	n/N	% (95% CI)	
HIV-1 RNA <400 copies/mL:					
Week 48	148/160	92.5 (87.3 to 96.1)	33/38	86.8 (71.9 to 95.6)	5.7 (-3.4 to 20.3)
Week 96	135/160	84.4 (77.8 to 89.6)	32/38	84.2 (68.7 to 94.0)	0.2 (-10.6 to 15.6)
HIV-1 RNA <50 copies/mL					
Week 48	137/160	85.6 (79.2 to 90.7)	33/38	86.8 (71.9 to 95.6)	-1.2 (-11.2 to 13.7)
Week 96	133/160	83.1 (76.4 to 88.6)	32/38	84.2 (68.7 to 94.0)	-1.1 (-12.0 to 14.5)
	Mean (95% CI) change from baseline		Mean (95% CI) change from baseline		
Mean change from baseline in HIV-1 RNA					
Week 48	-2.32 (-2.43 to -2.22)		-2.29 (-2.55 to -2.03)		-0.03 (-0.31 to 0.24)
Week 96	-2.30 (-2.42 to -2.19)		-2.28 (-2.57 to -2.00)		-0.02 (-0.33 to 0.29)
Change from baseline in CD4+ T-cell count					
Week 48	174 (153 to 196)		170 (125 to 215)		4 (-45 to 54)
Week 96	221 (197 to 246)		232 (180 to 285)		-11 (-69 to 47)
Virological failure/resistance					
Week 96	6/160: 3 had resistance-associated mutations in both the integrase and reverse transcriptase coding regions. The integrase mutations were N155H; L74L/M, V151I, N155H; and Y143C, S230R in the 3 pts. One additional pt who failed raltegravir developed a mutation only in the reverse transcriptase region. 2 pts had no resistance-associated mutations in either the integrase or reverse transcriptase coding regions		2/38: Both patients in whom efavirenz-based therapy failed had mutations conferring resistance to both nucleoside reverse transcriptase inhibitor and nonnucleoside reverse transcriptase inhibitor elements of their regimen.		

Other outcomes:

Week 96	Raltegravir 400 mg twice a day (N = 160) n (%)	Efavirenz 600 mg every day (N = 38) n (%)
One or more clinical adverse events	146 (91.3)	35 (92.1)

Serious clinical adverse events	16 (10.0)	3 (7.9)
Discontinued due to clinical adverse event	2 (1.3)	1 (2.6)
Drug-related* clinical adverse events†	82 (51.3)	28 (73.7)
Diarrhoea	11 (6.9)	4 (10.5)
Nausea	20 (12.5)	5 (13.2)
Vomiting	4 (2.5)	3 (7.9)
Flatulence	9 (5.6)	1 (2.6)
Dizziness	14 (8.8)	11 (28.9)
Headache	14 (8.8)	9 (23.7)
Abnormal dreams	10 (6.3)	7 (18.4)
Insomnia	13 (8.1)	4 (10.5)
Nightmares	0 (0.0)	4 (10.5)
Fatigue	8 (5.0)	2 (5.3)
Malaise	2 (1.3)	3 (7.9)
Anxiety	2 (1.3)	2 (5.3)
Lethargy	2 (1.3)	2 (5.3)
Disturbance in attention	1 (0.6)	2 (5.3)
One or more laboratory adverse events	38 (23.8)	11 (28.9)
Discontinued due to laboratory adverse event	1 (0.6)	0 (0.0)
Drug-related* laboratory adverse events†	19 (11.9)	3 (7.9)
Aspartate aminotransferase increased	7 (4.4)	2 (5.3)
Alanine aminotransferase increased	6 (3.8)	2 (5.3)

*Determined by investigator to be possibly, probably, or definitely related to any drug in the study regimen.

† Specific events occurring in at least 5% of patients in 1 or more treatment groups

Grade 3/4† Abnormalities for Prespecified Laboratory Tests

Week 96	Raltegravir 400 mg twice a day (N = 160) n (%)	Efavirenz 600 mg every day (N = 38) n (%)
Absolute neutrophil count <750 cells/mL	1 (0.6)	0 (0.0)
Haemoglobin <7.5 gm/dL	0	0
Platelet count <50,000/mL	0	0
Fasting total cholesterol >300 mg/dL	0 (0.0)	2 (5.3)
Fasting LDL-cholesterol ≥190 mg/dL	1 (0.6)	2 (5.3)

Fasting triglycerides >750 mg/dL	0 (0.0)	3 (7.9)
Fasting glucose >250 mg/dL	0	0
Total bilirubin >2.5 x ULN	0	0
Alkaline phosphatase >5 x ULN	1 (0.6)	0 (0.0)
Aspartate aminotransferase >5 x ULN	4 (2.5)	1 (2.6)
Alanine aminotransferase >5 x ULN	2 (1.3)	2 (5.3)
Creatinine	0	0
Pancreatic amylase >2 x ULN	4 (2.5)	0 (0.0)
Lipase >3 x ULN	2 (1.3)	0 (0.0)
Creatine kinase \geq 10 x ULN	10 (6.3)	1 (2.6)

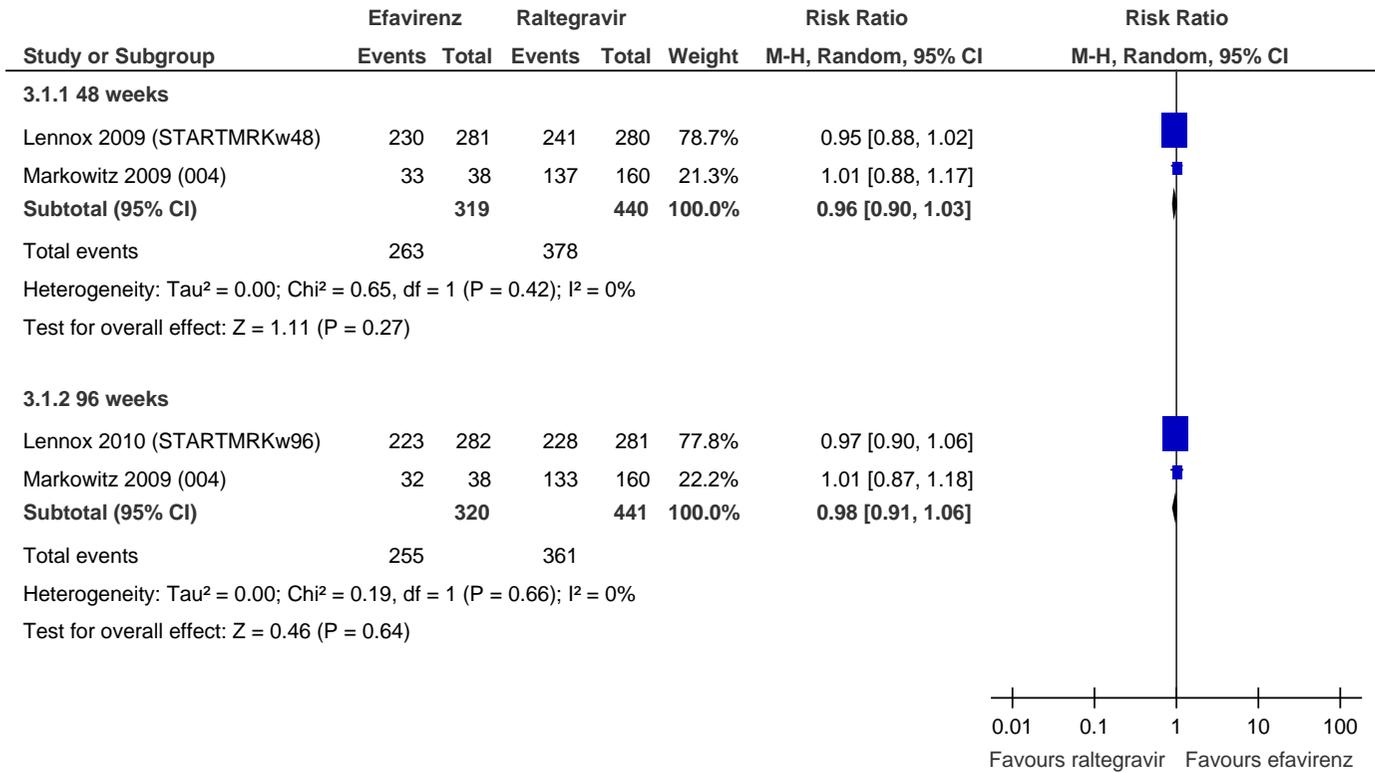
	Raltegravir N=160 n (%)	Efavirenz N=38 n (%)	p value
Mean change (mg/dL) in total cholesterol			
Week 48	-2.3	+20.7	<0.001
Week 96	+1.1	+24.0	0.002
Mean change (mg/dL) in HDL cholesterol			
Week 48	+4.8	+9.8	0.010
Week 96	+7.4	+13.0	0.017
Mean change (mg/dL) in LDL cholesterol			
Week 48	-7.5	+3.0	0.016
Week 96	-5.8	+4.4	0.045
Mean change (mg/dL) in triglycerides			
Week 48	-1.0	+49.5	0.068
Week 96	-10.8	+13.4	0.145
Mean change in the total cholesterol:HDL-cholesterol ratio			
Week 48	-0.6	-0.5	0.530
Week 96	-0.7	-0.7	0.689

Authors' conclusion

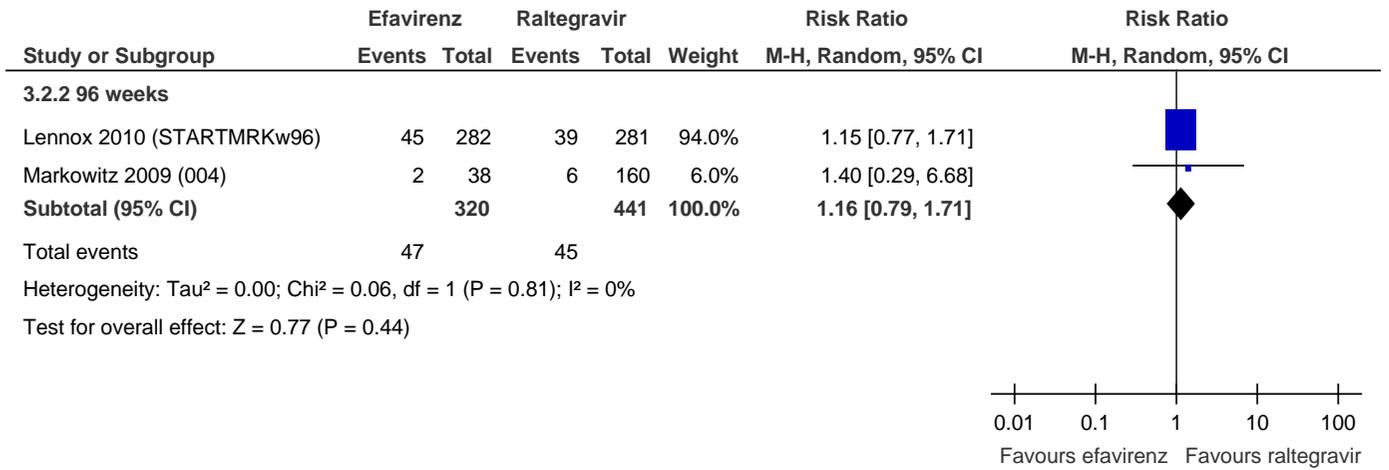
Raltegravir 400 mg twice daily in combination with 2 nucleoside reverse transcriptase inhibitors has demonstrated potent durable efficacy similar to that of an efavirenz-based regimen and has been generally well tolerated.

Forest plots for raltegravir versus efavirenz

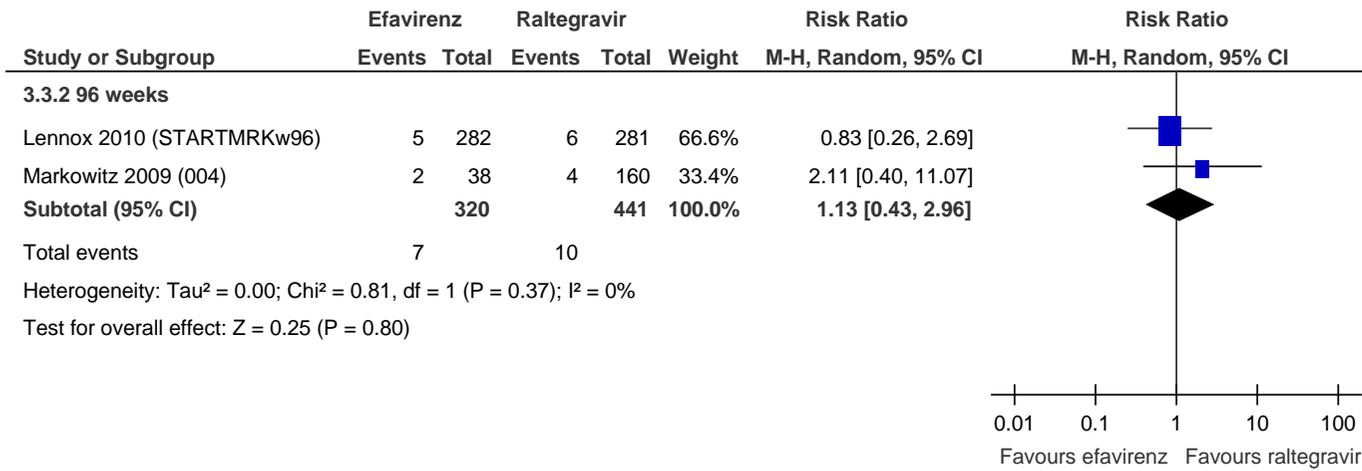
Viral suppression <50 copies/mL.



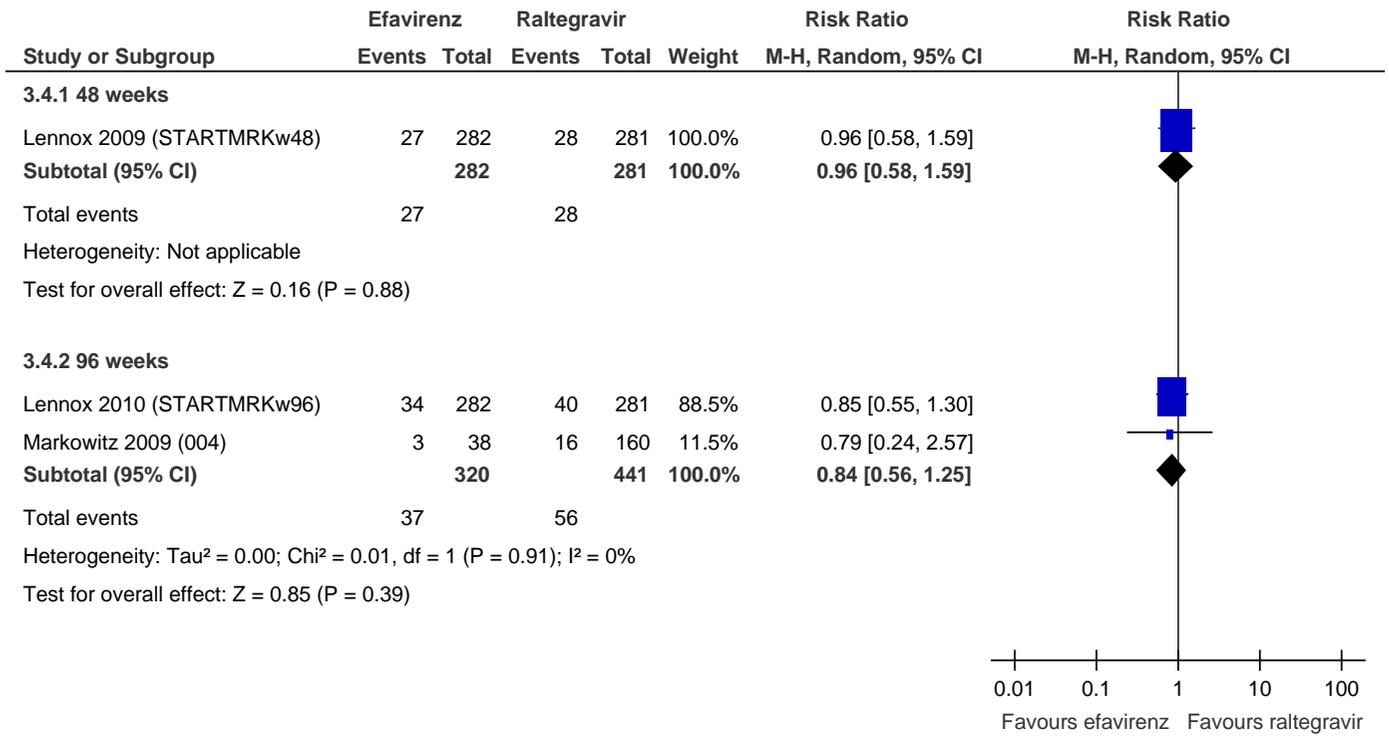
Virological failure.



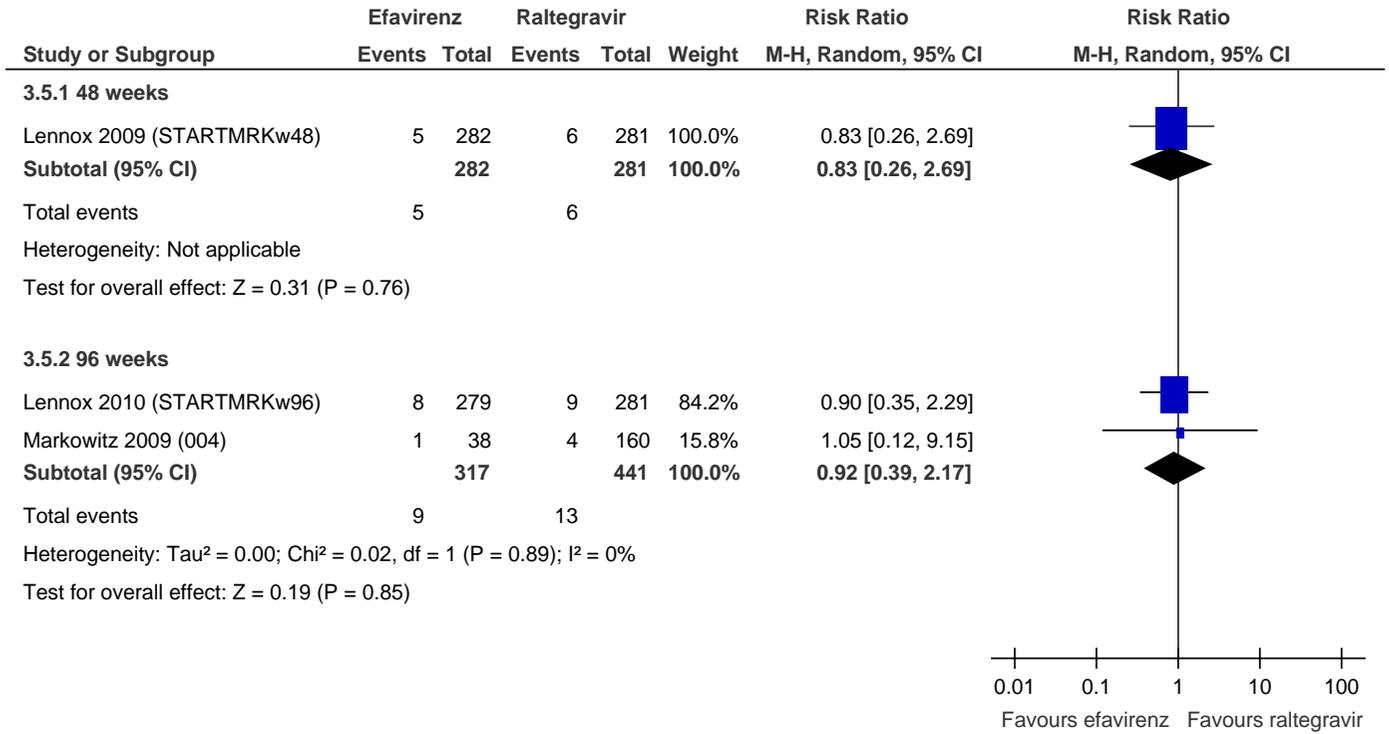
Drug resistance.



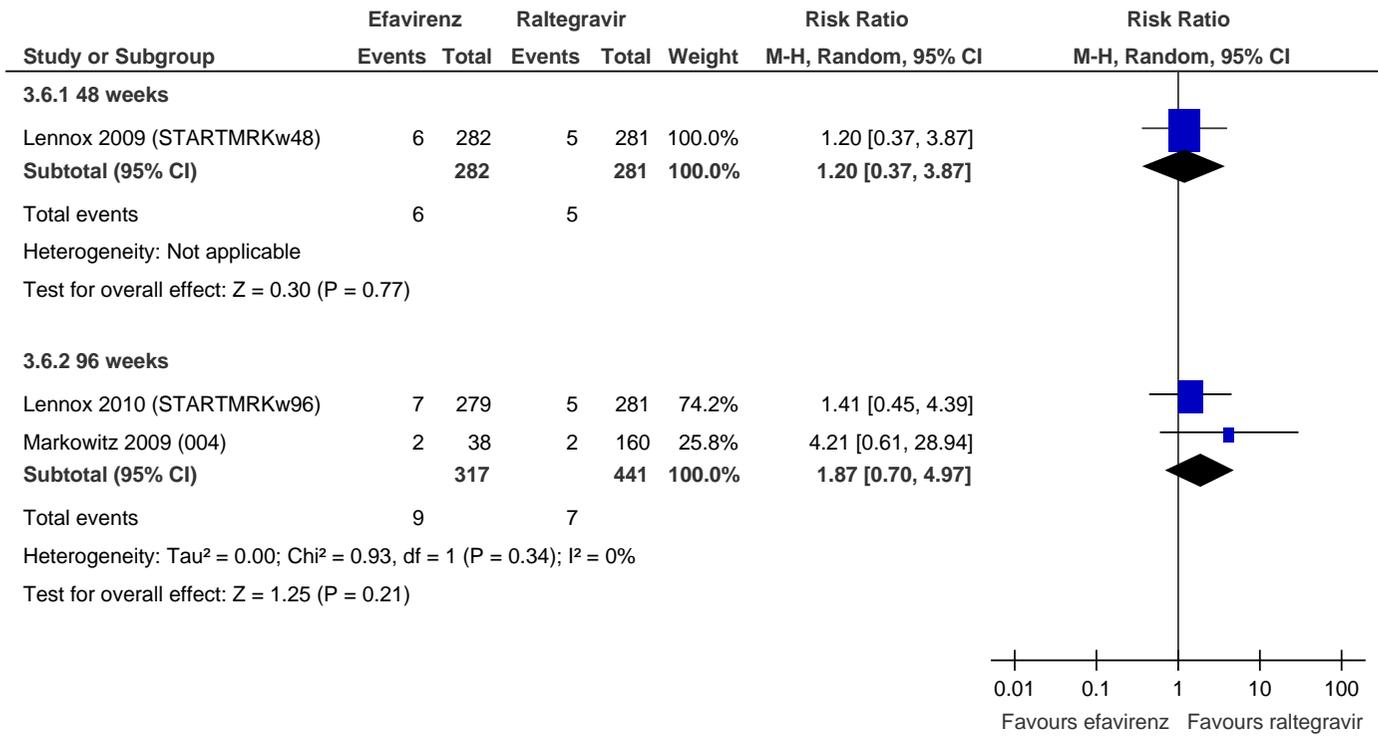
Serious adverse event.



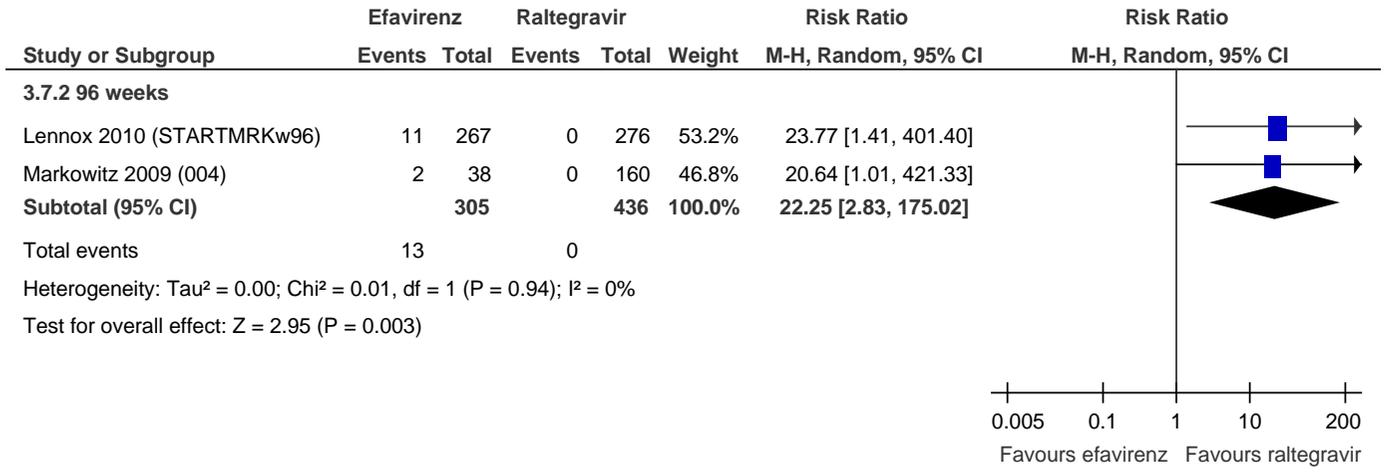
Grade 3 or 4 AST elevation.



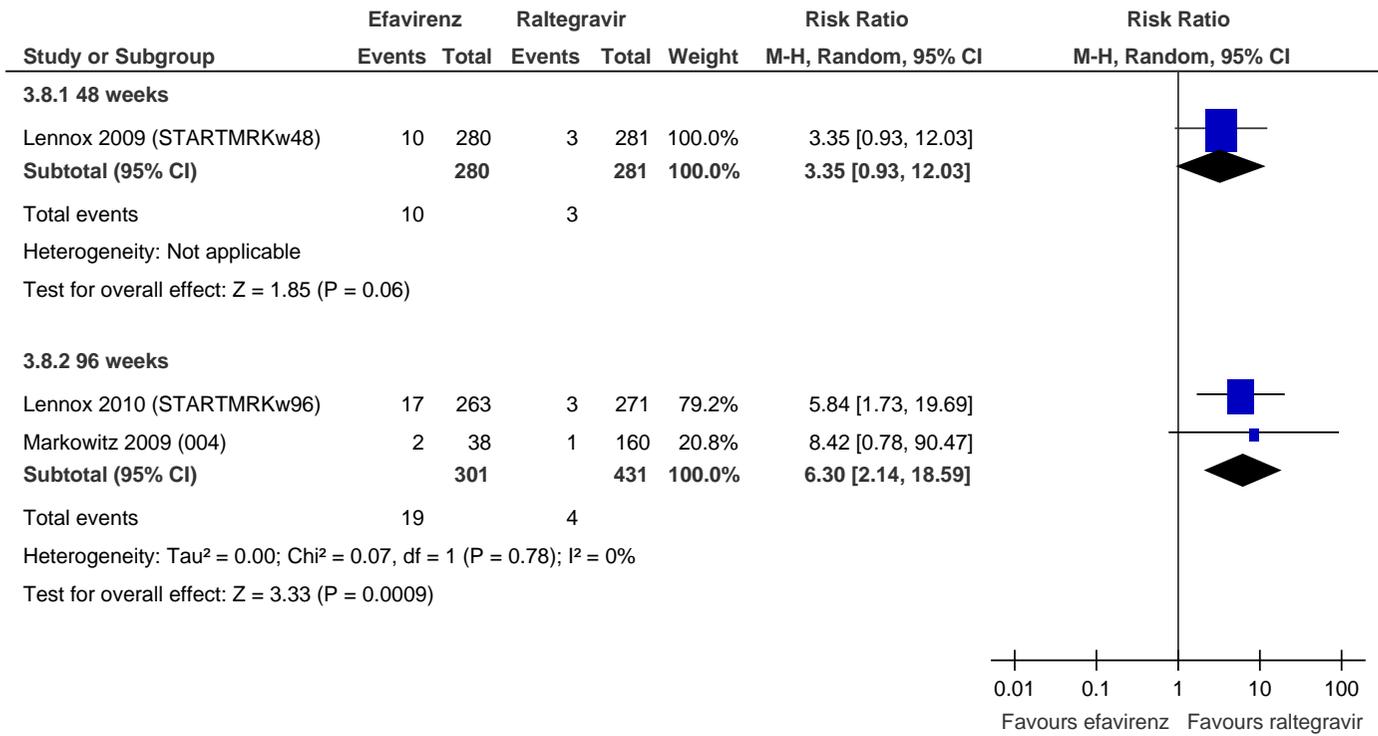
Grade 3 or 4 ALT elevation.



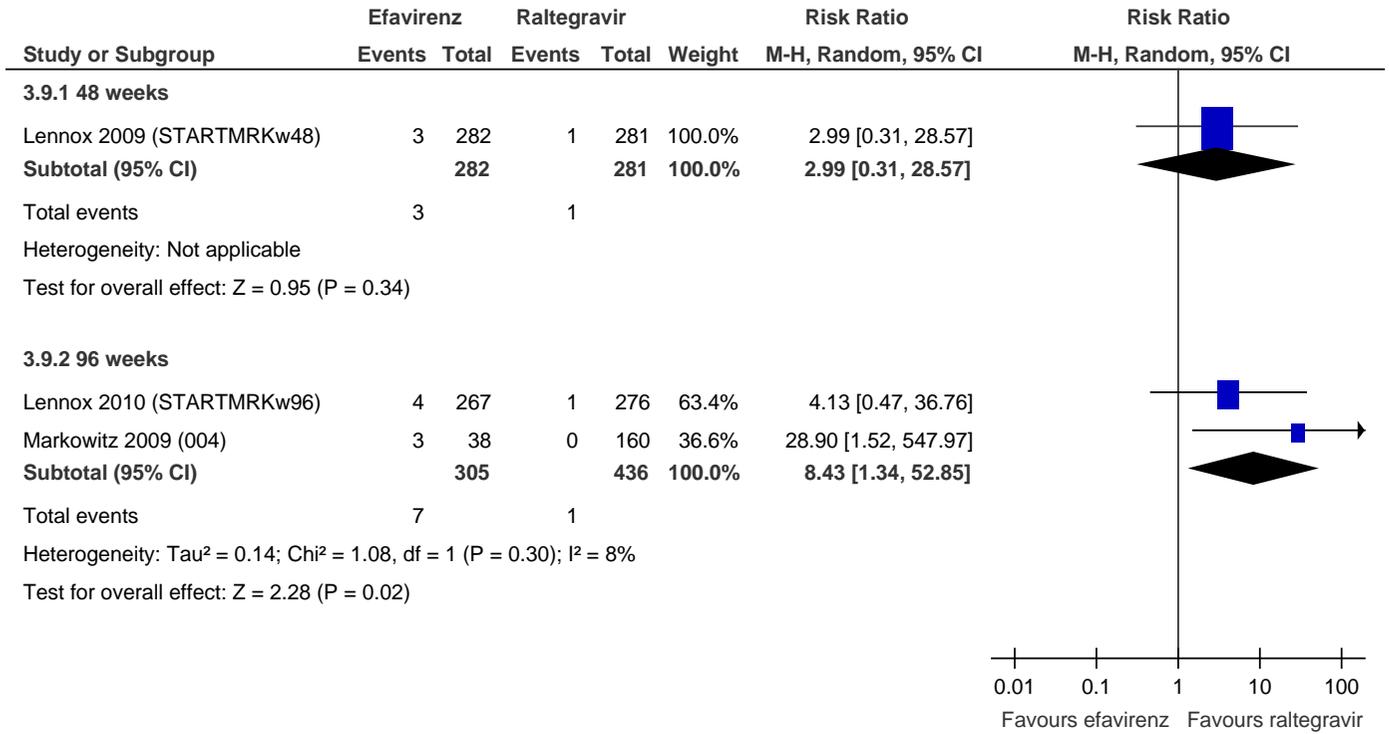
Grade 3 or 4 total cholesterol.



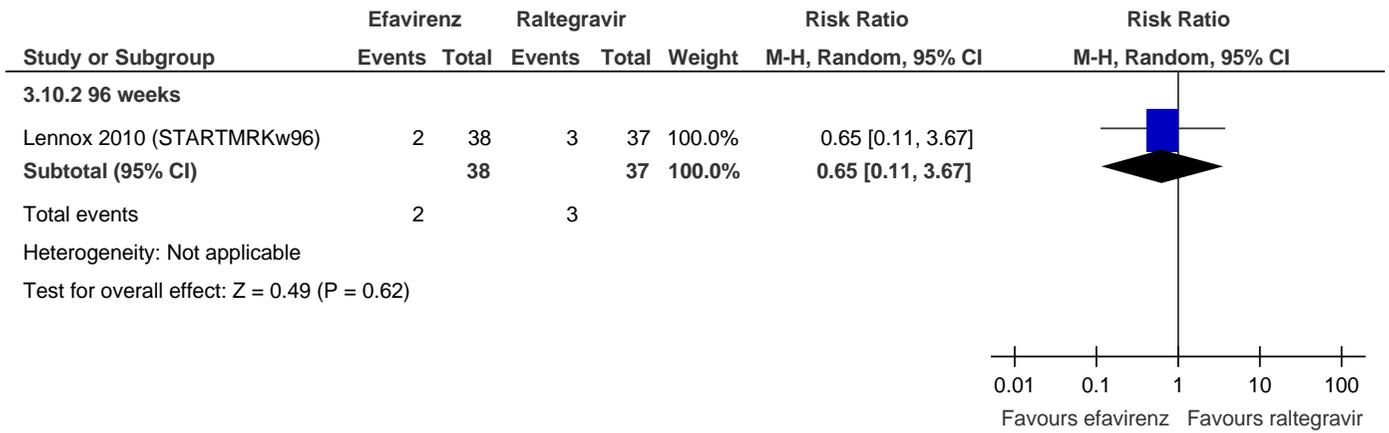
Grade 3 or 4 LDL cholesterol.



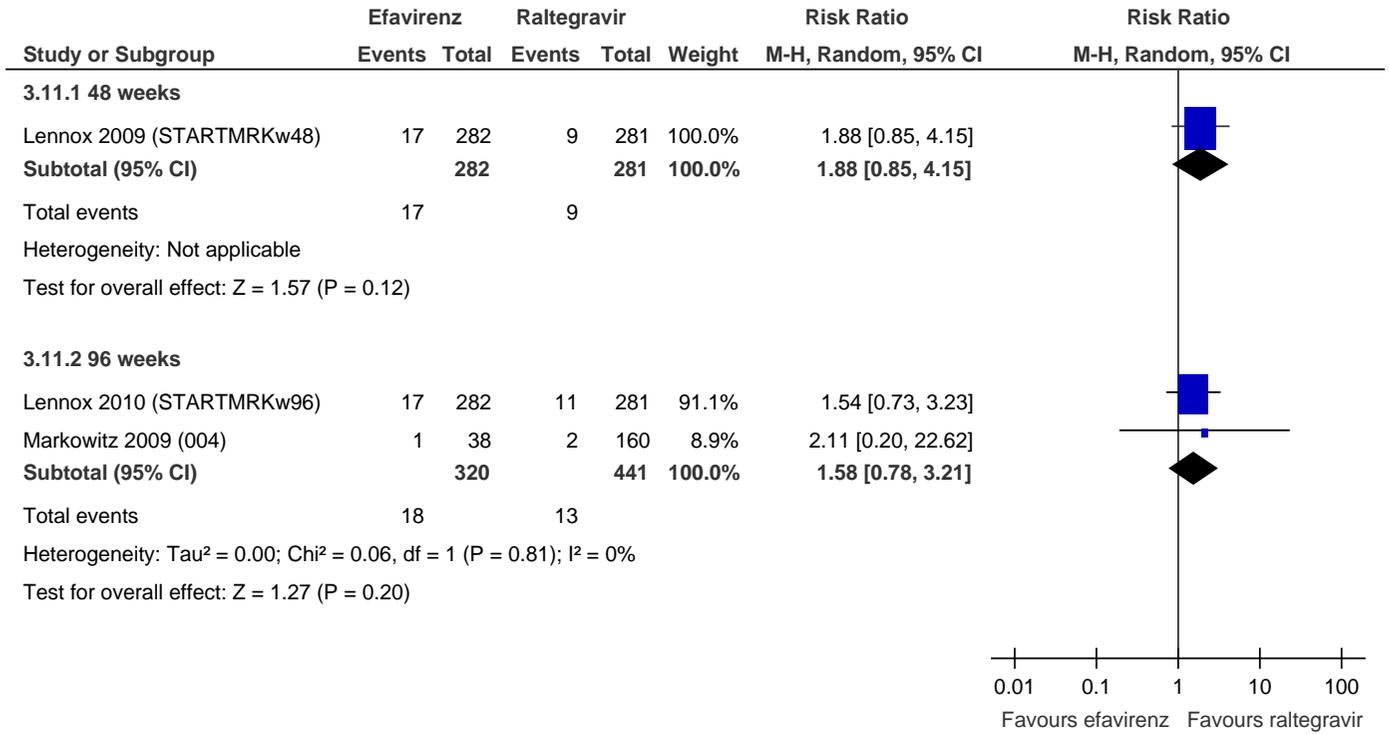
Grade 3 or 4 triglycerides.



Lipoatrophy (loss of 20% or more appendicular fat).



Discontinued due to adverse events.



NNT/NNH table for raltegravir versus efavirenz

Efavirenz and raltegravir were **equally effective** (outcomes of viral suppression, virological failure).

The only significant differences between the drugs were for the following *safety* outcomes:

	Efavirenz better	raltegravir better	ARR	NNT
Grade 3/4 total cholesterol	no	yes	cannot be calculated as raltegravir had no events	cannot be calculated as raltegravir had no events
Grade 3/4 LDL cholesterol	no	yes	49/1000	20
Grade 3 or 4 triglycerides	no	yes	17/1000	

20 people would need to be treated with raltegravir rather than efavirenz to avoid 1 case of Grade 3/4 LDL cholesterol

D Darunavir versus efavirenz

No randomised trials were found comparing darunavir versus efavirenz directly, so an indirect comparison was suggested using a) darunavir versus lopinavir/r and b) lopinavir/r versus efavirenz. This indirect comparison is only valid if there is little heterogeneity between the studies included in the two parts of the comparison.

a) darunavir versus lopinavir/r

One randomised trial was found comparing darunavir versus lopinavir/r:

- ARTEMIS
 - Ortiz, R., E. Dejesus, et al. (2008). "Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naive HIV-1-infected patients at week 48." AIDS**22**(12): 1389-1397.
 - Mills, A. M., M. Nelson, et al. (2009). "Once-daily darunavir/ritonavir vs. lopinavir/ritonavir in treatment-naive, HIV-1-infected patients: 96-week analysis." AIDS**23**(13): 1679-1688.
 - Nelson, M., P.-M. Girard, et al. (2010). "Suboptimal adherence to darunavir/ritonavir has minimal effect on efficacy compared with lopinavir/ritonavir in treatment-naive, HIV-infected patients: 96 week ARTEMIS data." Journal of Antimicrobial Chemotherapy**65**(7): 1505-1509.

b) lopinavir/r versus efavirenz

Three randomised trials were found comparing lopinavir/r versus efavirenz:

- LAKE
 - Echeverria, P., E. Negredo, et al. (2010). "Similar antiviral efficacy and tolerability between efavirenz and lopinavir/ritonavir, administered with abacavir/lamivudine (Kivexa), in antiretroviral-naive patients: a 48-week, multicentre, randomized study (Lake Study)." Antiviral Research**85**(2): 403-408.
- NCT00162643
 - Sierra-Madero, J., A. Villasis-Keever, et al. (2010). "Prospective, randomized, open label trial of Efavirenzvs Lopinavir/Ritonavir in HIV+ treatment-naive subjects with CD4+<200 cell/mm3 in Mexico." Journal of Acquired Immune Deficiency Syndromes: JAIDS**53**(5): 582-588
- ACTG5142:

- Riddler SA NEJM 2008, 358(20): 2095-106
- Stein, J. H., L. Komarow, et al. (2008). "Lipoprotein changes in HIV-infected antiretroviral-naive individuals after starting antiretroviral therapy: ACTG Study A5152s." Journal of Clinical Lipidology 2(6): 464-471.

Examples of factors that might cause heterogeneity of comparative treatment effects

A. Different quality or methods of randomized trials	<ul style="list-style-type: none"> i. Adequate concealment of randomisation ii. Blinding iii. Duration of follow-up iv. Loss to follow-up v. Cross-over
B. Confounding factors in relation to participant populations	<ul style="list-style-type: none"> i. Age ii. Sex iii. Genetic variation iv. Diagnostic workup v. Intensity of surveillance vi. Severity of pathology vii. Physiological reserve viii. Stage or duration of disease ix. Prior therapy x. Co-existing disease xi. Background therapy of concomitant treatments/advances in standard of care
C. Confounding factors in relation to circumstances	<ul style="list-style-type: none"> i. Health systems ii. Geography iii. Setting in hospital or ambulatory care iv. Date of trials
D. Different treatment (common reference and interventions)	<ul style="list-style-type: none"> i. Dose ii. Duration iii. Timing
E. Different outcome measures and methods of statistical analysis	<ul style="list-style-type: none"> i. Definition ii. Rating instrument iii. Frequency of measurement iv. Start point of measurement against duration or progression of disease or treatment, especially in time-to-event analyses

Reference	Ortiz 2008, Mills 2009, Nelson 2010	Echeverria 2010	Sierra-Madero 2010	Riddler 2008, Stein 2008	Comparability?
Name of study	ARTEMIS	LAKE	MEXICO	ACTG 5142	-
A. Different quality or methods of randomized trials					
i. Adequate concealment of randomisation	yes	not stated	yes	not stated	Probably OK
ii. Blinding	no – open label	no	no	no	OK
iii. Duration of follow-up	192 weeks of treatment	48 weeks of treatment	48 weeks of treatment	median follow-up was 112 weeks	Large variation from 48-192 weeks
iv. Loss to follow-up a) did not receive therapy; b) withdrawals (including insufficient efficacy, toxicity, adverse events, death) c) lost	total: 17% darunavir and 23% lopinavir; a) 3/343 pts (1%) + 0/346 pts; b) 41/343 (11%) + 70/346 (20%); c) 18/343 (5%) + 11/346 (3%)	a) none; b) 16/63 (25%) efavirenz and 9/63 (14%) lopinavir; c) 2/63 (3%) efavirenz and 14/63 (22%) lopinavir	a) none; b) 12/95 (13%) efavirenz and 28/94 (30%) lopinavir; c) 15/95 (16%) efavirenz and 11/94 (12%) lopinavir	a) none; b) 118/573 (21%): 19 died, 56 unable to attend clinic visits, 26 unwilling to adhere to the protocol, 17 other reasons; c) 46/573 (8%) could not be contacted	All studies should be viewed with caution because of the large (>20%) numbers of losses/ dropouts
v. Cross-over	none	none	none	none	OK
B. Confounding factors in relation to participant populations					
i. Age	mean 35.5 years on darunavir and 35.3 on lopinavir	mean 39 (±8.45) years efavirenz and 37(±9.41) lopinavir	median (IQR) 35 (29, 42) years	median 38 years	OK
ii. Sex	239/343 (70%) male on darunavir and 241/346 (70%) on lopinavir	86% male on efavirenz and 86.8% on lopinavir	161/189 (85%) male	80% male	OK
iii. Genetic variation	Black 80 (23%) darunavir and 71 (21%) lopinavir; Caucasian 137 (40%) and 153 (44%); Hispanic 77 (22%) and 77 (22%); Oriental/Asian 44 (13%) and 38 (11%); Other 4 (1%) and 5 (1%);	Race not stated	Race not stated	White 274 (36%); Black 314 (42%); Hispanic 146 (19%); Asian 15 (2%); Other or unknown 4 (1%)	unclear if comparable or not

Reference	Ortiz 2008, Mills 2009, Nelson 2010	Echeverria 2010	Sierra-Madero 2010	Riddler 2008, Stein 2008	Comparability?
	Missing 1 (1%) and 2 (1%)				
iv. Diagnostic workup	tested for clinical or laboratory evidence of significantly decreased hepatic function or decompensation; grade 3 or 4 laboratory abnormalities	HLAB* 5701 test was not determined at baseline (genetic test was not easily available at that time).	opportunistic infection excluded or treated	Genotyping for resistance to HIV-1 drugs was performed during screening	Difference diagnostic procedures prior to studies
v. Intensity of surveillance	Assessments at 2 wks, then every 4 wks until wk 16, at wk 24, and every 12 wks until wk 192	wk 4 and every 3 mo thereafter until wk 48	entry and at wks 4, 8, 16, 24, 32, and 48	entry, and at wks 1, 4, 8, 12, 16, 20, and 24 and every 8 wks thereafter	varied from 4-12 weeks
vi. Stage or duration of disease	Mean (SD) duration of infection 2.4 (3.6) years on darunavir and 2.5 (3.6) on lopinavir; median CD4 cell count 225cells/ml	Median time from HIV diagnosis: 20.9±57.9 months; mean CD4 cell count 193 (±122) cells/ml on efavirenz and 191 (±127) on lopinavir	CD4+ count <200/mm ³ required as inclusion criterion: median (IQR) CD4 cell count 56 (25, 117) cells/ml	median CD4 cell count 191cells/ml	Patients in Sierra-Madero 2010 had a much lower CD4+ cell count at baseline representing much more severe disease; exclude in sensitivity analysis
vii. Prior therapy	none	none	none	none	OK
viii. Activities score	not assessed	not assessed	not assessed	not assessed	OK
ix. Background therapy of concomitant treatments/advances in standard of care	tenofovir 300mg qd and emtricitabine 200mg qd	abacavir (600mg)/ lamivudine (300mg) (Kivexa®) once daily	zidovudine/lamivudine 300/150 mg bid	NRTIs: lamivudine (Epivir) for all pts (150 mg bd or 300mg once daily) plus the choice of 1 of 3 other agents: zidovudine (Retrovir) 300mg twice daily, stavudine extended release (XR) (Zerit XR) 100mg once daily (with pts weighing <60kg receiving 75mg), or tenofovir disoproxil fumarate (DF) (Viread)	unclear if it is OK to assume that all these backbones can be treated as identical

Reference	Ortiz 2008, Mills 2009, Nelson 2010	Echeverria 2010	Sierra-Madero 2010	Riddler 2008, Stein 2008	Comparability?
				300mg once daily. The choice of the 2nd NRTI was made by the site investigator before randomization; changes in NRTI were not allowed during the study	
C. Confounding factors in relation to circumstances					
i. Geography	26 countries (including North, Central and South America, Europe, Australia, Malaysia, Singapore, South Africa, Taiwan, Thailand)	19 centres in Spain (18) and Italy (1)	10 clinical sites in 5 states of Mexico	USA	Unclear if these are sufficiently similar
ii. Setting in hospital or ambulatory care	Outpatients	Outpatients	Outpatients	Outpatients	OK
iii. Date of trials: a) Enrollment dates; b) Cutoff date for outcomes	a) from 28 September 2005 (end date not stated) b) 13 June 2007 for 48 week analysis; 8 May 2008 for 96 week analysis	a) March 2005 to March 2006 b) not stated	a) January 2005 to January 2007; b) not stated	a) January 2003 to May 2004; b) not stated	ACTG 5142 recruited earlier than the other studies – unclear if the difference is important
D. Different treatment (common reference and interventions)					
Treatment Arm 1	LOPINAVIR/RITONAVIR	LOPINAVIR/ RITONAVIR	LOPINAVIR/ RITONAVIR	LOPINAVIR/ RITONAVIR	lopinavir arms
i. Dose	800/200mg total daily dose	lopinavir (400mg, 3 capsules)/ritonavir (100mg) twice daily	400/ 100 mg [three 133/ 33.3 mg capsules (fixed-dose, soft-gel formulation) bid]	400 mg lopinavir and 100 mg of ritonavir (Kaletra capsules) bd	OK
ii. Duration	192 weeks	48 weeks	48 weeks	112 weeks	Large variation from 48-192 weeks
iii. Timing	400/100mg bid or 800/200mg daily	400/100mg bid	twice daily	twice daily	
Treatment Arm 2	DARUNAVIR/ RITONAVIR	EFAVIRENZ	EFAVIRENZ	EFAVIRENZ	Efavirenz arms
i. Dose	800/100mg daily	600 mg daily	600 mg daily	600mg daily	OK
ii. Duration	192 weeks	48 weeks	48 weeks	112 weeks	Large variation from 48-112 weeks
iii. Timing	daily	daily	daily	daily	OK

Reference	Study type/quality	No. pts	Patient characteristics	Intervention	Comparison	Follow-up	Outcome measures	Funding
<p>Ortiz R, E Dejesus et al. (2008). "Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naive HIV-1-infected patients at week 48." <i>AIDS</i> 22(12): 1389-1397.</p> <p>Mills, A. M., M. Nelson, et al. (2009). "Once-daily darunavir/ritonavir vs. lopinavir/ritonavir in treatment-naive, HIV-1-infected patients: 96-week analysis." <i>AIDS</i> 23(13): 1679-1688.</p>	<p>RCT: ARTEMIS (AntiRetroviral Therapy with TMC114 ExaMined In naive Subjects)</p> <p>Allocation to treatment Random Method of randomisation: central randomization system (interactive voice response) Concealment : adequate Blinding not blinded (open label) Sample size calculation yes</p>	<p>Total N: 689</p>	<p>INCLUSION CRITERIA treatment-naive HIV-1-infected pts aged at least 18 years, with plasma HIV-1 RNA at least 5000 copies/ml</p> <p>EXCLUSION CRITERIA active AIDS-defining illness; any clinically significant disease; clinical or laboratory evidence of significantly decreased hepatic function or decompensation; acute viral hepatitis at screening or calculated creatinine clearance <70 ml/min; primary HIV infection or pregnant or breastfeeding. Pts with grade 3 or 4 laboratory abnormalities were not eligible with some exceptions (diabetes or asymptomatic glucose, triglyceride or cholesterol elevations) unless clinical assessment identified health risks. Pts coinfecting with chronic hepatitis B or C were allowed entry if their condition was clinically stable and they did not require treatment during the study period.</p>	<p>Drug(s): DRV/r 800/100mg qd + tenofovir 300mg qd and emtricitabine 200mg qd</p> <p>ITT n=343; PP n=340</p>	<p>Drug(s): lopinavir/ritonavir (LPV/r) 800/200mg total daily dose (400/100mg bid or 800/200mg qd depending on local regulator approval and investigator or pt prefer</p>	<p>Treatment duration: 192 weeks</p> <p>Assessments at: 2 wks, then every 4 wks until wk 16, 24, and every 12 wks until wk 192</p>	<p>Primary endpoint: non-inferiority of DRV/r 800/100 mg qd as compared with LPV/r 800/200 mg total daily dose in virologic response (a confirmed plasma HIV-1 RNA <50 copies/ml by per-protocol time-to-loss of virologic response (PP-TLOVR) at 48 weeks.</p> <p>Other endpoints: other virologic and immunologic parameters over 192 weeks (including proportion of pts with HIV-1 RNA <400 copies/ml, change in HIV-1 RNA and CD4 cell count change from baseline); evaluation of safety and tolerability; and in the event of non-inferiority, testing for superiority of DRV/r over LPV/r (planned analysis).</p> <p>Nelson 2010: Self-reported treatment adherence measured using the Modified Medication Adherence Self-Report Inventory (M-MASRI) questionnaire at wks 4, 12, 24, 36, 48, 60, 72, 84 and 96. The validity of these adherence measurements was assessed by correlation with self-reported</p>	<p>Gilead donated Truvada; Tibotec BVBA supported drafting the manuscript</p>

<p>Nelson M, P-M Girard et al. (2010). "Suboptimal adherence to darunavir/ritonavir has minimal effect on efficacy compared with lopinavir/ritonavir in treatment-naive, HIV-infected patients: 96 week ARTEMIS data." <u>Journal of Antimicrobial Chemotherapy</u> 65(7): 1505-1509.</p>	<p>ITT analysis Yes Setting: Outpatients; 26 countries (including North, Central and South America, Europe, Australia, Malaysia, Singapore, South Africa, Taiwan, Thailand)</p>	<p>Baseline comparability between groups: yes Age: mean 35.5 years on darunavir and 35.3 on lopinavir Gender: 239/343 (70%) male on darunavir and 241/346 (70%) on lopinavir Race: Black 80 (23%) darunavir and 71 (21%) lopinavir; Caucasian 137 (40%) and 153 (44%); Hispanic 77 (22%) and 77 (22%); Oriental/Asian 44 (13%) and 38 (11%); Other 4 (1%) and 5 (1%); Missing 1 (1%) and 2 (1%) Severity of disease: median CD4 cell count 225cells/ml Mean (SD) duration of infection 2.4 (3.6) years on darunavir and 2.5 (3.6) on lopinavir</p>		<p>ence or both) + tenofovir 300mg qd and emtricitabine 200mg qd ITT n=346; PP n=346</p>	<p>Follow-up after end of treatment : none</p>	<p>missed doses due to symptoms or side effects of HIV infection and/or antiretroviral medication for wks 4–96, and with plasma drug concentrations (wks 4–48). Pt-perceived distress caused by symptoms and side effects and their impact on adherence was assessed by a modified version of the validated Memorial Symptom Assessment Scale-Short Form (M-MSASSF) questionnaire at baseline and at wks 4, 12, 24, 48, 72 and 96. Doses of darunavir/ ritonavir or lopinavir/ ritonavir taken during the previous 30 days were calculated at each scheduled timepoint. Rates were transformed into a binary variable [adherent (>95%) and suboptimally adherent (≤95%)]. A 95% adherence level has been reported to be required to achieve optimal efficacy with protease inhibitor (PI)-based therapy.</p>	
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Main outcomes (Ortiz 2008):

Week 48	Darunavir	Lopinavir	Estimated difference between treatment responses
Wk 48 confirmed virologic response of HIV-1 RNA <50 copies/ml in the PP population	84% of 340 = 286	78% of 346 = 270	5.6% (95% CI, -0.1 to 11): the lower limit of the 95% CI was greater than -12% (P<0.001), demonstrating noninferiority of DRV/r qd as compared with LPV/r.
Median change from baseline in	137 cells/μL	141 cells/μL	

CD4 cell count (noncompleter = failure) at wk 48			
Virologic failure (HIV-1 RNA>50 copies/ml at any time before the cutoff date)	34/340 (10%)	49/346 (14%)	
Baseline and endpoint (last available timepoint during treatment) genotypes available: resistance	10: no pts developed an International AIDS Society (IAS-USA) protease inhibitor resistance-associated mutation (RAM), while one pt developed an IAS-USA nucleoside reverse transcriptase inhibitor (NRTI) RAM (M184I/V).	18: one pt developed two additional IAS-USA protease inhibitor RAMs (A71T and V77I) and 2 pts developed an IAS-USA NRTI RAM (both M184V).	

Other outcomes: Week 48

Incidence, n (%)	DRV/r (N=343)	LPV/r (N=346)	p value
Mean treatment exposure (weeks)	54.8	53.3	
≥1 adverse event	309 (90)	328 (95)	
≥1 serious adverse event	25 (7)	41 (12)	
≥1 grade 3 or 4 adverse event	64 (19)	75 (22)	
Total discontinuations	41 (12%)	56 (16%)	
≥1 adverse event leading to permanent discontinuation	12 (3)	24 (7)	p<0.05
Discontinuation due to virologic failure	2 (<1%)	6 (2%)	
Grade 2–4 adverse events at least possibly related to study treatment reported in ≥2% of pts (excluding laboratory abnormalities reported as adverse events)			
Gastrointestinal (all adverse events)	23 (7)	47 (14)	p<0.01
Diarrhoea	14 (4)	34 (10)	p<0.01
Nausea	6 (2)	10 (3)	
Rash (all types)	9 (3)	4 (1)	
Grade 2–4 laboratory abnormalities (incidence ≥2% of patients)			
Alanine aminotransferase	29 (8)	35 (10)	
Aspartate aminotransferase	32 (9)	31 (9)	

Hyperbilirubinemia	2 (<1)	11 (3)	p<0.0001 p<0.01
Triglycerides	10 (3)	38 (11)	
Total cholesterol	44 (13)	78 (23)	
Low-density lipoprotein	44 (13)	36 (10)	
Hyperglycemia	22 (6)	23 (7)	
Pancreatic amylase	23 (7)	17 (5)	
Neutrophil count	27 (8)	10 (3)	
Serious renal adverse events	0	0	
Discontinuation due to renal event	0	0	
Death (treatment-related)	0	0	
Death (not treatment-related)	1	3	

Week 96 (Mills 2009):

	DRV/r (N=343)	LPV/r (N=346)	difference, p value
Total discontinuations n (%)	59 (17%)	81 (23%)	
AEs (including ... deaths)	13 (4%); 1 death	32 (9%); 5 deaths	
Lost to follow-up	18 (5)	11 (3)	
Withdrawal of consent	11 (3)	10 (3)	
Virological failure	3 (1)	8 (2)	
Pregnancy	6 (2)	3 (1)	
Noncompliance to study protocol	3 (1)	7 (2)	
Other	5 (1)	10 (3)	
Viral load of less than 50 copies/ml at week 96	79% (271)	71% (246)	8.4% (P<0.001; 95% CI 1.9–14.8) and the lower limit of the 95% CI was greater than -12% (P<0.001), demonstrating noninferiority of DRV/r q.d. relative to LPV/r.
median change from baseline in CD4 cell count [noncompleter = failure (NC=F)]	171	188	p=0.57
virologic failure	12% of 343 (41)	17% of 346 (59)	P=0.0437
Analysis of samples from patients with a viral load at least 50	n=31	n=46	

copies/ml and paired baseline and endpoint genotypes: major (primary) protease inhibitor resistance-associated mutations	0	0		
one or two minor IAS-USA protease inhibitor resistance-associated mutations (almost all polymorphic); all remained susceptible to all protease inhibitors.	4	7		
nucleoside analogue reverse transcriptase inhibitor (NRTI) mutation (M184I or M184V)	2	4		
K70E mutation	0	1		
≥1 serious adverse event	34 (10)	55 (16)		
Any serious AE at least possibly related to PI	3 (1)	10 (3)		
Any AE leading to withdrawal	19 (5.5)	35 (10.1)		
Grade 2–4 AEs at least possibly related to study treatment (incidence ≥2% of patients)				
Any grade 2–4 AE	80 (23)	119 (34)	p<0.001	
Gastrointestinal AE (all)	23 (7)	52 (15)		
Diarrhoea	14 (4)	38 (11)		
Nausea	6 (2)	10 (3)		
Rash (all types)	9 (3)	5 (1)		
Grade 2–4 laboratory abnormalities (incidence ≥2% of patients)				
Alanine aminotransferase	38 (11)	40 (12)	p<0.01	
Aspartate aminotransferase	39 (11)	35 (10)		
Neutrophil count	30 (9)	11 (3)		
Hyperglycemia	28 (8)	26 (8)		
Pancreatic amylase	25 (7)	18 (5)		
Alkaline phosphatase	5 (2)	5 (2)		
Partial thromboplastin time	8 (2)	9 (3)		
Pancreatic lipase	8 (1)	8 (2)		
Hyperbilirubinemia	4 (1)	17 (5)		
Prothrombin time	2 (1)	7 (2)		
Total cholesterol	60 (18)	95 (28)		
Calculated low-density lipoprotein	62 (18)	50 (15)		
Triglycerides	15 (4)	46 (13)		p<0.001

median increases in triglycerides	0.1mmol/L (8.9mg/dL); 12%	0.6mmol/l (53.4mg/dl); 50%	p<0.001
median increases in total cholesterol	0.6mmol/L (23.4mg/dL); 15%	0.9mmol/l (35.1mg/dl); 23%	p<0.001
Serious renal adverse events	0	0	
Discontinuation due to renal event	0	0	

Nelson 2010: Mean adherence was similar between groups, ranging from 97.4% to 97.9% for darunavir/ritonavir and from 96.3% to 97.7% for lopinavir/ritonavir between weeks 4 and 96. The proportion of patients with mean adherence values >95% during the study period was high: darunavir/ritonavir 83%; lopinavir/ritonavir 78%. The proportion of adherent patients over 96 weeks ranged from 81% to 90% for darunavir/ritonavir and from 74% to 89% for lopinavir/ritonavir, and no statistically significant difference between the treatment groups was observed at any timepoint. Adherence did not vary significantly over time. In a logistical regression model including both treatment effect and adherence, virological response rates were higher in adherent compared with suboptimally adherent groups [odds ratio (OR): 2.3 (1.5–3.4)]. The difference in response rate for adherent versus suboptimally adherent patients was smaller for darunavir/ritonavir (6% difference, P=0.3312) than for lopinavir/ritonavir (25% difference, P<0.0001). Overall, the virological response rate was higher with darunavir/ritonavir versus lopinavir/ritonavir [logistical regression model, OR: 1.6 (1.09–2.3)]. In suboptimally adherent patients, a significantly higher virological response rate was seen with darunavir/ritonavir [76% (42/55)] versus lopinavir/ritonavir [53% (37/70)], P<0.01. For adherent patients, virological response rates were similar in both groups: darunavir/ritonavir 82% (221/269) and lopinavir/ritonavir 78% (196/252).

Patients with <50 copies/mL (TLOVR) at week 96 (% of those completing questionnaires)	Darunavir	Lopinavir	p value for comparison between treatment groups
Adherent (>95%)	221/269 (82%)	196/252 (78%)	NS
Sub-optimally adherent (95%)	42/55 (76%)	37/70 (53%)	p<0.01
p value for comparison between adherent and sub-optimally adherent within treatment group	0.3312	p<0.0001	

Patients reporting at least one missed dose due to symptoms were more likely to self-report suboptimal adherence (Kappa coefficients ranged from 0.16 to 0.32, P<0.001, all timepoints). Selfadherence measurements (self-reported missed doses due to symptoms weeks 4–48) were also correlated with plasma drug concentrations (weeks 4–48; P<0.01). Eleven percent (4/36) of darunavir/ritonavir patients had drug concentrations below the limit of detection (10ng/mL) at week 48 versus 14% (7/49) of lopinavir/ritonavir patients. Data for adherent patients were the same in both groups: 4% (7/199 and 7/189, respectively).

Authors' conclusion

Patients receiving once-daily DRV/r achieved high durable virologic response rates had a low rate of discontinuation due to virologic failure or adverse events or both, did not develop protease inhibitor resistance upon failure, and had suitable drug exposure. These benefits, coupled with the favorable safety and pharmacokinetic profile of DRV/r, suggest that DRV/r 800/100mg qd has the potential to become a first-line, once-daily treatment option for treatment-naïve patients.

Suboptimal adherence to darunavir/ritonavir has less impact on efficacy compared with suboptimal adherence to lopinavir/ritonavir. This finding, together with darunavir's more favourable tolerability profile may help to address the adherence challenges faced by treatment-naïve HIV-1-infected patients.

Reference	Study type/ quality	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Funding
Echeverria, P, E Negro et al. (2010). "Similar antiviral efficacy and tolerability between efavirenz and lopinavir/ritonavir, administered with abacavir/lamivudine (Kivexa), in antiretroviral-naïve patients: a 48-week, multicentre, randomized study (Lake	RCT: LAKE Allocation to treatment Random Method of randomisation: not stated Concealment: not stated Blinding not blinded Sample size calculation yes ITT analysis Yes Setting: Outpatients; 19 centres in Spain	Total N: 126	INCLUSION CRITERIA HIV1 infected, aged 18 years or above, antiretroviral naïve, with no history of a recent opportunistic infection (<4 weeks) or immunomodulating agents before baseline. EXCLUSION CRITERIA Baseline comparability between groups: yes Age: mean 39 (±8.45) years efavirenz and 37(±9.41) lopinavir Gender: 86% male on efavirenz and 86.8% on lopinavir	Drug(s): efavirenz (EFV) (600 mg) + abacavir (600mg)/ lamivudine (300mg) (Kivexa®) once daily n=63	Drug(s): lopinavir (400mg, 3 capsules)/ ritonavir (100mg) twice daily plus Kivexa® once daily n=63	Treatment duration: 48 weeks Assessments at: wk 4 and every 3 months thereafter until wk 48 Follow	Primary endpoint: % of responders (i.e. pts who completed 48 wks of study with the assigned treatment and maintained a viral load <50 copies/mL) Other endpoints: % of pts who experienced a virological failure; changes in CD4 cell count at week 48; changes in lipid and hepatic parameters at wk 48 from baseline, % of pts with serious (grades III and IV) adverse events; the % of	Glaxo Smith Kline Laboratories.

Study)." Antiviral Research 85(2): 403-408.	(18) and Italy (1)		Severity of disease: mean CD4 cell count 193(±122) cells/ml on efavirenz and 191(±127) on lopinavir Median time from HIV diagnosis: 20.9±57.9 months			-up after end of treatment: none	pts who discontinued the study throughout 48 weeks of followup; time to treatment failure (time to virological failure or treatment discontinuation for any reason)	
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Main outcomes:

48 weeks	Efavirenz (n=63)	Lopinavir (n=63)	p value
Discontinued	18	23	not stated
Lost to follow up	2	14	
Protocol deviation	1	0	
Adverse events grade I-II	10	6	
Adverse events grade III-IV	4	2	
Virological failure	1 (K103N, V179E, and M184V mutations in the transcriptase gene and the L33I mutation in the protease gene)	1 (M46L and L63P mutations in the protease gene with no mutations in the transcriptase gene)	
HIV1 RNA < 50 copies/mL at week 48 in the intention to treat analysis (Missing = Failure)	56.7% (36)	63.2% (40)	0.770

Other outcomes:

48 weeks	Efavirenz (n=63)	Lopinavir (n=63)	p value
Responders (finished study and RNA < 50 copies/mL; on treatment analysis)	87% (denominator unclear)	91.3% (denominator unclear)	0.382
Time to treatment failure	40.9±2.04 weeks	43.6±1.85 weeks	0.491
Increases in CD4 cell counts	from 193 cells/mL (±122) to 491 (±244), <i>P</i> = 0.001	from 191 cells/mL (±127) to 440 (±240), <i>P</i> = 0.002	0.126
Increase in total cholesterol	from 157±35 mg/dL to 205±28, <i>P</i> = 0.001	from 149±31 mg/dL to 193±46, <i>P</i> = 0.001	
Increase in HDL cholesterol	from 39±12 mg/dL to 49±11, <i>P</i> =	no significant increase but	

	0.001	data not shown	
Clinically evident body fat changes (moderate lipodystrophy)	0	1 (0.79%)	
Death	0	0	

Authors' conclusion

This exploratory analysis suggests similar virological effectiveness for efavirenz and lopinavir/r at 48 weeks, while slightly better immunological improvement was observed with efavirenz. The higher rate of discontinuations due to adverse events in the efavirenz group was mainly attributed to a higher incidence of hypersensitivity reaction related to the simultaneous use of abacavir and efavirenz.

Reference	Study type/ quality	No. pts	Patient characteristics	Intervention	Comparison	Follow-up	Outcome measures	Funding
Sierra-Madero J, A Villasis-Keever, et al. (2010). "Prospective, randomized, open label trial of Efavirenz vs Lopinavir/Ritonavir in HIV+ treatment-naïve subjects with CD4+<200 cell/mm ³ in Mexico." <i>JAIDS</i> 53 (5):	RCT: NCT00162643 Allocation to treatment Random Method of randomisation: using a central telephone Concealment: adequate Blinding not blinded Sample size calculation not stated ITT analysis Yes	Total N: 189	INCLUSION CRITERIA infected with HIV-1, aged 18 years or older, had not received previous antiretroviral treatment, and had CD4+ count <200/mm ³ ; required to have a plasma HIV-1 RNA level of at least 1000 copies/mL, no active opportunistic infection, a haemoglobin level >7 g/dL, a platelet count >50,000/mL, and a neutrophil count >1000/mL. Pts who had an opportunistic infection were allowed to participate after specific treatment for the infection was initiated and clinical symptoms controlled EXCLUSION CRITERIA active tuberculosis or any neoplasm	Drug(s): 600 mg of efavirenz (EFV) once daily + zidovudine / lamivudine 300/150 mg bid; changes to abacavir (300mg bid) and lamivudine (150mg bid) were allowed in cases of severe	Drug(s): fixed-dose lopinavir (LPV/r) 400/100 mg [three 133/ 33.3 mg capsules (fixed-dose, soft-gel formulation) bid] + zidovudine/lamivudine 300/150 mg bid; changes to abacavir (300mg bid) and lamivudine (150mg bid)	Treatment duration: 48 wks Assessments at: entry and at wks 4, 8, 16, 24, 32, and 48 Follow-up after end of	Primary endpoint: proportion of pts with HIV-1 RNA <50 copies/mL at wk 48. Other endpoints: proportion of pts with HIV-1 RNA <400 copies/mL at wk 48; change in CD4+ cell count from baseline through wk 48; adverse events, serious adverse events, discontinuations due to adverse events and grade 3 or 4 laboratory abnormalities.	National Council for Science and Technology

582-588.	Setting: Outpatients; 10 clinical sites in 5 states of Mexico		requiring chemotherapy Baseline comparability between groups: yes Age: median (IQR) 35 (29, 42) years Gender: 161/189 (85%) male Severity of disease: median (IQR) CD4 cell count 56 (25, 117) cells/ml	anemia or gastro-intestinal intolerance attributed to zidovudine n=95	were allowed in cases of severe anemia or gastro-intestinal intolerance attributed to zidovudine n=94	treatment: none		
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Main outcomes:

Patient Disposition After 48 Weeks	EFV, N = 95, n (%)	LPV/r, N = 94, n (%)	P
Completed 48 wks	68 (71)	55 (58)	0.05
HIV-RNA <50 copies/mL	67/95 (70)	50/94 (53)	0.017
Premature discontinuation:			
Virologic failure	7 (7)	17 (18)	0.02
Lost to follow-up	15 (16)	11 (12)	0.4
Adverse events			0.1
Death	2 (2)	5 (5)	
Tuberculosis	1 (1)	2 (2)	
Other	2 (2): rash, neurological toxicity	4 (4): gastrointestinal intolerance	
No. of samples from pts who failed virologically that could be amplified for genotypic analysis (1 sample was not available and the others had a viral load below 1000 copies/ mL)	3/7: all 3 pts had resistance associated mutations (2 K103N without nucleoside mutations and 1 G190A with K65R)	5/17: 1 of 5 genotypes had a single resistance associated mutation (M184V).	

Other outcomes:

Patient Disposition After 48 Weeks	EFV, N = 95, n (%)	LPV/r, N = 94, n (%)	P
Switched from zidovudine/lamivudine to abacavir/lamivudine because of anaemia	6	8	
Median CD4+ increase from baseline	234 cells/mm ³	239 cells/mm ³	P = 0.80

Adverse events resulting in drug discontinuation	5	11	
Serious adverse events (death, hospitalization, surgery)	17 (17.8%)	21 (22.3%)	
All grades 2–4 treatment-related AEs	68	68	
Most common grades 2–4 treatment-related AEs			
Gastrointestinal	11 (16.1)	15 (22)	
CNS disorders	24 (35)*	13 (19.1)†	
Rash	3 (4.4)	2 (2.9)	
Anaemia	9 (13.2)	9 (13.2)	
Lipids disorders	14 (20.5)	22 (32.3)	
LFT disorders	5 (7.3)	6 (8.8)	
Changes in total cholesterol			NS
Changes in low-density lipoprotein			NS
Changes in high-density lipoproteins			NS
Mean change in triglycerides	+48 mg/dL	+116 mg/dL	p<0.01

*20/24 AEs in the group of EFV, were attributed to the use of EFV (4 insomnia grade 2, 4 somnolence grade 2 to 4, 7 dizziness grade 2 and 3, 3 vivid dreams, and 2 headaches grade 2).

†AEs in the group of LPV/r were nonspecific and not attributed to the use of LPV/r, according to the investigators criteria (7 headaches grade 2, 2 somnolence grade 2, 2 dysaesthesias grades 2 and 3, 1 anxiety, and 1 dizziness).

Authors' conclusion

In antiretroviral therapy-naïve, HIV-infected subjects presenting to care with a CD4+ count <200/mm³, EFV-based HAART is virologically superior to LPV/r-based HAART. EFV was also virologically superior to LPV/r among patients presenting to care with CD4+ counts <100/mm³. Further evaluation of the longterm impact of these findings is warranted. Until then, based on the information of this trial and others (ACTG 5142, Castle, Artemis) it would seem appropriate for current guidelines to recommend the use of LPV/r with caution among HIV-infected patients who present to care with very advanced disease.

Reference	Study type/ quality	No. pts	Patient characteristics	Intervention	Comparison	Follow-up	Outcome measures	Funding
Riddler SA. Class-Sparing Regimens	RCT: ACTG5142 and AIDS Clinical Trials Group (ACTG) Study	Total N: 753; subst	INCLUSION CRITERIA HIV-1-infected male and female pts at least 13 years of age who had not received previous antiretroviral	Drug(s): 600mg of efavirenz (Sustiva tablets, Bristol-Myers	Drug(s): a) 400 mg lopinavir and 100	Treatment duration: Each	Primary endpoint: time to virologic failure and the time to	National Institute

<p>for Initial Treatment of HIV-1 Infection. NEJM 2008, 358(20): 2095-106.</p> <p>Stein JH, L Komarow et al. (2008). "Lipoprotein changes in HIV-infected antiretroviral-naïve individuals after starting antiretroviral therapy: ACTG Study A5152s." <u>Journal of Clinical Lipidology</u> 2(6): 464-</p>	<p>A5152s (Stein study)</p> <p>Allocation to treatment</p> <p>Random Method of randomisation: Randomization was stratified according to a permuted-block design on the basis of three factors: the screening level of plasma HIV-1 RNA (<100,000 vs. ≥ 100,000 copies/mL), the presence or absence of chronic hepatitis infection (B, C, or both), and the choice of NRTI</p> <p>Concealment: not stated</p> <p>Blinding</p> <p>not blinded</p> <p>Sample size calculation</p> <p>yes</p>	<p>udy</p> <p>n=82</p>	<p>therapy. All pts had a plasma HIV-1 RNA level of at least 2000 copies/mL with any CD4 cell count, and acceptable laboratory results</p> <p>EXCLUSION CRITERIA Genotyping for resistance to HIV-1 drugs was performed during screening if the site investigator suspected that the patient had been infected with HIV-1 for 1 year or less. Genotyping data were reviewed by the protocol chairs and virologist, and the patient was deemed to be ineligible for the study if any evidence of resistance to a study drug was present.</p> <p>Prior use of ART, known coronary artery disease, peripheral arterial disease, cerebrovascular disease, diabetes mellitus, significant kidney disease, and current use of lipid-lowering medications, insulin-sensitizing agents, antioxidant vitamin supplements, or hormones at > replacement doses. Drug treatment of diabetes mellitus and dyslipidemia were not permitted during the study</p> <p>Baseline comparability between groups: yes</p>	<p>Squibb) once daily plus two NRTIs (efavirenz group; n=250); the NRTIs used were lamivudine (Epivir, GlaxoSmithKline) for all pts (150 mg bd or 300mg once daily) plus the choice of 1 of 3 other agents: zidovudine (Retrovir, Glaxo SmithKline) 300mg twice daily, stavudine extended release (XR) (Zerit XR, investigational agent, Bristol-Myers Squibb) 100mg once daily (with pts weighing < 60kg receiving 75 mg), or tenofovir disoproxil fumarate (DF) (Viread, Gilead Sciences) 300mg</p>	<p>mg of ritonavir (Kaletra capsules, Abbott Laboratories) twice daily plus two NRTIs as for efavirenz group (lopinavir-ritonavir group n=253), or b) 533 mg lopinavir and 133 mg of ritonavir twice daily plus 600mg of efavirenz once daily (NRTI-sparing group n=250)</p>	<p>pt was scheduled for 96 wks of follow-up after the last enrollment; median follow-up was 112 weeks</p> <p>Assessments at:</p> <p>entry, and at wks 1, 4, 8, 12, 16, 20, and 24 and every 8 wks thereafter for the duration of the study</p> <p>Follow-up after end of</p>	<p>regimen failure among the three study groups. Virologic failure was defined as a lack of suppression of plasma HIV-1 RNA by 1 log₁₀ or rebound before week 32 or a lack of suppression to <200 copies/mL or rebound after week 32. Confirmation of suspected virologic failure was required within 4 weeks. Regimen failure was defined as the first of either virologic failure or toxicity-related discontinuation of any component of the initial randomized treatment regimen.</p> <p>Other endpoints:</p>	<p>of Allergy and Infectious Diseases, National Institutes of Health.</p>
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471.	ITT analysis Yes Setting: Outpatients; USA		Age: median 38 years Gender: 602/753 (80%) male Severity of disease: median CD4 cell count 191cells/ml Race: white 274 (36%); Black 314 (42%); Hispanic 146 (19%); Asian 15 (2%); Other or unknown 4 (1%)	once daily. The choice of the 2nd NRTI was made by the site investigator before randomization; changes in NRTI were not allowed during the study		treatment: none	proportions of pts with < 200 copies/mL of plasma HIV-1 RNA; proportions of pts with <50 copies/mL of plasma HIV-1 RNA; CD4 cell count; adverse events; resistance
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Main outcomes:

589 of 753 patients (78%) completed the protocol; Of the remaining 164 patients, 19 died, 56 were unable to attend clinic visits, 26 were unwilling to adhere to the protocol, 46 could not be contacted, and 17 had other reasons. There were no significant differences among the three study groups in the reasons for loss to follow-up or the time until patients were lost to follow-up (P = 0.66).

96 weeks	Efavirenz group; n=250	Lopinavir-ritonavir group n=253	NRTI-sparing group n=250	Comparisons
Virologic failure	60/250 (24%)	94/253 (37%)	73/250 (29%)	Efavirenz gp had significantly longer time to virologic failure than lopinavir-ritonavir gp (Hazard ratio 0.63 (95% CI 0.45-0.87), P=0.006); differences between the NRTI-sparing gp and the efavirenz gp (HR 0.86 (0.61-1.21) P=0.49) or the lopinavir-ritonavir gp (HR 1.30 (0.95-1.77), P=0.13) not significant.
Regimen failure	95/250 (38%)	127/253 (50%)	108/250 (43%)	There was a trend toward a longer time to regimen failure in the efavirenz gp than in the lopinavir-ritonavir gp (HR 0.75 (95% CI 0.57-0.98), P = 0.03), but the P value did not reach the significance level of 0.014 with adjustment for multiple comparisons. Differences between the NRTI-sparing gp and the efavirenz gp (HR 0.93, 95% CI 0.70-1.23), and the

				Lopinavir-ritonavir vs. NRTI-sparing therapy (HR 1.21, 95% CI 0.93-1.56) were not significant
HIV-1 RNA <200 copies/ mL at wk 96	93% (95% CI, 88 to 96)	86% (95% CI, 80 to 91)	92% (95% CI, 87 to 96)	Efavirenz vs. lopinavir-ritonavir P = 0.04; P>0.05 for each of the other pairwise comparisons.
HIV-1 RNA <50 copies/ mL at wk 96	89% (95% CI, 84 to 93) (223/250)	77% (95% CI, 71 to 83) (195/253)	83% (95% CI, 76 to 88)	Efavirenz vs. lopinavir-ritonavir P = 0.003; P>0.05 for each of the other pairwise comparisons.
median increase in the CD4 cell count at wk 96	230 cells/mm ³ (IQR 142 to 353)	287 cells/ mm ³ (155 to 422)	273 cells/ mm ³ (176 to 419)	Changes greater in lopinavir-ritonavir gp and the NRTI-sparing gp than in the efavirenz gp (P = 0.01 for the both comparisons by the Wilcoxon rank-sum test). At wk 48, there were no significant differences among the 3 gps in the change from baseline in the CD4 cell count.
Pts who had virologic failure and ≥1 drug-resistance mutations (excluding minor protease mutation)	22 of 250 (9%)	16 of 253 (6%)	39 of 250 (16%)	P<0.05 for the comparison between the NRTI-sparing group and both the efavirenz group and the lopinavir-ritonavir groups
NRTI-associated mutation M184V K65R	14 (30) 8 (17) 3 (7)	15 (19) 13 (17) 0	6 (11) 1 (2) 0	Ef vs. NRTI-sp: 0.02 Ef vs. NRTI-sp: 0.01; NRTI-sp vs. lop p<0.01 Lop vs. ef 0.05
Thymidine analogue-associated mutation (41L, 67N, 70R, 210W, 215Y/F, and 219Q/E were evaluated)	2 (4)	1 (1)	2 (4)	NS
NNRTI-associated mutation K103N	20 (43) 11 (24)	2 (3) 0	37 (66) 31 (55)	Ef vs. NRTI-sp: 0.03; lop vs. ef <0.001; NRTI-sp vs. lop <0.001 Ef vs. NRTI-sp: 0.002; lop vs. ef <0.001; NRTI-sp vs. lop <0.001
Any protease mutation	39 (85)	61 (78)	45 (80)	NS
Major protease mutation(30N, 32I, 33F, 46I, 47A/V, 48V, 50L/V, 82A/F/L/S/T, 84V, and 90M were evaluated)	0	0	2 (4)	NS
Mutation associated with two drug classes (only major	12 (26)	1 (1)	4 (7)	Ef vs. NRTI-sp: 0.01; Lop vs. ef <0.001; NRTI-sp vs. lop NS

protease mutations)				
Other outcomes:				
Treatment-limiting events, as Adverse events are those that occurred in 3% or more of patients in any study group. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129.				
Event n (%)	Efavirenz group; n=250	Lopinavir–ritonavir group n=253	NRTI-sparing group n=250	
Treatment-limiting event (determined by the site investigator; defined as those occurring in ≥2% pts in any study group)				
Pain or discomfort	10 (4)	5 (2)	3 (1)	
Fasting triglycerides*	0	4 (2)	11 (4)	
Macules, papules, or rash**	6 (2)	0	3 (1)	
Nausea	3 (1)	7 (3)	3 (1)	
Grade 3 or 4 clinical event				
Any new sign or symptom	42 (17)	46 (18)	43 (17)	
Pain or discomfort	14 (6)	14 (6)	19 (8)	
Diarrhoea or loose stool**	1 (<1)	8 (3)	7 (3)	
Nausea	7 (3)	4 (2)	8 (3)	
Macules, papules, or rash	6 (2)	2 (1)	7 (3)	
Headache	6 (2)	9 (4)	2 (1)	
Grade 3 or 4 laboratory abnormality				
Any abnormality* §	72 (29)	80 (32)	107 (43)	
Creatine kinase >5 times ULN	8 (3)	8 (3)	14 (6)	
Absolute neutrophil count <750/mm ³	11 (4)	18 (7)	12 (5)	
Fasting LDL cholesterol >190 mg/dl§	7 (3)	2 (1)	14 (6)	
Fasting triglycerides >750 mg/dl* ** §	6 (2)	16 (6)	34 (14)	
Aspartate aminotransferase, alanine aminotransferase or both >5 times ULN *	10 (4)	16 (6)	21 (8)	
Lipase >2 times ULN **	22 (9)	11 (4)	12 (5)	
Clinical lipoatrophy any grade *	8 (3)	3 (1)	0	
Deaths probably associated with a study drug	0	0	1 (hepato-toxicity)	

Median increase in limb fat as seen on DEXA from baseline to week 96 (P≤0.01 for each of the three pairwise comparisons)	0.05 kg	0.7 kg	1.15 kg
One or more new or recurrent conditions that define the presence of the acquired immunodeficiency syndrome (AIDS); differences were not significant	9/250 (4%)	16/253 (6%)	15/250 (6%)

*P<0.05 for the pairwise comparison between the efavirenz group and the NRTI-sparing group, with no adjustment for multiple testing

** P<0.05 for the pairwise comparison between the efavirenz group and the lopinavir-ritonavir group, with no adjustment for multiple testing.

§ P<0.05 for the pairwise comparison between the lopinavir-ritonavir group and the NRTI-sparing group, with no adjustment for multiple testing.

Stein 2008 substudy:

Changes in Lipids and Lipoproteins after 24 weeks of Antiretroviral Therapy: median (interquartile range)

	All	NRTIs + Efavirenz (PI-Sparing)	NRTIs + Lopinavir/ritonavir (NNRTI-Sparing)	Efavirenz + Lopinavir/ritonavir (NRTI-Sparing)	P _{KW} (Kruskal-Wallis) comparing all groups
Lipids					
Total cholesterol, mg/dL	27* (8 – 67)	18* (3 – 29)	21* (6 – 57)	65* (32 – 108)	<0.001
Triglycerides, mg/dL	44* (-4 – 126)	22 (-49 – 79)	72* (-1 – 186)	83* (11 – 164)	0.051
Direct LDL cholesterol, mg/dL	10* (-3 – 31)	6 (-5 – 24)	7 (-8 – 19)	26* (11 – 54)	<0.001
HDL cholesterol, mg/dL	9*(2 – 14)	9* (5 – 15)	3# (-1 – 13)	11* (7 – 17)	0.053
Total/HDL cholesterol ratio	-0.28 (-0.75 – 0.88)	-0.58* (-1.64 – -0.02)	0.02 (-0.99 – 1.29)	0.01 (-0.51 – 1.43)	0.017
Lipoproteins					
VLDL particles, nmol/L	29.6*(1.2 - 60.4)	13 (-16.6 - 33.4)	26.3* (2.8 - 60.3)	48.3* (14.2 - 84.4)	0.022
Large VLDL particles, nmol/L	1.1*(-0.2 - 6.7)	0.3 (-0.7 - 2.2)	3.2* (0.0 - 10.3)	1.2* (-0.1 - 11.3)	0.063
VLDL size, nm	3.2# (-5.2 - 11.1)	-0.2 (-5.2 - 7.4)	5.4# (-1.8 - 12.3)	2.6 (-10.4 - 12.4)	0.372
IDL particles, nmol/L	2 (-28 - 40)	-3 (-28 - 11)	-8 (-39 - 36)	18# (-5 - 76)	0.036
LDL particles, nmol/L	152* (-49 - 407)	64 (-65 - 167)	135# (-115 - 312)	414* (120 - 740)	0.003
Small LDL particles, nmol/L	130* (-98 - 417)	101 (-162 - 207)	127 (-162 - 357)	371* (-9 - 720)	0.039
LDL size, nm	-0.1 (-0.5 - 0.4)	0 (-0.3 - 0.6)	-0.1 (-0.6 - 0.4)	-0.3 (-0.5 - 0.1)	0.134
Lipoprotein (a), mg/ dL	5* (0-33)	3# (0-20)	4* (0 – 28)	7* (2 – 41)	0.309
HDL particles, μmol/L	6.0* (2.8 - 10.4)	5.3* (2.4 - 9.3)	5.1* (1.6 - 9.7)	8.3* (5.9 - 10.8)	0.069
Large HDL particles, μmol/L	0.5* (-0.9 - 2.8)	1.1 (-0.5 - 2.5)	0.1 (-1.1 - 2.6)	1.3# (-0.8 - 3.0)	0.663
HDL size, nm	0.1 (-0.2 - 0.3)	0.1 (-0.1 - 0.3)	0 (-0.2 - 0.4)	0.1 (-0.2 - 0.4)	0.799

Increase in BMI, kg/m ²	0.5 (-0.5 – +1.9)				similar in each arm; pKW=0.68
Waist circumference, cm	1.0 (-1.80 – 4.0)				0.910
Increases in glucose levels		+4 (0 – +9), p<0.05 from baseline	not stated	+5 (-3 – +12), p<0.05 from baseline	0.04

* p<0.01 compared to baseline, Wilcoxon signed rank probability test

0.01≤p<0.05 compared to baseline, Wilcoxon signed rank probability test

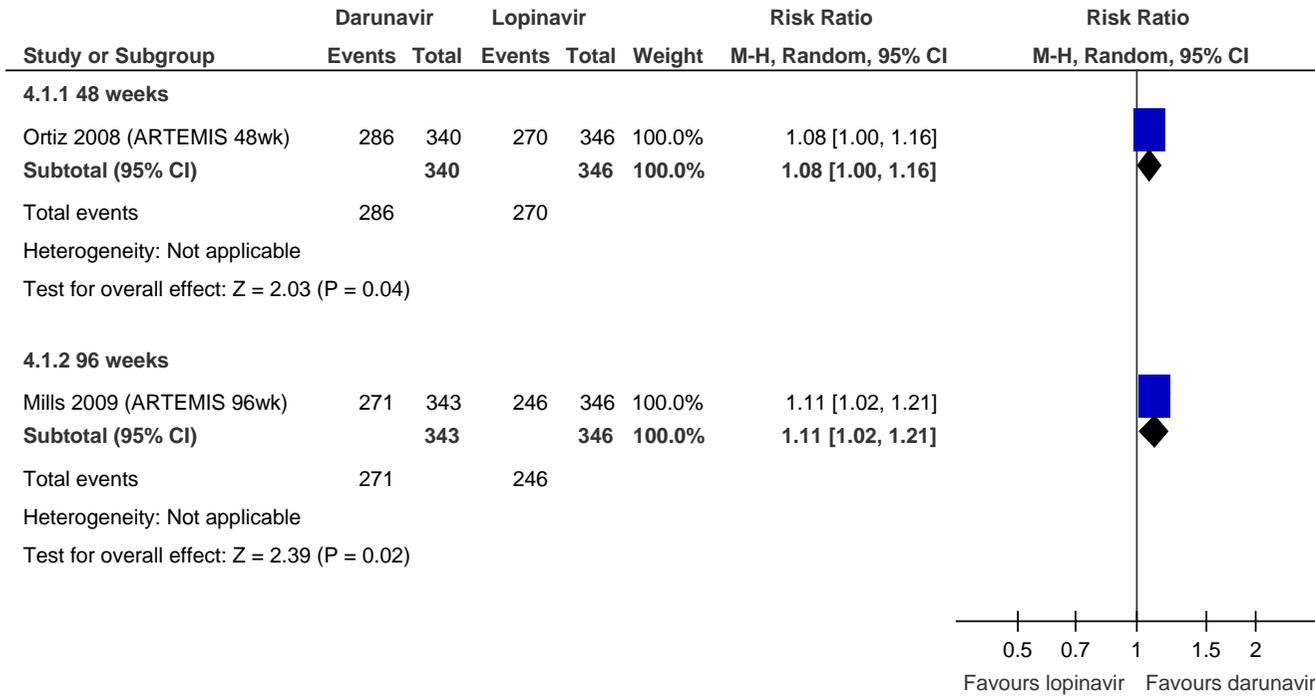
Authors' conclusion

Our study establishes the use of efavirenz plus two NRTIs as being more effective than lopinavir- ritonavir plus two NRTIs for initial therapy of HIV-1 infection, although the margin of superiority was moderate. Drug resistance was not a common outcome overall, but failure of efavirenz plus two NRTIs was often associated with NNRTI resistance, whereas failure of lopinavir-ritonavir plus two NRTIs was not associated with lopinavir resistance, and NRTI resistance was similar in the two groups. These results highlight the complexity of choosing initial therapy. Selection of initial therapy for an individual patient should take into consideration many factors, including virologic and immunologic response, tolerability, short-term and long-term toxicity, and the resistance consequences associated with virologic failure.

In this prospective study with randomized assignment to three class-sparing ART regimens, significant lipoprotein changes were observed. Total and small LDL particle concentrations increased, especially in the arms containing the PI lopinavir/ritonavir, as did total VLDL particles. HDL particles increased to a similar extent in all arms. Adverse changes in LDL and IDL were especially prominent in the arm with efavirenz + lopinavir/ritonavir. These changes were not related to changes in markers of insulin/glucose metabolism.

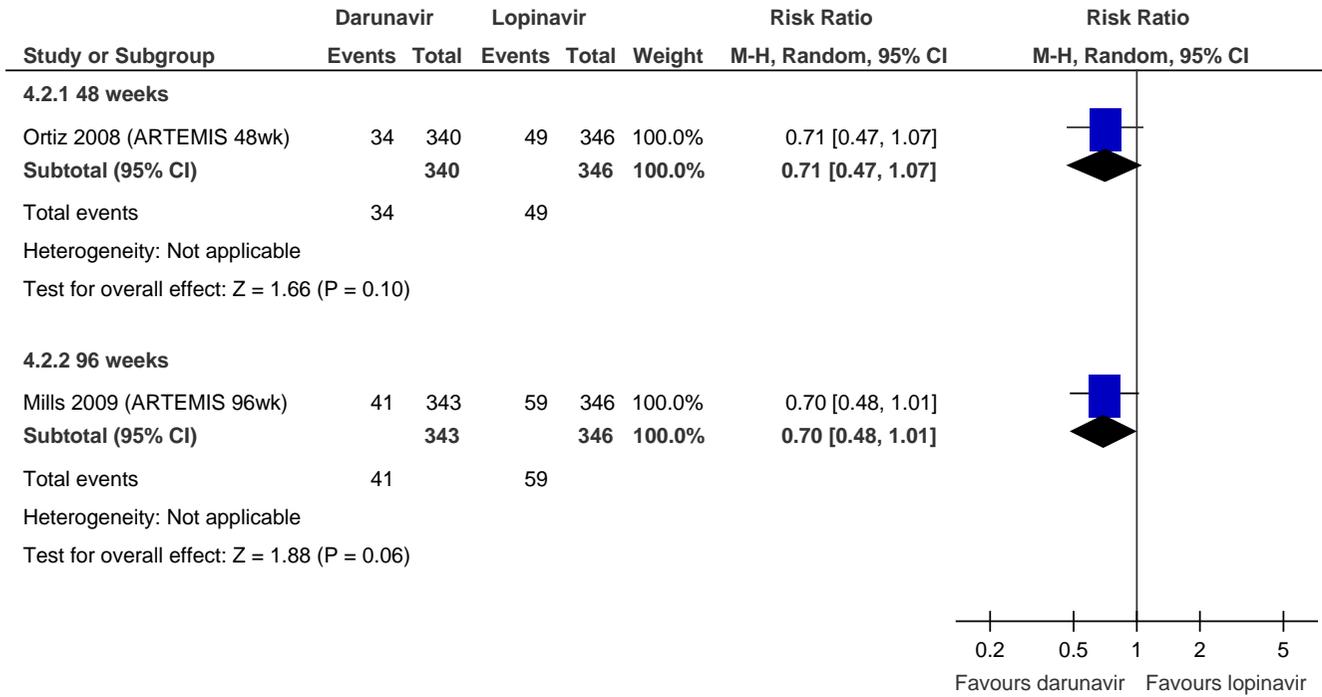
Forest plots Darunavir vs. lopinavir/r

Viral suppression <50 copies/mL.

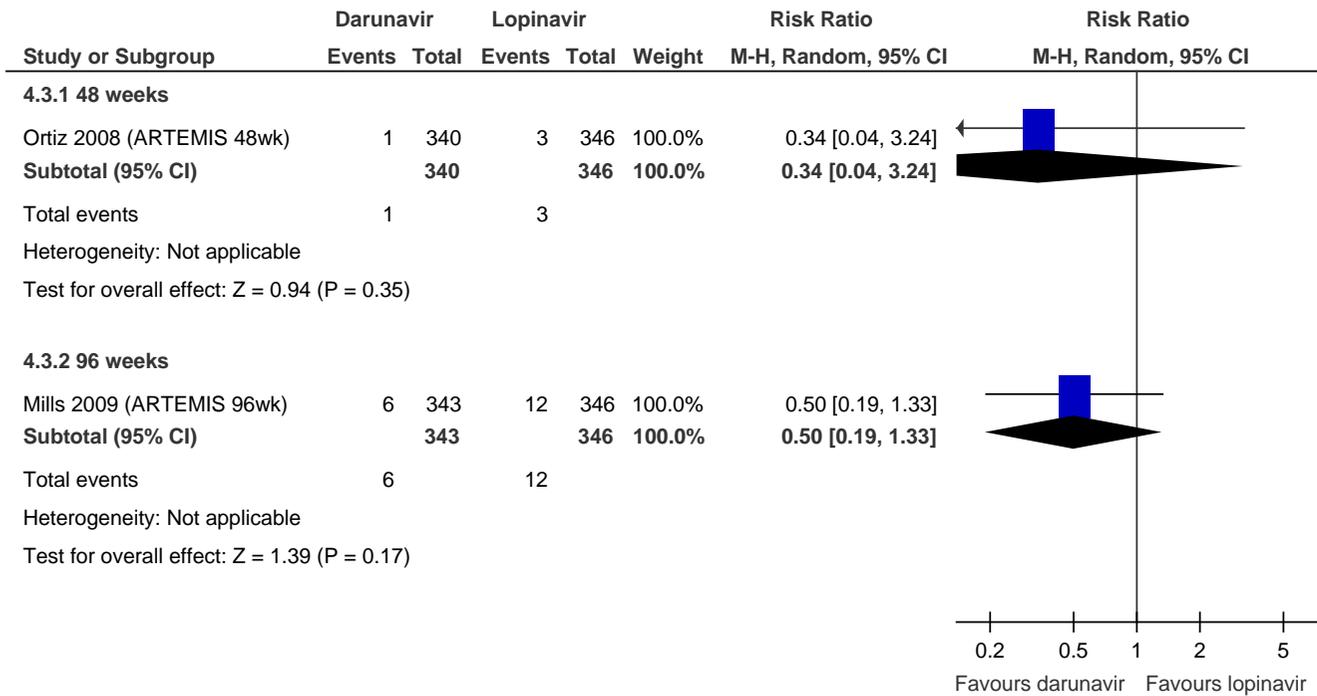


Viral suppression <50 copies/mL favours darunavir over lopinavir.

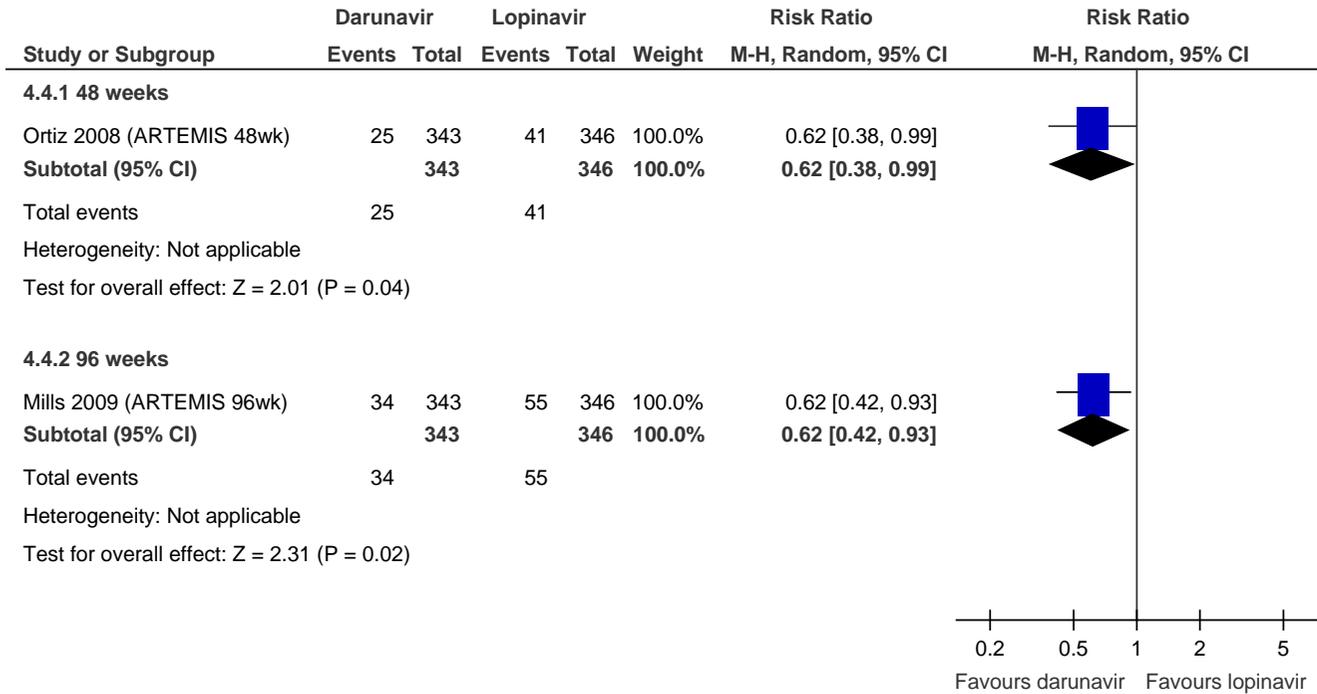
Virological failure.



Drug resistance.

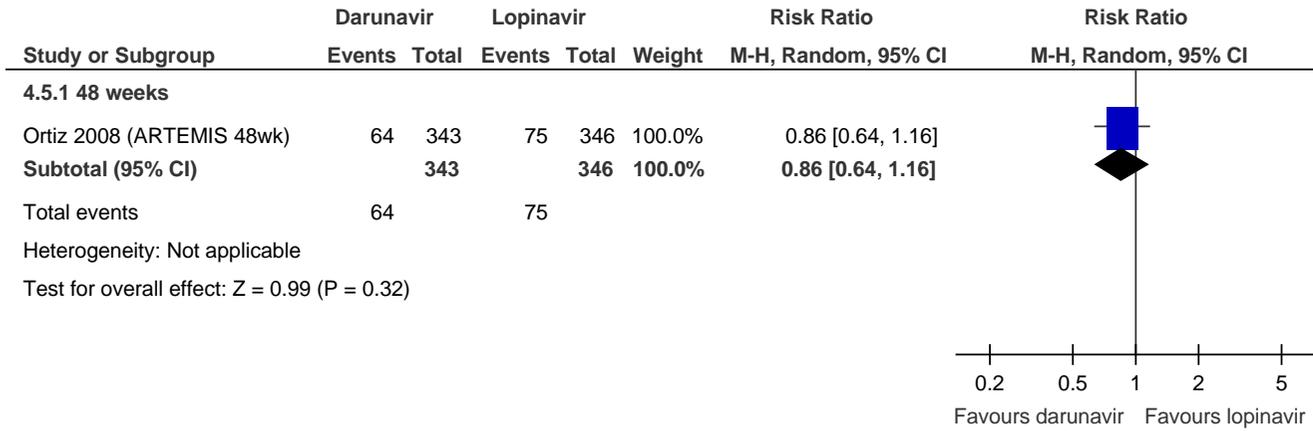


Serious adverse event.

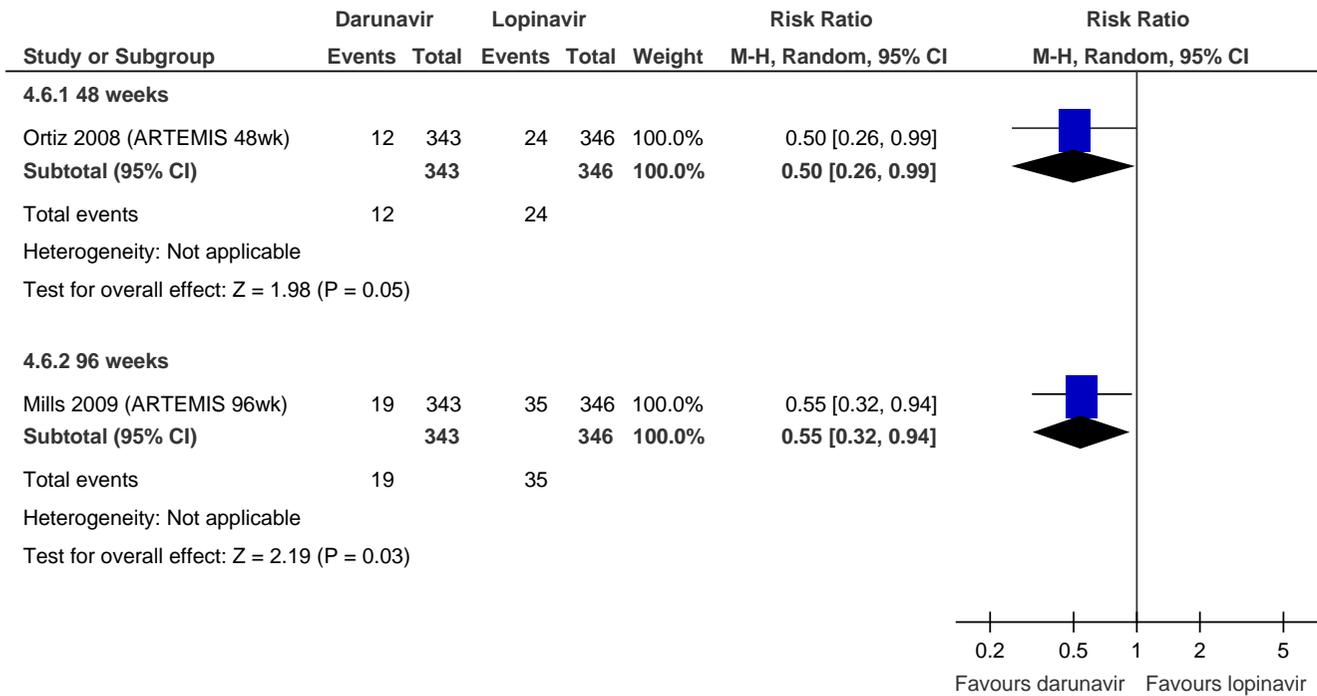


Serious adverse event favours darunavir over lopinavir.

Grade 3 or 4 adverse event.



Discontinuation due to adverse event.



Discontinuation due to adverse event favours darunavir over lopinavir.

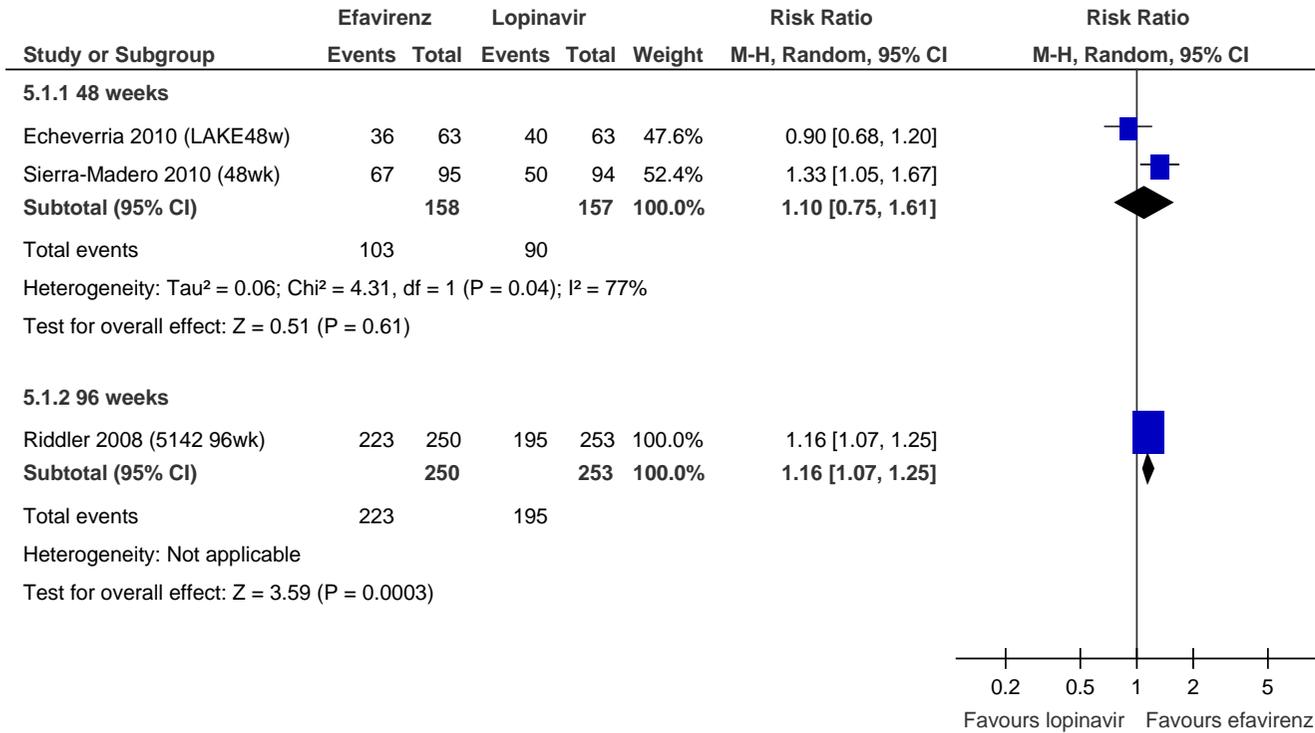
NNT/NNH table for darunavir versus lopinavir

	darunavir better	lopinavir better	ARR	NNT
Viral suppression <50 copies/mL	yes	no	78/1000	13
Serious adverse event	yes	no	45/1000	
Discontinuation due to adverse event	yes	no	35/1000	

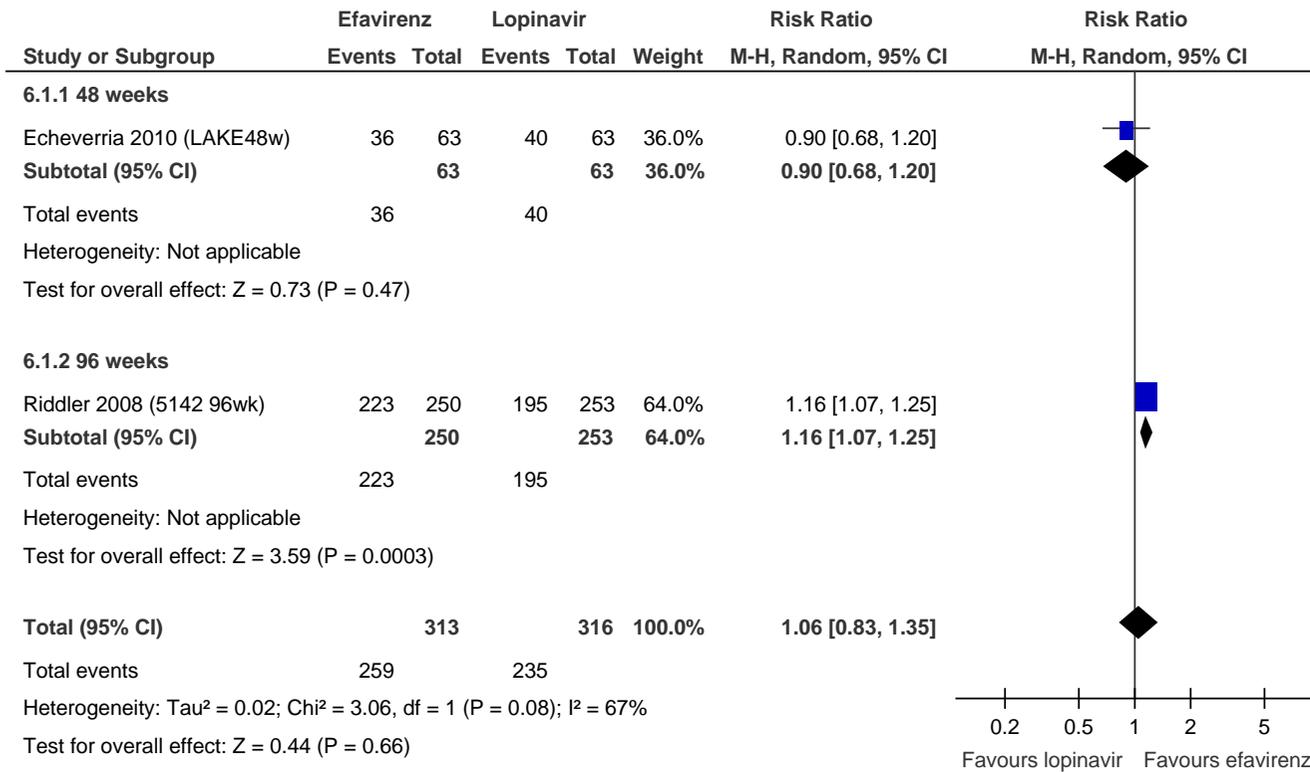
13 people would need to be treated with darunavir rather than lopinavir to gain 1 extra person with viral suppression.

Forest plots lopinavir/r vs. efavirenz

Viral suppression < 50 copies/mL

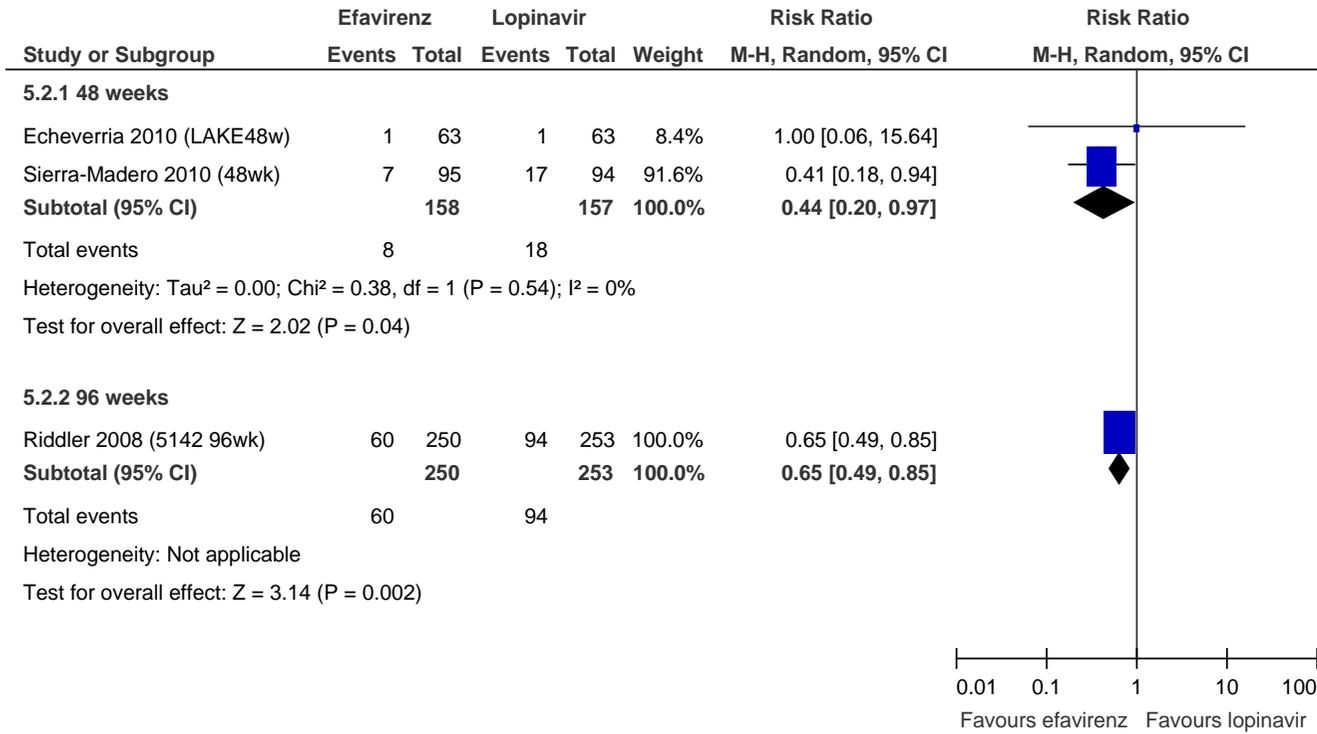


Sensitivity analysis for viral suppression excluding Sierra-Madero 2010 (due to heterogeneity of population)

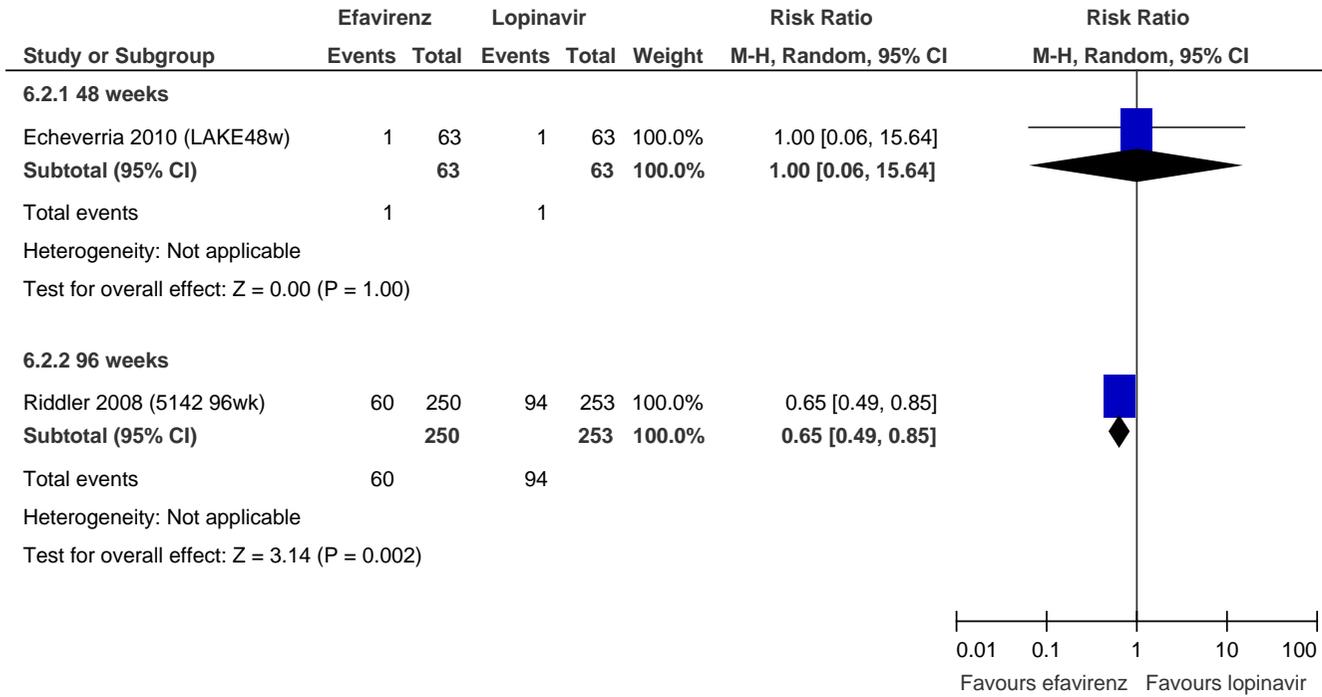


Heterogeneity between 48 and 96 week results.

Virological failure.

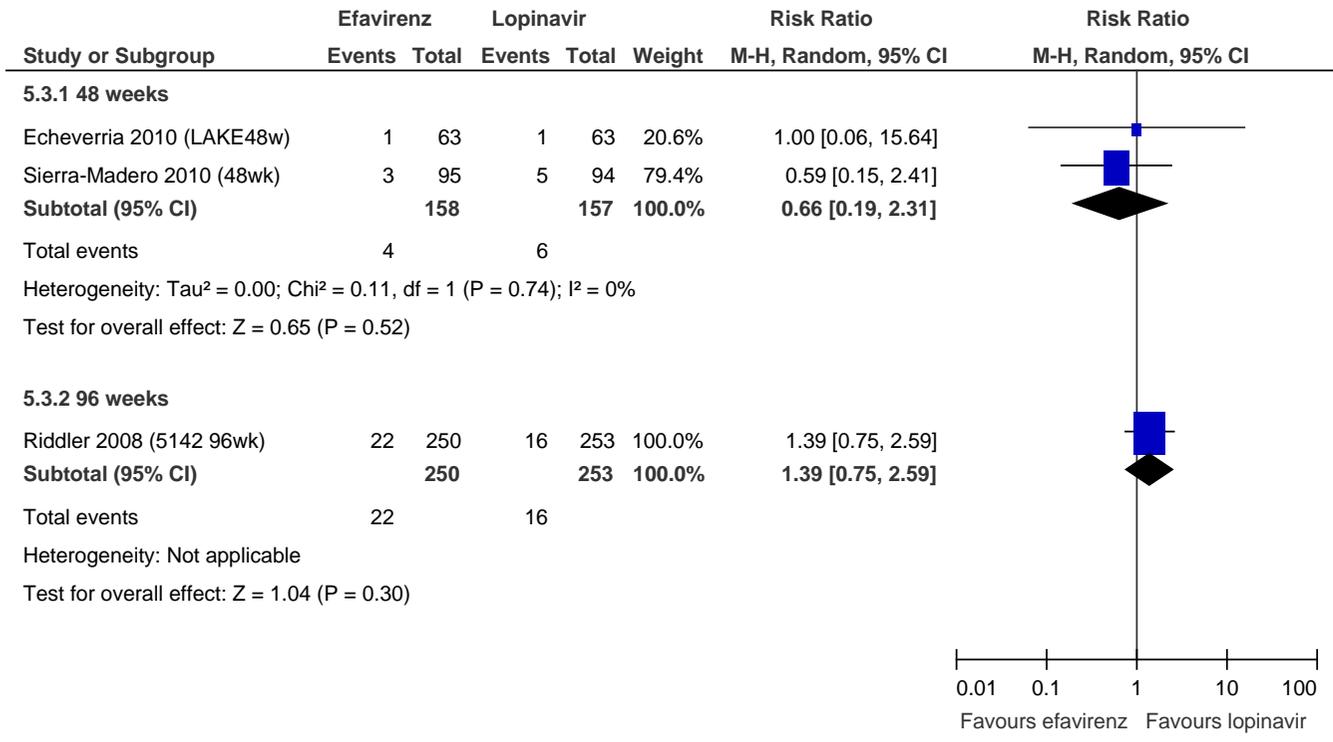


Sensitivity analysis for virological failure excluding Sierra-Madero 2010 (due to heterogeneity of population)

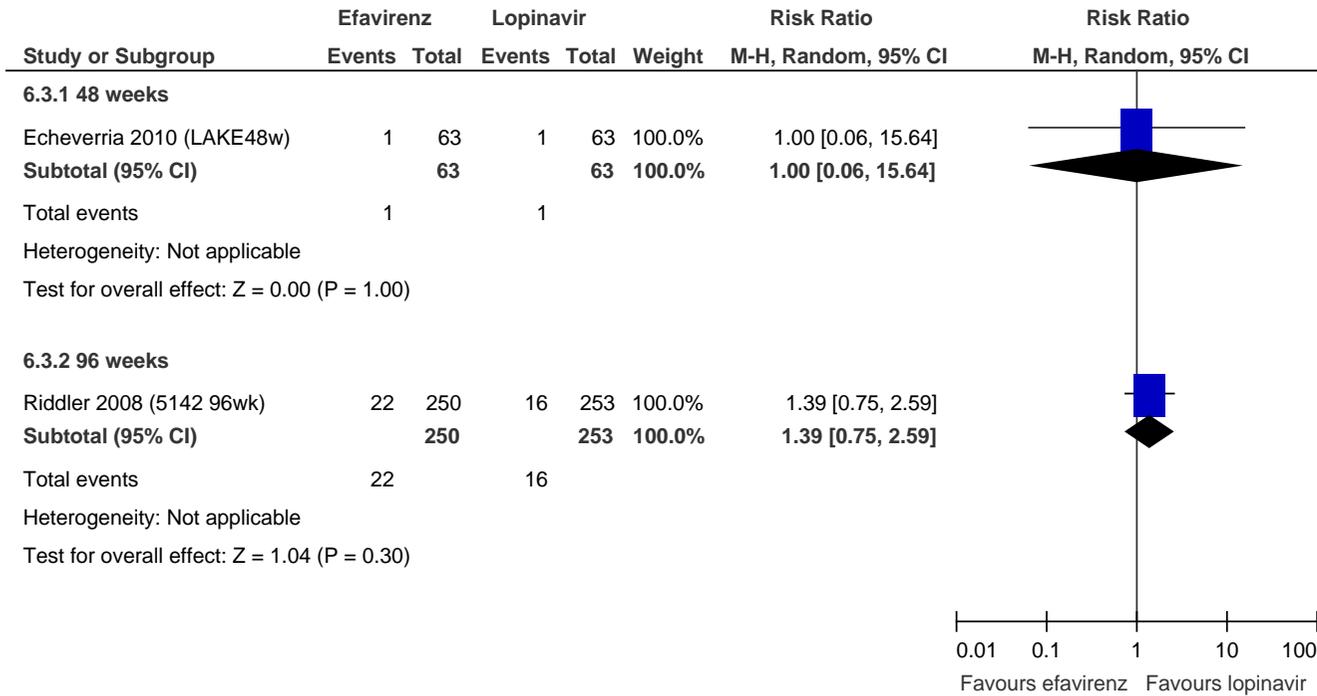


Virological failure favours efavirenz over lopinavir.

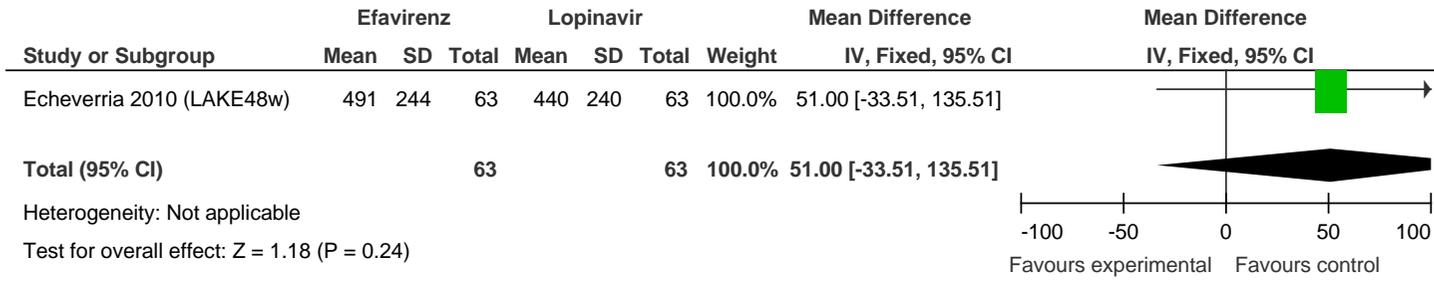
Drug resistance.



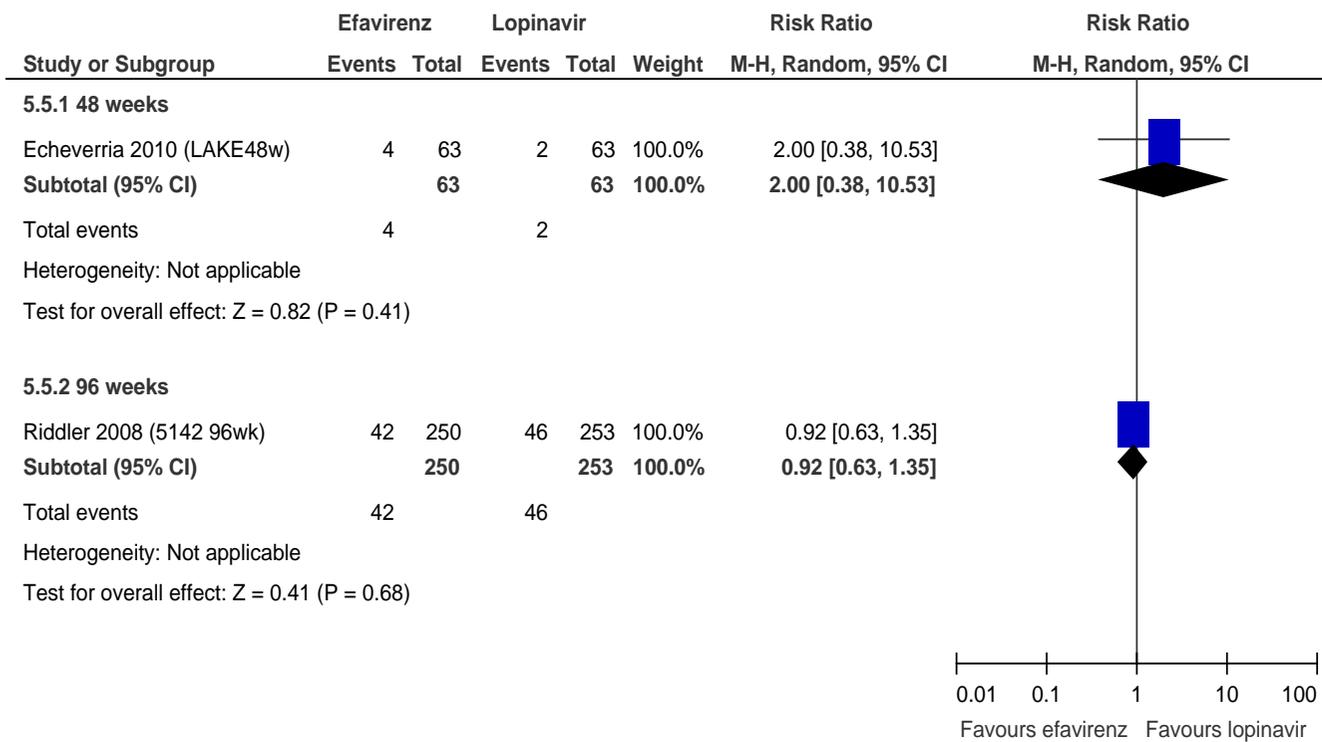
Sensitivity analysis for drug resistance excluding Sierra-Madero 2010 (due to heterogeneity of population)



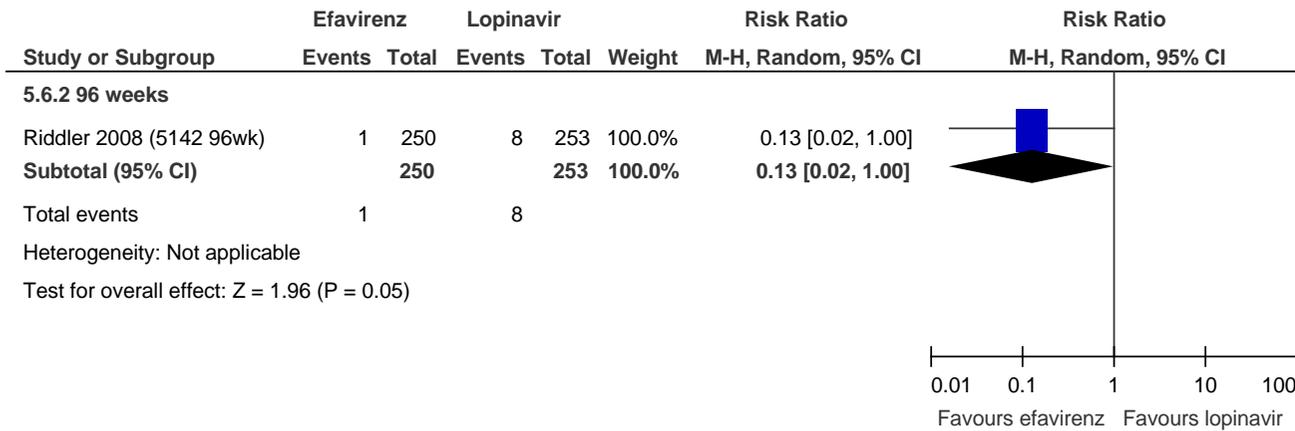
CD4 cell count.



Grade 3 or 4 clinical adverse events

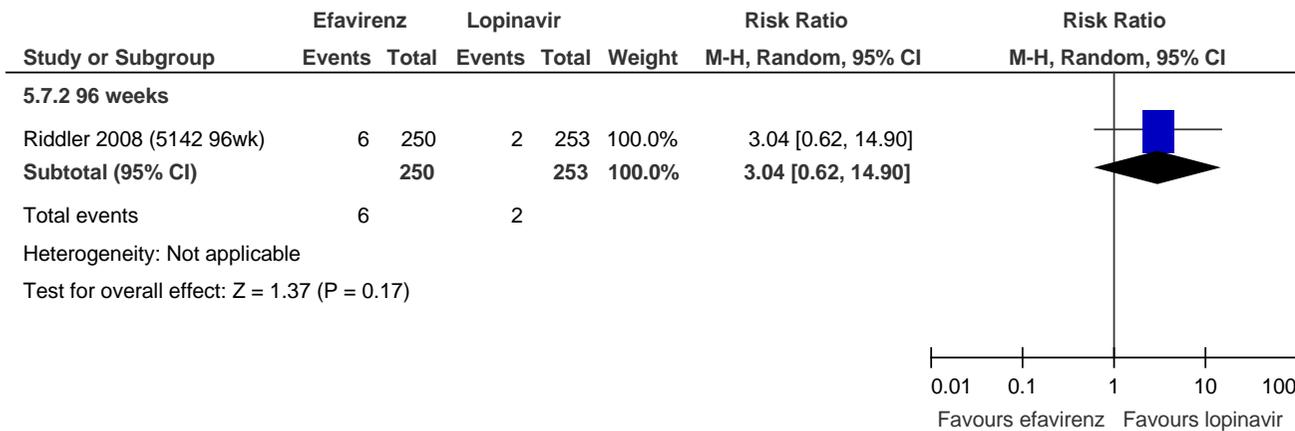


Grade 3 or 4 diarrhoea

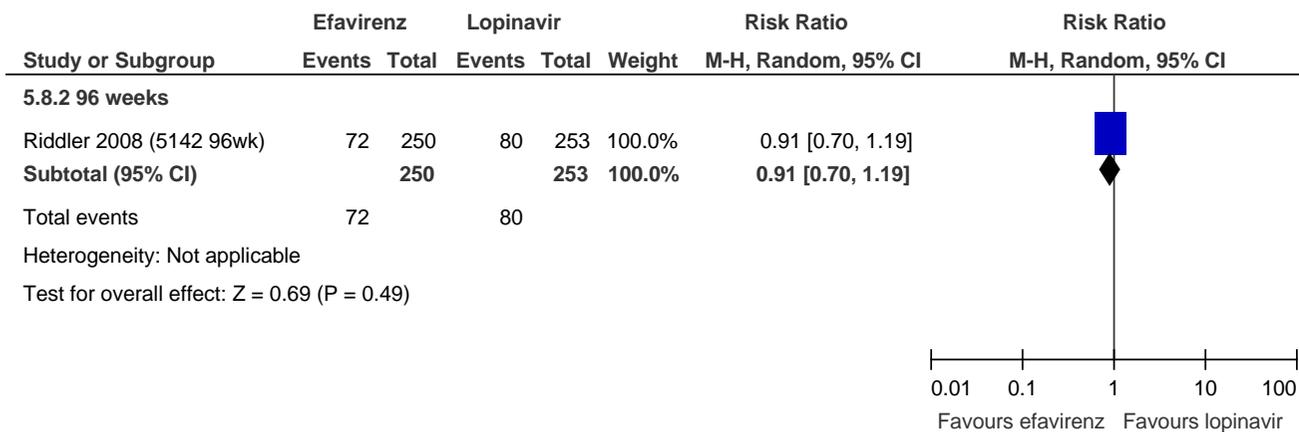


Grade 3 or 4 diarrhoea favours efavirenz over lopinavir.

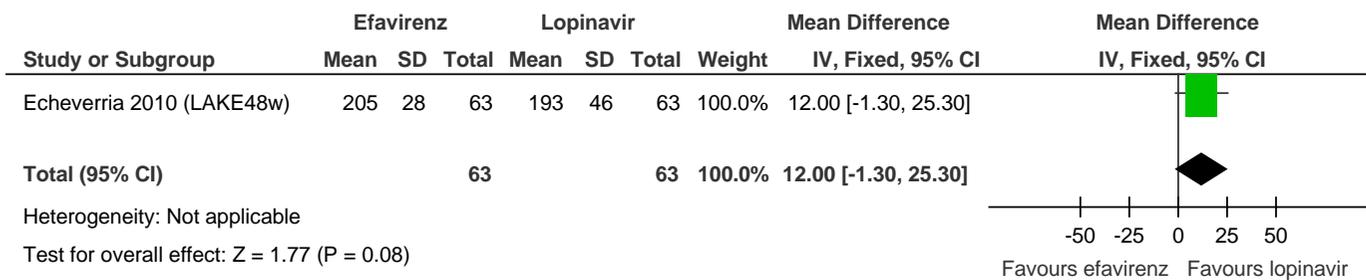
Grade 3 or 4 rash.



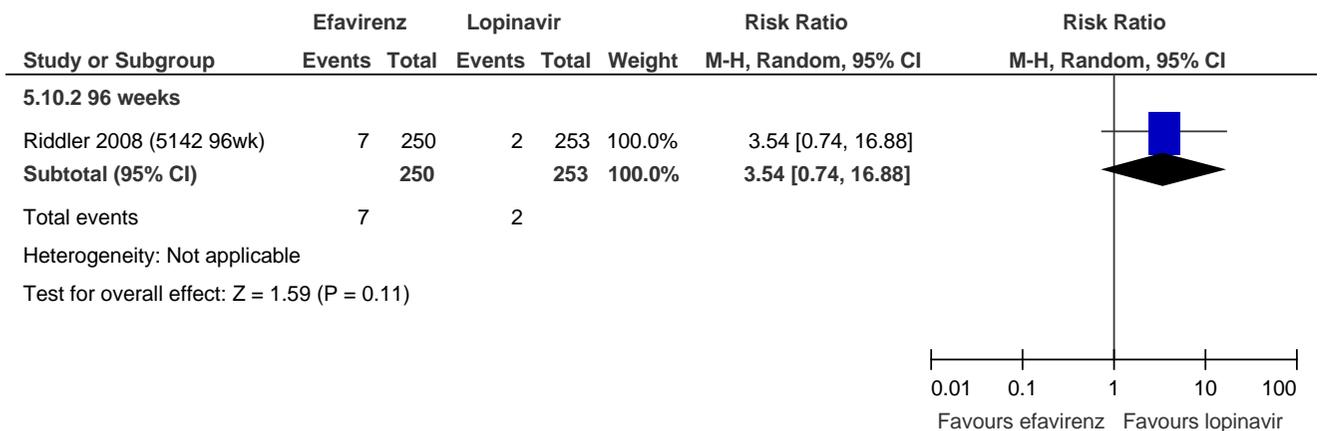
Grade 3 or 4 laboratory adverse event.



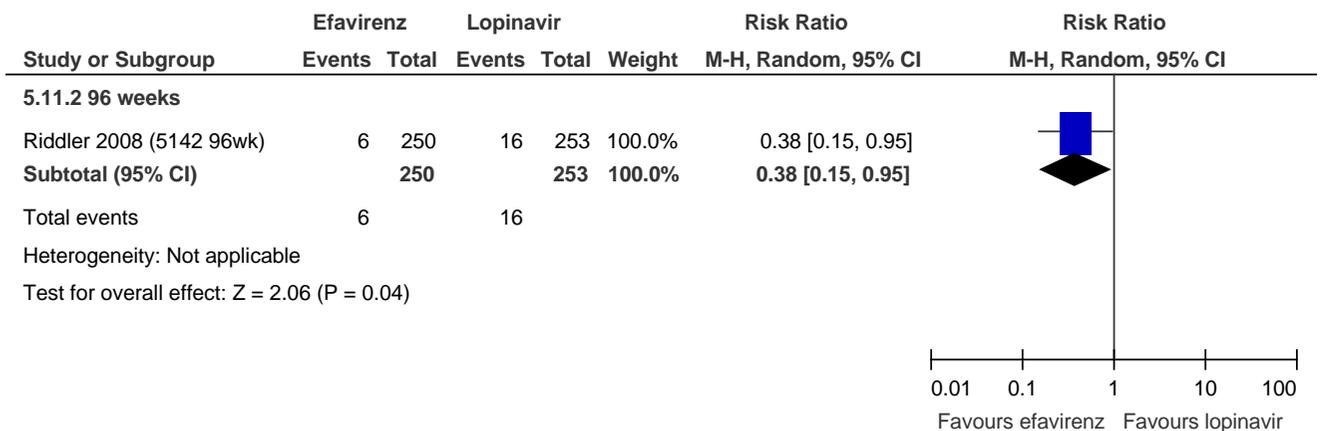
Total cholesterol.



Grade 3 or 4 LDL cholesterol.

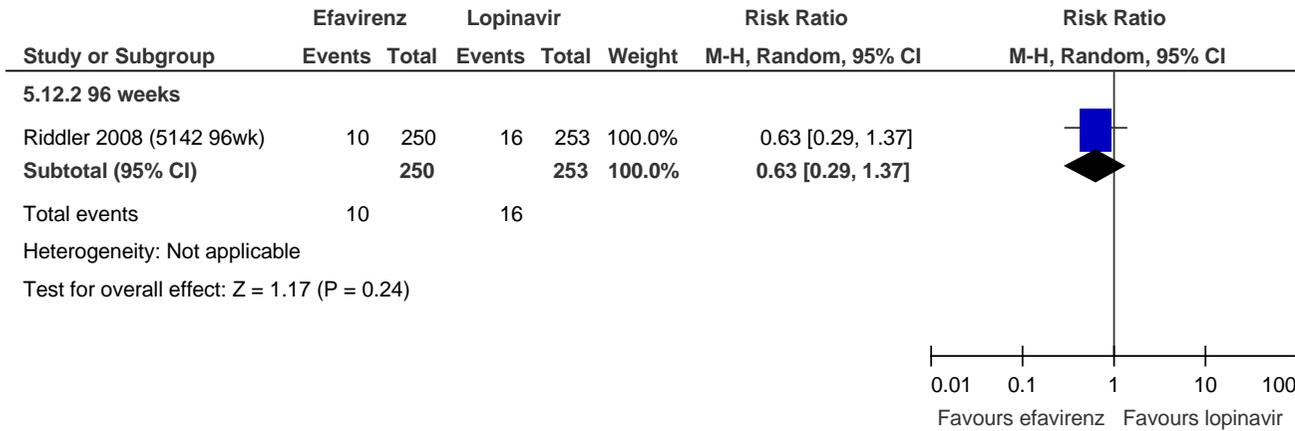


Grade 3 or 4 triglycerides.

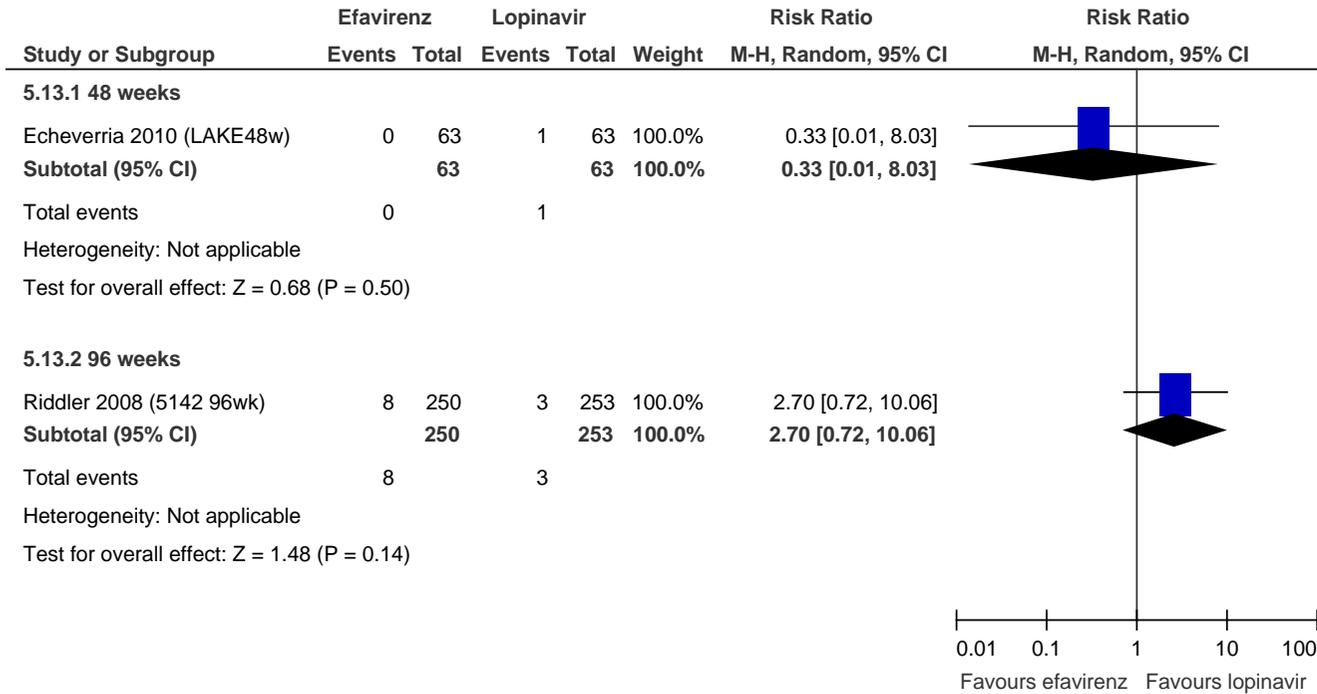


Grade 3 or 4 triglycerides favours efavirenz over lopinavir.

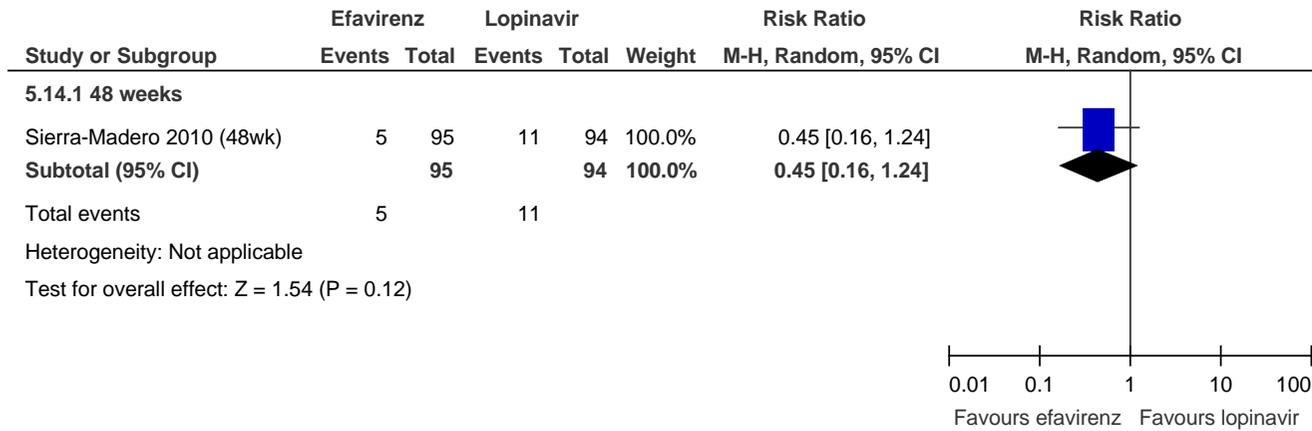
Grade 3 or 4 AST or ALT.



Lipodystrophy.



Discontinuation due to adverse event.



Excluding Sierra-Madero 2010 (due to heterogeneity of population) gives no data for this outcome.

NNT/NNH table for Efavirenz versus lopinavir

	Efavirenz better	Lopinavir better	ARR	NNT
Virological failure	yes	no	130/1000	8
Grade 3 or 4 diarrhoea	yes	no	28/1000	
Grade 3 or 4 triglycerides	yes	no	39/1000	

8 people would need to be treated with efavirenz rather than lopinavir to avoid 1 case of virological failure

Direct comparisons:

Comparison	Which drug is more effective?	NNT*	Which drug is safer?	NNH**
Efavirenz vs atazanavir	equally effective	-	Atazanavir better for the outcomes of drug resistance, grade 3/4 neurological events, grade 3/4 total cholesterol and grade 3/4 LDL cholesterol	20
Efavirenz vs rilpivirine	equally effective	-	25 people would need to be treated with efavirenz rather than rilpivirine to avoid 1 case of drug resistance. But this is at the expense of more laboratory adverse events and discontinuations due to adverse events. If 1000 people were treated with efavirenz rather than rilpivirine, there would be 40 fewer cases of drug resistance, but 67 more grade 3 or 4 laboratory adverse events and 43 more discontinuations due to adverse events.	trade-off between adverse events; NNH cannot be calculated
Efavirenz vs raltegravir	equally effective	-	raltegravir better for Grade 3/4 LDL cholesterol and Grade 3 or 4 triglycerides	20
Darunavir vs lopinavir	Viral suppression <50 copies/mL favours darunavir over lopinavir.	13	Darunavir better (fewer serious adverse events and 35 fewer discontinuations due to adverse events)	
Efavirenz vs lopinavir	Virological failure favours efavirenz over lopinavir.	8	Efavirenz better (grade 3 or 4 diarrhoea and 39 fewer with grade 3 or 4 triglyceride adverse events)	

* large NNT means a lot of people need to be treated to see a difference between the drugs on efficacy (i.e. difference between drugs small); - means no significant difference between drugs

** large NNH means a lot of people need to be treated to see a difference between the drugs on safety (i.e. difference between drugs small)

Efavirenz vs darunavir (indirect comparison)

If 1000 people were treated with darunavir rather than lopinavir, there would be 78 more people with viral suppression, 45 fewer serious adverse events and 35 fewer discontinuations due to adverse events.

If 1000 people were treated with efavirenz rather than lopinavir, there would be 130 fewer people with virological failure, 28 fewer with grade 3 or 4 diarrhoea and 39 fewer with grade 3 or 4 triglyceride adverse events.

The choice between efavirenz and darunavir therefore depends on the relative weight given to each outcome.

GRADE tables:

A Efavirenz versus atazanavir

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Efavirenz versus atazanavir	control	Relative (95% CI)	Absolute		
Viral suppression <50 copies week 48												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	97/108 (89.8%)	93/101 (92.1%)	RR 0.98 (0.9 to 1.06)	18 fewer per 1000 (from 92 fewer to 55 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								92.1%		18 fewer per 1000 (from 92 fewer to 55 more)		
Virological failure - Week 48												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	112/1043 (10.7%)	115/1033 (11.1%)	RR 0.97 (0.76 to 1.24)	3 fewer per 1000 (from 27 fewer to 27 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								7.9%		2 fewer per 1000 (from 19 fewer to 19 more)		
Virological failure - Week 96												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	129/929 (13.9%)	140/928 (15.1%)	RR 0.92 (0.74 to 1.15)	12 fewer per 1000 (from 39 fewer to 23 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								15.1%		12 fewer per 1000 (from 39 fewer to 23 more)		
Drug resistance (follow-up 96 weeks)												
2	randomised	no serious	no serious	no serious	no serious	none	71/1036 (6.9%)	18/1031	RR 3.94 (2.37	51 more per 1000 (from	⊕⊕⊕⊕	CRITICAL

	trials	limitations	inconsistency	indirectness	imprecision			(1.7%)	to 6.56)	24 more to 97 more)	HIGH	
								1.4%		41 more per 1000 (from 19 more to 78 more)		
Serious adverse event (follow-up 48 weeks)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ¹	none	14/114 (12.3%)	8/105 (7.6%)	RR 1.61 (0.7 to 3.69)	46 more per 1000 (from 23 fewer to 205 more)	⊕⊕⊕O MODERATE	CRITICAL
							7.6%			46 more per 1000 (from 23 fewer to 204 more)		
Grade 3 or 4 adverse event (follow-up 96 weeks)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	334/929 (36%)	311/928 (33.5%)	RR 1.07 (0.95 to 1.22)	23 more per 1000 (from 17 fewer to 74 more)	⊕⊕⊕⊕ HIGH	CRITICAL
							33.5%			23 more per 1000 (from 17 fewer to 74 more)		
Grade 3 or 4 neuropsychological event (follow-up 96 weeks)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	56/922 (6.1%)	24/926 (2.6%)	RR 2.34 (1.47 to 3.75)	35 more per 1000 (from 12 more to 71 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
							2.6%			35 more per 1000 (from 12 more to 71 more)		
Grade 3 or 4 diarrhoea (follow-up 96 weeks)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	17/922 (1.8%)	13/926 (1.4%)	RR 1.31 (0.64 to 2.69)	4 more per 1000 (from 5 fewer to 24 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
							1.4%			4 more per 1000 (from 5 fewer to 24 more)		
Grade 3 or 4 AST elevation (follow-up 96 weeks)												

1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/922 (1.3%)	20/926 (2.2%) 2.2%	RR 0.6 (0.3 to 1.23)	9 fewer per 1000 (from 15 fewer to 5 more) 9 fewer per 1000 (from 15 fewer to 5 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Grade 3 or 4 ALT elevation (follow-up 96 weeks)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	14/922 (1.5%)	18/926 (1.9%) 1.9%	RR 0.78 (0.39 to 1.56)	4 fewer per 1000 (from 12 fewer to 11 more) 4 fewer per 1000 (from 12 fewer to 11 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Grade 3 or 4 total cholesterol (follow-up 96 weeks)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	28/922 (3%)	13/926 (1.4%) 1.4%	RR 2.16 (1.13 to 4.15)	16 more per 1000 (from 2 more to 44 more) 16 more per 1000 (from 2 more to 44 more)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
Grade 3 or 4 LDL cholesterol (follow-up 96 weeks)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	44/922 (4.8%)	21/926 (2.3%) 2.3%	RR 2.1 (1.26 to 3.51)	25 more per 1000 (from 6 more to 57 more) 25 more per 1000 (from 6 more to 58 more)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
Grade 3 or 4 triglycerides (follow-up 96 weeks)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	22/922 (2.4%)	23/926 (2.5%) 2.5%	RR 0.96 (0.54 to 1.71)	1 fewer per 1000 (from 11 fewer to 18 more) 1 fewer per 1000 (from 12 fewer to 18 more)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT

Renal failure (follow-up 96 weeks)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/922 (0.9%)	10/926 (1.1%)	RR 0.8 (0.32 to 2.03)	2 fewer per 1000 (from 7 fewer to 11 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
							1.1%	2 fewer per 1000 (from 7 fewer to 11 more)				
Change in lumbar spine BMD (%; 0-96 weeks) (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	107	91	-	MD 1.55 higher (0.22 to 2.88 higher)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
Change in lumbar spine BMD (%; 0-96 weeks) - With TDF (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	54	43	-	MD 1.86 higher (0.02 to 3.7 higher)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
Change in lumbar spine BMD (%; 0-96 weeks) - With ABC (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	53	48	-	MD 1.21 higher (0.72 lower to 3.14 higher)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
Change in hip BMD (%; 0-96 weeks) (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	105	90	-	MD 0.33 higher (0.85 lower to 1.51 higher)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
Change in hip BMD (%; 0-96 weeks) - With TDF (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	54	42	-	MD 0.62 higher (1.24 lower to 2.48 higher)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
Change in hip BMD (%; 0-96 weeks) - With ABC (follow-up 96 weeks; Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	51	48	-	MD 0.14 higher (1.39 lower to 1.67 higher)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT

Bone fractures (follow-up 96 weeks)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	43/922 (4.7%)	37/926 (4%) 4%	RR 1.17 (0.76 to 1.79)	7 more per 1000 (from 10 fewer to 32 more) 7 more per 1000 (from 10 fewer to 32 more)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
Patients with 10% or more limb fat loss (week 96) (follow-up 96 weeks)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/109 (16.5%)	15/94 (16%) 16%	RR 1.03 (0.55 to 1.94)	5 more per 1000 (from 72 fewer to 150 more) 5 more per 1000 (from 72 fewer to 150 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Change in limb fat (% , 0-96 weeks) (Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	109	94	-	MD 13.63 lower (24.24 to 3.02 lower)	⊕⊕⊕⊕ HIGH	IMPORTANT
Change in limb fat (% , 0-96 weeks) - With TDF (Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	56	45	-	MD 12.5 lower (26.84 lower to 1.84 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Change in limb fat (% , 0-96 weeks) - With ABC (Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	53	49	-	MD 15 lower (30.78 lower to 0.78 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Change in trunk fat (% , 0-96 weeks) (Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	109	94	-	MD 15.34 lower (29.11 to 1.56 lower)	⊕⊕⊕⊕ HIGH	IMPORTANT
Change in trunk fat (% , 0-96 weeks) - With TDF (Better indicated by higher values)												

1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	56	45	-	MD 15.8 lower (34.58 lower to 2.98 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Change in trunk fat (% , 0-96 weeks) - With ABC (Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	53	49	-	MD 14.8 lower (35.06 lower to 5.46 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Change in visceral adipose tissue (% , 0-96 weeks) (Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	105	90	-	MD 14.04 lower (28.89 lower to 0.81 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Change in visceral adipose tissue (% , 0-96 weeks) - With TDF (Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	54	45	-	MD 14.7 lower (43.61 lower to 14.21 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Change in visceral adipose tissue (% , 0-96 weeks) - With ABC (Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	51	45	-	MD 13.8 lower (31.11 lower to 3.51 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Change in visceral:total adipose tissue (% , 0-96 weeks) (Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	105	90	-	MD 1.28 higher (4.41 lower to 6.97 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Change in visceral:total adipose tissue (% , 0-96 weeks) - With TDF (Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	54	45	-	MD 2 higher (5.66 lower to 9.66 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Change in visceral:total adipose tissue (% , 0-96 weeks) - With ABC (Better indicated by higher values)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	51	45	-	MD 0.4 higher (8.09 lower to 8.89 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT

Cognitive speed score (lower = better) (follow-up 48 weeks; Better indicated by lower values)												
1	randomised trials	serious ²	no serious inconsistency	no serious indirectness	no serious imprecision	none	9	8	-	MD 0 higher (0.07 lower to 0.07 higher)	⊕⊕⊕○ MODERATE	NOT IMPORTANT
Cognitive accuracy score (higher = better) (follow-up 48 weeks; Better indicated by higher values)												
1	randomised trials	serious ²	no serious inconsistency	no serious indirectness	no serious imprecision	none	9	8	-	MD 0.14 lower (0.32 lower to 0.04 higher)	⊕⊕⊕○ MODERATE	NOT IMPORTANT

¹ Wide confidence intervals

² Small sample size

B Efavirenz versus rilpivirine

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Efavirenz versus rilpivirine	control	Relative (95% CI)	Absolute		
Viral suppression <50 copies/mL (follow-up 48 weeks)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	561/682 (82.3%)	578/686 (84.3%) 84.3%	RR 0.98 (0.93 to 1.02)	17 fewer per 1000 (from 59 fewer to 17 more) 17 fewer per 1000 (from 59 fewer to 17 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Virological failure (follow-up 48 weeks)												
2	randomised trials	no serious limitations	serious ¹	no serious indirectness	no serious imprecision	none	33/682 (4.8%)	62/686 (9%) 9%	RR 0.55 (0.29 to 1.02)	41 fewer per 1000 (from 64 fewer to 2 more) 40 fewer per 1000 (from 64 fewer to 2 more)	⊕⊕⊕○ MODERATE	CRITICAL
Drug resistance (follow-up 8 weeks)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	16/682 (2.3%)	44/686 (6.4%) 6.4%	RR 0.38 (0.2 to 0.72)	40 fewer per 1000 (from 18 fewer to 51 fewer) 40 fewer per 1000 (from 18 fewer to 51 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Serious adverse event (follow-up 48 weeks)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	55/682 (8.1%)	45/686 (6.6%)	RR 1.23 (0.84 to 1.8)	15 more per 1000 (from 10 fewer to 52 more)	⊕⊕⊕⊕	CRITICAL

								6.6%		15 more per 1000 (from 11 fewer to 53 more)	HIGH	
Grade 3 or 4 rash (follow-up 48 weeks)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ²	none	3/682 (0.4%)	1/686 (0.1%)	RR 2.33 (0.34 to 15.83)	2 more per 1000 (from 1 fewer to 22 more)	⊕⊕⊕○ MODERATE	CRITICAL
								0.1%		1 more per 1000 (from 1 fewer to 15 more)		
Grade 3 or 4 laboratory adverse event (follow-up 48 weeks)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	118/670 (17.6%)	75/685 (10.9%)	RR 1.61 (1.23 to 2.11)	67 more per 1000 (from 25 more to 122 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
								11%		67 more per 1000 (from 25 more to 122 more)		
Grade 3 or 4 AST (follow-up 48 weeks)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	19/669 (2.8%)	14/685 (2%)	RR 1.39 (0.7 to 2.75)	8 more per 1000 (from 6 fewer to 36 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								2%		8 more per 1000 (from 6 fewer to 35 more)		
Grade 3 or 4 ALT (follow-up 48 weeks)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	23/678 (3.4%)	10/685 (1.5%)	RR 2.29 (1.09 to 4.8)	19 more per 1000 (from 1 more to 55 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								1.5%		19 more per 1000 (from 1 more to 57 more)		
Grade 3 or 4 total cholesterol (follow-up 48 weeks)												
2	randomised	no serious	no serious	no serious	serious ²	none	17/668 (2.5%)	1/685	RR 9.93 (1.83	13 more per 1000 (from 1	⊕⊕⊕○	NOT

	trials	limitations	inconsistency	indirectness				(0.1%)	to 53.94)	more to 77 more)	MODERATE	IMPORTANT
								0.1%		9 more per 1000 (from 1 more to 53 more)		
Grade 3 or 4 LDL cholesterol (follow-up 48 weeks)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ²	none	27/666 (4.1%)	5/685 (0.7%)	RR 5 (1.38 to 18.17)	29 more per 1000 (from 3 more to 125 more)	⊕⊕⊕○ MODERATE	NOT IMPORTANT
								0.7%		28 more per 1000 (from 3 more to 120 more)		
Grade 3 or 4 triglycerides (follow-up 48 weeks)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ²	none	15/668 (2.2%)	2/685 (0.3%)	RR 7.36 (1.67 to 32.39)	19 more per 1000 (from 2 more to 92 more)	⊕⊕⊕○ MODERATE	NOT IMPORTANT
								0.3%		19 more per 1000 (from 2 more to 94 more)		
Discontinuation due to adverse event (follow-up 48 weeks)												
2	randomised trials	no serious limitations	serious ¹	no serious indirectness	no serious imprecision	none	52/682 (7.6%)	23/686 (3.4%)	RR 2.29 (1.15 to 4.57)	43 more per 1000 (from 5 more to 120 more)	⊕⊕⊕○ MODERATE	CRITICAL
								3.4%		44 more per 1000 (from 5 more to 121 more)		

¹ Heterogeneity between studies

² Wide confidence intervals

C Efavirenz versus raltegravir

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Efavirenz versus raltegravir	control	Relative (95% CI)	Absolute		
Viral suppression <50 copies/mL - 48 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	263/319 (82.4%)	378/440 (85.9%)	RR 0.96 (0.9 to 1.03)	34 fewer per 1000 (from 86 fewer to 26 more)	⊕⊕⊕○ MODERATE	CRITICAL
								85.9%		34 fewer per 1000 (from 86 fewer to 26 more)		
Viral suppression <50 copies/mL - 96 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	255/320 (79.7%)	361/441 (81.9%)	RR 0.98 (0.91 to 1.06)	16 fewer per 1000 (from 74 fewer to 49 more)	⊕⊕⊕○ MODERATE	CRITICAL
								82.1%		16 fewer per 1000 (from 74 fewer to 49 more)		
Virological failure - 96 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	47/320 (14.7%)	45/441 (10.2%)	RR 1.16 (0.79 to 1.71)	16 more per 1000 (from 21 fewer to 72 more)	⊕⊕⊕○ MODERATE	CRITICAL
								8.8%		14 more per 1000 (from 18 fewer to 62 more)		
Drug resistance - 96 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/320 (2.2%)	10/441 (2.3%)	RR 1.13 (0.43 to 2.96)	3 more per 1000 (from 13 fewer to 44 more)	⊕⊕⊕○	CRITICAL

								2.3%		3 more per 1000 (from 13 fewer to 45 more)	MODERATE	
Serious adverse event - 48 weeks												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	27/282 (9.6%)	28/281 (10%)	RR 0.96 (0.58 to 1.59)	4 fewer per 1000 (from 42 fewer to 59 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								10%		4 fewer per 1000 (from 42 fewer to 59 more)		
Serious adverse event - 96 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	37/320 (11.6%)	56/441 (12.7%)	RR 0.84 (0.56 to 1.25)	20 fewer per 1000 (from 56 fewer to 32 more)	⊕⊕⊕○ MODERATE	CRITICAL
								12.1%		19 fewer per 1000 (from 53 fewer to 30 more)		
Grade 3 or 4 AST elevation - 48 weeks												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	5/282 (1.8%)	6/281 (2.1%)	RR 0.83 (0.26 to 2.69)	4 fewer per 1000 (from 16 fewer to 36 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								2.1%		4 fewer per 1000 (from 16 fewer to 35 more)		
Grade 3 or 4 AST elevation - 96 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/317 (2.8%)	13/441 (2.9%)	RR 0.92 (0.39 to 2.17)	2 fewer per 1000 (from 18 fewer to 34 more)	⊕⊕⊕○ MODERATE	CRITICAL
								2.9%		2 fewer per 1000 (from 18 fewer to 34 more)		
Grade 3 or 4 ALT elevation - 48 weeks												
1	randomised	no serious	no serious	no serious	no serious	none	6/282 (2.1%)	5/281	RR 1.2 (0.37 to	4 more per 1000 (from 11	⊕⊕⊕⊕	CRITICAL

	trials	limitations	inconsistency	indirectness	imprecision			(1.8%)	3.87)	fewer to 51 more)	HIGH	
								1.8%		4 more per 1000 (from 11 fewer to 52 more)		
Grade 3 or 4 ALT elevation - 96 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/317 (2.8%)	7/441 (1.6%)	RR 1.87 (0.7 to 4.97)	14 more per 1000 (from 5 fewer to 63 more)	⊕⊕⊕○ MODERATE	CRITICAL
								1.5%		13 more per 1000 (from 5 fewer to 60 more)		
Grade 3 or 4 total cholesterol - 96 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	13/305 (4.3%)	0/436 (0%)	RR 22.25 (2.83 to 175.02)	0 more per 1000 (from 0 more to 0 more)	⊕⊕○○ LOW	NOT IMPORTANT
								0%		0 more per 1000 (from 0 more to 0 more)		
Grade 3 or 4 LDL cholesterol - 48 weeks												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/280 (3.6%)	3/281 (1.1%)	RR 3.35 (0.93 to 12.03)	25 more per 1000 (from 1 fewer to 118 more)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
								1.1%		26 more per 1000 (from 1 fewer to 121 more)		
Grade 3 or 4 LDL cholesterol - 96 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	19/301 (6.3%)	4/431 (0.9%)	RR 6.3 (2.14 to 18.59)	49 more per 1000 (from 11 more to 163 more)	⊕⊕⊕○ MODERATE	NOT IMPORTANT
								0.9%		48 more per 1000 (from 10 more to 158 more)		
Grade 3 or 4 triglycerides - 48 weeks												

1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ²	none	3/282 (1.1%)	1/281 (0.4%)	RR 2.99 (0.31 to 28.57)	7 more per 1000 (from 2 fewer to 98 more)		NOT IMPORTANT
								0.4%		8 more per 1000 (from 3 fewer to 110 more)		
Grade 3 or 4 triglycerides - 96 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	7/305 (2.3%)	1/436 (0.2%)	RR 8.43 (1.34 to 52.85)	17 more per 1000 (from 1 more to 119 more)	⊕⊕⊕⊕ LOW	NOT IMPORTANT
								0.2%		15 more per 1000 (from 1 more to 104 more)		
Lipoatrophy (loss of 20% or more appendicular fat) - 96 weeks												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	2/38 (5.3%)	3/37 (8.1%)	RR 0.65 (0.11 to 3.67)	28 fewer per 1000 (from 72 fewer to 216 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
								8.1%		28 fewer per 1000 (from 72 fewer to 216 more)		
Discontinued due to adverse events - 48 weeks												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	17/282 (6%)	9/281 (3.2%)	RR 1.88 (0.85 to 4.15)	28 more per 1000 (from 5 fewer to 101 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								3.2%		28 more per 1000 (from 5 fewer to 101 more)		
Discontinued due to adverse events - 96 weeks												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/320 (5.6%)	13/441 (2.9%)	RR 1.58 (0.78 to 3.21)	17 more per 1000 (from 6 fewer to 65 more)	⊕⊕⊕⊕ MODERATE	CRITICAL
								2.6%		15 more per 1000 (from 6 fewer to 57 more)		

¹ Randomisation and allocation concealment not stated in one study

² Wide confidence intervals

D Darunavir versus lopinavir

Quality assessment							Summary of findings				Quality	Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Darunavir versus lopinavir	control	Relative (95% CI)	Absolute		
Viral suppression <50 copies/mL - 48 weeks												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	286/340 (84.1%)	270/346 (78%)	RR 1.08 (1 to 1.16)	62 more per 1000 (from 0 more to 125 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								78%				
Viral suppression <50 copies/mL - 96 weeks												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	271/343 (79%)	246/346 (71.1%)	RR 1.11 (1.02 to 1.21)	78 more per 1000 (from 14 more to 149 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								71.1%				
Virological failure - 48 weeks												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	34/340 (10%)	49/346 (14.2%)	RR 0.71 (0.47 to 1.07)	41 fewer per 1000 (from 75 fewer to 10 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								14.2%				

Virological failure - 96 weeks												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	41/343 (12%)	59/346 (17.1%)	RR 0.7 (0.48 to 1.01)	51 fewer per 1000 (from 89 fewer to 2 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								17.1%		51 fewer per 1000 (from 89 fewer to 2 more)		
Drug resistance - 48 weeks												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious ¹	none	1/340 (0.3%)	3/346 (0.9%)	RR 0.34 (0.04 to 3.24)	6 fewer per 1000 (from 8 fewer to 19 more)	⊕⊕⊕○ MODERATE	CRITICAL
								0.9%		6 fewer per 1000 (from 9 fewer to 20 more)		
Drug resistance - 96 weeks												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	6/343 (1.7%)	12/346 (3.5%)	RR 0.5 (0.19 to 1.33)	17 fewer per 1000 (from 28 fewer to 11 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								3.5%		18 fewer per 1000 (from 28 fewer to 12 more)		
Serious adverse event - 48 weeks												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	25/343 (7.3%)	41/346 (11.8%)	RR 0.62 (0.38 to 0.99)	45 fewer per 1000 (from 1 fewer to 73 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								11.9%		45 fewer per 1000 (from 1 fewer to 74 fewer)		
Serious adverse event - 96 weeks												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	34/343 (9.9%)	55/346 (15.9%)	RR 0.62 (0.42 to 0.93)	60 fewer per 1000 (from 11 fewer to 92 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								15.9%		60 fewer per 1000 (from 11 fewer to 92 fewer)		

											fewer to 92 fewer)		
Grade 3 or 4 adverse event - 48 weeks													
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	64/343 (18.7%)	75/346 (21.7%)	RR 0.86 (0.64 to 1.16)	30 fewer per 1000 (from 78 fewer to 35 more)	⊕⊕⊕⊕ HIGH	CRITICAL	
								21.7%					30 fewer per 1000 (from 78 fewer to 35 more)
Discontinuation due to adverse event - 48 weeks													
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/343 (3.5%)	24/346 (6.9%)	RR 0.5 (0.26 to 0.99)	35 fewer per 1000 (from 1 fewer to 51 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL	
								6.9%					34 fewer per 1000 (from 1 fewer to 51 fewer)
Discontinuation due to adverse event - 96 weeks													
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	19/343 (5.5%)	35/346 (10.1%)	RR 0.55 (0.32 to 0.94)	46 fewer per 1000 (from 6 fewer to 69 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL	
								10.1%					45 fewer per 1000 (from 6 fewer to 69 fewer)

[†] Wide confidence intervals

D Efavirenz vs lopinavir sensitivity analysis without Sierra-Madero

Quality assessment							Summary of findings				Importance	
							No of patients		Effect			Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Efavirenz	lopinavir sensitivity analysis without Sierra-Madero	Relative (95% CI)	Absolute		
Viral suppression < 50 copies/mL - 48 weeks												
1	randomised trials	very serious ^{1,2}	no serious inconsistency	no serious indirectness	no serious imprecision	none	36/63 (57.1%)	40/63 (63.5%)	RR 0.9 (0.68 to 1.2)	63 fewer per 1000 (from 203 fewer to 127 more)	⊕⊕○○ LOW	CRITICAL
								63.5%		64 fewer per 1000 (from 203 fewer to 127 more)		
Viral suppression < 50 copies/mL - 96 weeks												
1	randomised trials	very serious ^{1,2}	no serious inconsistency	no serious indirectness	no serious imprecision	none	223/250 (89.2%)	195/253 (77.1%)	RR 1.16 (1.07 to 1.25)	123 more per 1000 (from 54 more to 193 more)	⊕⊕○○ LOW	CRITICAL
								77.1%		123 more per 1000 (from 54 more to 193 more)		
Virological failure - 48 weeks												
1	randomised trials	very serious ^{1,2}	no serious inconsistency	no serious indirectness	serious ³	none	1/63 (1.6%)	1/63 (1.6%)	RR 1 (0.06 to 15.64)	0 fewer per 1000 (from 15 fewer to 232 more)	⊕○○○ VERY LOW	CRITICAL
								1.6%		0 fewer per 1000 (from 15 fewer to 234 more)		
Virological failure - 96 weeks												
1	randomised	very	no serious	no serious	no serious	none	60/250	94/253 (37.2%)	RR 0.65 (0.49	130 fewer per 1000 (from	⊕⊕○○	CRITICAL

	trials	serious ^{1,2}	inconsistency	indirectness	imprecision		(24%)		to 0.85)	56 fewer to 189 fewer)	LOW	
								37.2%		130 fewer per 1000 (from 56 fewer to 190 fewer)		
Drug resistance - 48 weeks												
1	randomised trials	very serious ^{1,2}	no serious inconsistency	no serious indirectness	serious ³	none	1/63 (1.6%)	1/63 (1.6%)	RR 1 (0.06 to 15.64)	0 fewer per 1000 (from 15 fewer to 232 more)	⊕○○○ VERY LOW	CRITICAL
								1.6%		0 fewer per 1000 (from 15 fewer to 234 more)		
Drug resistance - 96 weeks												
1	randomised trials	very serious ^{1,2}	no serious inconsistency	no serious indirectness	no serious imprecision	none	22/250 (8.8%)	16/253 (6.3%)	RR 1.39 (0.75 to 2.59)	25 more per 1000 (from 16 fewer to 101 more)	⊕⊕○○ LOW	CRITICAL
								6.3%		25 more per 1000 (from 16 fewer to 100 more)		
CD4 cell count (follow-up 48 weeks; Better indicated by higher values)												
1	randomised trials	very serious ^{1,2}	no serious inconsistency	no serious indirectness	serious ³	none	63	63	-	MD 51 higher (33.51 lower to 135.51 higher)	⊕○○○ VERY LOW	IMPORTANT
Grade 3 or 4 clinical adverse event - 48 weeks												
1	randomised trials	very serious ^{1,2}	no serious inconsistency	no serious indirectness	no serious imprecision	none	4/63 (6.3%)	2/63 (3.2%)	RR 2 (0.38 to 10.53)	32 more per 1000 (from 20 fewer to 303 more)	⊕⊕○○ LOW	CRITICAL
								3.2%		32 more per 1000 (from 20 fewer to 305 more)		
Grade 3 or 4 clinical adverse event - 96 weeks												
1	randomised trials	very	no serious	no serious	no serious	none	42/250	46/253 (18.2%)	RR 0.92 (0.63	15 fewer per 1000 (from	⊕⊕○○	CRITICAL

	trials	serious ^{1,2}	inconsistency	indirectness	imprecision		(16.8%)		to 1.35)	67 fewer to 64 more)	LOW	
								18.2%		15 fewer per 1000 (from 67 fewer to 64 more)		
Grade 3 or 4 diarrhoea - 96 weeks												
1	randomised trials	very serious ^{1,2}	no serious inconsistency	no serious indirectness	serious ³	none	1/250 (0.4%)	8/253 (3.2%)	RR 0.13 (0.02 to 1)	28 fewer per 1000 (from 31 fewer to 0 more)	⊕○○○ VERY LOW	IMPORTANT
								3.2%		28 fewer per 1000 (from 31 fewer to 0 more)		
Grade 3 or 4 rash - 96 weeks												
1	randomised trials	very serious ^{1,2}	no serious inconsistency	no serious indirectness	serious ³	none	6/250 (2.4%)	2/253 (0.8%)	RR 3.04 (0.62 to 14.9)	16 more per 1000 (from 3 fewer to 110 more)	⊕○○○ VERY LOW	CRITICAL
								0.8%		16 more per 1000 (from 3 fewer to 111 more)		
Grade 3 or 4 laboratory adverse event - 96 weeks												
1	randomised trials	very serious ^{1,2}	no serious inconsistency	no serious indirectness	no serious imprecision	none	72/250 (28.8%)	80/253 (31.6%)	RR 0.91 (0.7 to 1.19)	28 fewer per 1000 (from 95 fewer to 60 more)	⊕⊕○○ LOW	IMPORTANT
								31.6%		28 fewer per 1000 (from 95 fewer to 60 more)		
Total cholesterol (follow-up 48 weeks; Better indicated by lower values)												
1	randomised trials	very serious ^{1,2}	no serious inconsistency	no serious indirectness	no serious imprecision	none	63	63	-	MD 12 higher (1.3 lower to 25.3 higher)	⊕⊕○○ LOW	NOT IMPORTANT
Grade 3 or 4 LDL cholesterol - 96 weeks												
1	randomised trials	very serious ^{1,2}	no serious inconsistency	no serious indirectness	serious ³	none	7/250 (2.8%)	2/253 (0.8%)	RR 3.54 (0.74 to 16.88)	20 more per 1000 (from 2 fewer to 126 more)	⊕○○○ VERY	NOT IMPORTANT

								0.8%		20 more per 1000 (from 2 fewer to 127 more)	LOW	
Grade 3 or 4 triglycerides - 96 weeks												
1	randomised trials	very serious ^{1,2}	no serious inconsistency	no serious indirectness	no serious imprecision	none	6/250 (2.4%)	16/253 (6.3%)	RR 0.38 (0.15 to 0.95)	39 fewer per 1000 (from 3 fewer to 54 fewer)	⊕⊕○○ LOW	NOT IMPORTANT
								6.3%		39 fewer per 1000 (from 3 fewer to 54 fewer)		
Grade 3 or 4 AST or ALT - 96 weeks												
1	randomised trials	very serious ^{1,2}	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/250 (4%)	16/253 (6.3%)	RR 0.63 (0.29 to 1.37)	23 fewer per 1000 (from 45 fewer to 23 more)	⊕⊕○○ LOW	CRITICAL
								6.3%		23 fewer per 1000 (from 45 fewer to 23 more)		
Lipodystrophy - 48 weeks												
1	randomised trials	very serious ^{1,2}	no serious inconsistency	no serious indirectness	serious ³	none	0/63 (0%)	1/63 (1.6%)	RR 0.33 (0.01 to 8.03)	11 fewer per 1000 (from 16 fewer to 112 more)	⊕○○○ VERY LOW	IMPORTANT
								1.6%		11 fewer per 1000 (from 16 fewer to 112 more)		
Lipodystrophy - 96 weeks												
1	randomised trials	very serious ^{1,2}	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/250 (3.2%)	3/253 (1.2%)	RR 2.7 (0.72 to 10.06)	20 more per 1000 (from 3 fewer to 107 more)	⊕⊕○○ LOW	IMPORTANT
								1.2%		20 more per 1000 (from 3 fewer to 109 more)		

¹ Randomisation and/or allocation concealment not stated

² Large drop-out

³ Wide confidence intervals

Appendix 3: GRADE Tables

3.3. Switch studies: simplification – PI monotherapy

Design: RCTs, Systematic reviews

Population: ART experienced, stable on ART, undetectable VL

Intervention: regimen simplification- PI monotherapy (darunavir or lopinavir)

Outcomes: Viral load, CD4 count, HIV resistance, adverse events, clinical events

NB Outcomes data extracted from main report of study at primary time point (e.g. 48 weeks). Data not extracted again for other time points in the same paper, or other papers from the same study, where this would double count the same patients (e.g. at week 96); data from secondary reports of the same study only added to analysis if different outcomes reported (not in main paper).

Systematic reviews

**Mathis, S., B. Khanlari, et al. (2011). "Effectiveness of Protease Inhibitor Monotherapy versus Combination Antiretroviral Maintenance Therapy: A Meta-Analysis." PLoS ONE [Electronic Resource] 6(7):

This meta-analysis includes data from 10 trials (cut off date for search August 2010): 9 included among those reported below (covering the OK pilot study, OK04, KalMo, Cohn study, KALESOLO, MONOI and MONET trials) plus Echeverria P, Domingo P, Gutierrez M, Mateo G, Fuster M, et al. (2010) Saquinavir/ritonavir monotherapy as a new nucleoside sparing maintenance strategy in long-term virologically suppressed HIV-infected patients. *Curr HIV Res* 8: 467–70. This was excluded from our review as it assesses saquinavir, which is not used as monotherapy.

Our analysis below includes 18 studies (9 overlapping with Mathis review, plus 5 more papers covering aspects of the MONET trial; 3 more OK04; and one paper describing the KAMON2 trial published as an abstract in 2011).

MONET trial

1. ** Arribas, J. R., A. Horban, et al. (2010). "The MONET trial: darunavir/ ritonavir with or without nucleoside analogues, for patients with HIV RNA below 50 copies/ml." AIDS **24**(2): 223-230.

Reference	Study type and methodological quality	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Arribas, J. R., A. Horban, et al. (2010). "The MONET trial: darunavir/ ritonavir with or without nucleoside analogues, for patients with HIV RNA below 50 copies/ml." AIDS 24 (2): 223-230.	<p>RCT</p> <p>Allocation to treatment Random Method of randomisation: unclear Concealment: unclear Blinding not blinded Sample size calculation stated ITT analysis Yes Setting: Outpatients</p>	<p>Total N: 256 10 pts were excluded from the per protocol population (4 monotherapy, 6 triple therapy). 8 of these pts had a history of virological failure before the trial, 1 was imprisoned and 1 left the investigational site indefinitely. Data from 246 pts (123 per arm) were included in the per protocol population. All 256 pts in the</p>	<p>INCLUSION CRITERIA HIV RNA levels below 50 copies/ml on stable triple antiretroviral regimen for at least 24 weeks and no history of virological failure since first starting antiretrovirals. EXCLUSION CRITERIA not stated Baseline comparability between groups: Pts on triple therapy were more likely to be on their 1st antiretroviral regimen (36%) than pts on monotherapy (23%); pts on triple therapy were more likely to be protease inhibitor-naive (28%) than on monotherapy (23%). By hepatitis C serology, 22 (17%) patients had hepatitis C antibodies on monotherapy and 12 (9%)</p>	<p>n=127 Drug(s): darunavir / ritonavir 800/100 mg once daily</p>	<p>n=129 Drug(s): triple therapy arm of two nucleoside analogues (selected by the investigators) and darunavir / ritonavir 800/100 mg once daily. Nucleoside analogues used at baseline</p>	<p>Treatment duration: 48 weeks Assessments at: screening, baseline and then weeks 4, 12, 24, 36 and week 48 Follow-up after end of treatment: none</p>	<p>Primary endpoint: treatment failure, defined as two consecutive HIV RNA levels above 50 copies/ml at week 48, or discontinuation of randomized treatment [commonly known as time to loss of virological response (TLOVR)] Other endpoints: Safety assessments included</p>	Janssen-Cilag

		ITT population were included in the safety analysis.	<p>on triple therapy. At baseline, 13 patients had HIV RNA levels above 50 copies/ml (nine on monotherapy and 4 on triple therapy), despite having results below 50 copies/ml at screening; 2 of these elevations were above 400 copies/ml. These pts were still included in both the per protocol and ITT analyses.</p> <p>Age: mean 44 years Gender: 81% male Severity of disease: mean CD4 cell count 574 cells/ml Duration of disease: median 8 years of known HIV infection, and median of 6.5 years treatment with antiretrovirals</p>		were: tenofovir + emtricitabine (46%), tenofovir + lamivudine (7%), abacavir + lamivudine (31%), zidovudine + lamivudine (10%), or other (6%).		reported adverse events data, clinical laboratory tests (haematology, clinical chemistry, fasting lipids, and urinalysis), physical examination and anthropometric measurements. Clinical and laboratory abnormalities													
<p>Main outcomes: Summary HIV RNA less than 50 copies/ml at week 48, for the per protocol (PP) and intent to treat (ITT) populations.</p> <table border="1"> <thead> <tr> <th>Response</th> <th>Monotherapy (%)</th> <th>Triple therapy (%)</th> <th>Delta (95% CI)</th> </tr> </thead> <tbody> <tr> <td>HIV RNA<50 (PP)</td> <td>86.2 (n=106/123)</td> <td>87.8 (n=108/123)</td> <td>-1.6% (-10.1, +6.8%) i.e. non-inferior</td> </tr> <tr> <td>HIV RNA<50 (ITT)</td> <td>84.3 (n=107/127)</td> <td>85.3 (n=110/129)</td> <td>-1.0% (-9.9, +8.8%) i.e. non-inferior</td> </tr> </tbody> </table> <p>Other outcomes: Median CD4 cell counts remained stable over time in both treatment arms (no data shown).</p>									Response	Monotherapy (%)	Triple therapy (%)	Delta (95% CI)	HIV RNA<50 (PP)	86.2 (n=106/123)	87.8 (n=108/123)	-1.6% (-10.1, +6.8%) i.e. non-inferior	HIV RNA<50 (ITT)	84.3 (n=107/127)	85.3 (n=110/129)	-1.0% (-9.9, +8.8%) i.e. non-inferior
Response	Monotherapy (%)	Triple therapy (%)	Delta (95% CI)																	
HIV RNA<50 (PP)	86.2 (n=106/123)	87.8 (n=108/123)	-1.6% (-10.1, +6.8%) i.e. non-inferior																	
HIV RNA<50 (ITT)	84.3 (n=107/127)	85.3 (n=110/129)	-1.0% (-9.9, +8.8%) i.e. non-inferior																	

	Monotherapy arm (n=127):	Triple therapy (n=129):
Protocol defined treatment failures:	20	19
confirmed HIV RNA elevations	11	7
missing HIV RNA data	0	3
discontinued for adverse events	4	0
discontinued for other reasons	5	9
Of the protocol defined treatment failures:		
HIV RNA levels below 50 copies/ml at week 48	18/20 (90%)	17/19 (89%)
Of those with confirmed HIV RNA elevations, number who changed their antiretrovirals as recommended in the trial protocol	7/ 11 (either adding NRTIs, or switching back to pretrial antiretrovirals)	0/7

Genotypic data were available for 35 of 61 (57%) patients with at least one HIV RNA result above 50 copies/ml (22 and 13 patients in the monotherapy and triple therapy arms, respectively). Thirty-three of these patients showed genotypic and phenotypic sensitivity to all boosted protease inhibitors and NRTIs. One protease inhibitor-pretreated patient in the triple therapy arm had a single genotype, showing resistance to lamivudine (M184V) and to protease inhibitors (V82IT, L90M), when the HIV RNA level was 78 copies/ml. However, the virus was phenotypically sensitive to DRV/r (fold change=1.2). All subsequent visits showed HIV RNA levels below 50 copies/ml. Also, one protease inhibitor-pretreated patient in the monotherapy arm had a single DRV mutation (L33F), when the HIV RNA level was 63 copies/ml at one visit (week 12). However, the virus was phenotypically sensitive to DRV (fold change=0.8) and HIV RNA was suppressed below 50 copies/ml for this patient for all subsequent visits to week 48.

	Monotherapy arm (n=127):	Triple therapy (n=129):
Serious adverse events	9 pts	9 pts
Discontinued study medication for adverse events	8 pts	3 pts
Deaths	0	0
Grade 1–4 adverse events of the nervous system	16% (20 pts)	16% (21 pts)
Grade 1–4 psychiatric adverse events	9%	9%
Discontinued darunavir for grade 3 headache, considered to be drug related	1 pt	0
Grade 2 rash, considered drug-related	1 pt	1 pt
Discontinued the trial for rash	0	0
Grade 3 elevations in alanine aminotransferase and/or aspartate aminotransferase (these patients all had either acute infection with HCV (two cases), presence of HCV antibodies (five cases) or acute hepatitis A infection (one case). Six of these eight patients showed transient elevations in liver enzymes, with values at grade 1 or below at week 48)	6 pts	2 pts

Treatment emergent grade 3 elevations in total cholesterol, sustained for at least two consecutive visits	5 pts	2 pts
At least one red blood cell result below the lower limit of normal ($<4.12 \times 10^{12}/l$)	22.8%	42.6%

Authors' conclusion

Once-daily DRV/r monotherapy has been shown to be noninferior HIV RNA suppression at week 48 (85.4%) compared with a standard control arm of two nucleosides and DRV/r (86.4%). Almost all patients on DRV/r monotherapy had full HIV RNA suppression, at week 48 in the MONET trial: although this strategy warrants further evaluation, these data suggest that a switch to DRV/r monotherapy can be considered in treatment-experienced patients who have a history of HIV RNA levels below 50 copies/ml on other treatments, but who are wishing to avoid toxicities related to nucleoside analogues, non-nucleosides or other antiretrovirals.

2. ** Clumeck, N., A. Rieger, et al. (2011). "96 week results from the MONET trial: a randomized comparison of darunavir/ritonavir with versus without nucleoside analogues, for patients with HIV RNA <50 copies/mL at baseline." Journal of Antimicrobial Chemotherapy **66**(8): 1878-1885.

Reference: Clumeck, N., A. Rieger, et al. (2011). "96 week results from the MONET trial: a randomized comparison of darunavir/ritonavir with versus without nucleoside analogues, for patients with HIV RNA <50 copies/mL at baseline." Journal of Antimicrobial Chemotherapy **66**(8): 1878-1885.

MONET trial: methodology as above except this paper reports 96 week outcomes

Main outcomes:

Efficacy endpoint, week 96	Monotherapy n=127	Triple therapy n=129	Difference (95% CI)
HIV RNA <50 copies/mL, switch=failure, TLOVR, per protocol	95/122 (78%)	101/123 (82%)	-4.2% (-14.3%, +5.8%)
HIV RNA <50 copies/mL, switch=failure, TLOVR, ITT	95/127 (75%)	104/129 (81%)	-5.8% (-16.0%, +4.4%)

Median CD4 counts remained stable over time in both treatment arms (no data shown).

	Monotherapy arm (n=127):	Triple therapy (n=129):
Protocol defined treatment failures:	32	25
confirmed HIV RNA elevations	15	11
withdrew from the trial before week 96 (started new antiretrovirals)	17 without prior virological failure	14 (12 without virological failure; 1 known virological failure)

		failure; 1 missing data)
Of the confirmed HIV RNA elevations: HIV RNA levels below 50 copies/ml at week 96/most recent visit	11/15	10/11
Of those with confirmed HIV RNA elevations, number who changed their antiretrovirals as recommended in the trial protocol	9/15 (either adding nucleoside reverse transcriptase inhibitors (NRTIs) or switching back to pre-trial antiretrovirals)	0/11

76 pts (41 on monotherapy, 35 on triple therapy) had at least one HIV RNA result >50 copies/mL during the trial and were genotyped. Genotyping was successful for 48 patients (21 and 27 patients in the monotherapy and triple therapy arms, respectively). 46 of these 48 pts (96%) showed genotypic and phenotypic sensitivity to all boosted PIs and NRTIs. Major IAS–USA PI mutations were detected in one pt per treatment arm, during short-term elevations in HIV RNA. In the monotherapy arm, the L33F mutation was detected at a single visit, when the HIV RNA level was 63 copies/mL. In the triple therapy arm, PI mutations detected before the trial re-emerged, when the HIV RNA level was 78 and 50 copies/mL during an interruption of treatment. Both pts remained phenotypically sensitive to darunavir during follow-up, with sustained HIV RNA ,50 copies/ mL during the trial and no change in antiretroviral treatment.

	Monotherapy arm (n=127):	Triple therapy (n=129):
Serious adverse events	13 pts (10.2%)	13 pts (10.1%)
Deaths	0	0
Grade 1–4 adverse events of the nervous system	25 (19.4%)	29 (22.8%)
Grade 2–4 adverse events of the nervous system	10 (7.8%)	10 (7.9%)
Grade 1–4 psychiatric adverse events	20 (15.5%)	15 (11.8%)
Grade 2–4 psychiatric adverse events	9 (7.0%)	11 (8.7%)
Grade 3 nervous system or psychiatric adverse event	1 (pt discontinued treatment for headache)	2: 1 pt had grade 3 depression and 1 had a loss of libido.
Neuropsychiatric adverse events that would suggest CNS viraemia	0	0
Grade 3–4 abnormalities in alanine aminotransferase *	8 (6.3%)	3 (2.4%)
Grade 3–4 abnormalities in aspartate transaminase *	5 (3.9%)	3 (2.4%)
Grade 3–4 abnormalities in lipase	4 (3.2%)	3 (2.4%)
Grade 3–4 abnormalities in low-density lipoprotein	12 (9.4%)	10 (7.8%)
Grade 3–4 abnormalities in total cholesterol	14 (11.0%)	5 (3.9%)
of whom elevations at a single timepoint only	8/14	2/5
sustained elevations	6/14	3/5
Grade 3–4 abnormalities in triglycerides	4 (3.2%)	1 (0.8%)

Grade 3–4 abnormalities in haemoglobin	0	2 (1.6%)
Grade 3–4 abnormalities in neutrophils	0	2 (1.6%)
Grade 1–4 haematuria of which grade 3 (severe)	4 1 (this pt had stopped taking tenofovir at the baseline visit)	12 (of whom 8 receiving tenofovir) 6
Clinical adverse events at least one grade 1–4 adverse event	112 (86.8%)	109 (84.5%)

*Elevations in alanine transaminase and aspartate transaminase were associated with acute or chronic infection with hepatitis A or hepatitis C.

Authors' conclusion

These results suggest that the strategy of switching to darunavir/ritonavir monotherapy can be considered in treatment-experienced patients who have a history of HIV RNA levels <50 copies/mL on other treatments, but who wish to avoid toxicities related to nucleoside analogues, non-nucleosides or other antiretrovirals. If necessary, patients who show low-level elevations in HIV RNA during darunavir/ritonavir monotherapy can be successfully re-intensified with nucleoside analogues to re-suppress HIV RNA below detectable levels.

3. * Garvey, L., C. Higgs, et al. (2010). "Changes in cerebral function parameters in HIV-1 infected subjects undergoing a treatment simplification to darunavir/ritonavir :A randomized, prospective study." *Antiviral Therapy* **15**: A70. 12TH Int Workshop on Adverse drug reactions and co-morbidities P42 (**conference abstract**)- published *AIDS Research and Human retroviruses* 2011; 27 (7): 701-703 (**letter**)
According to the protocol this study should be excluded as it is only published as a letter (very small sub-sample of MONET, n=6)
4. * Gazzard, B., A. Hill, et al. (2011). "Cost-efficacy analysis of the MONET trial using UK antiretroviral drug prices." *Applied Health Economics & Health Policy* **9**(4): 217-223.

Reference: Gazzard, B., A. Hill, et al. (2011). "Cost-efficacy analysis of the MONET trial using UK antiretroviral drug prices." *Applied Health Economics & Health Policy* **9**(4): 217-223.

MONET trial: methodology as above except the purpose of this analysis was to calculate the potential cost savings from the use of DRV/r monotherapy in the UK. The UK costs per patient with HIV RNA <50 copies/mL at week 48 (responders) were calculated using a 'switch included' analysis to account for additional antiretrovirals taken after initial treatment failure. By this analysis, efficacy was 93.5% versus 95.1% in the DRV/r monotherapy and triple therapy arms, respectively. *British National Formulary* 2009 values were used.

Main outcomes:

Before the trial, the mean annual cost of antiretrovirals was £6906 for patients receiving NNRTI-based HAART, and £8348 for patients receiving PI-based HAART. During the MONET trial, the mean annual per-patient cost of antiretrovirals was £8642 in the triple therapy arm, of which 55% was from NRTIs and 45% from PIs. The mean per-patient cost in the monotherapy arm was £4126, a saving of 52% versus triple therapy. The mean cost per responder was

£9085 in the triple therapy arm versus £4413 in the DRV/r monotherapy arm.

Authors' conclusion

Based on the MONET results, the lower cost of DRV/r monotherapy versus triple therapy in the UK would allow more patients to be treated for fixed budgets, while maintaining HIV RNA suppression at <50 copies/mL. If all patients meeting the inclusion criteria of the MONET trial in the UK were switched to DRV/r monotherapy, there is the potential to save up to £60 million in antiretroviral drug costs from the UK NHS budget.

5. * Pulido, F., J. R. Arribas, et al. (2011). "Analysis of drug resistance during HIV RNA viraemia in the MONET trial of darunavir/ritonavir monotherapy." *Antiviral Therapy* **16**(1): 59-65.

Reference: Pulido, F., J. R. Arribas, et al. (2011). "Analysis of drug resistance during HIV RNA viraemia in the MONET trial of darunavir/ritonavir monotherapy." *Antiviral Therapy* **16**(1): 59-65.

MONET trial: methodology as above except this paper only reports on drug resistance.

Main outcomes:

The results are a duplicate of those reported in the Arribas 2010 paper reported above and are not data extracted again to avoid double counting the same patients.

Authors' conclusion

Drug resistance to PIs in the MONET trial was uncommon.

6. *Winston, A., G. Fatkenheuer, et al. (2010). "Neuropsychiatric adverse events with ritonavir-boosted darunavir monotherapy in HIV-infected individuals: a randomised prospective study." *HIV Clinical Trials* **11**(3): 163-169

Reference: Winston, A., G. Fatkenheuer, et al. (2010). "Neuropsychiatric adverse events with ritonavir-boosted darunavir monotherapy in HIV-infected individuals: a randomised prospective study." *HIV Clinical Trials* **11**(3): 163-169

MONET trial: methodology as above except this paper reports clinician-reported neuropsychiatric events (clinical adverse events graded by severity as either grade 1 (mild), grade 2 (moderate), grade 3 (severe), or grade 4 (life-threatening) and whether adverse events were related to study medication using the Division of AIDS 2007 classification system) and patient-reported neuropsychiatric events (self-scored memory and concentration assessment using part of the Functional Assessment of HIV Infection (FAHI) questionnaire, and an assessment of cognitive function) over 48 weeks.

Main outcomes:

Grade 1–4 central nervous system and psychiatric adverse events by treatment arm		
	DRVrMono (n=127)	DRVrNRTI (n=129)
All CNS adverse events, n (%)	20 (15.7%)	21 (16.3%)
Areflexia	0	1
Burning sensation	0	1
Carotid artery stenosis	1	0
Disturbance in attention	0	1
Dizziness	1	3
Dysgeusia	1	1
Headache	10	9
Hypoesthesia	2	1
Intracranial hypotension	1	0
Nervous system disorder	0	1
Parosmia	2	0
Post herpetic neuralgia	1	0
Cervical radiculitis	0	2
Sciatica	0	1
Syncope	2	0
Tremor	0	1
Trigeminal neuralgia	1	0
All psychiatric adverse events, n (%)	12 (9.4%)	12 (9.3%)
Anxiety disorder	0	1
Apathy	1	0
Depression	7	3
Drug dependence	0	2
Insomnia	0	3
Libido decreased	1	1
Nightmare	0	1
Obsessive-compulsive disorder	1	0
Psychotic disorder	1	0
Sleep disorder	4	5
Stress	0	1

Most of these events were grade 1 (mild) in severity and not judged to be related to study medication. The most frequently observed CNS adverse event was headache (reported by 19 patients), while the most frequently observed psychiatric adverse event was depression (reported by 10 patients). Of the 32 grade 1–4 neuropsychiatric adverse events in the DRVrMono arm, two were grade 2–4 and drug related (both cases were of headache); of the 33 grade 1–4 neuropsychiatric adverse events in the DRVrNRTI arm, three were judged grade 2–4 and drug related (headache, migraine, and cervical radiculitis). One patient in the DRVrMono arm discontinued darunavir for a grade 3 headache.

Change from baseline in FAHI cognitive functioning score:

Study group	Week 24		Week 48		<i>P</i> value for difference in change between study treatment groups at week 48, Student <i>t</i> test.
	Mean ± <i>SD</i>	No. of subjects	Mean ± <i>SD</i>	No. of subjects	
Overall	0.2 ± 2.8	211	0.1 ± 2.6	206	0.76
DRVrMono	0.1 ± 2.7	99	0.0 ± 2.7	95	
DRVrNRTI	0.4 ± 2.9	112	0.1 ± 2.5	111	

Authors' conclusion

In this exploratory analysis, no differences in the evolution of neuropsychiatric adverse events over 48 weeks are observed in HIV-infected subjects randomised to switch antiretroviral therapy to darunavir/ritonavir with or without nucleoside reverse transcriptase inhibitors.

- * The MONET trial: week 144 analysis of efficacy of darunavir/ritonavir monotherapy versus DRV/r + 2NRTIs, for patients with HIV RNA < 50 copies/mL at baseline. [J. Arribas](#), N. Clumeck, M. Nelson, A. Hill, Y. van Delft, C. Moecklinghoff. abstract no. MOPE216, IAS 2011 (**conference abstract**)
Same patients and outcome measures as above – not data extracted again as would be double counting.

Reference: The MONET trial: week 144 analysis of efficacy of darunavir/ritonavir monotherapy versus DRV/r + 2NRTIs, for patients with HIV RNA < 50 copies/mL at baseline. [J. Arribas](#), N. Clumeck, M. Nelson, A. Hill, Y. van Delft, C. Moecklinghoff. abstract no. MOPE216, IAS 2011 (**conference abstract**)

MONET trial: methodology as above except this paper reports results at week 144.

Main outcomes:

By Week 144, HIV RNA < 50 copies/mL (ITT, TLOVR, Switch=Failure) was 69% versus 75% in the DRV/r monotherapy and triple therapy arms (difference = -5.9%, 95% C.I. -16.9%, +5.1%); by a switch included analysis, HIV RNA < 50 copies/mL was 84% versus 83.5% (difference = +0.5%, 95% C.I.: -8.7%, +9.7%). 21 and 13 patients had two consecutive HIV RNA results above 50 copies/mL in the DRV/r monotherapy arm and triple therapy arm respectively, of whom 18/21 (86%) and 10/13 (77%) had HIV RNA < 50 copies/mL at Week 144. One patient per arm showed a major IAS-USA PI mutation. HIV RNA at baseline and Hepatitis C co-infection were significantly associated with transient viraemia during the trial ($p < 0.05$ for each comparison); treatment arm was not

associated with virological failure in any analysis.

Authors' conclusion

In this study for patients with HIV RNA < 50 copies/mL at baseline, switching to DRV/r monotherapy showed non-inferior efficacy to DRV/r + 2NRTI in the switch included analysis, but not in the primary TLOVR switch equals failure analysis.

- *Fox, J., B. Peters, et al. (2011). "Improvement in vitamin D deficiency following antiretroviral regime change: Results from the MONET trial." AIDS Research & Human Retroviruses 27(1): 29-34.

The aim of this substudy of the MONET trial was to describe the factors associated with vitamin D deficiency at the baseline visit, and investigate the impact of changes in antiretroviral treatment during the trial on changes in vitamin D levels. This is not one of the specified outcomes – exclude.

MONOtherapy Inhibitor protease (MONOI) study performed at 32 Agence Nationale de Recherche sur le SIDA et les Hépatites Virales (ANRS) sites in France (Clinical trial registration NCT00421551)

- ** Katlama, C., M. A. Valantin, et al. (2010). "Efficacy of darunavir/ritonavir maintenance monotherapy in patients with HIV-1 viral suppression: a randomized open-label, noninferiority trial, MONOI-ANRS 136." AIDS 24(15): 2365-2374

Reference	Study type and methodological quality	No pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Katlama, C., M. A. Valantin, et al. (2010). "Efficacy of darunavir/ritonavir maintenance monotherapy in patients with HIV-1 viral suppression: a	RCT Allocation to treatment Random Method of randomisation: unclear Concealment: adequate	Total N: 225	INCLUSION CRITERIA: HIV-1-infected pts ≥18 years of age on triple antiretroviral drug regimen; plasma HIV-1 RNA < 400 copies/ml for the past 18 months, based on ≥4 viral load measurements, and < 50 copies/ml at screening; no history of virologic failure while on a protease inhibitor-	n=112 Drug(s): darunavir monotherapy	n=113 Drug(s): triple drug darunavir - containing regimen	Treatment duration: 96 weeks Assessments at: randomization and at weeks 4, 8	Primary endpoint: the proportion of patients with treatment success by week 48 (Treatment failure: virologic failure [2 consecutive	Janssen-Cilag provided darunavir ; financial support from Agence Nationale de

<p>randomized open-label, noninferiority trial, MONOI-ANRS 136." AIDS 24(15): 2365-2374</p>	<p>Blinding not blinded Sample size calculation stated ITT analysis Yes Setting: Outpatients</p>	<p>containing regimen; documented CD4 lymphocytes nadir > 50 cells/ml and acceptable laboratory results at screening. First phase: darunavir 600/100 mg twice daily was introduced for 8 weeks as a component of a triple drug regimen instead of the protease inhibitor, NNRTI or third NRTI. Pts whose HIV viral load remained < 50 copies/ml 4 weeks after darunavir induction and who had no severe adverse event or darunavir-related toxicity were included.</p> <p>EXCLUSION CRITERIA: Pts with a history of HIV-related neurological disease or with hepatitis B coinfection</p> <p>Baseline comparability between groups: yes</p> <p>Age: median 45 (IQR 39–56) triple therapy and 46 (IQR 41–51) monotherapy Gender: 87 (77%) male triple therapy and 83 (74%) monotherapy Severity of disease: median</p>		<p>and every 8 weeks thereafter</p> <p>Follow-up after end of treatment: none</p>	<p>measurements of HIV-1 RNA >400 copies/ml within 2 weeks]; treatment modification [any] or discontinuation; withdrawal; pts with a single value of HIV-1 RNA > 400 copies/ ml and a missing second HIV-1 RNA measurement.</p> <p>Other endpoints: proportion of pts with HIV-1 RNA level < 50 copies/ml and < 400 copies/ ml at each study visit, changes in CD4 cell count and emergence of resistance mutations. For these secondary endpoints, missing data due to missed</p>	<p>Recherche sur le SIDA et les Hépatites Virales, Paris, France (ANRS-MONOI ANRS 136 trial)).</p>
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			CD4 cells at baseline 582 (IQR 390–780) triple therapy and 585 (457–757) monotherapy Duration of disease: median 8.9 (IQR 4.2–15.6) years triple therapy and 11.7 (6.5–15.9) monotherapy Duration of ART: median 7.8 (IQR 3.0–11.3) years triple therapy and 8.7 (4.6–11.3) monotherapy				evaluations were ignored.	
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Main outcomes:

48 weeks	Darunavir/r triple therapy	Darunavir/r monotherapy	Difference (%)	90% Confidence interval
Therapeutic success (PP)	101/102 (99.0%)	96/102 (94.1%)	-4.9	(-9.1 to -0.8)
Therapeutic success (ITT)	104/113 (92.0%)	98/112 (87.5%)	-4.5	(-11.2 to +2.1)

Other outcomes:

HIV-1 RNA response to treatment.

	Darunavir/r triple therapy	Darunavir/r monotherapy	Difference	95% Confidence interval
All HIV-1 RNA <50 copies/ml (PP)	82/102 (80.4)	75/102 (73.5)	-6.86	-18.4 to +4.7
All HIV-1 RNA <50 copies/ml (ITT)	91/113 (80.5)	82/112 (73.2)	-7.32	-18.3 to +3.7

	Monotherapy arm (n=112):	Triple therapy (n=113):
Protocol defined treatment failures:	11	9
confirmed HIV RNA elevations	3*	0
adverse events	4	5
pregnancy	1	0
other reasons	3	1
withdrew consent	3	3

*1 low adherence to therapy; 1 had a viral load at week 24 of 411 copies/ml with an adequate darunavir trough concentration of 3480 ng/ml; 1 had discontinued therapy at week 32 with a viral load of 484,569 copies/ml; all 3 patients resuppressed HIV-1 RNA after the addition of two NRTIs. From the three observed virologic failures, one patient had the V11I mutation at failure, but the mutation was also found retrospectively in a previous sample 7 years prior to study entry. No darunavir resistance-associated mutations were found in the other two patients at failure. No darunavir

resistance mutations were also found in the 13 other patients having two consecutive plasma HIV-1 RNA more than 50 copies/ml (11 in the darunavir/r monotherapy group and two in the darunavir/r triple therapy).

At week 48, the median CD4 cell count was 574 cells/ml [interquartile range (IQR) 452–825, median increase 36 cells/ml, IQR-71 to +100] on darunavir/r triple therapy and 621 cells/ml (IQR 481–778, median increase 6 cells/ml, IQR -53 to +93) on darunavir/r monotherapy (P=0.58 by the Wilcoxon rank-sum test).

Adverse events:

	Darunavir/r monotherapy N=112	Darunavir/r triple therapy N=113
Treatment-limiting event, n (%):		
CNS disorders	2 (2%)	0
Hepatic aminotransferase >5 times ULN	0	1 (1%)
Lipodystrophy	1 (1%)	1 (1%)
Hyperglycemia	1 (1%)	0
Hypertriglyceridemia	0	1 (1%)
Diarrhoea	0	1 (1%)
Asthenia	0	1 (1%)
Grade 3 or 4 clinical event:		
Any new sign or symptom	13 (12%)	11 (10%)
Infectious disease events	3 (3%)	2 (2%)
Cardiovascular events	1 (1%)	2 (2%)
Grade 3 or 4 laboratory abnormality:		
Hepatic aminotransferase >5 times ULN	1 (1%)	2 (2%)
Creatine kinase >5 times ULN	0	1 (1%)
Fasting triglycerides >750 mg/dl	1 (1%)	0
Fasting cholesterol >400 mg/dl	0	1 (1%)

Authors' conclusion

Darunavir/r monotherapy exhibited efficacy rate over 85% with concordant results in the magnitude of difference with darunavir/r triple drug regimen in both intent-to-treat and per protocol analyses, but discordant conclusions with respect to the noninferiority margin. Patients failing on darunavir/r monotherapy had no emergence of new darunavir resistance mutations preserving future treatment options.

OK Pilot study

1. ** Arribas J et al (2005). Lopinavir/r as single drug therapy for maintenance of HIV-1 viral suppression. 48-week results of a randomised controlled open label proof of concept pilot clinical trial (OK study) JAIDS 2005, 40: 280-287.

Reference	Study type/ methodological quality	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Arribas J et al (2005). Lopinavir/r as single drug therapy for maintenance of HIV-1 viral suppression. 48-week results of a randomised controlled open label proof of concept pilot clinical trial (OK study) JAIDS 2005, 40: 280-287.	RCT Allocation to treatment Random Method of randomisation: adequate (computer-generated) Concealment: adequate Blinding not blinded Sample size calculation pilot trial: 21 patients per arm the study had a statistical power of 80% to detect a 41% difference between treatment arms ITT analysis Yes Setting:	Total N: 42	INCLUSION CRITERIA: at least 18 years old, no history of virologic failure while receiving a protease inhibitor, receiving 2 NRTIs (or tenofovir and 1 nucleoside) and lopinavir/r (400/100 mg b.i.d.) for at least 4 weeks, had had <50 copies of HIV RNA/mL for at least the prior 6 months. EXCLUSION CRITERIA: pregnancy, serum hepatitis B surface antigen, need for treatment with agents known to have potential major interactions with lopinavir/r, major psychiatric disease. Baseline comparability between groups: yes Age: median 42 (range 25-54) years Gender: 17 (81%) male on monotherapy and 18 (86%) male on triple therapy	n=21 Drug(s): lopinavir/r (400/100 mg b.i.d.)	n=21 Drug(s): 2 NRTIs (or tenofovir and 1 nucleoside).	Treatment duration: Assessments at: baseline, 1, 2, 4, 8, 12, 16, and 24 weeks and every 12 weeks thereafter until week 48.	Primary endpoint: proportion of pts with <500 copies/mL of HIV RNA of plasma at 48 weeks. Secondary efficacy outcomes: proportion of pts with <50 copies/mL of HIV RNA at week 48, time to loss of virologic suppression through week 48, HIV resistance, changes in the CD4 cell count, frequency and severity of treatment-related adverse events, incidence of laboratory abnormalities, changes in clinical	Abbott Laboratories

	Outpatients		Severity of disease: median CD4 cells/ μ l: 662 (IQR 446–740) on monotherapy and 585 (331–721) on triple therapy				and laboratory values	
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Main outcomes/Effect Size:

In an intent-to-treat analysis, with missing HIV RNA level values or change in randomized therapy considered to be >500 copies/mL, 81% (17/21, 95% CI: 64% to 98%) of the patients in the monotherapy group and 95% (20/21, 95% CI: 86% to 100%) of the patients in the triple-therapy group maintained an HIV RNA level of <500 copies/mL at week 48 (P = 0.34; Fisher exact test).

Other outcomes:

All patients who had an HIV RNA level of <500 copies/mL at week 48 were also below detection limit using the <50-copies/mL cutoff. The 95% CI for the difference in response rates at week 48 was -33.4% to +4.9%.

At 72 weeks, percent of patients <50 copies/mL (intention to treat) were 81% (monotherapy arm) and 90.5% (triple-therapy arm). The 95% CI for this difference in response rates at week 72 was -30.5% to +11.4%.

At week 48:	Monotherapy arm (n=21):	Triple therapy (n=21):
Discontinuation due to noncompliance	1	0
Discontinuation due to adverse event	0	1 (hyperlipidemia not responding to lipid-lowering drugs)
Loss of virologic suppression	3 (nucleosides were added back)	0

In patients with loss of virologic suppression after starting lopinavir/r monotherapy, development of primary or active site mutations in the protease was not detected by standard genotyping.

No significant change in CD4 cell count was seen in any group from baseline to week 48. The mean increase from baseline in CD4 cell counts at week 48 was 70 cells/mL for the monotherapy group and 8 cells/mL for the triple-therapy group (P = 0.36; Mann–Whitney U test).

Adverse events:

	Darunavir/r monotherapy N=21	Darunavir/r triple therapy N=21
Grade 3 hypertriglyceridemia	0	1
Grade 3 hypercholesterolemia	1	1

Authors' conclusion

Most of the patients maintained with lopinavir/ritonavir monotherapy remain with undetectable viral load after 48 weeks. Failures of lopinavir/ritonavir monotherapy were not associated with the development of primary resistance mutations in the protease gene and could be successfully reinduced adding back prior nucleosides.

2. *Pulido, F., R. Delgado, et al. (2008). "Long-term (4 years) efficacy of lopinavir/ritonavir monotherapy for maintenance of HIV suppression." *Journal of Antimicrobial Chemotherapy* **61**(6): 1359-1361. (comment: long term FU of OK and OK4 trials of PI monotherapy arm – cohort analysis)
Long-term cohort follow up of the 21 patients in the Arribas 2005 OK pilot trial (exclude – no comparator)

OK04 study

1. ** Pulido, F., J. R. Arribas, et al. (2008). "Lopinavir-ritonavir monotherapy versus lopinavir-ritonavir and two nucleosides for maintenance therapy of HIV." *AIDS* **22**(2): F1-9.

Reference	Study type and methodological quality	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Pulido, F., J. R. Arribas, et al. (2008). "Lopinavir-ritonavir monotherapy versus lopinavir-ritonavir and two nucleosides for maintenance therapy	RCT Allocation to treatment Random Method of randomisation: adequate (computer-generated) Concealment: adequate Blinding not blinded Sample size	Total N: 205	INCLUSION CRITERIA at least 18 years old, no previous suspected or confirmed virological failure while receiving a protease inhibitor, receiving two nucleoside reverse transcriptase inhibitors (or one nucleoside plus tenofovir DF) and lopinavir-ritonavir soft gel capsule (400/100 mg bid) for at least 4 weeks and had <50 copies of HIV RNA/mL for at least the	n=103 Drug(s): LPV/r	n=102 Drug(s): LPV/r + 2 NRTIs	Treatment duration: Assessments at: at baseline, week 4, week 12, and every 12 weeks thereafter until week 48 Follow-up	Primary endpoint: proportion of pts without therapeutic failure at 48 weeks, defined as any of: i) 2 consecutive measurements of HIV RNA >500 copies/mL separated by at least 2 weeks [pts on monotherapy who failed by this definition were not considered therapeutic failures if at the time of failure there was no evidence of lopinavir-ritonavir genotypic	Abbott Laboratories and the Fundació n de Investigació n Mèdica Mutua Madrileña (MUTUA 2005-066).

<p>of HIV." AIDS 22(2): F1-9.</p>	<p>calculation stated ITT analysis Yes Setting: Outpatients</p>		<p>prior 6 months. Pts with a single transitory episode of detectable viral load ('blip', defined as an HIV RNA viral load >50 copies/mL preceded and followed by one HIV-RNA viral load <50 copies/mL without changes in antiretroviral treatment) during the prior 6 months could also been included.</p> <p>EXCLUSION CRITERIA: pregnancy, serum hepatitis B surface antigen in pts treated with lamivudine, emtricitabine or tenofovir DF, need for treatment with agents known to have potential major interactions with lopinavir-ritonavir, major psychiatric disease</p> <p>Baseline comparability between groups: yes</p> <p>Age: median 41 (range 28-78) years on monotherapy and 42 (26-65) years on triple therapy</p> <p>Gender: 79 (78%) male on monotherapy and 84 (82%) on triple therapy</p>			<p>after end of treatment:</p>	<p>resistance, were reinduced with two nucleosides and were suppressed to <50 copies/mL of HIV RNA at 48 weeks]; (ii) change of randomized therapy for reasons different from re-induction in the monotherapy group; (iii) treatment discontinuation; (iv) loss to follow-up; (v) for patients re-induced in the monotherapy group: decrease in HIV RNA <1 log₁₀ 4 weeks after reinduction or failure to reach HIV RNA <50 copies/mL 16 weeks after reinduction).</p> <p>Other endpoints: proportion of pts with virological failure (HIV RNA >50 or >500 copies/ mL, according to the analysis) through week 48. Missing data, early termination of participation in the study, or re-induction with nucleosides in the monotherapy group were considered to be failures in these analyses. Also</p>	
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			Severity of disease: median CD4 cells per µl: 474 (IQR 340–660) on monotherapy and 473 (307–673) on triple therapy				development of HIV resistance and changes in the CD4 cell count.	
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Main outcomes:

At week 48:	Monotherapy arm (n=103):	Triple therapy (n=102):
Randomised but not dosed	3	4
Discontinuations	4 (3 loss to follow-up, 1 change of therapy)	7 (3 adverse events, 4 loss to follow-up)
Loss of virologic suppression (per protocol analysis)	6/100 (2 therapeutic failure [1 resistance, 1 did not maintain virological suppression after resuming baseline nucleosides]; 4 resuppressions on NRTIs)	3/98
ITT analysis (missing HIV RNA level values or change in randomized therapy, including successful reinduction with nucleosides in the monotherapy group, were considered to be failures)	85% not failures (85/100)	90% not failures (88/98)
If those randomised but not dosed considered failures:	82.5% (85/103)	88.2% (90/102)

Other outcomes:

The mean increase from baseline in CD4 cell counts at week 48 was 65 cells/mL for the monotherapy group and 31cells/mL for the triple therapy group (P=0.31; Mann- Whitney U test).

Study drug-related adverse events of at least moderate severity occurred in three patients in the triple therapy group (3%) and none (0%) in the monotherapy group (P=0.08). The three adverse events in the triple therapy group were diarrhoea (two patients) and insomnia. These three adverse events resulted in treatment discontinuation.

At week 48:	Monotherapy arm (n=103):	Triple therapy (n=102):
Grade 3 or 4 hypertriglyceridaemia	3	3
Grade 3 or 4 hypercholesterolemia	10	4
Grade 3 or 4 aspartate aminotransferase (AST) or alanine aminotransferase (ALT)	4	2

elevations (5 of the 6 pts were coinfecting with hepatitis C virus)		
<p>In both treatment groups there were no statistically significant changes from baseline in fasting total cholesterol, high-density lipoprotein cholesterol or triglycerides. No patient discontinued the study because of elevated lipid or aminotransferase levels.</p> <p>There were 15 patients (11 in the monotherapy group, four in the triple therapy group) who qualified for genotypic testing due to a HIV RNA >500 HIV RNA copies/mL. Protease inhibitor associated mutations were detected in three subjects, two (2%) in the monotherapy group, and one (1%), in the triple group (P=0.56; Fisher exact test). All three subjects had exhibited more than one episode of viraemia >500 copies/mL. Reverse transcriptase mutations were detected in two subjects, one in the monotherapy group and one in the triple therapy group.</p> <p>Authors' conclusion 48 weeks of lopinavir-ritonavir monotherapy with reintroduction of nucleosides as needed was non-inferior to continuation of two nucleosides and lopinavir-ritonavir in patients with prior stable suppression. However, episodes of low level viremia were more common in patients receiving monotherapy.</p>		

2. ** Arribas, J. R., R. Delgado, et al. (2009). "Lopinavir-ritonavir monotherapy versus lopinavir-ritonavir and 2 nucleosides for maintenance therapy of HIV: 96-week analysis." Journal of Acquired Immune Deficiency Syndromes: JAIDS **51**(2): 147-152.

Reference: Arribas, J. R., R. Delgado, et al. (2009). "Lopinavir-ritonavir monotherapy versus lopinavir-ritonavir and 2 nucleosides for maintenance therapy of HIV: 96-week analysis." Journal of Acquired Immune Deficiency Syndromes: JAIDS 51 (2): 147-152.		
OK04 trial: methodology as above except 96 week outcomes (not analysed again as double counting)		
Main outcomes/Effect Size:		
At week 96: (Only Patients Randomized and Dosed)	Monotherapy arm (n=100):	Triple therapy (n=98):
Still receiving randomized therapy	77	76
Therapeutic failure	13	22
Loss of virologic control (confirmed HIV RNA >500 copies/mL)	6	5
Reinduction with nucleosides due to HIV RNA >500 copies/mL	5	NA
Reinduction with nucleosides due to HIV RNA >50 HIV RNA copies/mL but <500 copies/mL	7	NA
Lost to follow-up	8	9

Death (Myocardial infarction after cocaine use, with HIV RNA <50 copies per millilitre)	1	0
Change in randomized treatment (not due to reinduction)	1	0
Discontinuation due to adverse events	0	8 (p = 0.003)

By an intention to treat analysis in which missing data and reinduction with nucleosides are considered failures, 77.6% (76 of 98) of patients receiving triple therapy had an HIV RNA <50 copies per millilitre compared with 77% (77 of 100) of patients receiving monotherapy (P = 0.865; log rank). At week 96, by observed treatment analysis in which missing data or change in therapy is censored and reinduction with nucleosides is considered failure, 94.4% of patients receiving triple therapy had an HIV RNA <50 copies per millilitre compared with 86.4% of patients receiving monotherapy (P = 0.06; log rank).

At week 96, proportion of patients without therapeutic failure according to our primary end point definition (for which the 10 patients with successful reinductions are not considered failures) was 78% in the triple therapy group and 87% in the monotherapy group (difference: 29%; 95% CI: 220% to +1.2%, P = 0.09). The upper limit of the CI for the difference (+1.2%) fulfilled the preestablished criteria for noninferiority of the monotherapy group.

Other outcomes:

The mean increase from baseline in CD4 cell counts at week 96 was 71 cells per microliter in the monotherapy group and 47 cells per microliter in the triple therapy group (difference not statistically significant).

In total, after 2 years of follow-up, proportion of patients rebounding with isolates containing major protease inhibitor mutations was 2% in the monotherapy group and 2% in the triple therapy group.

At week 96, 8 patients had discontinued randomized therapy due to adverse events in the triple therapy group vs. none in the monotherapy group (P = 0.003).

In both treatment groups, there were no statistically significant changes from baseline in fasting total cholesterol, high-density lipoprotein cholesterol, or triglycerides. No patient discontinued the study because of elevated lipid or aminotransferase levels.

At week 96:	Monotherapy arm (n=100):	Triple therapy (n=98):
Grade 3 or 4 hypertriglyceridaemia	8	6
Grade 3 or 4 hypercholesterolemia	11	7
Grade 3 or 4 aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations (10 of the 11 pts were coinfectd with hepatitis C virus)	7	4

Authors' conclusion

The 96 week results of the OK04 trial continue to support the efficacy and safety of the lopinavir–ritonavir monotherapy strategy. Although episodes of low-level viremia were more frequent in the monotherapy group, we did not observe an increased risk of resistance development and most of these patients could be resuppressed restarting nucleosides. The toxicity of the monotherapy regimen was lower than the toxicity of the triple regimen.

3. *Pulido, F., I. Perez-Valero, et al. (2009). "Risk factors for loss of virological suppression in patients receiving lopinavir/ritonavir monotherapy for maintenance of HIV suppression." *Antiviral Therapy* **14**(2): 195-201

Exclude – this is looking at the cohort of 121 patients on monotherapy in OK and OK04 studies and correlating risk factors for risk of suppression (no comparator)

4. * F. Pulido, J. Arribas and OK04 Study Group. No effect of HCV infection on virological response 96 weeks after simplification to lopinavir/ritonavir (LPV/r) monotherapy (MT) in the OK04 trial. MOPE217. 6th IAS Conference. 17th-20th July 2011. Rome. Italy (Conference abstract)

Reference: F. Pulido, J. Arribas and OK04 Study Group. No effect of HCV infection on virological response 96 weeks after simplification to lopinavir/ritonavir (LPV/r) monotherapy (MT) in the OK04 trial. MOPE217. 6th IAS Conference. 17th-20th July 2011. Rome. Italy (Conference abstract)

OK04 trial: methodology as above except this paper assessed the impact of baseline anti-HCV+ on 96 week outcomes in the OK04 study (i.e. sub-group analysis; not analysed again).

Main outcomes/Effect Size:

HIV-RNA <50 copies/mL, missing data or change of therapy = failure [M/C=F]: monotherapy HCV+: 70.5% (n=44), HCV-: 82.1% (n=56), p=0.23; triple therapy HCV+: 74% (n=50), HCV-: 81.3% (n=48), p=0.47

HIV-RNA <50 copies/ml, missing data or change of therapy for reasons other than virological failure are censored [Virological failure (VF)]: monotherapy HCV+: 90.9% (n=44), HCV-: 83.9% (n=56), p=0.38; triple therapy HCV+: 94% (n=50), HCV-: 95.8% (n=48), p=1.0.

Authors' conclusion

In the OK04 trial, patients with anti-HCV+ at baseline on LPV/r MT did not have higher rates of virological failure than anti-HCV-patients.

5. *McKinnon, J. E., R. Delgado, et al. (2011). "Single genome sequencing of HIV-1 gag protease resistance mutations at virologic failure during the OK04 trial of simplified versus standard maintenance therapy." *Antiviral Therapy* 16(5): 725-732.

Reference: McKinnon, J. E., R. Delgado, et al. (2011). "Single genome sequencing of HIV-1 gag protease resistance mutations at virologic failure during the OK04 trial of simplified versus standard maintenance therapy." *Antiviral Therapy* 16(5): 725-732.

OK04 study: In this paper, the authors report developing a single genome sequencing (SGS) assay of HIV-1 gag and protease to assess the emergence of low-frequency drug-resistant variants during virological rebound.

Main outcomes/Effect Size:

Major protease resistance mutations: 3/11 monotherapy and 3/4 triple therapy; median number of minor protease resistance mutations 3.0 monotherapy and 3.5 triple therapy.

Authors' conclusion

Although more subjects on monotherapy had virological rebound, this was not associated with more frequent emergence of variants encoding PI resistance mutations in gag or protease detected by SGS.

Cahn study (NCT00159224):

**Cahn, P., J. Montaner, et al. (2011). "Pilot, Randomized Study Assessing Safety, Tolerability and Efficacy of Simplified LPV/r Maintenance Therapy in HIV Patients on the 1 PI-Based Regimen." *PLoS ONE [Electronic Resource]* 6(8): e23726. [ClinicalTrials.gov NCT00159224](http://ClinicalTrials.gov/NCT00159224)

Reference	Study type and methodological quality	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Cahn, P., J. Montaner, et al. (2011). "Pilot, Randomized Study	RCT Allocation to treatment Random Method of	Total N: 80	INCLUSION CRITERIA: HIV-1 infected adults: i) on their first ART regimen, composed of any two NRTIs plus LPV/r or a PI/r combination; and ii) virologically suppressed	n=41 Drug(s): Lopinavir/ r 133.3/ 33.3 mg	n=39 Drug(s): standard HAART regimen	Treatment duration: 1 year Assessme	Primary endpoint: % pts with plasma HIV-1 RNA level <200 copies/ml at Day 360 Other endpoints: %	Abbott Canada

<p>Assessing Safety, Tolerability and Efficacy of Simplified LPV/r Maintenance Therapy in HIV Patients on the 1 PI-Based Regimen." PLoS ONE [Electronic Resource] 6(8): e23726.</p>	<p>randomisation: adequate Concealment: adequate Blinding not blinded Sample size calculation stated ITT analysis Yes Setting: Outpatients</p>		<p>(HIV-1 RNA viral load <50 copies/ml) at least 6 months prior to study entry and a CD4+ T-cell count ≥ 100 cells/mm³. EXCLUSION CRITERIA: HBsAg+, active TB or opportunistic infection, active malignancy (except Kaposi's Sarcoma), ALT/AST >5x ULN, uncontrolled substance abuse or psychiatric illness that could preclude compliance with protocol; pregnant or lactating; received an investigational drug within 30 days prior to study initiation; had modified ART within 3 months of study entry or intending to do so during the study Baseline comparability between groups: yes Age: mean 39 (9.3) years Gender: 84% male Severity of disease: mean (SD) CD4+ T-cell count and log₁₀ HIV-1 RNA 383 (195) cells/mm³ and 1.68 (0.08) log₁₀ copies/ml, respectively</p>	<p>soft gel capsules; 3 capsules BID orally with food</p>		<p>nts at: Screening / Baseline (Day - 1) and Days 15, 30, 60, 90, 120, 150, 180, 240, 300, and 360. Follow-up after end of treatment:</p>	<p>pts with plasma HIV-1 RNA <50 copies/mL at Day 360; time to confirmed virologic rebound (≥ 200 copies/ml and ≥ 50 copies/ml) or meeting the criteria for virologic failure (pts with viral load test >50 copies/ml and second viral load >200 copies/ml) through Day 360; mean change in Viral Load and CD4+ T-cell count from baseline to final assessment; impact on patient-reported outcomes (PROs) assessed by Symptoms Distress Module (SDM; higher values indicate worse PROs); treatment emergent adverse events (AE), changes in vital signs and clinical laboratory data, metabolic toxicity</p>	
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			Duration of disease: mean (SD) time since initial HIV diagnosis 3.3 (3.0) years					
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Main outcomes/Effect Size:

2/41 monotherapy discontinued (adverse event); 7/39 standard therapy discontinued (1 adverse event; 1 protocol violation, 1 virological failure; 3 withdrawal of consent; 1 other)

In an ITT analysis using the LOCF principle, 37 of the 39 patients (95%) in the ST group and 40 of the 41 patients (98%) in the IM group had plasma HIV-1 RNA <200 copies/ml (OR= 0.46; 95% CI: 0.04–5.31; P= 0.611).

Other outcomes:

Patients with plasma HIV-1 RNA <50 copies/ml at 360 days, applying again the LOCF principle, there were 36/39 patients (92%) for the ST and 39/41 (95%) for the IM group (OR =0.61; 95% CI: 0.097–3.897; P =0.671). Four (10%) patients on LPV/r were intensified with 2 NRTIs and all of them regained virologic control, as demonstrated by achieving a plasma HIV-1 RNA <50 copies/mL following the intensification.

For time to first confirmed virologic rebound of ≥200 plasma HIV-1 RNA copies/ml, a hazard ratio (95% CI) of 2.62 (0.26–24.20) for IM versus ST was calculated, which was not statistically significant (P= 0.405). Similarly, the time to first confirmed virologic rebound of ≥50 HIV-1 RNA copies/ml was comparable in the two groups with an estimated hazard ratio (95% CI) of 4.19 (0.90–19.43), P= 0.067.

Parameter	Visit	Standard Therapy		Monotherapy		Total		p value
		N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	
Absolute CD4+ T-cell count	Baseline	39	401.2 (222.5)	41	364.6 (164.3)	80	382.5 (194.5)	0.404
	360 days	32	478.6 (246.4)	39	453.8 (249.4)	71	465.0 (246.6)	0.678
	Change	32	56.8 (168.93)	39	89.3 (196.18)	71	74.6 (183.84)	0.463
Viral load log ₁₀ RNA copies/ml	Baseline	39	1.689 (0.063)	41	1.680 (0.087)	80	1.684 (0.076)	0.592
	360 days	31	1.692 (0.079)	39	1.734 (0.249)	70	1.715 (0.193)	0.369
	Change	31	0.006 (0.032)	39	0.055 (0.245)	70	0.033 (0.184)	0.361

Symptoms Distress Module	Baseline		31.8		31.7			
	360 days		29.6		26.2			
	Change		P =0.094		P= 0.003			P= 0.131

The most frequent adverse events were diarrhoea (19%), headache (18%), influenza (16%), nasopharyngitis (13%), back pain (10%), hypertriglyceremia (8%) and insomnia (8%). Adverse events were predominantly mild in severity and judged unrelated to the study drug. There were three SAEs reported by two patients in the IM group (1 thrombocytopenia, 1 upper abdominal pain and 1 pneumonia) and five SAEs reported by three patients in the ST group, of which seven were considered severe and one in the IM group was moderate. All SAEs were considered unrelated to the study drug.

Authors' conclusion

At day-360, virologic efficacy and safety of LPV/r appears comparable to that of a PI+2NRTIs HAART. These results suggest that our individualized, simplified maintenance strategy with LPV/r-monotherapy and protocol-mandated NRTI re-introduction upon viral rebound, in virologically-suppressed patients merits further prospective long-term evaluation.

Gutmann study (MOST)

1. **Gutmann, C., A. Cusini, et al. (2010). "Randomized controlled study demonstrating failure of LPV/r monotherapy in HIV: the role of compartment and CD4-nadir." AIDS **24**(15): 2347-2354. Monotherapy Switzerland/Thailand study (MOST)

Reference	Study type and methodological quality	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Gutmann, C., A. Cusini, et al. (2010). "Randomized controlled study demonstrating failure of LPV/r monotherapy in	RCT Allocation to treatment Random Method of randomisation: unclear	Total N: 60	INCLUSION CRITERIA HIV patients with fully suppressed viral load EXCLUSION CRITERIA: previous history of virologic	n=29 Drug(s): Lopinavir/ r 400/100 mg	n=31 Drug(s): triple therapy	Treatment duration: 48 weeks Assessments at: baseline, then every	Primary endpoint: treatment failure in the CNS or genital compartment. As expected HIV RNA levels in the compartments are not fully established,	This study has been financed in the framework of the Swiss HIV Cohort

<p>HIV: the role of compartment and CD4-nadir." AIDS 24(15): 2347-2354.</p>	<p>Concealment: unclear Blinding not blinded Sample size calculation Yes. Also, defined study termination criteria in the case of an unexpectedly high degree of treatment failure in blood. Premature study termination was mandated if more than six (20%) of the first 30 patients on monotherapy failed treatment. Failure was defined as two consecutive plasma HIV RNA levels more than 400 cell/ml. ITT analysis Yes Setting: Outpatients</p>		<p>treatment failure with any drug combination or documented protease inhibitor resistance.</p> <p>Baseline comparability between groups: yes</p> <p>Age: mean 46+/-11 years standard therapy and 42+/-7 years monotherapy Gender: Male: 24 (77%) standard and 19 (66%) monotherapy Severity of disease: median CD4 465 (IQR 356–625) standard and 498 (IQR 360–670) monotherapy</p>	<p>twice daily monotherapy</p>		<p>6 weeks to week 24 and every 8 weeks thereafter</p> <p>Follow-up after end of treatment: none</p>	<p>compartment failure was defined as an HIV RNA level one log above the respective value at baseline. If baseline values were undetectable, a level of 40cp/ml was assumed. However, as the trial was terminated when recruitment reached 60% of plan, the analysis of primary endpoints was not possible. The focus of investigations therefore shifted to explaining these failures and looking for predictive factors.</p>	<p>Study, supported by the Swiss National Science Foundation (SHCS Project 490) and by a grant of the Swiss National Science Foundation (SNF Grant 3247B0-114006).</p>
<p>Main outcomes/Effect Size: Six patients reached HIV-RNA failing criteria (all on monotherapy). With a median of 4.2 log₁₀ cp/ml, CSF HIVRNA in the five failures who consented to lumbar puncture was higher than the respective level in blood plasma (median 3.4 log₁₀ cp/ml, P=0.15).</p> <p>Five of the six failing patients presented with clinical symptoms at the time of failure: one patient had sialadenitis, four had neurological symptoms such as headache, dizziness, visual disturbance, deficit in concentration and ataxic gait. There was no history of previous neurological symptoms in all four failing patients. None of the other patients during the trial presented with signs or symptoms of acute neurological discomfort. In all failing</p>								

patients, viral RNA was completely resuppressed after switching to previous triple therapy.

Genotypic resistance testing performed in CSF and in plasma of the failing patients did not reveal any mutation associated with drug either in the protease or in the reverse transcriptase region. All clinical findings, especially CNS symptoms, resolved completely after treatment switch.

Cerebrospinal fluid was examined in all 60 patients at baseline and in 45 patients at study termination (25 monotherapy with blood viral load <400, five failing monotherapy, 15 continued treatment patients with blood viral load <50). At baseline, three patients had low level HIV-RNA in CSF (82, 56, and 43 cp/ml). Two of the three were randomized to continuous therapy [efavirenz+TDF+3TC and TDF+FTC+atazanavir, ritonavir-boosted (ATV/r)] and both had undetectable HIV-RNA in CSF and blood at study termination. The third patient with 1.6 log₁₀ (43) cp/ml, was randomized to monotherapy. At week 37, when the study was prematurely terminated, his viral load in CSF was 2.4 log₁₀ (250) cp/ml, whereas blood viral load was undetectable. One additional patient on triple therapy had a detectable viral load in CSF of 1.6 log₁₀ (45) cp/ml at week 48, whereas plasma viral load was undetectable. At this time, he was switched from TDF+FTC+ATV/r to monotherapy. Eighteen weeks later, at the termination visit, viral load in CSF was 3.4 log₁₀ (2300) cp/ml, whereas viral load in plasma was 2.2 log₁₀ (170) cp/ml.

Among all non-failing patients (viral load <400) at study termination, none of the 15 patients still under continued treatment had an HIV-RNA value in CSF more than 1.6 log₁₀ (40) cp/ml, as opposed to eight of 25 monotherapy patients (32%, P=0.01, Fisher's exact). Only four of the eight did reach the predefined CSF-failing criteria (>2.6 log₁₀ cp/ml). Interestingly, three of the four CSF-failures had a plasma HIV-RNA value between 1.6 and 2.6 log₁₀ (40–400) cp/ml. In all four patients, HIV RNA was more than one log higher in CSF than in blood. Mean CD4 nadir in cases with isolated CSF failures was not significantly different than in the monotherapy patients who had undetectable HIV-RNA in CSF at termination; 171/ml (IQR 123–251) vs. 211/ml (IQR 168–272), P=0.28.

Only patients on monotherapy (≥6 weeks, n=42) were included in the analysis of risk factors for treatment failure (n=6). In univariate analysis, the following parameters were not associated with treatment failure in blood: age, sex, therapy prior to baseline and duration of HIV-RNA suppression less than 50 cp/ml, CDC classification, RNA set point, hepatitis C virus coinfection, length of therapy, peripheral blood mononuclear cell-associated HIV-DNA and RNA, hemoglobin and platelets. Cholesterol showed a trend for lower baseline cholesterol (t-test; P=0.053), with failures having lower baseline cholesterol levels compared with nonfailures (4.5+/-0.7 vs. 5.3+/-1.1). Median nadir CD4 cell count in failing patients was 56/ml (IQR 19-126) vs. 194/ml (IQR 99-257) in nonfailing patients (P=0.026; Mann-Whitney-U). Similarly, median baseline CD4 cell count was 335/ml (IQR 301–373) vs. 554/ml (IQR 413–720, P=0.019; Mann-Whitney-U). Cox regression analysis revealed a significant difference between the number of failures in patients with low (<200/ml) and high CD4 nadir (P<0.01). No monotherapy failure occurred in patients with nadir CD4 cell count more than 200 cells/ml.

Evaluation of frequency of blips as a proxy for decreased potency of monotherapy showed that low level rebound (40–400 cp/ml) was significantly more frequent in the monotherapy arm (8 vs. 2% with HIV RNA 40–400 cp/ml under monotherapy vs. continued treatment among 191 vs. 210 RNA determinations per group; P<0.01. No significant difference in changes in CD4 cell count was detectable between the monotherapy and continued

treatment arms.

Results of HIV-RNA determination in the genital tract showed no marked elevation of HIV-RNA in the genital secretions. Neuropsychological tests demonstrated no significant changes.

Authors' conclusion

Maintenance of HIV therapy with LPV/r alone should not be recommended as a standard strategy; particularly not in patients with a CD4 cell count nadir less than 200/ml. Further studies are warranted to elucidate the role of the central nervous system compartment in monotherapy-failure.

KALESOLO Trial

1. **Meynard, J.-L., V. Bouteloup, et al. (2010). "Lopinavir/ritonavir monotherapy versus current treatment continuation for maintenance therapy of HIV-1 infection: the KALESOLO trial." Journal of Antimicrobial Chemotherapy 65(11): 2436-2444. NCT00140751

Reference	Study type and methodological quality	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Meynard, J.-L., V. Bouteloup, et al. (2010). "Lopinavir/ritonavir monotherapy versus current treatment continuation for maintenance therapy of HIV-1 infection: the	RCT Allocation to treatment Random Method of randomisation: adequate Concealment: adequate Blinding not blinded Sample size calculation	Total N: 186	INCLUSION CRITERIA HIV-1 infection; age >18 years; no previous history of virological failure on a PI; HIV-1 RNA <50 copies/mL for at least 6 months; no change in antiretroviral treatment in last 3 months; no opportunistic	n=87 Drug(s): lopinavir/ritonavir monotherapy (400/100 mg twice a day)	n=99 Drug(s): continue current cART	Treatment duration: 48 weeks Assessments at: screening/baseline and every 12 week period thereafter for 48 weeks	Primary endpoint: % pts with viral load <50 copies/mL at week 48 without modification of antiretroviral treatment during the study. Modifications of treatment included any change except dosing adaptation or replacement by a fixed combination. Pts lost to follow-up or with no HIV-1 RNA	Institut de Médecine et d'Epidémiologie Appliquée (IMEA), Paris.

<p>KALESOLO trial." Journal of Antimicrobial Chemotherapy 65(11): 2436-2444.</p>	<p>stated ITT analysis Yes Setting: Outpatients</p>		<p>infection in the last 6 months. Patients with triple NRTI regimen could be included. EXCLUSION CRITERIA: pregnancy; hepatitis B treated with lamivudine or tenofovir DF Baseline comparability between groups: yes Age: median 43 (IQR 39–50) combination therapy and 44 (39–51) monotherapy Gender: male: 75 (76%) combination and 63 (72%) monotherapy Severity of disease: median CD4 cell count 525 (IQR 357–688) combination and 494 (371–630) monotherapy</p>			<p>Follow-up after end of treatment: at week 96 (only subset of patients followed up)</p>	<p>measurement at Week 48 were considered as failures (missing= failure) Other endpoints: % pts with viral load <400 copies/mL at Week 48 without modification of antiretroviral treatment during the study, % pts with viral load <50 copies/mL at Week 48 with treatment intensification not considered as failure. Success with treatment intensification allowed was defined in lopinavir/ ritonavir monotherapy group by a viral load <50 copies/mL at Week 48 even if NRTIs had been reintroduced; in the current cART group, success was defined by a viral load of <50 copies/mL at Week 48 without change of treatment. Variation in CD4 cell count, evolution of biological</p>	
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			Duration of disease: median duration since HIV-1 infection 10 years				parameters, evolution of DEXA scan parameters, treatment adherence, clinical and biological safety.
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Main outcomes/Effect Size:

At Week 48, 73/87 patients (84%) in the lopinavir/ritonavir monotherapy group were virologically suppressed to <50 copies/mL for the primary endpoint compared with 87/99 patients (88%) in the current cART group. The percentage difference between the two groups was -4.0% with a 90% two-sided CI -12.4% to +4.5%. Non-inferiority was therefore not demonstrated on the primary outcome.

	lopinavir/ritonavir monotherapy	current cART
Therapeutic failure:	14/87	12/99
Plasma HIV-1 RNA was ≥50 copies/mL	5	0
Missing RNA value	0	5
Changed their regimen during the trial	9 (clinician's assessment virological failure 8 + 1 adverse events [dyslipidaemia])	7 (lipodystrophy, n=1; altered renal function, n=2; and unspecified, n=4)

If antiretroviral treatment intensification was taken into account to evaluate therapeutic success at Week 48 (plasma HIV-1 RNA <50 copies/mL, addition of NRTIs allowed in lopinavir/ ritonavir monotherapy group), the proportions of patients meeting the primary endpoint were 87/99 (88%) in the current cART group and 79/87 (91%) in the lopinavir/ritonavir monotherapy group (difference, 2.9; 90% CI, -4.5 to +10.4).

Other outcomes:

In the current cART group, median CD4 counts increased from 525 to 604 cells/mm³ between baseline and Week 48 and in the lopinavir/ritonavir monotherapy group, from 494 to 592 cells/mm³.

Failures of lopinavir/ritonavir monotherapy did not show acquired resistance mutations in the protease gene.

Changes from inclusion to Week 48 in fasting triglycerides, total cholesterol, LDL-cholesterol, HDL-cholesterol and creatinine clearance were assessed. The only difference between treatment groups was fasting total cholesterol change, which was significantly higher in the lopinavir/ritonavir monotherapy group (+0.42 mmol/L) than in the current cART group (+0.08 mmol/L; P=0.04).

Seventy patients were included in a DEXA substudy (not data extracted).

	lopinavir/ritonavir monotherapy	current cART
Grade 3–4 biological events	3 (total cholesterol increase, n=1; serum alanine aminotransferase (ALT) increase, n=1; serum aspartate aminotransferase (AST) and ALT increase, n=1; the increase in serum AST and ALT was related to acute hepatitis C).	3 (total cholesterol and triglycerides increase, n=1; triglycerides increase, n=2)

Thirteen patients in the current cART group experienced at least one episode of diarrhoea versus 34 in the lopinavir/ritonavir group (P<0.001).

Authors' conclusion

Lopinavir/ritonavir monotherapy did not achieve non-inferiority versus cART for maintaining plasma HIV-1 RNA at <50 copies/mL. Nevertheless, the incidence of virological failure was low (mostly with HIV-1 RNA <400 copies/mL) and easily managed by treatment intensification.

KalMo Study

1. **Nunes, E. P., M. Santini de Oliveira, et al. (2009). "Monotherapy with Lopinavir/Ritonavir as maintenance after HIV-1 viral suppression: results of a 96-week randomized, controlled, open-label, pilot trial (KalMo study)." *HIV Clinical Trials* **10**(6): 368-374.

Reference	Study type and methodological quality	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Nunes, E. P., M. Santini de Oliveira, et al. (2009). "Monotherapy with Lopinavir/Ritonavir as maintenance after HIV-1 viral suppression: results of a 96-week randomized,	RCT Allocation to treatment Random Method of randomisation: adequate Concealment: adequate Blinding not blinded Sample size	Total N: 60	INCLUSION CRITERIA HIV-1 infected, ≥18 years, virologic suppression <80 copies/mm ³ (lower limit of Nucleic Acid Sequence Based Amplification [NASBA] assay, most widely available at that time in Brazil), on a stable HAART regimen for at least 6 months, CD4 levels >200 cells/mm ³ at screening, and CD4 nadir	n=30 Drug(s): lopinavir/ritonavir monotherapy 400 + 100 mg bid	n=30 Drug(s): maintain current HAART regimen	Treatment duration: 96 weeks Assessments at: baseline and at Weeks 2, 4, and 12, and then every 12 weeks until Week	Primary endpoint: proportion of patients with PVL <80 copies/mL of HIV RNA at Week 96 on intention-to-treat (ITT) analysis with all missing data counting as failure Other endpoints: VF was defined as two consecutive	partially supported by Abbott Laboratories

<p>controlled, open-label, pilot trial (KalMo study)." HIV Clinical Trials 10(6): 368-374.</p>	<p>calculation not stated ITT analysis Yes Setting: Outpatients</p>		<p>> 100 cells/mm³. EXCLUSION CRITERIA: Pregnant or breastfeeding women; previous history of an AIDS-defining condition, virologic failure, or intolerance to lopinavir</p> <p>Baseline comparability between groups: yes</p> <p>Age: median 39 (IQR 31–46) monotherapy and 40 (31–46) current cART Gender: male: 17 (54.8%) monotherapy and 20 (69.0%) current cART Severity of disease: CD4 count: median 538 (IQR 365–738) monotherapy and 510 (355–608) current cART</p>			<p>96. Follow-up after end of treatment: none</p>	<p>measures of HIV-1 PVL >500 copies/mL within an interval of 4 (±1) weeks. Incidence of AIDS-defining illnesses; CD4 cells count changes during the study period; and incidence of antiretroviral-related clinical and laboratory adverse events including changes in anthropometric measures and lipids profile.</p>	
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Main outcomes/Effect Size:

At Week 96, by ITT analysis, 26/30 (86.7%; 95% CI, 74.5–98.8) and 24/30 (80.0%; 95% CI, 65.7–94.3) subjects in the control and monotherapy arms remained virologically suppressed ($p = .48$).

	lopinavir/ritonavir monotherapy	current cART
Discontinuations:	6	3
virological failure	1 (no resistance; successfully resuppressed)	1 (no resistance)
grade 3 diarrhea	1	0
lost to follow-up	1	0
pregnancy	2	1

tuberculosis	1	0
imprisonment	0	1

On-treatment analysis including only patients who completed 96 weeks of follow-up without discontinuation for reasons other than VF showed 96% efficacy in both groups (24/25 patients in the monotherapy group and 26/27 patients in the control group).

Other outcomes:

At Week 96, no statistically significant differences in median CD4 count changes were observed between the control and the monotherapy arms (42 [IQR 35 to 133] and 91 [IQR -55 to 169], respectively; $p = .93$). No AIDS-defining conditions occurred during the study period. One case of tuberculosis in the monotherapy group was not considered to be associated with immunosuppression, because it was a localized presentation (vertebral tuberculosis); at the last visit before this diagnosis, the patient did not show a significant decrease in CD4 count or loss of virologic suppression.

More patients in the monotherapy arm experienced gastrointestinal side effects (24 vs. 10 in monotherapy and maintenance arms, respectively; $p = .001$), including one study discontinuation due to diarrhoea. No other statistically significant differences were detected between the two study arms. In the control arm, five subjects had their regimen changed due to drug-related toxicities, three patients switched from stavudine to tenofovir, one patient switched from indinavir to atazanavir, and one patient switched from didanosine to lamivudine.

	lopinavir/ritonavir monotherapy	current cART
Grade 3–4 abnormality of triglycerides	0	2
Grade 3 abnormalities of cholesterol	2	3

No other clinically significant laboratory abnormalities of grades 3 or 4 were observed in any of the study groups.

Authors' conclusion

Switching from various HAART regimens to LPV/r monotherapy in patients who were virologically suppressed and without a history of previous virologic failure was effective, safe, and well tolerated through 96 weeks.

KAMON 2

H. Hasson, L. Galli, G. Gallotta, V. Neri, P. Blanc, M. D'Annunzio, G. Morsica, S. Bagaglio, S. Sollima, A. Lazzarin, C. Uberti Foppa. HAART simplification with lopinavir/ ritonavir monotherapy in HIV/HCV coinfecting patients starting anti-HCV treatment: final results of a randomised, proof-of-principle clinical trial (KAMON 2 Study) IAS 2011: abstract no. CDB358 (**conference abstract**)

Reference	Study type/ methodologic quality	Number of patients	Patient characteristics	Intervention	Comparison	Length follow- up	Outcome measures	Source funding
H Hasson, L Galli, G Gallotta, V Neri, P Blanc, M D'Annunzio, G Morsica, S Bagaglio, S Sollima, A Lazzarin, C Uberti Foppa. HAART simplification with lopinavir/ ritonavir monotherapy in HIV/HCV coinfecting patients starting anti-HCV treatment: final results of a randomised, proof-of-principle clinical trial (KAMON 2 Study) IAS 2011: abstract no. CDB358 (conference abstract)	RCT Allocation to treatment Random Method of randomisation : unclear Concealment: unclear Blinding not blinded Sample size calculation not stated ITT analysis Yes Setting: Outpatients	Total N: 30 11 pts (36.6%) discontinued : 2 (1 in each arm, 6.7%) for toxicity (95%CI: -0.108+0.108) . Among 9 withdrawn pts, 4 (36%) in A and 3 (27%) in B discontinued treatment for HCV virological failure; 2 (18%) were lost to follow-up.	INCLUSION CRITERIA HIV/HCV coinfecting pts naïve for HCV treatment and requiring the start of anti-HCV therapy; stable HAART (>6 months); no previous virological failure or resistance to Protease Inhibitors; CD4+ >350cells/ mm ³ EXCLUSION CRITERIA Compensated cirrhosis Baseline comparability between groups: Baseline characteristic (age, gender, previous IDV use, HCV genotype, HIV duration, CD4 count, ALT) were not significantly different between A and B arms, except for Hb [13.9 (13.3-14.7) g/dL vs 15 (14.6-16.1) g/dL; p=0.017] Age: not stated Gender: not stated Severity /Duration of disease: not stated	n=15 Drug(s): LPV/r monotherapy plus anti-HCV therapy (Peg-IFNα 2a + ribavirin (0.8-1.2 g/ die depending on body weight))	n=15 Drug(s): LPV/r + Tenofovir/ emtricitabine plus anti-HCV therapy (Peg-IFNα 2a + ribavirin (0.8-1.2 g/ die depending on body weight))	Treatment duration: 48 weeks Assessments at: 48 and 72 weeks Follow-up after end of treatment: 24 weeks	Primary endpoint: the proportion of reduction or discontinuation of anti-HCV therapy through week 48. Other endpoints: virological response; CD4 count; blood counts and biochemistry	Not stated
Main outcomes: Sustained virological response was observed in 8/15 (53%) patients on monotherapy vs 10/15 pts (67%) under HAART. One transient HIV blip (RNA >50 copies/mL and ≤400 copies/mL) was observed in arm B.								

Other outcomes:							
Bioparameter Serum concentration and Units	Baseline			48 weeks		72 weeks	
	A	B	P-value	A	B	A	B
<i>Immuno-virologic</i>							
CD4-count $\times 10^3$ -Cells/mL	543-(402-663)	570-(451-842)	NS	267-(183-474)	321-(272-432)	556-(340-633)	456-(417-553)
HIV-RNA-copies/mL	49	49	NS	49	49	49	49
<i>Hepatic-toxicity</i>							
ALT-U/L	66-(52-137)	85-(39-113)	NS	28-(18-40)	27-(24-52)	21-(19-44)	29-(16-63)
AST-U/L	42-(35-99)	42-(33-56)	NS	25-(22-33)	26-(23-36)	22-(19-30)	22-(16-30)
Lactic-acid-mM/L	1.0-(0.89-1.32)	1.5-(1.12-1.9)	P=0.045	1.14-(0.80-1.53)	1.37-(0.80-2.0)	1.43-(0.8-1.62)	1.45-(0.9-2.0)
Bilirubin-total-mg/dL	0.87-(0.68-1.03)	0.86-(0.7-1.11)	NS	0.51-(0.4-0.8)	0.59-(0.3-0.8)	0.6-(0.39-0.8)	0.6-(0.32-0.76)
Gamma-GT-U/L	104-(46-152)	91-(46-174)	=	39-(29-121)	37-(28-49)	39-(28-66)	27-(24-56)
Amylase-U/L	33-(30-40)	38-(34-62)	NS	29-(27-55)	45-(24-61)	31-(27-56)	38-(24-61)
Albumin-g/L	42-(39-45.4)	43.1-(41.3-46)	NS	41-(36.2-44.7)	42.2-(41-45.4)	43-(41.3-43.2)	44-(41-45)
<i>Metabolic-toxicity</i>							
Insulin-U/L	12-(6-17)	15.95-9.2-19)	NS	12.4-(7.17)	18.8-(10.6-26)	13.9-(7-17)	18.8-(10.6-26)
Glucose-mg/dL	80-(76-85)	88-(84-95)	NS	77-(72-83)	84-(77-88)	86-(79-88)	89-(84-93)
Cholesterol-total-mg/dL	162-(153-196)	176-(160-205)	NS	174-(153-200)	175-(153-192)	186-(170-201)	190-(162-205)
HDL-Cholesterol-mg/dL	44-(29-49)	44-(40-50)	NS	35.5-(33-46)	39-(33-48)	36.5-(33-46)	39-(33-53)
LDL-Cholesterol-mg/dL	84-(69-101)	98-(82-120)	NS	79-(71-111)	88-(68-119)	86.5-(71-111)	109-(80-118)
Triglycerids-mg/dL	129-(97-149)	138-(105-199)	NS	189-(128-311)	157-(128-230)	221-(128-311)	156-(119-224)
Haemoglobin-mg/dL	14.3-(13.4-14.5)	15.3-(14-16)	P=0.017	11.3-(10.7-12.3)	12.4-(11.6-13.3)	12.7-(11.8-13.9)	14.6-(12.4-15.2)
White-Blood-Cells- $\times 10^3$ -Cells/mL	6-(4.8-7)	5.85-(5.1-7.34)	NS	2.7-(1.8-3.7)	3-(1.8-5)	4.5-(3.4-6)	5-(3.7-6.46)
Neutrophils- $\times 10^3$ -Cells/mL	3-(2.5-3.5)	2.79-(2.4-4.49)	NS	1.4-(1.0-1.7)	1.5-(0.9-2.8)	2.32-(1.6-3.0)	2.5-(1.9-5.01)
Platelets- $\times 10^3$ -cells/mL	214-(191-233)	206-(160-233)	NS	143-(116-177)	114-(100-186)	195-(147-224)	177-(125-223)

HCV virological efficacy was higher among 2/3 than 1/4 genotypes. Most biochemical parameters improved significantly during treatment in particular the hepatic AST and ALT ; Gamma-GT decreased more in arm B (p=0.0185). Neutrophils increased more in arm B (p=0.0093). Blood glucose and total cholesterol slightly increased in each arm during the study, without exceeding normal values; conversely, triglycerides significantly increased in arm A.

Authors' conclusion

PI monotherapy + anti-HCV drugs was safe and effective as HAART + anti-HCV drugs

Atazanavir /r monotherapy

*Pulido F et al. Atazanavir/ritonavir monotherapy for maintenance of virologic suppression: 48 week primary analysis of the 96 week multicenter, open-label, single-arm, pilot OREY study. EACS

Year: 2009 Abstract-No: PS4/6 Session: PS4 - Antiretroviral Therapy I Category: 7.5 Treatment Simplification (**conference abstract**)

Further analysis of this publication showed that it should be excluded as it was not a randomised comparison of PI monotherapy versus continuation of combination therapy; all patients were switched to monotherapy.

Wilkin study: ClinicalTrials.gov identifier: NCT00084019

*Wilkin, T. J., J. E. McKinnon, et al. (2009). "Regimen simplification to atazanavir-ritonavir alone as maintenance antiretroviral therapy: final 48-week clinical and virologic outcomes." *Journal of Infectious Diseases* **199**(6): 866-871. ClinicalTrials.gov identifier: NCT00084019; AIDS Clinical Trials Group (ACTG) protocol 5201

This was a single-arm study - exclude

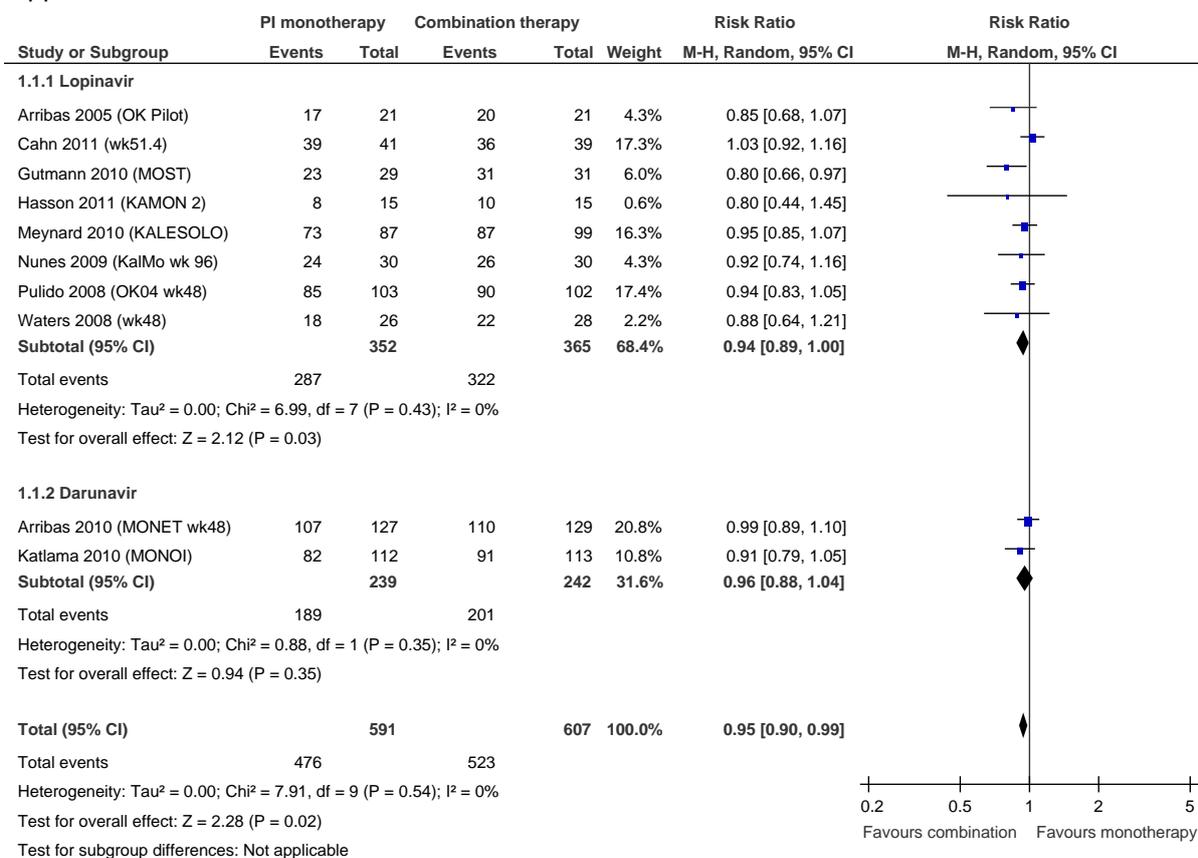
Waters study

Waters L, Jackson A, Singh K, Higgs C, Mandalia S, et al. (2008) The impact of continued HAART versus lopinavir/ritonavir monotherapy (mLPV/r) on body fat and bone mineral density (BMD) as measured by DEXA: 48 week results of a randomised study. XVII International AIDS Conference, August 3-8, 2008, Mexico City, Mexico Abstract CDB0193.(P88).

Reference	Study type/ methodologic quality	No. pts	Patient characteristics	Intervention	Comparison	Length follow- up	Outcome measures	Source funding
Waters L, Jackson A, Singh K, Higgs C, Mandalia S, et al. (2008) The impact of continued HAART versus lopinavir/ritonavir monotherapy (mLPV/r) on body fat and bone mineral density (BMD) as measured by DEXA: 48 week results of a randomised study. XVII International AIDS Conference, August 3-8, 2008, Mexico City, Mexico Abstract CDB0193.(P88). (conference abstract)	RCT Allocation to treatment Random/ Method of randomisation : unclear Concealment: unclear Blinding not blinded Sample size calculation not stated ITT analysis Yes Setting: Outpatients	Total N: 54	INCLUSION CRITERIA Subjects on suppressive HAART (2 NRTI and NNRTI or PI/r) with <5 PI mutations EXCLUSION CRITERIA: not stated Baseline comparability between groups: yes Age: not stated Gender: not stated Severity /Duration of disease: not stated	n=26 Drug(s): lopinavir/ ritonavir monotherapy	n=28 Drug(s): continue HAART	Treatment duration: 48 weeks Assessments at: not stated Follow-up after end of treatment: none	Primary endpoint: viral load, CD4, safety parameters , QoL, DEXA scans	Not stated
<p>Main outcomes: Viral load <50 at 48 weeks: 18/26 monotherapy and 22/28 HAART.</p> <p>Other outcomes: Change in DEXA not significant for either arm. Small median increase in limb fat on monotherapy (13.3% vs. 7% on HAART, p=0.92) and an increase of 15.3% in trunk fat on monotherapy vs. 0.5% on HAART (p=0.05).</p> <p>Authors' conclusion Switch to monotherapy is associated with maintained viral suppression and greater increase in trunk fat than HAART. Limb fat and BMD were similar and stable at 48 weeks.</p>								

Forest plots for comparisons of PI monotherapy versus combination therapy.

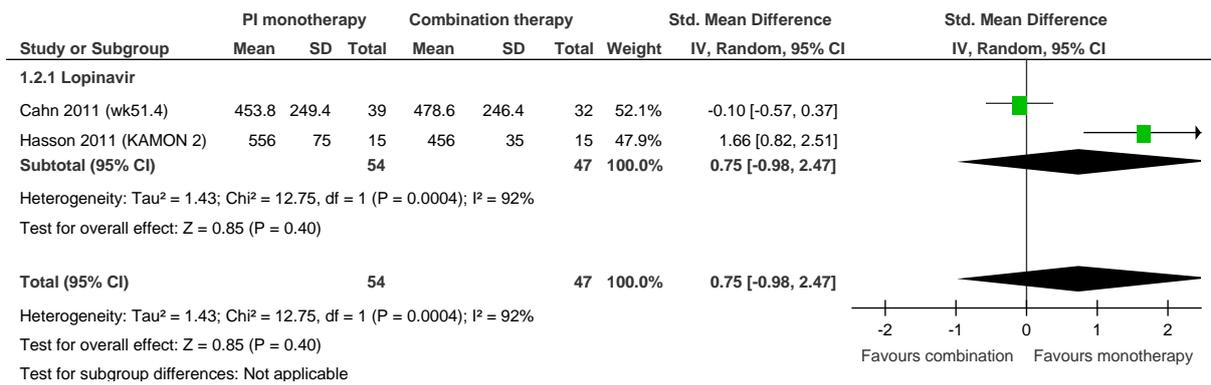
Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.1 Virological suppression.



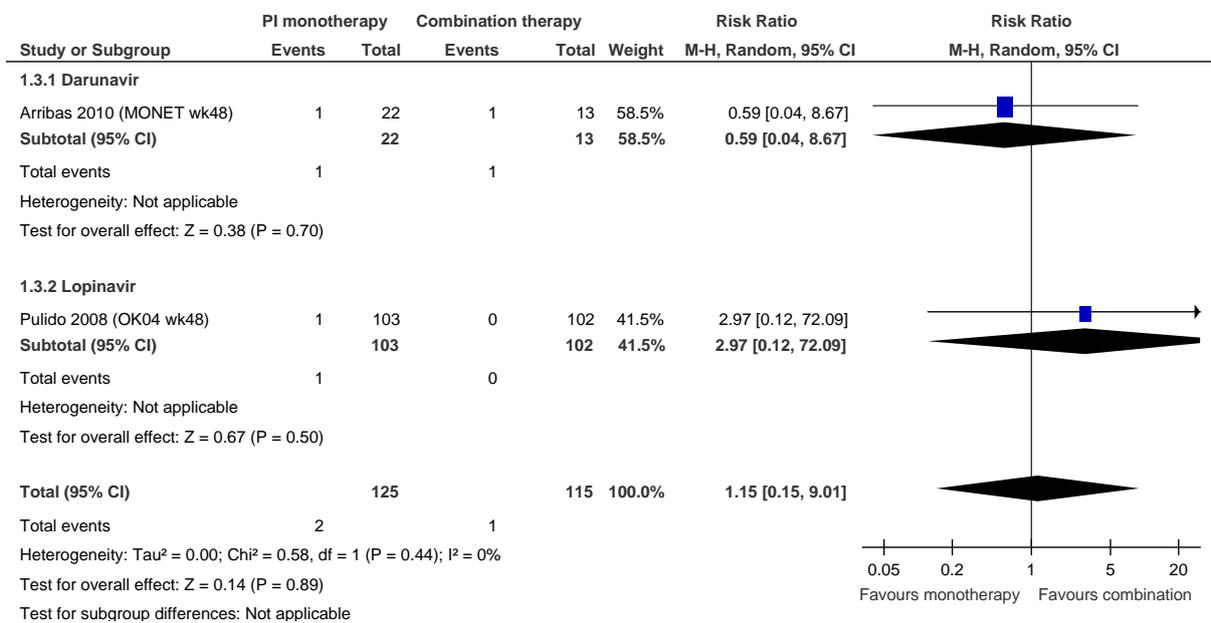
Combination therapy was superior to monotherapy for virological suppression.

There were no significant differences between the groups for the outcomes of CD4 count; drug resistance; serious adverse events; grade 3 nervous system or psychiatric adverse events; Grade 3 raised LFTs; Grade 3-4 abnormalities in lipase; Grade 3 abnormalities in total cholesterol; Grade 3-4 abnormalities in low-density lipoprotein; Grade 3-4 abnormalities in triglycerides; Grade 3-4 abnormalities in haemoglobin; Grade 3-4 abnormalities in neutrophils; Grade 3 or 4 infectious disease events; Grade 3 or 4 cardiovascular disease events; Lipodystrophy (any grade) or CNS disease (including Functional Assessment of HIV infection).

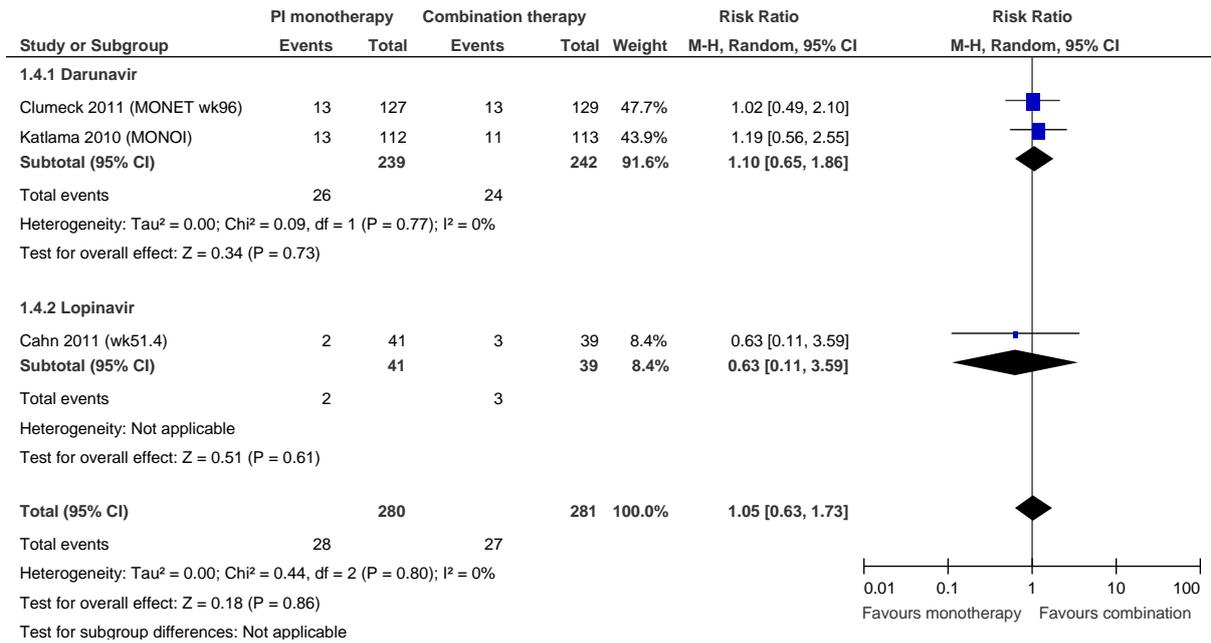
Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.2 CD4 count.



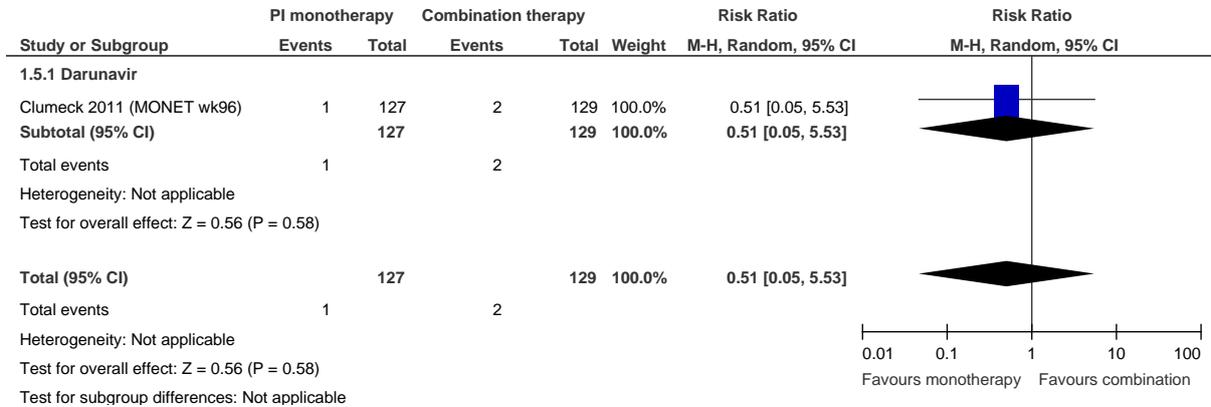
Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.3 Drug resistance.



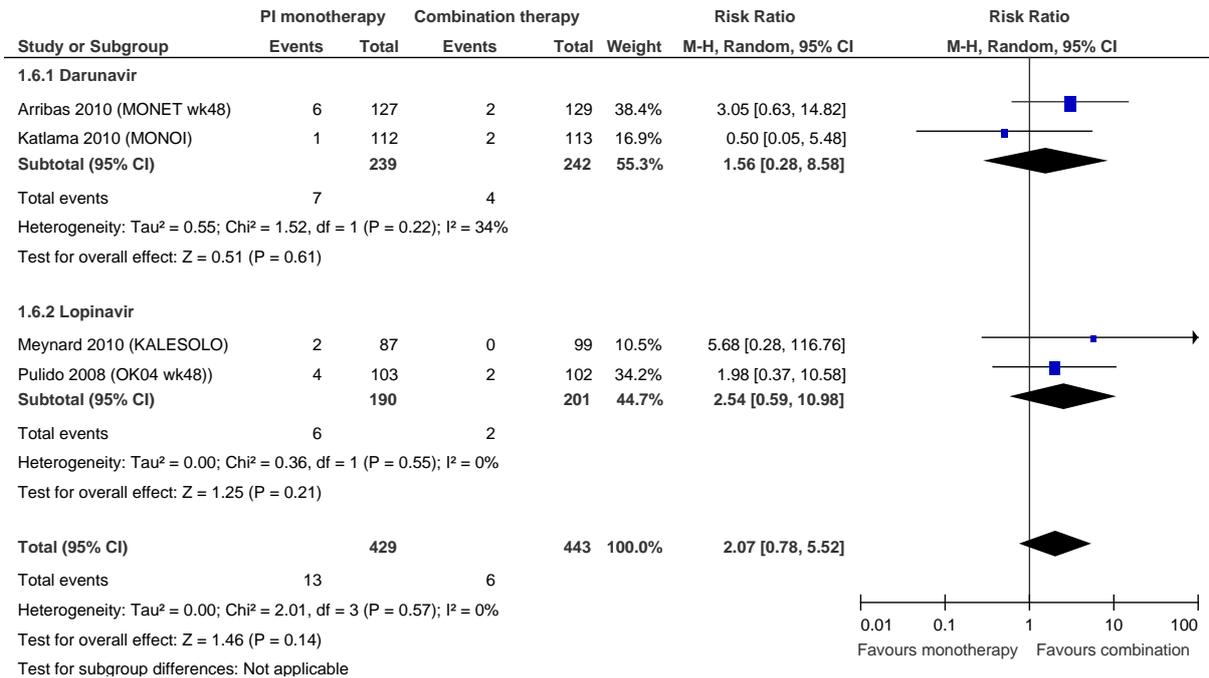
Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.4 Serious adverse events.



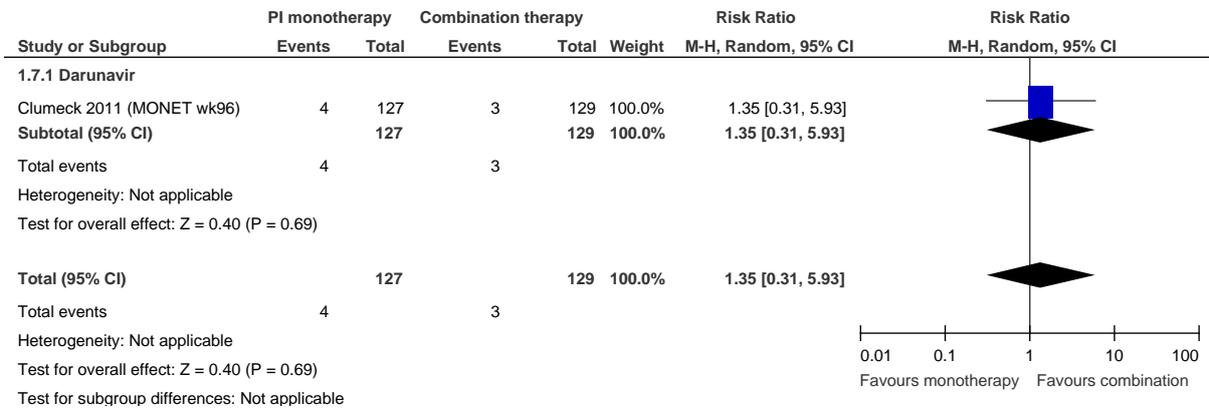
Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.5 Grade 3 nervous system or psychiatric adverse event.



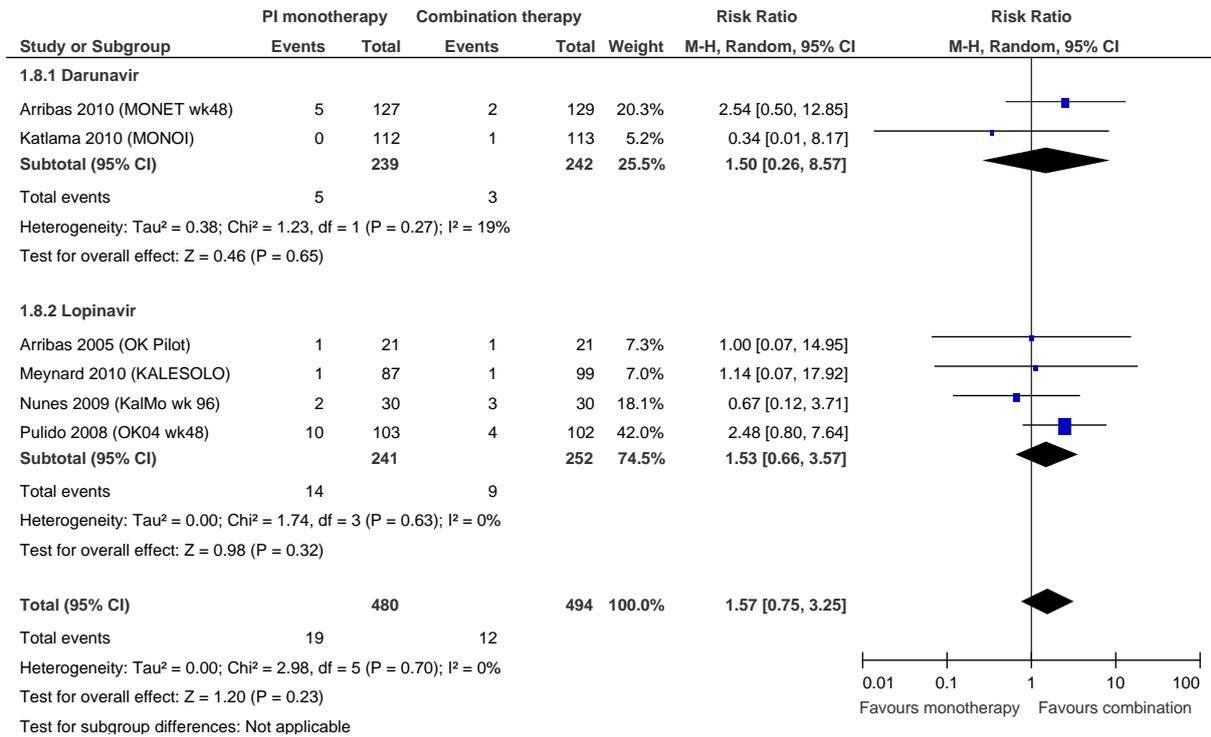
Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.6 Grade 3 raised LFTs.



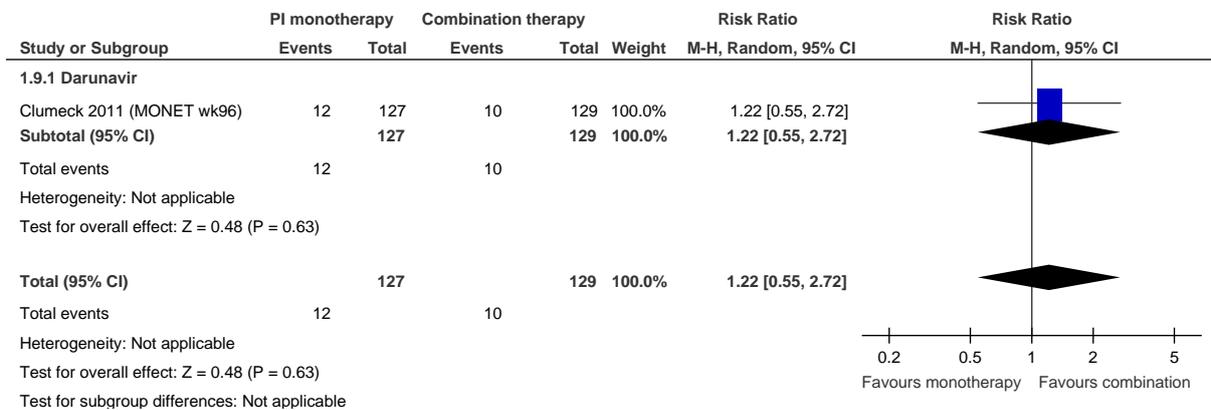
Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.7 Grade 3-4 abnormalities in lipase.



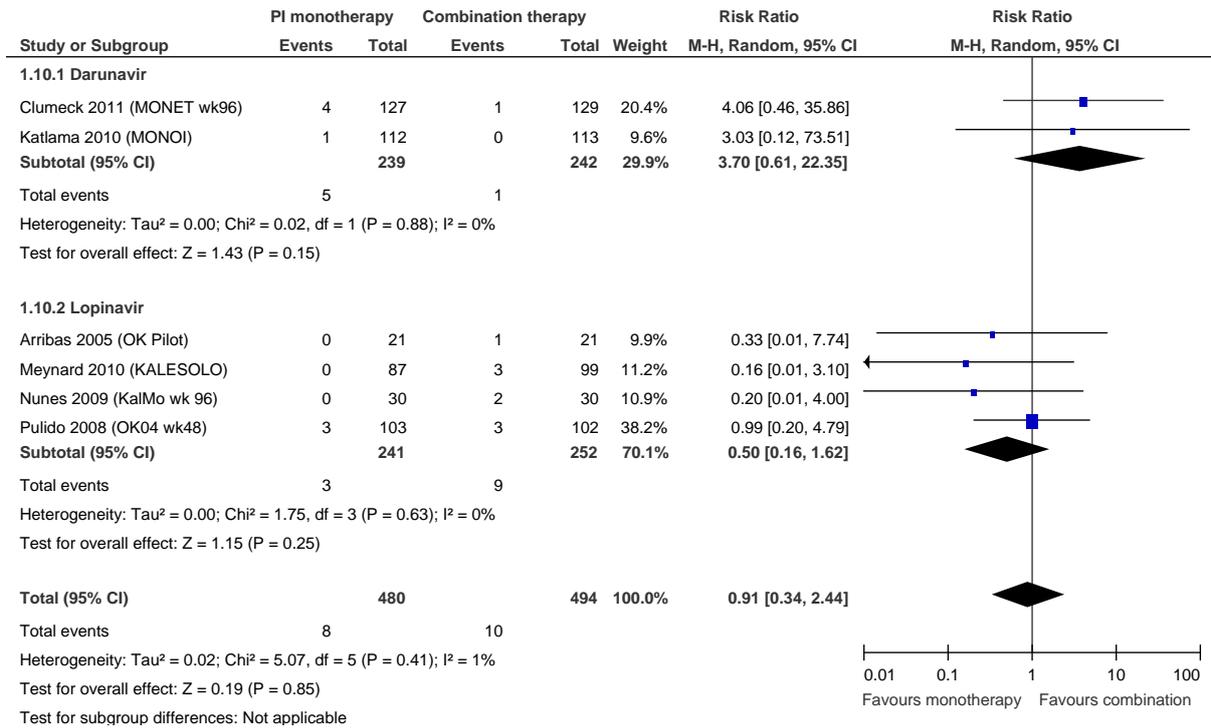
Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.8 Grade 3 abnormalities in total cholesterol.



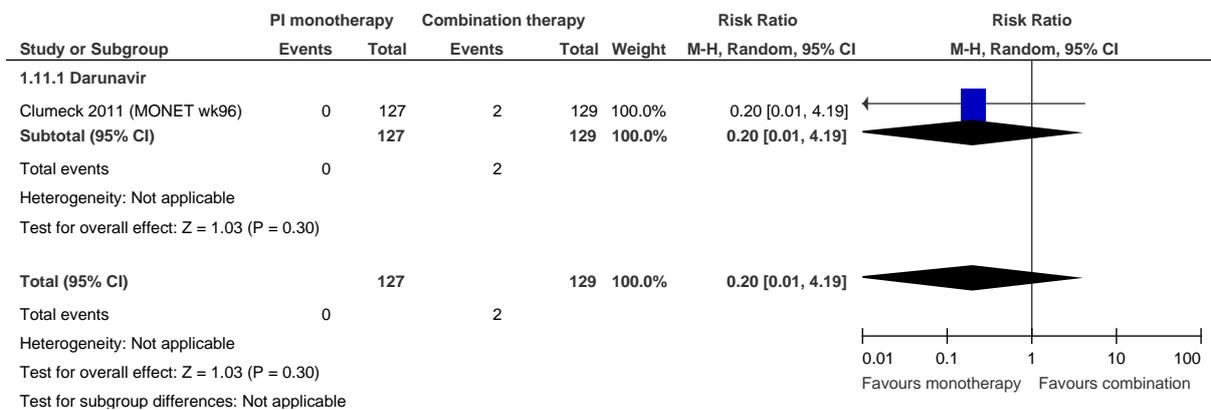
Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.9 Grade 3-4 abnormalities in low-density lipoprotein.



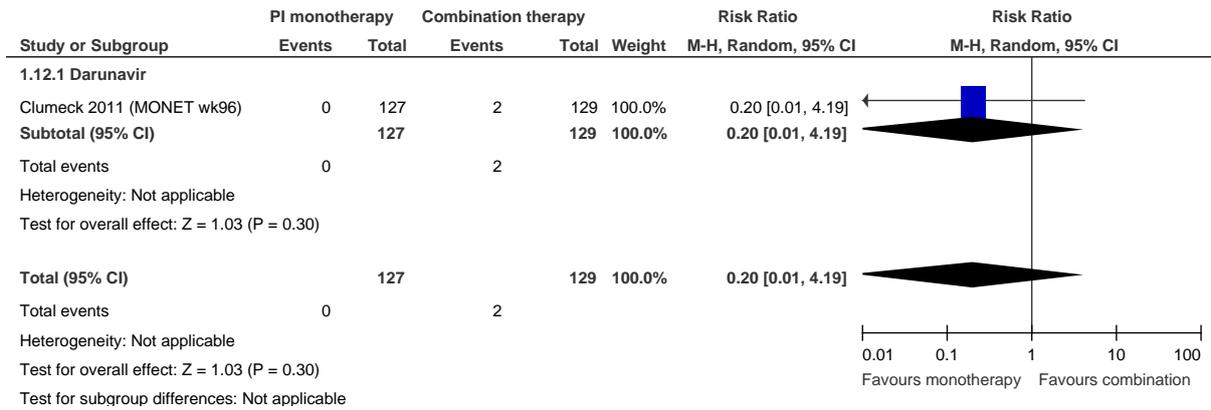
Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.10 Grade 3-4 abnormalities in triglycerides.



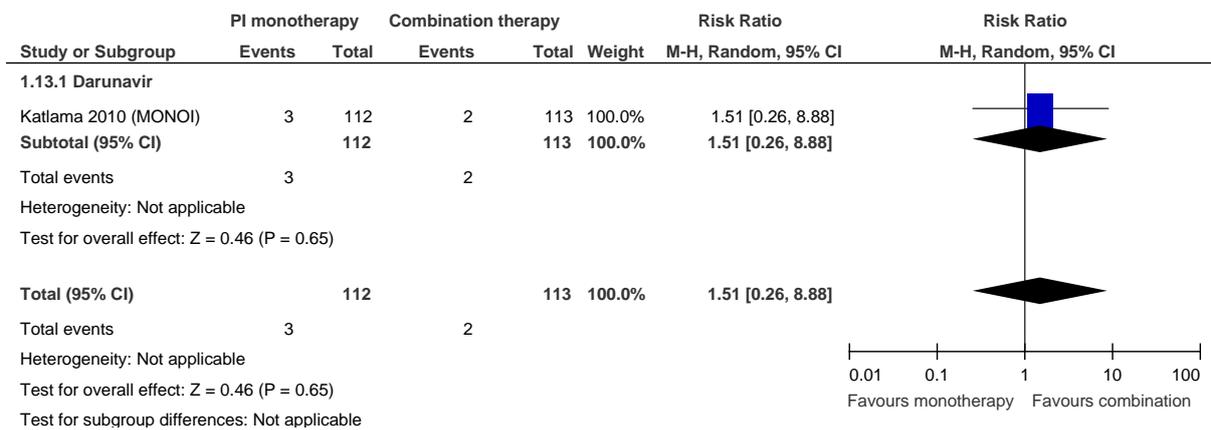
Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.11 Grade 3-4 abnormalities in haemoglobin.



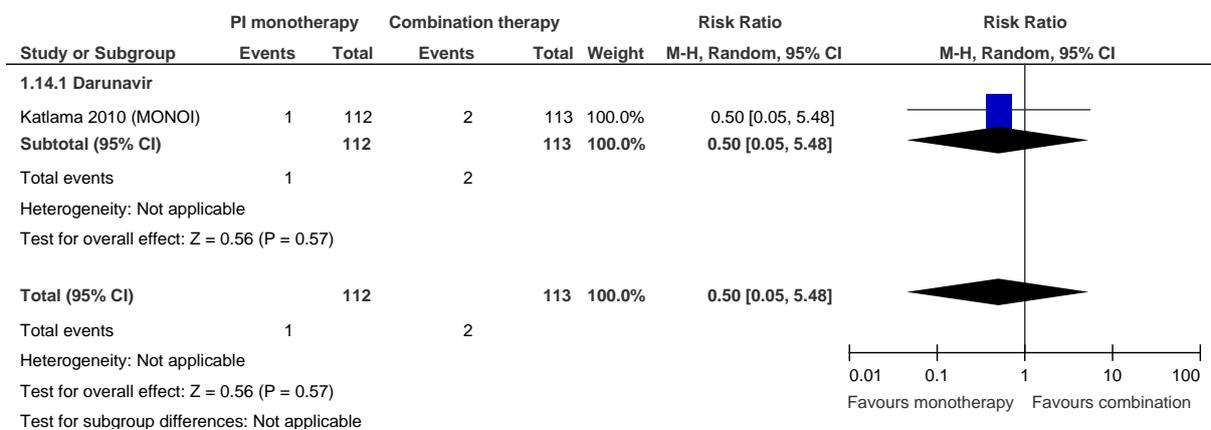
Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.12 Grade 3-4 abnormalities in neutrophils.



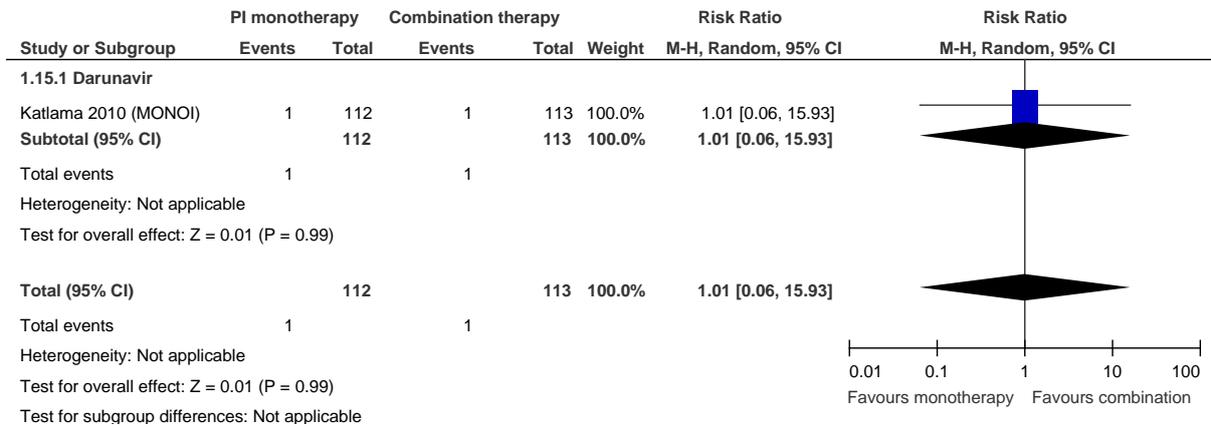
Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.13 Grade 3 or 4 infectious disease events.



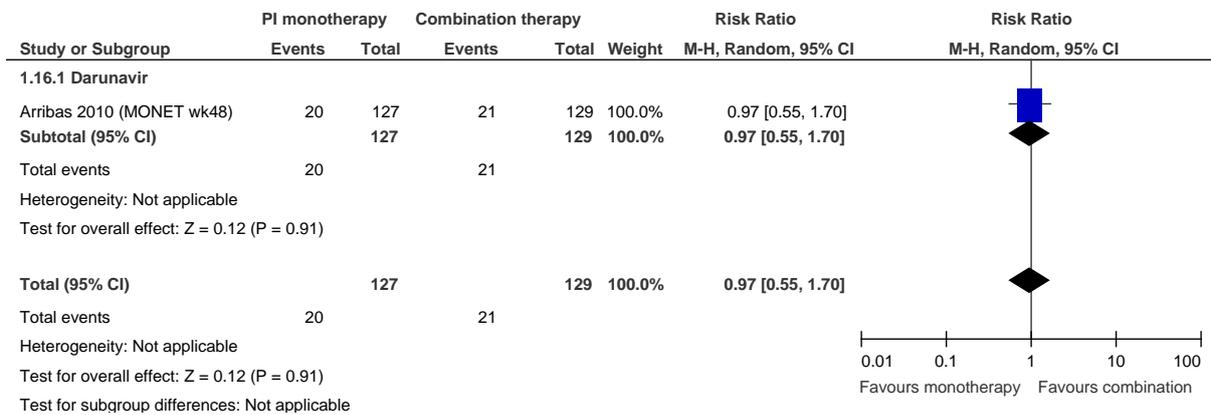
Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.14 Grade 3 or 4 cardiovascular disease events.



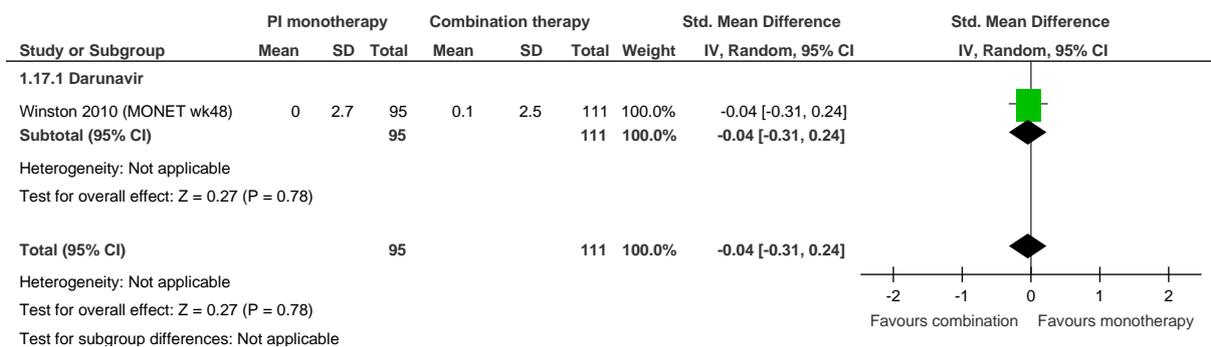
Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.15 Lipodystrophy (any grade).



Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.16 CNS disease (any grade).



Forest plot of comparison: 1 PI monotherapy versus combination therapy, outcome: 1.17 Functional Assessment of HIV infection.



GRADE table for PI monotherapy versus combination therapy for HIV

The outcomes have been classified as follows:

Viral suppression: Critical for decision-making (9/9); CD4 count: Critical for decision-making (8/9); Drug resistance: Critical for decision-making (7/9); Serious adverse events: Important for decision-making (6/9); any grade 3-4 adverse event outcomes: Important for decision-making (5/9); lipodystrophy (any grade) or CNS disease (any grade): Important for decision-making (4/9); change in Functional Assessment of HIV infection: not important for decision-making (3/9).

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	PI monotherapy versus combination therapy	control	Relative (95% CI)	Absolute		
Virological suppression (follow-up 48-96 weeks; viral load <50)												
10	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	476/591 (80.5%)	523/607 (86.2%)	RR 0.95 (0.9 to 0.99)	43 fewer per 1000 (from 9 fewer to 86 fewer)	⊕⊕⊕○ MODERATE	CRITICAL
								87.3%		44 fewer per 1000 (from 9 fewer to 87 fewer)		
Virological suppression - Lopinavir (follow-up 48-96 weeks; viral load < 50)												
8	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	287/352 (81.5%)	322/365 (88.2%)	RR 0.94 (0.89 to 1)	53 fewer per 1000 (from 97 fewer to 0 more)	⊕⊕⊕○ MODERATE	CRITICAL
								88.1%		53 fewer per 1000 (from 97 fewer to 0 more)		
Virological suppression - Darunavir (follow-up 48 weeks; viral load <50)												

2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	189/239 (79.1%)	201/242 (83.1%)	RR 0.96 (0.88 to 1.04)	33 fewer per 1000 (from 100 fewer to 33 more)	⊕⊕⊕ MODERATE	CRITICAL
							82.9%	33 fewer per 1000 (from 99 fewer to 33 more)				
CD4 count (follow-up 48-51.4 weeks; measured with: CD4 cell count; Better indicated by higher values)												
2	randomised trials	serious ¹	very serious ²	no serious indirectness	serious ³	none	54	47	-	SMD 0.75 higher (0.98 lower to 2.47 higher)	⊕○○○ VERY LOW	CRITICAL
CD4 count - Lopinavir (follow-up 48-51.4 weeks; measured with: CD4 cell count; Better indicated by higher values)												
2	randomised trials	serious ¹	very serious ²	no serious indirectness	serious ³	none	54	47	-	SMD 0.75 higher (0.98 lower to 2.47 higher)	⊕○○○ VERY LOW	CRITICAL
Drug resistance (follow-up 48 weeks; genotypic testing)												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	2/125 (1.6%)	1/115 (0.9%)	RR 1.15 (0.15 to 9.01)	1 more per 1000 (from 7 fewer to 70 more)	⊕○○○ VERY LOW	CRITICAL
							3.9%	6 more per 1000 (from 33 fewer to 312 more)				
Drug resistance - Darunavir (follow-up 48 weeks; genotypic testing)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	1/22 (4.5%)	1/13 (7.7%)	RR 0.59 (0.04 to 8.67)	32 fewer per 1000 (from 74 fewer to 590 more)	⊕○○○ VERY LOW	CRITICAL
							7.7%	32 fewer per 1000 (from 74 fewer to 591 more)				
Drug resistance - Lopinavir (follow-up 48 weeks; genotypic testing)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ⁴	none	1/103 (1%)	0/102 (0%)	RR 2.97 (0.12 to 72.09)	0 more per 1000 (from 0 fewer to 0 more)	⊕⊕○○	CRITICAL

								0%		0 more per 1000 (from 0 fewer to 0 more)	LOW	
Serious adverse events (follow-up 48-96 weeks; monitoring)												
3	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	28/280 (10%)	27/281 (9.6%)	RR 1.05 (0.63 to 1.73)	5 more per 1000 (from 36 fewer to 70 more)	⊕⊕⊕O MODERATE	IMPORTANT
								9.7%		5 more per 1000 (from 36 fewer to 71 more)		
Serious adverse events - Darunavir (follow-up 48-96 weeks; monitoring)												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	26/239 (10.9%)	24/242 (9.9%)	RR 1.1 (0.65 to 1.86)	10 more per 1000 (from 35 fewer to 85 more)	⊕⊕⊕O MODERATE	IMPORTANT
								9.9%		10 more per 1000 (from 35 fewer to 85 more)		
Serious adverse events - Lopinavir (follow-up 51.4 weeks; monitoring)												
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ⁴	none	2/41 (4.9%)	3/39 (7.7%)	RR 0.63 (0.11 to 3.59)	28 fewer per 1000 (from 68 fewer to 199 more)	⊕⊕OO LOW	IMPORTANT
								7.7%		28 fewer per 1000 (from 69 fewer to 199 more)		
Grade 3 nervous system or psychiatric adverse event (follow-up 96 weeks; monitoring)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	1/127 (0.8%)	2/129 (1.6%)	RR 0.51 (0.05 to 5.53)	8 fewer per 1000 (from 15 fewer to 70 more)	⊕OOO VERY LOW	IMPORTANT
								1.6%		8 fewer per 1000 (from 15 fewer to 72 more)		
Grade 3 nervous system or psychiatric adverse event - Darunavir (follow-up 96 weeks; monitoring)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	1/127 (0.8%)	2/129 (1.6%)	RR 0.51 (0.05 to 5.53)	8 fewer per 1000 (from 15 fewer to 70 more)	⊕OOO VERY LOW	IMPORTANT
								1.6%		8 fewer per 1000 (from		

										15 fewer to 72 more)		
Grade 3 raised LFTs (follow-up 48 weeks; monitoring)												
4	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	13/429 (3%)	6/443 (1.4%)	RR 2.07 (0.78 to 5.52)	14 more per 1000 (from 3 fewer to 61 more)	⊕○○○ VERY LOW	IMPORTANT
								1.7%		18 more per 1000 (from 4 fewer to 77 more)		
Grade 3 raised LFTs - Darunavir (follow-up 48 weeks; monitoring)												
2	randomised trials	serious ¹	serious ⁵	no serious indirectness	very serious ⁴	none	7/239 (2.9%)	4/242 (1.7%)	RR 1.56 (0.28 to 8.58)	9 more per 1000 (from 12 fewer to 125 more)	⊕○○○ VERY LOW	IMPORTANT
								1.7%		10 more per 1000 (from 12 fewer to 129 more)		
Grade 3 raised LFTs - Lopinavir (follow-up 48 weeks; monitoring)												
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ⁴	none	6/190 (3.2%)	2/201 (1%)	RR 2.54 (0.59 to 10.98)	15 more per 1000 (from 4 fewer to 99 more)	⊕⊕○○ LOW	IMPORTANT
								1%		15 more per 1000 (from 4 fewer to 100 more)		
Grade 3-4 abnormalities in lipase (follow-up 96 weeks; monitoring)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	4/127 (3.1%)	3/129 (2.3%)	RR 1.35 (0.31 to 5.93)	8 more per 1000 (from 16 fewer to 115 more)	⊕○○○ VERY LOW	IMPORTANT
								2.3%		8 more per 1000 (from 16 fewer to 113 more)		
Grade 3-4 abnormalities in lipase - Darunavir												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	4/127 (3.1%)	3/129 (2.3%)	RR 1.35 (0.31 to 5.93)	8 more per 1000 (from 16 fewer to 115 more)	⊕○○○ VERY LOW	IMPORTANT
								2.3%		8 more per 1000 (from 16 fewer to 113 more)		
Grade 3 abnormalities in total cholesterol (follow-up 48-96 weeks; monitoring)												

6	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	none	19/480 (4%)	12/494 (2.4%)	RR 1.57 (0.75 to 3.25)	14 more per 1000 (from 6 fewer to 55 more)	⊕⊕OO LOW	IMPORTANT
								2.7%		15 more per 1000 (from 7 fewer to 61 more)		
Grade 3 abnormalities in total cholesterol - Darunavir (follow-up 48 weeks; monitoring)												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	5/239 (2.1%)	3/242 (1.2%)	RR 1.5 (0.26 to 8.57)	6 more per 1000 (from 9 fewer to 94 more)	⊕OOO VERY LOW	IMPORTANT
								1.2%		6 more per 1000 (from 9 fewer to 91 more)		
Grade 3 abnormalities in total cholesterol - Lopinavir (follow-up 48-96 weeks; monitoring)												
4	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ⁴	none	14/241 (5.8%)	9/252 (3.6%)	RR 1.53 (0.66 to 3.57)	19 more per 1000 (from 12 fewer to 92 more)	⊕⊕OO LOW	IMPORTANT
								4.3%		23 more per 1000 (from 15 fewer to 111 more)		
Grade 3-4 abnormalities in low-density lipoprotein (follow-up 96 weeks; monitoring)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	none	12/127 (9.4%)	10/129 (7.8%)	RR 1.22 (0.55 to 2.72)	17 more per 1000 (from 35 fewer to 133 more)	⊕⊕OO LOW	IMPORTANT
								7.8%		17 more per 1000 (from 35 fewer to 134 more)		
Grade 3-4 abnormalities in low-density lipoprotein - Darunavir (follow-up 96 weeks; monitoring)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	none	12/127 (9.4%)	10/129 (7.8%)	RR 1.22 (0.55 to 2.72)	17 more per 1000 (from 35 fewer to 133 more)	⊕⊕OO LOW	IMPORTANT
								7.8%		17 more per 1000 (from 35 fewer to 134 more)		
Grade 3-4 abnormalities in triglycerides (follow-up 48-96 weeks; monitoring)												
6	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	8/480 (1.7%)	10/494 (2%)	RR 0.91 (0.34 to 2.44)	2 fewer per 1000 (from 13 fewer to 29 more)	⊕OOO	IMPORTANT

								3%		3 fewer per 1000 (from 20 fewer to 43 more)	VERY LOW	
Grade 3-4 abnormalities in triglycerides - Darunavir (follow-up 48-96 weeks; monitoring)												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	5/239 (2.1%)	1/242 (0.4%)	RR 3.7 (0.61 to 22.35)	11 more per 1000 (from 2 fewer to 88 more)	⊕○○○ VERY LOW	IMPORTANT
								0.4%				
Grade 3-4 abnormalities in triglycerides - Lopinavir (follow-up 48-96 weeks; monitoring)												
4	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	very serious ⁴	none	3/241 (1.2%)	9/252 (3.6%)	RR 0.5 (0.16 to 1.62)	18 fewer per 1000 (from 30 fewer to 22 more)	⊕⊕○○ LOW	IMPORTANT
								3.9%		20 fewer per 1000 (from 33 fewer to 24 more)		
Grade 3-4 abnormalities in haemoglobin (follow-up 96 weeks; monitoring)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	0/127 (0%)	2/129 (1.6%)	RR 0.2 (0.01 to 4.19)	12 fewer per 1000 (from 15 fewer to 49 more)	⊕○○○ VERY LOW	IMPORTANT
								1.6%		13 fewer per 1000 (from 16 fewer to 51 more)		
Grade 3-4 abnormalities in haemoglobin - Darunavir (follow-up 96 weeks; monitoring)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	0/127 (0%)	2/129 (1.6%)	RR 0.2 (0.01 to 4.19)	12 fewer per 1000 (from 15 fewer to 49 more)	⊕○○○ VERY LOW	IMPORTANT
								1.6%		13 fewer per 1000 (from 16 fewer to 51 more)		
Grade 3-4 abnormalities in neutrophils (follow-up 96 weeks; monitoring)												

1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	0/127 (0%)	2/129 (1.6%)	RR 0.2 (0.01 to 4.19)	12 fewer per 1000 (from 15 fewer to 49 more)	⊕○○○ VERY LOW	IMPORTANT
								1.6%		13 fewer per 1000 (from 16 fewer to 51 more)		
Grade 3-4 abnormalities in neutrophils - Darunavir (follow-up 96 weeks; monitoring)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	0/127 (0%)	2/129 (1.6%)	RR 0.2 (0.01 to 4.19)	12 fewer per 1000 (from 15 fewer to 49 more)	⊕○○○ VERY LOW	IMPORTANT
								1.6%		13 fewer per 1000 (from 16 fewer to 51 more)		
Grade 3 or 4 infectious disease events (follow-up 48 weeks; monitoring)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	3/112 (2.7%)	2/113 (1.8%)	RR 1.51 (0.26 to 8.88)	9 more per 1000 (from 13 fewer to 139 more)	⊕○○○ VERY LOW	IMPORTANT
								1.8%		9 more per 1000 (from 13 fewer to 142 more)		
Grade 3 or 4 infectious disease events - Darunavir (follow-up 48 weeks; monitoring)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	3/112 (2.7%)	2/113 (1.8%)	RR 1.51 (0.26 to 8.88)	9 more per 1000 (from 13 fewer to 139 more)	⊕○○○ VERY LOW	IMPORTANT
								1.8%		9 more per 1000 (from 13 fewer to 142 more)		
Grade 3 or 4 cardiovascular disease events (follow-up 48 weeks; monitoring)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	1/112 (0.9%)	2/113 (1.8%)	RR 0.5 (0.05 to 5.48)	9 fewer per 1000 (from 17 fewer to 79 more)	⊕○○○ VERY LOW	IMPORTANT
								1.8%		9 fewer per 1000 (from 17 fewer to 81 more)		

Grade 3 or 4 cardiovascular disease events - Darunavir (follow-up 48 weeks; monitoring)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	1/112 (0.9%)	2/113 (1.8%)	RR 0.5 (0.05 to 5.48)	9 fewer per 1000 (from 17 fewer to 79 more)	⊕○○○ VERY LOW	IMPORTANT
								1.8%				
Lipodystrophy (any grade) (follow-up 48 weeks; monitoring)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	1/112 (0.9%)	1/113 (0.9%)	RR 1.01 (0.06 to 15.93)	0 more per 1000 (from 8 fewer to 132 more)	⊕○○○ VERY LOW	IMPORTANT
								0.9%				
Lipodystrophy (any grade) - Darunavir (follow-up 48 weeks; monitoring)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	1/112 (0.9%)	1/113 (0.9%)	RR 1.01 (0.06 to 15.93)	0 more per 1000 (from 8 fewer to 132 more)	⊕○○○ VERY LOW	IMPORTANT
								0.9%				
CNS disease (follow-up 48 weeks; monitoring)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/127 (15.7%)	21/129 (16.3%)	RR 0.97 (0.55 to 1.7)	5 fewer per 1000 (from 73 fewer to 114 more)	⊕⊕⊕○ MODERATE	IMPORTANT
								16.3%				
CNS disease - Darunavir (follow-up 48 weeks; monitoring)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/127 (15.7%)	21/129 (16.3%)	RR 0.97 (0.55 to 1.7)	5 fewer per 1000 (from 73 fewer to 114 more)	⊕⊕⊕○ MODERATE	IMPORTANT
								16.3%				
Functional Assessment of HIV infection (follow-up 48 weeks; measured with: Change in Functional Assessment of HIV Infection score; Better indicated by higher values)												

1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	95	111	-	SMD 0.04 lower (0.31 lower to 0.24 higher)	⊕⊕⊕○ MODERATE	NOT IMPORTANT
Functional Assessment of HIV infection - Darunavir (follow-up 48 weeks; measured with: Change in Functional Assessment of HIV Infection; Better indicated by higher values)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	95	111	-	SMD 0.04 lower (0.31 lower to 0.24 higher)	⊕⊕⊕○ MODERATE	NOT IMPORTANT

¹ randomisation and allocation concealment unclear in some studies

² I² > 80% indicates inconsistency between studies

³ Wide confidence intervals indicates imprecision

⁴ Very small numbers of events

⁵ I² between 20 and 50% indicates some inconsistency