THE LANCET

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"The question for attendees in Rome, and the global community, is whether we have the political will to mobilise the resources needed to arrest the HIV epidemic 30 years after it first emerged."

See **Comment** page 206

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The Castleman's Study

Announcing a New Clinical Trial for Patients With Multicentric Castleman's Disease

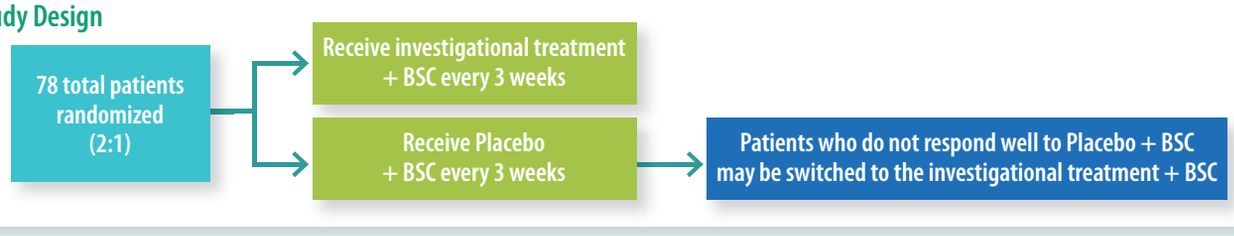
About Multicentric Castleman's Disease (MCD)

MCD is a rare disorder characterized by abnormal noncancerous growths in the lymphatic tissues at multiple sites throughout the body and by systemic manifestations such as fever, night sweats, fatigue, anorexia, and wasting. Also known as giant lymph node hyperplasia or angiofollicular lymph node hyperplasia, MCD can also be misdiagnosed as malignant lymphoma. There is no currently approved treatment for MCD.

Study Overview

Ortho Biotech Oncology Research and Development, a unit of Centocor Research and Development, Inc., is conducting a pivotal, registration study on MCD. The primary objective is to demonstrate that an investigational medicine plus best supportive care (BSC) is better than Placebo + BSC in patients with symptomatic MCD. The investigational medicine is a chimeric monoclonal antibody that blocks the function of the cytokine IL-6.

Study Design



Key Inclusion Criteria

- Symptomatic MCD with measurable tumors confirmed by biopsy
- Age ≥18 years
- Adequate organ function
- On stable or decreasing doses of steroids

Key Exclusion Criteria

- HIV positive, HHV-8 positive
- Previous lymphoma
- Uncontrolled important medical condition
- Known allergy to antibodies or protein products

The Castleman's Study will be conducted in approximately 24 countries worldwide. As this trial presents a unique opportunity for patients with MCD, you may wish to consider referring your patients with this condition. To find out more, please visit:

www.CastlemansResearch.com

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Image courtesy of Sean Carney.

The Wakley Prize 2011

We are looking for the *brightest* and *sharpest* essays about health from professionals and students

In 1823, reformer Thomas Wakley chose to call his medical journal *The Lancet* as a play on words: his publication would both illuminate, like a lancet window, and "cut out the dross", like a surgical instrument.

This year, we would like to invite entrants for the Wakley Prize to do the same. We are looking for the brightest and sharpest essays about a topic of importance to health.

We invite submissions from professionals or students in any health-related specialty. Essays should be no longer than 2000 words and must be submitted by October 11, 2011 through the journal's electronic submission system, specifying "Wakley Prize" as the article type. The winner, as judged by *Lancet* editors (with authors' identities masked), will receive £2000 and publication in the final issue of the year. We hope the winning essay will move, entertain, and cast fresh light on the medical world.

To submit an essay go to:

http://ees.elsevier.com/thelancet/default.asp

THE LANCET

Women's progress UN Women, a new agency to guide global efforts towards gender equality, has issued its first report on women's access to justice in their home and working lives. More women should be put on the front line of law enforcement, and receive access to justice, legal, and health services in "one-stop shops", the report states.

Desperation in Somalia The UN High Commissioner for Refugees (UNHCR) has expressed concern over the rates of malnutrition in Somali refugees who have fled into neighbouring countries to escape the crippling drought. The UNHCR reports that more than 135 000 Somalis have left the nation since the beginning of the year, and that more than a quarter is dispersed.

Patent progress The Medicines Patent Pool has announced a "milestone" licensing agreement with Gilead over several antiretroviral drugs that are still in clinical development. The licence will allow generic versions of tenofovir, emtricitabine, and pipeline drugs cobicistat and elvitegravir, alone or as a new combination product, to enter the market shortly after they become available in rich countries.

Corbis

EU blocks Egyptian sprouts The European Food Safety Authority has issued a moratorium on the import of Egyptian seeds, beans, and sprouts until Oct 31, 2011. A batch of fenugreek seeds from an Egyptian company has been linked to the deaths of 49 people in the EU early this summer from *Escherichia coli* infection. All of the fenugreek seeds from the company will be destroyed.

GMB Akash/Panos

Safe water Revised *WHO guidelines for drinking-water quality* call on governments and water companies for a primary prevention approach to stop the avoidable 2 million deaths per year from waterborne diseases. The guidelines include risk assessments on specific waterborne hazards based on scientific evidence, and will form the groundwork for national laws and regulations.

Mental health challenges The US National Institutes of Health have added global mental health to their series of Grand Challenges. A Delphi consensus process identified 40 top challenges, the most important of which were integration of screening into routine primary care, reduction of the cost of effective drugs, and improvement of access and care for children in low-income countries.

Co-infection control Most cases of co-infection with tuberculosis and HIV in Latin America and the Caribbean are going unrecognised and untreated, according to the Pan American Health Organization. Public health experts want to better coordinate programmes that target both diseases, to ensure people with HIV are tested for tuberculosis and vice versa.

Abortion warning Russian politicians are aiming to reduce the number of abortions in the country by targeting advertisements by service providers. In a bill expected to pass without opposition, 10% of advertisement space would be given over to warnings about possible negative health consequences. Russia has one of the world's highest abortion rates and a declining population.

Dietary data The US National Institutes of Health have created the Biomarkers of Nutrition for Development (BOND) programme, which aims to promote a unified approach for choosing appropriate biomarkers to assess diet and nutrition globally. BOND will be available worldwide, and be used to provide essential data, for example as part of nutrition surveys.

Where's the beef? The Japanese Government is proposing strict guidelines for the hygienic preparation of dishes containing raw beef after several people died earlier this year from beef-related food poisoning. The government is also considering setting up standards for raw chicken and horse meat, which might come into action at a later date.

Budget crisis The Government of Spain is to inject an additional €8 million into the country's public health system next year to stave off regional budget shortfalls and ensure suppliers are paid. Proposed cuts in health spending in response to the national debt crisis are strongly opposed by health-care unions and anti-austerity protestors.

Pentobarbital victory Danish drug firm Lundbeck has introduced a new policy to prevent the use of its drug pentobarbital for executions by US prison authorities. All purchasers must now agree not to redistribute pentobarbital without Lundbeck's written permission. The decision follows the publication in *The Lancet* of an open letter from David Nicholl and colleagues calling on the company to restrict access to the drug.

For the **UN women report on access to justice** see http://progress.unwomen.org

For the **Medicines Patent Pool agreement with Gilead** see http://www.medicinespatentpool.org/LICENSING/Current-Licences/Medicines-Patent-Pool-and-Gilead-Licence-Agreement

For the **WHO drinking water guidelines** see http://www.who.int/water_sanitation_health/events/press_backgrounder/en/index.html

For the **Grand Challenges in Global Mental Health** see http://grandchallengesgmh.nimh.nih.gov

For more on **tuberculosis/HIV co-infection in the Americas** see http://new.paho.org/hq/index.php?option=com_content&task=view&id=5636&Itemid=1926

For the **BOND programme** see http://www.nichd.nih.gov/global_nutrition/programs/bond/about.cfm

For the **open letter to Lundbeck about pentobarbital** see Correspondence *Lancet* 2011; **377:** 2079

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THE LANCET

HIV/AIDS and the road to Rome

On July 17–20, the sixth International AIDS Society conference on HIV pathogenesis, treatment, and prevention will take place in Rome, Italy. To coincide with the meeting, this issue of *The Lancet* is dedicated to HIV/AIDS.

Among the highlights of the conference will be the latest data for new antiretroviral therapy to improve treatment options and expand patient choice. We publish the results of two phase 3 randomised trials, ECHO and THRIVE, which find that in combination regimens in treatment-naive patients, rilpivirine, a new non-nucleoside reverse transcriptase inhibitor, is as safe and effective as efavirenz, the recommended first-choice treatment option. Although rilpivirine has a higher virological failure rate, it has far fewer side-effects than does efavirenz, and will therefore be a valuable treatment option for this patient population.

A hugely contentious area is the role of concurrency as a driver in the HIV epidemic, particularly in sub-Saharan Africa. To date, empirical evidence is limited by flaws in the data. A study that will no doubt ignite further discussion is by Frank Tanser and colleagues, who use a sophisticated geographical approach to analyse data from repeated population-based surveys in an area of KwaZulu-Natal, South Africa. They assess whether multiple concurrent partnerships in men are an important driver of HIV incidence in this population. The authors found that the mean number of lifetime partners—and not multiple concurrent partnerships—is associated with an increase in risk of HIV acquisition. That is not to say that concurrency does not play a part in the epidemic. Indeed, Tanser points out that concurrency might have had a role earlier in this epidemic when disease was concentrated mainly in high-risk groups. He reinforces the need for simple clear messages aimed at reduction of numbers of partners, concurrent or otherwise.

A prominent focus at the meeting will be on biomedical prevention. In 2008, *The Lancet*'s Series on HIV prevention deplored the scarce attention given to prevention efforts. But the recent reinvigoration of prevention, especially by antiretroviral-based prevention trials such as CAPRISA 004, HPTN 052, and iPrEx, ushers in new hope and brings the otherwise separate strategies of prevention and treatment closer together. Indeed, the results of HPTN 052, which showed that people on treatment are less likely to transmit HIV, points to prevention benefits accruing every day as a result of the 6·6 million people currently on antiretroviral drugs. In Rome, WHO will release guidelines recommending treatment of HIV-positive partners in serodiscordant relationships irrespective of CD4 cell count to prevent sexual transmission of HIV. The ethical and operational challenges of this new prevention opportunity will provoke much discussion.

Nancy Padian and colleagues review the developments in HIV prevention since *The Lancet* Series, and emphasise the urgent need for implementation science and establishing the population-level effect of combination prevention. One intervention that remains slow to implement is prevention of mother-to-child transmission. The goal of elimination of paediatric infections is hindered by WHO guidelines specifying that CD4 cell count testing be required for uptake. In the absence of these facilities, Malawi has chosen to offer all HIV-infected pregnant women lifelong antiretroviral therapy, an approach supported by Erik Schouten and colleagues in a Viewpoint and described further in a World Report. Malawi should be commended for taking such a bold public health approach.

Perhaps one of the biggest challenges facing the HIV community is scaling up of access to treatment at a time of financial constraint. Treatment 2.0, led by WHO and UNAIDS, will address the need for innovation and efficiency gains in HIV programmes, such as optimisation of drug regimens, simplification of diagnosis, and adaptation of delivery systems to enable sustained universal access to HIV treatment for those who need it, as well as to maximise the preventive benefits of antiretroviral therapy. This initiative is hugely important and will help to respond to some of the clinical and scientific challenges that Ken Mayer refers to in his Comment, to turn the promise of antiretroviral-based prevention into a concrete strategy for epidemic control.

Recent scientific progress and renewed high-level commitments have re-energised the HIV community with new opportunities to change the course of the epidemic. But one challenge for Rome will be to ensure that the scientific evidence remains connected to the realities in countries, such as barriers of stigma and discrimination. Equity and human rights must remain at the heart of all future HIV/AIDS programmes. ■ *The Lancet*

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For the **THRIVE trial** see **Articles** page 229

For **more on the ECHO and THRIVE trials** see **Comment** page 201

For **Tanser and colleagues' cohort study** see **Articles** page 247

For **more on the concurrency debate** see **Comment** page 203

For ***The Lancet* Series on HIV Prevention** see http://www.lancet.com/series/hiv-prevention

For **Padian and colleagues' paper** see **Review** page 269

For **Schouten and colleagues' paper** see **Viewpoint** page 282

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Warning: a hard habit to break

Per Lindgren/Rex Features

On July 7, the *WHO Report on the Global Tobacco Epidemic, 2011*, was launched in Montevideo, Uruguay. The report focuses on warning people about the dangers of tobacco use through health-warning labels on packaging and national anti-tobacco mass media campaigns. With governments banning tobacco advertisements, the tobacco industry relies primarily on cigarette packaging as a marketing method. Health-warning labels on tobacco packages and media campaigns have been effective in reducing tobacco use and encouraging people to stop. In 2009–10, these campaigns reached 1·9 billion individuals in 23 countries.

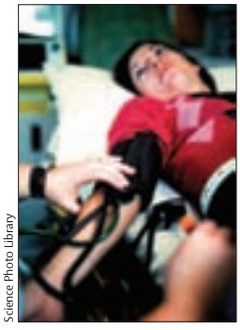
Worldwide, nearly 6 million people per year die from tobacco-related illnesses, including cancers, heart disease, and stroke. The number of deaths is projected to increase to 8 million per year by 2030, with 80% of deaths in countries with low and middle incomes. The death toll from tobacco use could be at least 1 billion in this century. Drastic action is needed to prevent tobacco-related illnesses and deaths. Since 2008, as a result of laws enacted in 16 countries to ban smoking in public places, more than 385 million people have been newly protected from the harms associated with tobacco smoke. Iceland's Parliament is considering a proposal led by the former health minister Siv Fridleifsdottir, in May, to ban tobacco products from general sale, only allowing them to be dispensed by registered pharmacies with special licences.

Tobacco manufacturers pay governments nearly US$133 billion in excise tax revenues, but governments spend less than $1 billion on tobacco-control policies—only 3% of this amount is spent in low-income and middle-income countries. Therefore, people in these countries are less likely to be well informed about the detrimental effects of tobacco use than are those in high-income countries. Governments, especially in low-income and middle-income countries, have to increase spending on anti-tobacco campaigns and health communication. Whatever the cost, it will be a small price that will save perhaps billions of dollars in terms of health care and, most importantly, millions of lives. ■ *The Lancet*

For the **WHO report** see http://whqlibdoc.who.int/publications/2011/9789240687813_eng.pdf

For more on **Iceland's policy for prescription cigarettes** see http://www.icenews.is/index.php/2011/05/30/iceland-to-ban-tobacco/#more-24041

Cardiovascular disease in women—often silent and fatal



Science Photo Library

On June 21, two US organisations, WomenHeart: The National Coalition for Women with Heart Disease and the Society for Women's Health Research, released *2011 10Q Report: Advancing Women's Heart Health Through Improved Research, Diagnosis and Treatment*. The report emphasises the burden of cardiovascular disease in women and the disappointing lack of research into this predicament.

Although cardiovascular disease is the number one killer of both men and women in the USA, more women die yearly—close to 500 000. Women are twice as likely as men to have heart failure, 1·5 times more likely to die within a year of a heart attack, and twice as likely to have a poor outcome after a coronary artery bypass graft. Furthermore, the cardiovascular mortality rate is rising in women younger than 55 years. Women often have non-chest-pain-specific cardiovascular symptoms. Two-thirds of women who die suddenly of coronary heart disease have no symptoms, probably reflecting a distinct microvasculature cause of cardiovascular disease in women.

Women's cardiovascular risk factors are understudied. Psychosocial factors such as depression and stress are more common in women than men, and pregnancy-related complications (eg, gestational diabetes, hypertension, pre-eclampsia) significantly increase cardiovascular disease later in life. The exact nature of oestrogen's protective effect on premenopausal cardiovascular risk remains unclear.

Guidelines for management of cardiovascular disease are primarily targeted at men because women are under-represented in clinical trials. Only a third of trials in cardiovascular disease publish sex-specific results even though US regulations require sex stratification. Although cardiovascular disease contributes 25% of total mortality and morbidity in the USA, relevant cardiovascular research receives only 4% of National Institute of Health funding.

Many American women are unaware of the risk posed by cardiovascular disease, which is an order of magnitude greater than that of breast cancer. Education and advocacy is needed across ethnic and socioeconomic strata to make women aware that the biggest threat to their health is their heart. Researchers must also redouble their efforts to study and improve outcomes for women at risk of cardiovascular disease. ■ *The Lancet*

For the **report on cardiovascular disease in women** see http://www.womenheart.org/documents/upload/FINAL-TO-PRINTER-6-15-11.pdf

Rilpivirine: a step forward in tailored HIV treatment

See Articles page 229 and 238

The results of two highly anticipated clinical trials, ECHO[1] and THRIVE,[2] are reported in *The Lancet*. These studies assessed the efficacy and safety of the latest antiretroviral drug against HIV-1 infection, rilpivirine.

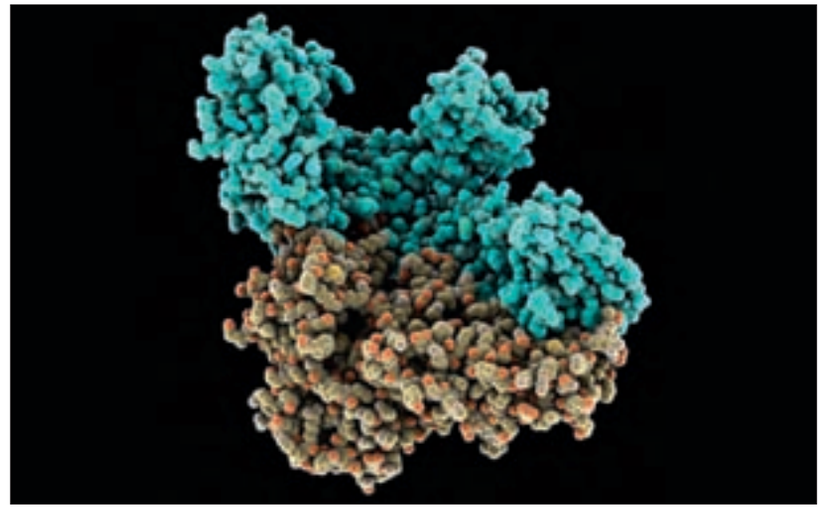
Despite the encouraging case of cure in a patient with HIV-1 infection after treatment for acute myeloid leukaemia with a stem-cell transplantation from a *CCR5* delta32 homozygous donor,[3] no feasible HIV-eradication strategy exists. Standard care is aimed at suppression of plasma viral loads below the limit of detection. This strategy has unequivocally changed the outcome for individuals infected with HIV. However, lifelong treatment is needed because the virus rebounds from latently infected cells once antiretroviral treatment is withdrawn. Furthermore, life expectancy of individuals infected with HIV and treated with combination antiretroviral therapy is lower than that of the general population.[4] This excess mortality has been partly attributed to toxic effects of antiretrovirals. Therefore treatment not only needs to be directed at improved efficacy but also at improved tolerability for the patient. Here, the short-term and long-term side-effects in combination with the convenience of a regimen (ie, dosing frequency and the number of pills or the availability of a coformulation) guide therapy choices from the expanding range of antiretrovirals.

In this context, the ECHO and THRIVE investigators report two large international randomised, double-blind, double-dummy, phase 3 clinical trials comparing efavirenz with rilpivirine in combination with two nucleoside or nucleotide reverse transcriptase inhibitors (N[t]RTIs) in treatment-naive adults with HIV-1 infection.

Rilpivirine (TMC278) is the newest member of the class of non-nucleoside reverse transcriptase inhibitors (NNRTIs) that inhibit the HIV-1 reverse transcriptase in an allosteric manner.[5] Nevirapine was approved as the first NNRTI by the US Food and Drug Administration (FDA) in 1996, followed by delavirdine in 1997 and efavirenz in 1998. The first next-generation NNRTI, etravirine (TMC125), was approved in 2007 for the treatment of patients with evidenced virological failure and resistance to NNRTI in a two-pill twice-daily regimen.[6,7] The newest NNRTI, rilpivirine, is the result of rational drug design.

The efficacy of efavirenz is established,[8] and it is recommended as the first-choice treatment option for treatment-naive adults with HIV-1 infection in combination with two N(t)RTIs, emtricitabine and tenofovir.[9] Efavirenz is generally well tolerated and the most common side-effects are rash and CNS toxic effects, necessitating a regimen switch in some patients. Efavirenz is teratogenic and has a low genetic barrier for drug resistance, usually leading to substantial cross-resistance with nevirapine and delavirdine.[10]

THRIVE and ECHO were designed to assess non-inferiority of rilpivirine to efavirenz. The rationale was sound because of the promising efficacy and safety results of a phase 2b clinical trial.[11] These two parallel and independently run trials were started as a first and second confirmatory trial.[12] Both trials were identical in design; in THRIVE the background N(t)RTIs were investigator-selected (emtricitabine/tenofovir, abacavir/lamivudine, or zidovudine/lamivudine) and in ECHO were fixed (emtricitabine/tenofovir). FDA approval—which was the reason to report two independent trials[12]—was granted before publication.[13] From both studies, 1368 patients with a median baseline viral load of 5 $\log_{10}$ copies per mL and a median CD4 cell count of 256 cells per µL received at least one dose of rilpivirine or efavirenz.[14] Analysis (time to loss of virological response) of the proportion of patients with a plasma viral load lower than the limit of detection (<50 copies per mL) at 48 weeks showed that rilpivirine was not inferior to efavirenz. The proportion of patients with a confirmed response at week 48 was 83% in ECHO and 86% in THRIVE for rilpivirine compared



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Molecular model of the HIV-1 virus reverse transcriptase enzyme

with 83% and 82%, respectively, for efavirenz. Analyses of patients who received at least one dose of study drug and the more conservative per-protocol analysis showed that the non-inferiority criteria were met. Response rates for patients stratified with a baseline viral load of 100 000 copies or fewer per mL were 90% for rilpivirine versus 84% for efavirenz, and 77% for rilpivirine versus 81% for efavirenz in patients with more than 100 000 copies per mL.

Rilpivirine had a better tolerability with fewer grade 2–4 adverse events (16% in the rilpivirine *vs* 31% in the efavirenz group)[14] and fewer adverse events leading to discontinuation of the regimen (3% in the rilpivirine group *vs* 8% in the efavirenz group). Adverse events commonly attributed to efavirenz, such as rash or CNS side-effects, were less often reported in patients in the rilpivirine group than in the efavirenz group.[14] Lipid perturbations were significantly lower in the rilpivirine group than in the efavirenz group although no significant difference in the ratio of total cholesterol to HDL was reported. Both rilpivirine and efavirenz can be coformulated with emtricitabine or tenofovir in a one-pill once-daily regimen, and an open-label comparative study of the triple combination is ongoing (NCT01309243).

Of note, nearly 11% of patients in the rilpivirine group had virological failure compared with nearly 6% in the efavirenz group.[14] The authors suggest that this difference might be because of an increased effect on virological failure of suboptimum adherence to rilpivirine than occurred with efavirenz. In an analysis of the pooled data, the proportion of patients with virological failure with baseline viral load of 100 000 copies or fewer per mL was 5·2% (19 of 368 patients) for rilpivirine and 4·8% (16 of 330 patients) for efavirenz.[15,16] The proportion of patients with virological failure and baseline viral load of more than 100 000 copies per mL was 17% (53 of 318) for rilpivirine and 7% (23 of 352) for efavirenz.[15,16] These data suggest that a baseline viral load of more than 5 $\log_{10}$ copies per mL was a predictor of virological failure in the rilpivirine group. This consideration has been adopted in the FDA recommendations.[13]

What do the trials teach us about cross-resistance? In those patients who failed therapy, 63% in the rilpivirine group developed at least one NNRTI-resistance-associated mutation (mainly E138K, but also K101E, H221Y, V189I, Y181C, or V90I) compared with 54% in the efavirenz group (mainly K103N, but also V106M, Y188C, or K101E). Of the patients with virological failure on rilpivirine who were phenotypically resistant to rilpivirine, 45%, 87%, and 90% were cross-resistant to nevirapine, efavirenz, and etravirine, respectively,[1,15] practically excluding further use of NNRTIs in these patients. This outcome is different from efavirenz resistance, which generally leaves etravirine[6,7] and probably rilpivirine[15] as alternative treatment options. Additional studies are needed to clarify these issues. Also unresolved is the question of why proportionally more NRTI-resistance-associated mutations were reported in patients who had virological failure on rilpivirine (68%, mainly M184I) than efavirenz (32%, mainly M184V).[15] Because of the importance of the remaining questions about virological failure and cross-resistance, we believe that the absence of a fully published pooled analysis is a missed opportunity.

However, rilpivirine should be embraced as an example of the continuous effort to generate patient-tailored drugs that are highly convenient, have minimal side-effects, and are sufficiently efficacious. The presented data show that rilpivirine is a valid and safe alternative to efavirenz in the treatment of antiretroviral-naive patients infected with HIV-1 and is associated with fewer side-effects. However, although apparently non-inferior, rilpivirine should be started cautiously as patients with a baseline plasma viral load of more than 100 000 copies per mL were more prone to virological failure (and development of resistance). Additional studies explaining the increased rate of virological failure with rilpivirine and studies about resistance or cross-resistance are warranted. The results of ongoing trials assessing the potential and safety of switching from a protease-inhibitor-based (NCT01252940) or efavirenz-based (NCT01286740) regimen to rilpivirine in virologically suppressed patients are eagerly anticipated to expand the rational use of rilpivirine in daily practice.

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RS and BAD declare that they have no conflicts of interest. ZD coordinated an FP7 project with Tibotec (ie, money provided by EU not by Tibotec [THINC 2008-2010]).

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The concurrency debate: time to put it to rest

The debate over the centrality of concurrency in the maintenance of generalised, heterosexual HIV epidemics still smoulders,[1] mostly because of substantial flaws in both evidence that supports and that refutes the hypothesis that concurrent sexual partners drive the epidemic in sub-Saharan Africa.[2,3] Nevertheless, international organisations and national agencies have already begun to scale up partner-reduction campaigns that specifically target concurrency.[4]

The key challenge for empirical tests of the importance of concurrent sexual partnerships is that concurrency is postulated to increase the risk of transmission of the virus, rather than acquisition. Therefore an individual-level analysis should estimate the effect of the behaviour of an individual's partners on his or her own risk of HIV infection. A traditional approach would entail the collection of detailed sexual histories from individuals and all of their partners—a costly and time-consuming proposition.[2]

In *The Lancet,* Frank Tanser and colleagues[5] make innovative use of geolocated data in an effective empirical test of the concurrency hypothesis. To avoid the cumbersome and often incomplete process of sexual-network mapping, the investigators measured mean sexual-risk behaviour in women's likely partners. Information about partners was collected from men, and incident infections in women were assessed in association with the number of partners and rate of concurrency reported by men in the geographical area. The researchers support the method with data from this well-characterised population, in which they have documented that women select most of their sexual partners from within a fixed geographical radius. Thus this analysis makes a crucial contribution to our understanding by addressing the primary shortcoming of the methods in previous studies. The overarching finding was that increases in lifetime numbers of partners for men, not concurrency, raised the individual risk of seroconversion in women from the same area.

Despite the strength of the design, Tanser and colleagues' study does not provide the final definitive answer about whether concurrency maintains the spread of HIV. The investigators acknowledge that the behavioural survey in men was taken well before many of the women seroconverted, and so they had to assume no substantial shifts in men's sexual behaviour over the study's duration. Most importantly, the prevalence of concurrency was

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calculated as the percentage of men who reported being in more than one sexual relationship at the time of the survey. This definition of concurrency attenuates the key result of the investigation—the number of sexual partners was assessed over a man's lifetime, but concurrency was the present point-prevalence in the community.

These limitations notwithstanding, the strong dose-effect of number of partners argues strongly for the importance of the number of lifetime male partners in driving the epidemic. Analyses of areas characterised by high numbers of lifetime male partners and little concurrency, and vice versa, also corroborate this finding.[5] Although regions with large numbers of partners and low concurrency were associated with high incidence of infection in women, no association between incidence and areas with high concurrency and low numbers of partners existed.[5]

Tanser and colleagues' report clearly contributes to the concurrency debate in substantial methodological ways, but even the investigators acknowledge that concurrency could have been an important driver at early stages of the epidemic. This debate should be put to rest. Concurrency is a subset of multiple partners: both contribute to sexual-network formation, and therefore both probably play a part in the epidemic's spread, even if they are not risk factors with the same effects at the same times in the same regions.

We agree with Tanser and colleagues that messages focusing on concurrency alone could diminish the importance of multiple partners, and so could be dangerous. Messages aimed at reductions in both multiple and concurrent partners might have diluted effects (as the researchers suggest), but this contention should be supported by empirical data about how target populations understand such messages—eg, the zero-grazing campaign in Uganda from 1986 to 1991 might have been an effective way to address both.[6]

Messages should be explicit about the behavioural change required and appropriate for the local context. Studies in Kenya[7] and Tanzania[8] suggest that many young people do not understand global catchphrases such as those about faithfulness, with interpretations ranging from the importance of trust in relationships to the value of being a good or honest person. Essentially, Tanser and colleagues' study reinforces the need for simple, unambiguous prevention messages to discourage individuals from having several sexual partners, whether concurrent or not.

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Test and treat in HIV: success could depend on rapid detection

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In *The Lancet*, Kimberly Powers and colleagues[1] present a mathematical model of HIV transmission to project the population-level effectiveness of three approaches to the provision of universal HIV testing and immediate initiation of antiretroviral therapy for HIV prevention (a test-and-treat intervention) in Lilongwe, Malawi. Antiretrovirals reduce infectiousness to others by reducing viral loads in the blood and genital secretions of patients with HIV.[2,3] This study follows closely on from the exciting results of HPTN-052,[4] the first phase 3 randomised trial of antiretroviral therapy to prevent HIV transmission in serodiscordant couples for whom the

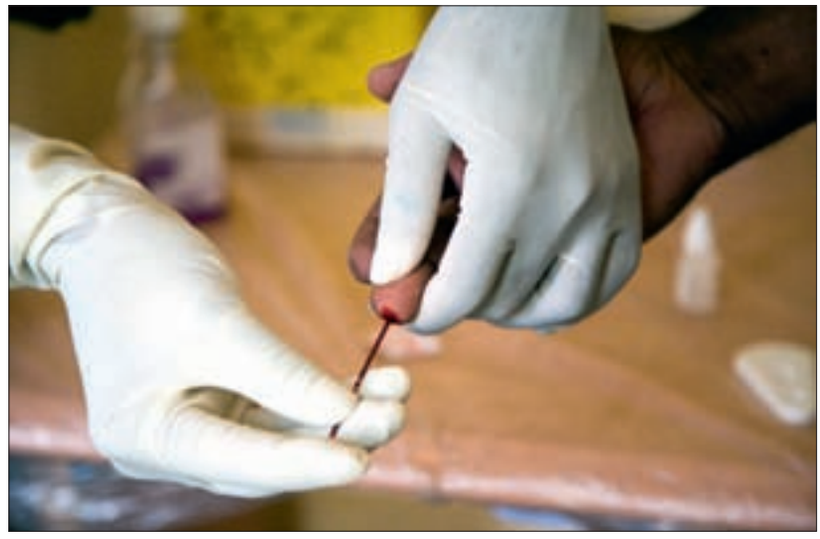
partner with HIV does not meet the criteria for starting antiretrovirals (CD4 cell count of 350–550 cells per μL). HPTN-052 received wide media coverage earlier this year when interim analysis showed 96% fewer HIV transmission events in couples who began treatment immediately than in couples who started at a later date (one *vs* 27 transmission events).

Powers and colleagues' study originates from the research group that spearheaded HPTN-052 and did pioneering work on the identification of acute HIV infection in Africa. Test-and-treat strategies have been assessed in several previous mathematical modelling studies.[5,6] Powers and colleagues' report stands out because of the unusually comprehensive data about sexual partnerships and viral loads from acute HIV cases, which allow consideration of differential per-contact transmissibility by disease stage and more precise estimation of the likely importance of early HIV infection for epidemic dynamics in the context of test and treat. Early HIV infection is potentially very important because this disease stage, although constituting only a brief period in the natural history of HIV (generally defined as about the first 6 months after infection), has a disproportionate effect on disease spread because it is characterised by a high viral load and thus a high per-contact transmission risk.[7,8]

Powers and colleagues estimate that nearly 40% of incident infections in Lilongwe result from early-stage HIV infections; this estimate is greater than that assumed by Granich and colleagues in a 2009 modelling study,[5] which concluded that universal yearly HIV testing of adults followed by immediate highly active antiretroviral therapy for individuals who test positive (ie, a test-and-treat strategy) could reduce HIV prevalence from 15% to less than 1% within the next 50 years. Conclusions from Powers and colleagues' study are less favourable, with the key finding being that if individuals within the first 6 months of their HIV infection are indeed responsible for a high proportion of all transmission events, a substantial proportion needs to be rapidly identified and treated during this stage to have any prospect of the large decreases in HIV prevalence projected by Granich and colleagues. The importance of early HIV in transmission is sensitive to epidemic stage and assumptions about the frequency of partner change and concurrent relationships, and will thus probably vary between populations.

This requirement of rapid detection of incident infection adds substantially to the already formidable logistical challenges and costs of attempting to implement test-and-treat strategies. HIV infection is still a stigmatising disease, making regular repeat HIV testing and counselling difficult to scale up. And antiretroviral therapy for prevention needs high levels of adherence for life. Economies of scale and differential pricing have resulted in very low unit costs for the widely used HIV testing and care commodities in resource-poor settings, but detection of early HIV infection would need more expensive kits that can detect antigen and antibodies, along with other changes to the HIV testing strategy.[9,10] Other concerns related to test-and-treat strategies include the risk of accelerating the emergence of antiviral resistance or risk compensation (ie, adoption of more risky sexual behaviours when an individual feels protected by treatment[11]) and the ethics of treating individuals to protect their contacts.[12]

Test-and-treat strategies are beginning to be investigated in community-wide cluster-randomised trials and demonstration projects, building on the impressive scale-up of HIV-care programmes in Africa during the past 5 years. Should these trials be modified to incorporate the need to better address early HIV infection? Of course this would be ideal, and investigators and implementers should be aware of this aspect of HIV epidemiology and aim to collect data in the most informative way possible, even if practicalities dictate against inclusion of specific components targeting this stage. Alternatively, combined HIV-prevention strategies could be used, because populations targeted for repeat testing could then be well placed to receive interventions aimed at HIV-negative



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participants as well. Such prevention strategies include male circumcision and pre-exposure prophylaxis with oral tablets or vaginal gels containing tenofovir.[13]

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Antiretrovirals for HIV prevention: translating promise into praxis

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The road between Vienna and Rome has been a historic thoroughfare for centuries, but in the past year the distance has symbolised the move from aspirations that antiretroviral drugs could decrease HIV incidence to a secure scientific foundation for an invigorated strategy of epidemic control. Findings from the CAPRISA 004 study,[1] presented at the Vienna International AIDS Conference in August, 2010, showed that a tenofovir-containing gel reduced HIV incidence by about 39% in uninfected women in South Africa. Subsequently, the iPrEx study[2] demonstrated that oral tenofovir-emtricitabine decreased HIV transmission by about 44% among men who have sex with men (MSM). In both studies, participants who were highly adherent derived the greatest prophylactic benefit. At this month's International AIDS Society meeting in Rome, announcement of results from the HPTN 052 study will show that people infected with HIV whose CD4 counts were 350 cells per µL or greater when they initiated treatment were 96% less likely to transmit HIV to uninfected spouses than those who started later.[3]

The past year has not only had unmitigated successes. The FEM-PrEP study[4] assessing oral tenofovir-emtricitabine pre-exposure prophylaxis (PrEP) in women in sub-Saharan African was prematurely terminated because the intervention did not appear to be efficacious. In *The Lancet*, a Viewpoint by Salim Abdool Karim and colleagues[5] could help to explain this surprising result, because protection in CAPRISA 004 was associated with vaginal tenofovir concentrations exceeding 1 ng/mL. Oral tenofovir has been shown to achieve vaginal tissue concentrations that are less than 1% of those observed after women applied the topical gel, so topical chemoprevention could trump oral tenofovir.[6,7] Another possible reason for the poor efficacy of the intervention in FEM-PrEP could be because of non-adherence, which attenuated the benefits seen in CAPRISA 004 and iPrEx, and is the Achilles heel of chemoprevention. Analyses that might inform either hypothesis are underway.

In the next few years additional understanding will come from studies of PrEP in injecting drug users and heterosexual discordant couples, and a comparison of

whether oral or topical PrEP is more protective for women, but residual questions remain. Concerns have been expressed about the reliance on tenofovir-based regimens for primary prevention because the drug is a mainstay of treatment, based on the worry that chemoprophylaxis will result in resistance that could compromise efforts to expand access to drugs, since second-line treatment regimens are more expensive. Studies of alternative chemoprophylaxis regimens with drugs that are not as frequently used, such as maraviroc, are being initiated. Several years of study will be needed to establish whether alternatives to tenofovir-based chemoprophylaxis are as effective. Less frequent PrEP dosing could save money and limit toxic effects, and studies are underway in Africa and Asia on the acceptability and effectiveness of different intermittent PrEP strategies.

In a severe economic downturn, with less than a third of people infected with HIV who need antiretroviral treatment (based on WHO criteria) accessing drugs,[8] concerns regarding how best to use scarce resources loom large. The conclusions from HPTN 052 would suggest that earlier initiation of treatment could yield a substantial prevention benefit, but it is important to consider that a significant proportion of new HIV infections do not occur in the context of stable discordant couples. To optimise the prevention benefit from antiretroviral treatment that decreases new HIV transmissions, culturally tailored strategies to seek out, test, and treat patients are needed, which massively scale up testing. Such strategies should decrease the pool of people who are unaware of their infection, and offer them earlier treatment and behavioural counselling to decrease risk compensation and to promote ongoing drug adherence (figure). A successful public health strategy would also need to carefully assess the risk practices of those who test HIV negative, since a subset will benefit from chemoprophylaxis. The algorithm of who should be offered PrEP will need to be adjusted to mirror local realities, since the AIDS pandemic is really a set of localised micro-epidemics. Clinical effectiveness studies have already suggested that oral PrEP could be cost saving when offered to high-risk MSM in the USA,[9] and microbicidal gel could be cost effective for some young South African women.[10]

If the Vienna conference was a harbinger of a new era of chemoprevention, the meeting in Rome will be a sober reminder of the costs of success. Hard decisions will need to be made by international funders as to how best to deploy finite resources to achieve the greatest benefit for those most in need. Much as the International AIDS Conference in Vancouver, in 1996, ushered in the era of highly active antiretroviral treatment, and the meeting in Durban, 2000, shone the spotlight on the urgency of making antiretrovirals available to those in the developing world, these two European meetings highlight the reality that in the short term, in the absence of an effective AIDS vaccine, we have the tools at our disposal to reduce substantially the 2·5 million new infections that are expected to occur each year for the next few years.[8] The question for attendees in Rome, and the global community, is whether we have the political will to mobilise the resources needed to arrest the HIV epidemic 30 years after it first emerged.

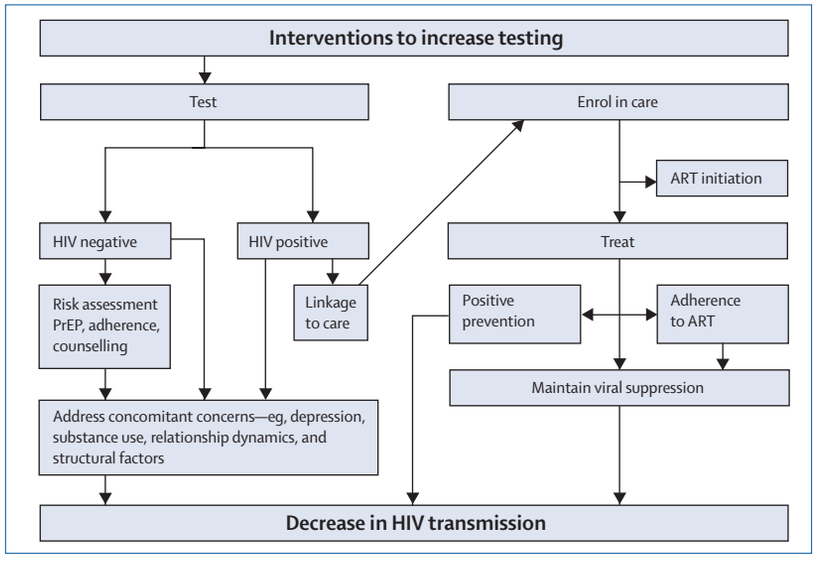

***Figure*: Combination antiretroviral prevention**
ART=antiretroviral treatment. PrEP=pre-exposure prophylaxis.

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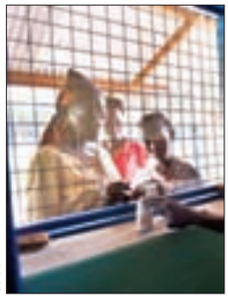
Treatment as prevention—a double hat-trick



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In the absence of a cure or a vaccine, new HIV infections continue to accumulate 30 years into the pandemic. By contrast, over the past 15 years, highly active antiretroviral therapy (HAART) has prevented progression to AIDS and death for millions of people. More recently, it has become increasingly apparent that HAART has a secondary preventive effect on HIV and tuberculosis transmission. As a result, the International AIDS Society, with the support of key international agencies, organised the International Treatment as Prevention Workshop.[1] At the end of the Workshop, it had become clear that treatment as prevention has progressed from a testable hypothesis to an urgent implementation priority.

Plasma HIV-1 RNA concentration is now accepted as a key driver of HIV transmission, and appropriate use of HAART is highly effective in reducing plasma HIV-1 RNA to undetectable levels, consequently decreasing HIV transmission. This reduction applies to vertical transmission,[2] serodiscordant heterosexual couples,[3] and injection drug use.[4,5] Lower community viral load, caused by the expansion of HAART coverage, has been associated with declining numbers of new HIV diagnoses in Taiwan,[6] British Columbia, Canada,[7,8] and San Francisco, USA.[9]

HPTN 052—a randomised trial of HIV serodiscordant couples—was halted by the data and safety monitoring board after a planned interim analysis.[10] The study[11] included HIV serodiscordant couples in whom the HIV-infected partner had CD4 cell counts between 350 and 550 cells per µL. Participating couples were randomly assigned so that the HIV-infected partner would receive immediate or deferred (defined as started after a CD4 cell count below 250 cells per µL, or an incident AIDS event) HAART. The investigators reported an impressive 96% decrease in the risk of HIV transmission with immediate HAART. Of note, immediate HAART was also associated with a 30% decrease in the combined endpoint of disease progression and death, and an 83% reduction in the incidence of extra-pulmonary tuberculosis.

For the past decade, we have struggled with the substantial tension between those advocating for the need to rigorously pursue every question before implementing treatment as prevention initiatives and those advocating for the research to be done as part of an implementation strategy. Nowadays, particularly in the wake of the compelling—although yet to be reported in detail—HPTN 052 results, we are no longer in equipoise. The evidence is clear: treatment conclusively prevents morbidity, mortality, and transmission. From this point on, these three endpoints should be considered together. Further, we urgently need new normative guidelines that fully incorporate treatment as prevention, without caveats. It would be unethical not to offer immediate HAART to serodiscordant couples.[12]

Starting immediately, we must deploy so-called Smart HAART Roll Out initiatives that incorporate a strong implementation science component so that evidence-based best practices can be adequately delineated. The entire cascade of care must be dissected and assessed as part of these efforts. Seek, Test, Treat, and Retain (STTR) initiatives[13] partially address one dimension of a much more complex picture.

Mathematical modelling has previously suggested that progressive expansion of HAART coverage would

lead to proportional decreases in new HIV infections.[14] At the extreme, a universal test-and-treat strategy was suggested as a possible means to eliminate HIV;[15] however, others have contested this view.[16] Research efforts are currently being deployed to address some of these important questions.[17,18] Unequivocal answers are urgently needed. Moreover, in view of present fiscal challenges and the impracticality of amassing evidence specific to every geographical region, culture, affected group, and population, it will be essential to foster collaboration, data harmonisation, and efficiency at all stages.

The evidence is in: treatment is prevention. Treatment dramatically prevents morbidity and mortality, HIV transmission, and tuberculosis. Furthermore, treatment prevents HIV transmission in vertical, sexual, and injection drug use settings; indeed, a very welcome double hat-trick. The challenge remains to optimise the impact of this valuable intervention. Failure to do so is not an option.

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Treatment 2.0: catalysing the next phase of scale-up

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Treatment 2.0 is an initiative coordinated by UNAIDS and WHO to provide leadership and technical guidance to catalyse the next phase of scale-up in HIV treatment.[1] Radical simplification, innovation in drug design and diagnostics, renewed commitment and resources, and adapted delivery systems will be crucial to reach universal and sustainable coverage of treatment for those in need. The Treatment 2.0 framework is guiding UNAIDS, WHO, and partners to scale up treatment over the next decade.

In 2003, WHO published *The public health approach to antiretroviral therapy: overcoming constraints*,[2] in which the organisation laid out a strategic rationale for the rapid

scale-up of antiretroviral therapy (ART) in low-income and middle-income countries—the report paved the way for the 3 by 5 initiative of UNAIDS and WHO. Key elements of the public health approach include using standardised treatment protocols and simplified clinical monitoring, optimising the use of human resources, involving people living with HIV in programme design and implementation, and minimising costs. In 2006, all UN member states committed to the goal of universal access by 2010.[3]

Dedicated AIDS financing rose from US$1·6 billion in 2001 to $15·9 billion in 2009,[4] with substantial increases in domestic and international funding, in particular through the Global Fund to Fight AIDS, Tuberculosis and Malaria, the US President's Emergency Plan for AIDS Relief, and other bilateral programmes and private-sector contributions. Preliminary data indicate that, by the end of 2010, more than 6 million adults and children were receiving ART, compared with only 30 000 in 2003.[5] This achievement is a major one but, with coverage of less than half of those eligible, still far short of universal access.

WHO's guidelines about ART were first published in 2002, with revisions in 2003, 2006, and 2010.[5,6] The 2010 guidelines reflect the evidence that earlier starting of ART (≤350 CD4 cells per μL) is cost effective, improves health outcomes, and reduces HIV and tuberculosis transmission.[7–9] The enormous potential of ART to both save lives and prevent new infections underscores the urgency of achieving universal access.

Mike Kalloffel/Still Pictures

HIV clinic in Malawi

The world faces a $10 billion annual shortfall in financing for AIDS in a context of global economic constraints and competing demands.[4,10,11] Access to HIV and non-HIV health services in many poor countries is limited by fragile health systems and often fragmented health services. 10 million people who are eligible do not have access to ART, with structural barriers, such as discriminatory laws and outdated drug control policies, exacerbating inequities in access.[10]

Treatment 2.0 is designed to maximise the efficiency and effectiveness of HIV treatment through focus on five priorities: optimising drug regimens, advancing point-of-care and other simplified platforms for diagnosis and monitoring, reducing costs, adapting delivery systems, and mobilising communities.

In the short term, there are many avenues being pursued to optimise currently available drugs and regimens, including studies aimed at dose reduction, simplified process chemistry, and one-pill-per-day formulations. Efforts are underway to standardise simplified platforms for diagnosis and treatment monitoring with available technologies. Reduced costs can be achieved through commodity price reductions, use of market and trade flexibilities, and efficiency gains across HIV programmes. Best practice in decentralisation and integration of service delivery is being documented and promoted, and communities are mobilising to create demand, to participate in the design, management, and delivery of services, and to promote and protect human rights.

In the medium term, efforts will focus on re-invigorating the research pipeline to develop new drug regimens, matched against target product profiles that maximise potency, robustness, and barriers to resistance, minimise toxicities and drug interactions, and emphasise simple formulations. Similarly, target profiles will be advanced to research and develop new technologies for point-of-care and other simplified diagnostic platforms.

The non-drug costs of treatment substantially outweigh the cost of the drugs themselves.[12] Guidance will be developed to improve patients' care while achieving efficiency gains through adapting service delivery. The focus will be on optimising service delivery approaches that are family-centred, that are available at the periphery of the health-care system, that integrate HIV prevention, diagnosis, and treatment, and (depending on local specificities) other areas of health care, such as tuberculosis,

viral hepatitis, maternal and child health, sexual and reproductive health, harm reduction, and primary care.

A group of technical, civil society, research, and funding partners met on Feb 7, 2011, in Geneva, Switzerland and laid the groundwork for a well-coordinated and accountable operational plan to achieve the goals of Treatment 2.0. The details of this plan will be published in July, 2011, at the 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention.

The ongoing commitment of all stakeholders is crucial. Good-quality improvements that maximise efficiency, ensure effective outcomes for HIV and broader health, and strengthen overall health and community systems are essential to achieve sustained and universal access.

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The publication date of the plan has changed since the original electronic publication of this comment

Let there be light: The Wakley Prize 2011

In 1823, reformer Thomas Wakley chose to call his medical journal *The Lancet* as a play on words: his publication would both illuminate, like a lancet window, and "cut out the dross" like a surgical instrument. In his introduction to the first issue, Wakley signalled his intent to make his publication accessible to as wide an audience as possible, promising to "exclude from our pages the semibarbarous phraseology of the Schools, and adopt as its substitute, plain English diction".

This year, we would like to invite entrants for the Wakley Prize to do the same. We are looking for the brightest and sharpest essays about a topic of importance to health. Whether you are a medical student starting your first year, a mid-career researcher working on a health-related project, a retiring consultant looking back on decades of change and innovation, or a front-line nurse or paramedic describing the day-to-day challenges you face, we want to hear your story, and your opinions.

We invite submissions from professionals or students in any health-related specialty. Essays should be no longer than 2000 words and must be submitted by Oct 11, 2011 through the journal's electronic submission system, specifying "Wakley Prize" as the article type. The winner, as judged by *Lancet* editors (with authors' identities masked), will receive £2000 and publication in the final issue of the year. We hope the winning essay will move, entertain, and cast fresh light on the medical world.

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To **submit an essay** go to http://ees.elsevier.com/thelancet/default.asp

Offline: A seeker of silences


Richard Horton


Richard Horton


Richard Horton


Richard Horton


Richard Horton

This is the story of a people entirely invisible to the world, a people with no voice and, presently, no future. It is the story of a people to whom many of the great powers, thanks to their colonial histories, owe a special obligation.

*

Dr Ali Dakwar led us through the Ein El Hilweh Palestinian refugee camp in Saida (Sidon), 40 km south of Beirut. He has spent most of his working life with the United Nations Relief and Works Agency (UNRWA), orchestrating care and services for Palestinian refugees who lost their original homes in Israel during the wars of 1948 and 1967. Now, he leads a maternal and child health project on behalf of charity, Medical Aid for Palestinians (MAP). About 280 000 Palestinian refugees live across Lebanon in 12 officially designated refugee camps. Half of this population is under 24 years of age. Families suffer almost complete social, economic, and political exclusion. Housing is Dickensian in its inadequacy. Adults have no right to vote. Education is poor. Unemployment is high (well over 50%). Those who are of working age are prevented from joining anything but the most low-skilled occupations (a bright and promising young Palestinian born in Lebanon is not allowed, for example, to become a doctor working in Lebanese society). And the health of refugees is precarious. 60% of Palestinian refugee children are anaemic, as are 40% of their mothers.

*

The Ein El Hilweh camp is the biggest in the country. About 100 000 refugees live within one square kilometre. The feeling inside the camp is one of extreme intensity—overcrowding, poverty, dangerous and almost slum-like conditions. UNRWA is the main service provider. But the MAP team of Dr Ali, seven midwives, and three nurses bridges gaps where UNRWA lacks resources. Some of the biggest gaps are in maternal and child health. There is no free passage into or out of the camp to access care in Lebanese health facilities. I needed a permit to enter and my passport was closely scrutinised by Lebanese army guards at one of the camp's checkpoints. 20 doctors work inside the camp. Dr Khaled Abou Shakra and Dr Kassem Mohammad work in one of two UNRWA health centres. They were both born in the camp and completed their schooling there. After finishing medical degrees in Russia, they returned to continue clinical training in the Palestinian Red Crescent Society hospital system that exists for Palestinians in the camps. They work with one other doctor and a dentist, together with a small team of nurses. 300 patients pass through their clinic each day.

*

One MAP project, begun in 2008, is run with another non-governmental organisation, Naba'a (Developmental Action Without Borders). The team is composed of a GP, gynaecologist, paediatrician, urologist, and nurse. Part of their work is preventive, educating families to recognise health problems before they become too severe (for example, by using dolls to teach about the functions of blood and the signs of anaemia). They also act as a drop-in clinic, kindergarten, community advice centre, advocacy organisation, and a means to mobilise informal networks of mothers to amplify neglected health messages (eg, on personal hygiene). This work is often confronted with deep cultural taboos. Educating women about safer sex and condom use may be seen as promoting "promiscuity". The creation of this MAP/Naba'a clinic has been a huge achievement. As the paintings of children on the walls of the clinic illustrate, this work is a testament to the community's commitment to participation, tolerance, equality, and protection. In a setting of sometimes bleak possibility, the work of MAP, with friends from UNRWA and other NGOs, is offering a vital lifeline to a future free of political oppression and international isolation.

*

How likely is that hopeful future? In truth, it feels distant. But thanks to people—Huda Zurayk, Rita Giacaman, Iman Nuwayhid, to name only three—who have dedicated their professional lives to the health and futures of a population that has been utterly disenfranchised by their host country and by the international community, it is possible to glimpse a way ahead. That way might come from providing a voice through science—reporting the realities of camp life to those who might prefer us to be unaware of the existence of not only the camps but also their inhabitants. Journals have a part to play too.

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Quest for an effective AIDS vaccine takes a new tack

Clinical and immunological breakthroughs in 2009 and 2010 are pulling AIDS vaccine research out of the doldrums of previous years. John Maurice reports on the latest developments.

In their battle with HIV, vaccine researchers have become used to ups and downs. Since their early encounters with the elusive virus in the mid-1980s, the downs have clearly outnumbered the ups. Late 2009, however, saw an upward turn. "In the last couple of years", says Seth Berkley, immediate past president of the International AIDS Vaccine Initiative (IAVI)*, "we've seen more progress than over the past decade. There is no doubt in my mind that we are now at a critical turning point and the pace of progress is clearly accelerating." Catherine Hankins, chief scientific adviser at UNAIDS, is also elated: "Recent exciting developments", she says, "have given a tremendous boost to the entire field of HIV protection."

Three developments stand out. First, on Sept 3, 2009, a team of scientists from the IAVI Neutralizing Antibody Center at the Scripps Research Institute in California, USA, announced that they had culled, from the sera of about 1800 HIV-infected people in Thailand, Australia, the UK, the USA, and several African countries, two antibodies capable of neutralising a wide range of HIV strains circulating throughout the world. These antibodies proved to be far more potent than the handful of broadly neutralising antibodies discovered up to then. "They are probably 100 times better", team leader Dennis Burton, professor of immunology and microbial science at the Scripps Institute, told *IAVI Report*, a quarterly IAVI publication. "Some of them hit 90% of the world's [HIV] isolates."

Over the past year, other teams working under the aegis of the US National Institutes of Health (NIH) have found several more "extraordinarily potent" broadly neutralising antibodies, Berkley says. "This shows us that humans can make antibodies that cover all the HIV strains. So we're in a rapid race now to figure out how to use these antibodies to make a powerful vaccine. I can't predict when the problem will be solved. But I know it will be."

> **"'We have to hit this epidemic with everything we've got. But without a vaccine, we're not going to nail it down. And we can be certain now, in the light of recent progress, that we will have a good vaccine. Just don't ask me to give you a time-frame.'"**

Second, on Sept 24, 2009, the US National Institute of Allergy and Infectious Diseases (NIAID) reported the results of a large-scale clinical trial held in Thailand—the largest HIV vaccine trial so far. The vaccine protected 31% of 8000 vaccinated trial participants, thus becoming the first vaccine to show protective efficacy against HIV. For Hankins at UNAIDS, the findings of this trial were "quite surprising and very exciting". Needless to say, she adds, "a 31% protective efficacy rate does not qualify a vaccine for further development, but it does provide proof that an AIDS vaccine can work". To many researchers the news signified that HIV, however biologically wily, was not invincible.

Third, on May 3, this year, a team at the Oregon Health and Science University, Beaverton, OR, USA, reported that in 13 of 24 monkeys infected with the most highly virulent strain known of SIV, the simian cousin of HIV, a novel vaccine they had constructed with cytomegalovirus (CMV) as a vector brought the infection under complete control. In many of the monkeys, no SIV was detectable at necropsy even with very sophisticated probes. An advantage of using CMV as a vector is that it can replicate indefinitely: a single dose of a CMV-vectored vaccine should provide lifelong protection. The downside is the risk of CMV disease in immunosuppressed people and also in fetuses, since the virus crosses the placental barrier. The Oregon researchers are working on ways of reducing this risk by attenuating the infective potential of the virus.

How close these results will bring researchers to the final goal of making a vaccine that can stop the epidemic is still anyone's guess. Berkley is decidedly, if cautiously, excited by these advances. "They have brought us to the edge of a solution, but we still face a number of serious pitfalls. One is the difficulty of the science that is needed to produce an effective vaccine."

Back in the mid-1980s, however, when the quest for a vaccine started, scientists thought the task would

*On July 1, Seth Berkley left IAVI to head GAVI Alliance

Getty Images

An IAVI team discovered two new antibodies against several HIV strains in 2009

Press Association Images

A technician works on blood samples of volunteers in Thailand's HIV vaccine trial

be easy. Research had produced successful antibody-based vaccines against other viral infections, such as measles, poliomyelitis, hepatitis B. Why would HIV be different? As it turned out, of course, HIV was found to be very different. Its thick sugar-coated surface and extremely high immunological variability allow it, within the first few days of infection, to slip by the body's immune system and to settle down for life in the chromosomes of the infected individual's T cells. In 1994, the decision by the NIAID to withdraw its support of work on the two leading first-generation AIDS vaccines, both antibody-based, marked the end of the first chapter in the AIDS vaccine story.

The second chapter logically turned to the second part of the immune system: cell-mediated immunity (CMI). This system targets and destroys the cells in the body already infected by viruses, as well as triggering substances that inhibit viruses from replicating and spreading through the body. Would it also be able to block initial HIV infection? The complete failure, in 2007, of the most promising CMI based-AIDS vaccine in the pipeline produced a resounding "no", which brought the second chapter to a precipitous close. In a large phase 3 trial undertaken in several countries, the vaccine not only failed to prevent HIV infection or to reduce viral load in vaccine recipients but even increased the risk of HIV infection. Since most of the 30 or so vaccine candidates in the pipeline at that time were (and still are) CMI-based, the close of this chapter left many researchers floundering for a new way forward.

Today, having swung from antibody to cellular immunity over two decades of HIV/AIDS research, the pendulum seems to be settling in a broad midway position that encompasses both parts of the immune system. As Berkley puts it, "we believe the ideal vaccine will have both antibody and CMI. On the CMI side, you're going to see a different pipeline with more exciting vectors, like the CMV replicating vector, which gives a strong, broad immune response". On the antibody side, he says, there will be a new range of candidates that are likely to be based on the new broadly neutralising antibodies discovered in 2009.

In this third chapter, moreover, the emphasis has turned away from a frenetic race to produce and test as many vaccine candidates as quickly as possible in large clinical trials in favour of a more selective, flexible process that gives precedence to smaller trials underpinned by the findings of basic science. Of the 270 clinical AIDS vaccine trials undertaken so far on 123 candidates, 27 are still underway on 26 different candidates. Of these candidates, 24 are in a very early (phase 1) stage and two in a midway (phase 2) stage. Most are based on CMI. But only a few, according to Berkley, will continue.

Meanwhile, other approaches to dealing with the HIV/AIDS epidemic are progressing. Trials of vaginal microbicidal gels are, for the first time, showing strong promise. Male circumcision, too, is having a documented effect on the epidemic in some African countries. And drug treatment is producing spectacular results: witness the recent report of a study showing that antiretroviral drugs taken by an HIV-infected individual can reduce transmission of HIV to an uninfected sexual partner by 96%. Taken by enough infected people, therefore, drug treatment could be expected to halt or reduce spread of the epidemic throughout a community. However, finding enough infected people early enough will be a major obstacle, says Berkley. "To stop an infection with drugs, you need to diagnose it and begin treatment within 7–10 days of the start of the infection. The cost and effort to find enough infected people early enough would be enormous." Plus, of course, the cost of lifelong treatment—about US$7000 per person in the developing world, according to an IAVI calculation. An IAVI cost analysis showed that even a vaccine costing as much as $800 per dose would be more cost effective than would drug treatment in a developing country context. Most vaccines on the market today cost between $3·50–7·00, suggesting substantial cost savings compared with antiretroviral drugs. Treatment is visibly changing the AIDS landscape, Berkley admits, but it is not the final solution.

For Hankins the final solution is going to be a judicious mix of several approaches. "We have a toolbox containing a variety of promising tools", she says. "We have to hit this epidemic with everything we've got. But without a vaccine, we're not going to nail it down. And we can be certain now, in the light of recent progress, that we will have a good vaccine. Just don't ask me to give you a time-frame."

With several international agencies and more than 50 public-sector and private-sector entities, plus more than 30 industry, philanthropic, and non-governmental organisations all committed to AIDS vaccine research, hope is surely justified that an effective vaccine against the virus will emerge sooner rather than later.

John Maurice

Battles with donors cloud Malawi's HIV prevention plan

Malawi is taking bold steps to prevent mother-to-child transmission of HIV, but funding difficulties could hamper the new initiative. John Donnelly reports from the capital Lilongwe.

On a routine medical check-up in June, Grace James, 8 months pregnant, was surprised twice. First, a counsellor at Bwaila Hospital told her she had tested positive for HIV. Second, she learned that starting this month the Government of Malawi would be giving all HIV-positive pregnant women free antiretroviral drugs irrespective of their CD4 cell count.

It meant that 23-year-old James would be eligible for the drugs in the last weeks of her pregnancy, and the treatment would continue for the rest of her life. She took the abundance of news calmly—no tears, no head in her hands, no outward grieving. "I really didn't expect to hear that I was HIV positive", she said. "I had no idea. As much as I'm concerned about it, I'm not worried. I know once I get on the medication I should be fine."

Malawi's decision marks an unusual stand by a developing country against WHO guidelines for treatment of a disease. In 2010, the WHO lowered the point for starting antiretroviral AIDS drugs when an HIV-positive patient's CD4 cell count dropped below 350. Malawi officials, after a series of internal discussions and talks with its international partners, decided that following such guidance meant too many women who needed treatment would not be getting it: only a few HIV-positive pregnant women had access to reliable CD4 testing, which until now precluded them from receiving the treatment they needed.

"We felt we had to do something", Frank Chimbwandira, director of HIV/AIDS Service for the Ministry of Health, told *The Lancet*. "We found that we didn't test all the positive women for CD4 count, and even those we did, there wasn't any systematic follow-up. We needed to protect the mother and the baby better, so we decided to put the HIV-positive women on treatment for life, which would save the mother and the baby."

But the path leading to this ground-breaking policy has not been easy. The country is now in the centre of several contentious disagreements with donors that could threaten the delivery of parts of its basic health service packages. In the most significant standoff, the UK Department for International Development, Malawi's largest bilateral donor with US$121 million donated per year, suspended future funding in May after President Bingu wa Mutharika ordered the expulsion of the British high commissioner over a leaked cable that referred to the President as "autocratic and intolerant of criticism".

> **"'Given our experiences in Malawi, the WHO guidelines just don't work because of the lack of access to CD4 testing…'"**

Other development partners also are using the power of the purse to register disappointment or to try to force change on a host of issues, including Malawi's enforcement of an anti-homosexuality law and government threats to freedom of speech and association. The World Bank is withholding $40 million in funding pending further reviews and Germany suspended $16·5 million in funding because of the anti-gay laws. Additionally, the country suffered a serious blow when the Global Fund to Fight AIDS, Tuberculosis and Malaria rejected a $565 million plan due to mostly technical reasons. In total, 40% of Malawi's budget comes from foreign donors.

Through it all, President Mutharika has stated it is time for Malawi to become far less dependent on donors. His sharp tone has been puzzling to many because of the country's strong partnerships over the past 6 or 7 years with donors, which helped lead to substantial gains, including putting 270 000 people on antiretroviral treatment since 2004.

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Now, due to the tense relationship, many wonder who will fund existing health programmes, much less new initiatives such as treating all HIV-positive pregnant women.

The standoff "is a big blow for the country", said Helen Magombo, policy adviser in Development Finance and Essential Services at Oxfam. "While we do not condone the situation regarding human rights in Malawi, we are also not accepting the withholding of aid by donors in Malawi. We hope that all parties understand the real impact this could have on the people who really need the assistance."

In the Ministry of Health, meanwhile, senior officials insist that the plan to treat all HIV-positive pregnant women will not be affected by the troubles with donors. "We will move ahead on this—there's

Alfredo Caliz/Panos

A nurse visits a pregnant woman who has HIV at her home in Sopali village, Malawi

Dominic Chavez

Willie Samute, Malawi's Secretary for Health at the Ministry of Health in Lilongwe

no question, it's a priority", said Willie Samute, the Secretary for Health. He said the first year was estimated to cost $5 million. The cost reflected the ministry's decision to use a regimen of tenofovir, lamivudine, and efavirenz that have few side-effects and cost $176 per person per year, compared with $65 for the most common first-line regimen in Malawi.

Erik Schouten, HIV adviser for Management Sciences for Health in Malawi and a former technical adviser in the Department of HIV and AIDS at the Ministry of Health for 7 years, said too few women now receive the proper services. In the third quarter of 2010, the latest statistics available, 51% of HIV-positive pregnant women in Malawi received prevention of mother-to-child transmission services (PMTCT).

"There's tension between the path we've chosen and the individual approach that is impossible to implement", said Schouten. "Given our experiences in Malawi, the WHO guidelines just don't work because of the lack of access to CD4 testing. We don't believe a PMTCT programme based on CD4 counting is ever going to have much of an impact here."

At Bwaila Hospital, which used to be called Bottom Hospital in Lilongwe, the capital, because it sits in lowlands while Kamuzu Central Hospital is on top of a hill, the policy change was news to some of the nurses who work in the antenatal clinic. But all said they favoured it.

In the middle of a waiting room, with more than 160 pregnant women sitting on benches holding onto pieces of cardboard paper with their number in the line, Stelia Tsilzani, senior psychiatric enrolled nurse, said that many HIV-positive women had difficult births. "This new policy is a very good idea because it will prevent some of the complications that arise during labour", she said. "They will be in better health when they come to deliver."

Dorothy Kaliwa, the district principal nursing officer, who oversees 266 nurses in the Lilongwe area, said there was no doubt the policy would save many lives. "We used to lose a lot of the women in giving birth, and these were women who had been tested, [and] even had received their CD4 count, but some would not come back to receive the treatment", she said. "Some people live very far away from here, and they often missed out on the visits or on treatment."

Still, some health workers said they worried about potential problems. Some speculated it could keep some women away from check-ups because they would be fearful that others would learn of their HIV status. Others wondered whether the government could sustain the effort. "My fear is that the ARVs [antiretrovirals] are expensive and I wonder whether the government could purchase all the drugs needed for the pregnant women who test positive for HIV", said Sylvia Kandiyesa, a nurse midwife at Salima District Hospital, a 2-h drive east of Lilongwe.

Watching are several interested parties. One is the US Government, which is one of the partners funding the training of 3600 health workers in June for the new policy of treating all HIV-positive pregnant women.

"We actively support the national HIV programme", said Thomas Warne, an HIV adviser with the US Centers for Disease Control and Prevention in Malawi. "Malawi decided to pursue this strategy based on its assessment of what will be the best prevention and treatment option for women and their families, and complex considerations regarding future resources, impact, and sustainability."

He said that the funding costs were "substantial. Because of this, the US Government, like other donors, is not in a position to advocate either way" for this particular approach. "Instead, we should just do our best to support the country's decisions and planning, as Malawi determines the best way to improve the long-term health and productivity of its population."

But he added, "Putting HIV-infected women on antiretroviral therapy in pregnancy is the best thing for the woman's and baby's health."

Another interested partner is WHO. In Geneva, senior HIV officials in WHO also said that the choice was Malawi's, and that they were watching closely. Officials urged Malawi to closely evaluate the programme.

Ying-Ru Lo, coordinator of Prevention in the Health Sector Department of HIV/AIDS at WHO, said in an email that "the Malawi experience could serve as an important contribution to the development of the next generation of guidelines" for HIV/AIDS treatment internationally.

Around sub-Saharan Africa, more than 400 000 babies are born with HIV every year. And worldwide around 350 000 women die at the late stages of pregnancy and during childbirth, including tens of thousands who have AIDS-related complications.

Malawi officials said they could do much more to protect mother and child, and the treatment of all HIV-positive pregnant women was an important step in that direction.

"Our biggest challenge will be the funding", said Chimbwandira, the director of HIV/AIDS Service at the Ministry. "But we decided that this was very essential. This is something we're doing for the mothers and the children in our country."

John Donnelly

Book

Building the momentum to prevent HIV in MSM

Larry Kramer, on accepting the Tony Award last month from the Theatre Guild-American Theatrical Society for *The Normal Heart* as Best Revival of a Play said: "To gay people everywhere, whom I love so dearly...we are a very special people, an exceptional people, and...our day will come." My day came in 1982 when I secured an Assistant Professorship in the Department of Medicine at the University of California, San Francisco. I set about establishing a behavioural medicine clinic fully integrated into general medicine practices, researching chronic disease prevention, and teaching interns and residents about psychological issues. One guest speaker, a social worker, led a discussion with the residents about the special medical needs of gay men. He was dead a month later from what later became known as AIDS.

The "special and exceptional people" cited by Kramer had lived through the 1970s and fought for human rights in the USA. That was followed in 1981 with the scourge of AIDS that could have knocked the wind out of the gay community. Instead, the community rallied and used its skills and talents to advocate for resources to develop community-based systems of care and prevention, and to ensure that human rights were not trampled.

Unleashing that energy and skill to build a global movement to improve HIV prevention and care services for men who have sex with men (MSM) is long overdue. Momentum is building and Chris Beyrer and co-authors make an important contribution. *The Global HIV Epidemics among Men Who Have Sex with Men* documents the extent of the HIV epidemic and outlines what needs to happen to ensure that everything possible is being done to prevent and treat HIV infection in MSM worldwide.

This volume documents the need in terms of the numbers, but also addresses the scenarios in which HIV epidemics among MSM exist in low-income and middle-income countries. The first scenario they describe, characterising the HIV epidemic in most of Latin America, is one in which MSM are the predominant exposure mode for HIV infection in the population. In these countries MSM are ten to over

> **"At best, most governments and donor agencies have ignored HIV among MSM. At worst, MSM are stigmatised and prosecuted."**

100 times more likely to have HIV than the general population. By contrast, eastern Europe and central Asia have the highest rates of HIV among injection drug users (IDUs), but MSM are still several times more likely to have HIV than the general population. A different scenario is found in sub-Saharan Africa where HIV is widespread among heterosexuals, but even in these contexts MSM can have two to 20 times higher prevalence of HIV than the general population estimates. South, southeast, and northeast Asia are characterised by epidemics that have equal contributions from MSM, IDUs, and heterosexuals, although MSM are still at least ten times more likely to have HIV than the general population.

The needs come not only from the numbers. Beyrer and his co-authors document well the lack of prevention technologies focused on male-to-male transmission. They note that much effort has been expended on encouraging voluntary HIV counselling, testing, and behavioural interventions to decrease rates of unprotected anal intercourse by encouraging less risky sexual behaviours. Although important, such strategies are probably insufficient to produce immediate or lasting change in HIV transmission. Male circumcision may be effective for reducing acquisition of HIV through anal intercourse but we will never know for sure because of the challenges of conducting a trial to prove efficacy. Antiretroviral-based prophylactic approaches provide the best opportunity for managing HIV among MSM. In the wake of the IPREX, CAPRISA 004, and HPTN 052 trials, it is now time to accelerate efforts to determine if similar benefits can be obtained with rectal use of these or similar compounds. In some countries, like Peru where the epidemic is concentrated in MSM, providing universal access to care with MSM-sensitive services could actually change the overall trajectory of disease spread.

Kramer's use of the term "exceptional people" referred to the gay community's creativity, resilience, and energy to ensure that the response to HIV was all that it could be in resource-rich countries of the world. But not everyone views homosexual exceptionality in a positive light. Many parts of the world view same-sex relations as abnormal, deviant, sinful, and illegal. At best, most governments and donor agencies have ignored HIV among MSM. At worst, MSM are stigmatised and prosecuted. Homosexuality is criminalised in just less than half of the UN member states with punishment ranging from jail time to the death penalty.

Beyrer and his colleagues show us that MSM are everywhere in the world and disproportionately affected by the HIV epidemic. They highlight how MSM are underserved nearly everywhere and that the global response to HIV will stall without access to treatment and prevention services in the context of protection of fundamental human rights. The HIV global epidemic among MSM is only beginning to be addressed. Beyrer's book is a key part of the momentum that will continue to propel us in the right direction.

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The Global HIV Epidemics among Men Who Have Sex with Men
Chris Beyrer, Andrea L Wirtz, Damian Walker, Benjamin Johns, Frangiscos Sifakis, Stefan D Baral. World Bank, 2011. Pp 400. US$35·00. ISBN 9780821387269

Profile

Bertrand Audoin: promoting a global strategy for IAS

IAS

If there is one driving force for Bertrand Audoin's work in HIV/AIDS, it is having witnessed from a young age the stigma and discrimination that people with the disease face. An idealistic French 20-something, Audoin was working for Alliance Française in Auckland, New Zealand, in the early 1990s when he heard his friends talk about people they knew who were HIV positive and refer to them as "'people we should avoid'. That really struck me", he says.

Instead of heeding his friends' words, however, Audoin started doing voluntary work to promote HIV prevention in the gay community. "It was before we had treatment for AIDS and there were misconceptions about the epidemic, whether you can protect yourself and whether condoms were effective", he told *The Lancet*. It was a couple of months into this work that Audoin's best friend told him that he was HIV positive; he had been keeping it a secret because he was worried about the reaction he would receive from people. This revelation and his friend's fears made Audoin "realise that there was a lot of work to be done to fight stigma and discrimination" in HIV and that he wanted to be involved in this effort.

Upon returning to France in 1996, he started working for Sidaction, a French HIV/AIDS non-governmental organisation. "I thought it would just be for a few months", he laughs, "but I left last February". The 42-year-old is now the new Executive Director of the International AIDS Society (IAS)—the world's leading association of HIV professionals, with over 16 000 members in 196 countries. Although a substantial change, Audoin does not seem fazed by his new job. "Sidaction brings together scientists, doctors, nurses, all medical staff, and activists and communities, the same way that IAS does through its membership and the conferences", he says.

Audoin tells *The Lancet* that IAS has four priority areas, which were decided by the Governing Council in November, 2010. These are: a cure for HIV, with a focus on a global scientific strategy; advocating for drug harm reduction programmes and policies, particularly through expanding access to opioid substitution therapy; championing HIV and human rights, with a focus on HIV professionals (for example, campaigning against HIV travel bans); and promoting social and political science research and the key role it plays in the HIV response. "My job is to deliver on these", says Audoin, who took up his IAS position in February this year. He says that he wants to make sure IAS members get what they want from the society—the best scientific information, position statements, if expected, and the promotion of IAS's vision to broader audiences.

Françoise Barré-Sinoussi, who won the Nobel Prize for Physiology or Medicine in 2008 for being one of the discoverers of HIV, has worked closely with Audoin since 2005, when she became a board member of Sidaction, and has no doubt that he will succeed. She describes Audoin as "very easy to work with, friendly, and open-minded". Barré-Sinoussi says that, although not a scientist himself (Audoin has an educational background in marketing, human resources management, and finance), he supports programmes and interventions that are evidence based and is very open to scientific discussions. And, she adds that "he has a lot of charisma".

This attribute has certainly helped him keep HIV/AIDS on the agenda in France. After becoming General Director of Sidaction in March, 2000, Audoin was a key player in the organisation's expansion to fund HIV work in developing countries. His leadership helped to increase the money raised for the charity from €7 million a year to €22 million—95% of this income was from individual donations. "I succeeded in involving more people in the general audience", says Audoin. But it was by no means an easy task. "10 years ago there was a simple message, compared to a very complicated one now that not everyone was getting. Yes, there are treatments available but once you have HIV you remain HIV positive for the rest of your life." And, he says, he still had to fight false ideas. "Even 5–6 years ago, some people thought you got HIV/AIDS from being bitten by a mosquito", he explains. Audoin's hard work paid off. The increase in donations meant that Sidaction was able to start HIV treatment and prevention programmes in 32 developing countries in sub-Saharan Africa, eastern Europe, and Asia.

Barré-Sinoussi, who as President-Elect of IAS will become the society's new President in 2012, believes that Audoin's astute management and fundraising skills will be crucial for promoting international research towards a cure for HIV—a new priority area for IAS that she is already actively involved in. "I'm convinced working with Bertrand it will be easier to connect with stakeholders and get funding for this and be successful", she says. Audoin says that IAS would like to launch the global scientific strategy for an HIV cure at the XIX International AIDS Conference in Washington, DC, USA, in July, 2012. He explains why IAS wants to take forward the idea for a cure internationally. "Some members of IAS are working on basic science and there are a few scientific themes but no coordination between them…it is a misused opportunity to deliver better results in the epidemic. IAS is the right place for a global strategy. We could deal with the epidemic but we want to find a way forward to potentially end the epidemic."

Udani Samarasekera

Profile

Kamiar and Arash Alaei: championing HIV/AIDS initiatives in Iran

Kamiar Alaei recounts with enthusiasm the way he and his older brother Arash recently transformed the health of some Iranian prisoners. The doctors offered advice on everything from basic hygiene and quitting smoking to dealing with drug addiction and HIV. What makes their work remarkable is that they were inmates too, after being sentenced in 2008 for "communicating with an enemy government". When Kamiar, who was released earlier this year and is finishing a Doctor of Public Health degree at the SUNY Albany School of Public Health in New York, accepted the 2011 Jonathan Mann Award for Global Health and Human Rights on behalf of the brothers last month, his feelings were bittersweet; Arash is still in prison and could be there until 2014.

The Alaeis pioneered a national HIV/AIDS response in Iran that addressed social factors like stigma as directly as it did medical issues, such as access to antiretrovirals. This holistic approach reflects the values instilled in the brothers during their childhood in Kermanshah, western Iran. Their father was a scholar of Persian literature who dedicated hours to teaching poor students for free and they were also inspired by Ibn Sina, a renowned 11th-century Iranian physician, who devoted himself to the community.

The brothers studied medicine in Tehran during the 1990s and, in 1997, Kamiar noticed how a patient with HIV in his hospital was kept quarantined simply because health-care workers were scared. Realising the extent of this fear about HIV, the brothers set up a clinic in Kermanshah to treat people with HIV. A serendipitous change of government that year ushered in a more progressive rule under Mohammad Khatami, which eased the barriers to the Alaeis' work. Their room was no bigger than a storage cupboard, but they knew that location is everything. Situating the clinic between a health clinic and a marriage guidance centre put it at the heart of community activity. While the patients had serious medical needs, their main concern was their social exclusion. "We turned into social workers, visiting our patients' homes to educate their families, and even matchmaking occasionally", says Kamiar. The Alaeis were also pivotal in ensuring that the government provided free antiretrovirals.

Without realising it, the brothers intuitively implemented integrated care approaches that were being promoted in global health, for instance, providing HIV care alongside treatment for other sexually transmitted diseases and for drug addiction. They called these "triangular clinics", which were later set up in 67 Iranian cities. Designing a programme that is more innovative than many in developed countries—giving methadone and free needles to drug addicts—is no mean feat in such a conservative country. Kamiar says one factor in their success was giving patients what they wanted. He calls it a "restaurant approach". "If people want tea, you give them tea. You don't make them drink coffee." They also brought religious leaders on board by talking about comparative evils in Islam: for the clerics "if condoms and needle exchanges are bad, then HIV is worse", says Kamiar. Imprisonment was one of the country's biggest risk factors for contracting HIV, so in 2001 the brothers set up the first HIV clinic in Kermanshah prison.

The brothers' work soon gained international recognition. WHO advised the rest of the Middle East and North African region to emulate the clinics, and the Global Fund to Fight AIDS, Tuberculosis and Malaria gave US$15·8 million for a national plan to control HIV, drug addiction, and tuberculosis, designed by the Alaeis. All this happened within just 5 years of treating their first HIV patient. Buoyed by this response, they embarked on health diplomacy initiatives with countries like Afghanistan and Tajikistan. Between 2002 and 2007, Arash was Director of the International Education and Research Cooperation of the Iranian National Research Institute of Tuberculosis and Lung Disease. But the country's political climate changed with the election to Mahmoud Ahmadinejad in 2005. Soon, the brothers' activities were restricted, and while Arash stayed in Tehran, Kamiar started a Masters degree at Harvard. On one of Kamiar's trips home in 2008, the pair were arrested "We just focused on HIV/AIDS, never on politics. We are so confused", Kamiar says.

The doctors have global support. Michel Sidibé, Executive Director of UNAIDS, told *The Lancet* "Although the government of Iran finds it difficult to acknowledge, let alone address, the HIV-related needs of men who have sex with men and sex workers, I saw first hand exemplary harm reduction and other HIV-prevention programmes for people who use drugs during my recent visit to Iran. The world's health depends on bridging different views through inclusive dialogue to find pragmatic, evidence and rights-based solutions. So, I was pleased to learn of the release of Dr Alaei. I hope it will enable him to resume his contribution to the exceptional AIDS response in Iran as well as much needed dialogue on ensuring universal access to HIV prevention, treatment, care and support."

Kamiar's attitude remains impressively positive. There was no question that they would stop their work even in prison. "Instead of a 1-hour workshop, we could now work with them for 24 hours a day, 7 days a week". They shored up prisoners' wellbeing too by encouraging them to learn languages, play sports, or paint murals. Moving forward is the only option, Kamiar says: "Even if you get arrested, keep doing your job. As long as you are alive, until the last moment of your life, keep doing your job."

Priya Shetty

AFP/Getty Images

Kamiar Alaei

MCT via Getty Images

Arash Alaei

The art of medicine

Should health professionals play the global health security card?

The health of all peoples is fundamental to the attainment of peace and security. So, at least, argues the constitution of WHO drafted more than half a century ago. Recent experience of an epidemic of epidemics has driven home this message. From pandemic H1N1 influenza A and pathogenic avian influenza, through to severe acute respiratory syndrome and the HIV/AIDS pandemic, we seem to have entered an era of deep microbial unease. Perhaps nothing reflects this underlying mood shift more poignantly than the growing tendency to articulate international health policy in the metaphors and vocabulary of security. What began in the year 2000 with the unprecedented step taken by the UN Security Council in designating a disease—HIV/AIDS—as a threat to international peace and security, has become a staple and defining aspect of global health politics in the past decade. The rise of the new health security paradigm has even seen some health issues becoming formally incorporated into national security strategies.

But should health issues and security concerns be married in this most intimate of ways? Should health professionals be playing the security card in international politics? That, of course, depends very much on which version of "health security" is under consideration. So far the strongest security card has probably been played by those working in the field of biosecurity and bioweapons. Here, the worlds of health and security collide inescapably because state or non-state groups might deliberately weaponise diseases to achieve political ends. Expert opinion remains divided about the likelihood and extent of such an attack. However, the intentional release of sarin gas in Tokyo's subway system by the Aum Shinrikyo cult in 1995 represented an early warning sign. That was a chemical attack, but the release provoked wider fears about the possibility of future biological attacks. The terrorist attacks of Sept 11, 2001, and the "anthrax letters" posted to prominent addresses in the USA just a month later, only added to those concerns.

Playing this security card has certainly proved influential in terms of freeing up resources and galvanising leadership. Biosecurity arguments formed the impetus behind the creation of various national initiatives and research bodies on both sides of the Atlantic, as well as the formation of the Global Health Security Initiative—an informal, international partnership of states seeking to strengthen their response capabilities in relation to the threat of biological, chemical, and radionuclear terrorism. Yet that does not mean the biosecurity community has had an easy ride. Public health experts have vocally and repeatedly pointed to the uncomfortable tension between the fundamentally different professional cultures that exist between public health communities, on the one hand, and security and counter-terrorism communities, on the other. Occasionally, this clash of cultures has provoked discussions within WHO about the extent to which an international organisation devoted to public health can become involved in responding to bioweapons incidents without undermining its perceived neutrality and objectivity. Others have questioned whether recourse to the security card to raise resources is a good thing in and of itself. Surely it is not just the volume of resources that matters, but also the balance of how those resources are allocated. Here further concerns have surfaced about the perceived narrowness of much biosecurity funding and its uncertain contribution to wider public health objectives. Playing the biosecurity card, in short, has proved a double-edged sword.

A somewhat different security card has been played by those working within the framework of national security. Here the focus has been predominantly on the threat posed by naturally emerging and re-emerging infectious diseases in the context of an increasingly globalised and interdependent world economy. This case for linking health and national security is strong in that a naturally occurring infectious disease could be just as damaging as an attack by a foreign power in terms of causing significant morbidity, mortality, and economic disruption. It is a case backed up by an influential national intelligence estimate produced by the US National Intelligence Council. The *Global Infectious Disease Threat and Its Implications for the United States* found that since 1973 at least 30 previously unknown disease agents have been identified, and that during that same period at least 20 older infectious diseases have re-emerged, frequently in drug-resistant form. The case tends to be all the more persuasive because the widespread perception of microbes as "invaders" coming from "outside" maps neatly onto a pre-existing idea of national security involving the protection of populations against external threats.

To be sure, such a national security framing of infectious diseases has distinct policy advantages as well. Bringing the dramatic connotations of security into play helps garner political attention and lubricates the flow of resources for tackling these issues. Both of those things are necessary if countries around the world are to be prodded into creating—and maintaining—effective pandemic preparedness plans. But none of this has shielded the health security framework from controversy either. Although many developing countries are just as keen to protect their populations against future pandemic threats as their western counterparts, some have voiced concerns about how more powerful states might use—or even abuse—the imperatives of "security"

to override their country's political sovereignty in times of an international public health crisis. Unlike much of the technical language used by health professionals working internationally, "security" is a politically deeply charged and sensitive notion—the pursuit of which has in the past enabled states to override legal constraints and justify a range of extraordinary and also controversial practices. Not surprisingly, playing the national security card in relation to pandemic threats has bred considerable apprehension and distrust in some quarters. It too, in other words, has proved a double-edged sword.

There is still plenty of space, then, in the market place of health security ideas for a third—and altogether different—security card to be played by those working with a broader notion of human security. The human security advocates seek to recalibrate security practices around the needs of individuals rather than just of states, and have been just as keen in that vein to harness the idea of security for their global health efforts. Within the human security framework, the premature loss of life caused by disease continues to represent one of the greatest threats to people around the world. Moreover, in many low-income countries it is not so much the spectre of armed conflict or bioterrorism that constitutes the greatest security threat for most people, but rather the absence of more effective and affordable health care. In this framework, the most pervasive threats to security are not seen to emanate from those acute and highly infectious diseases that can spread rapidly between countries, or those that could be deliberately released by a terrorist group; they stem instead from a range of illnesses that remain endemic in many low-income countries hampered by a weak public health infrastructure—for example, malaria, tuberculosis, and HIV/AIDS. Hence human health security is not principally concerned about future pandemics, but about already existing endemics, especially in the developing world.

One of the greatest policy advantages of this idea of human health security is that—comparatively—it has courted much less political controversy among health professionals. It is true that difficult questions remain about the operational utility of the concept. After all, the human security framework works in broad brush strokes and adopts a logic that renders virtually any lethal disease (including non-communicable diseases) a credible security threat. But where, then, should health rank in relation to all the other pressing human insecurities, like threats to economic security, food security, environmental security, and so forth? And exactly which global health issues should be prioritised? There is concern that many human health security initiatives have tended to reflect the priorities of wealthy donors, rather than being closely matched up to the health conditions and priorities on the ground. That said, it certainly remains the case that the much softer connotations of the human security approach seem to have largely escaped the feelings of disquiet and concern provoked by the other two security cards. That is no doubt a substantial achievement, but one which has a political flip side as well: the human security approach seems to have been less effective in mobilising wider political support and freeing up designated resources than the previous two. The distance that still needs to be travelled to achieve the health-related Millennium Development Goals is testament to that more limited legacy. Although playing the human health security card is much less of a double-edged sword for health professionals, perhaps it is not much of a sword in terms of galvanising attention, leadership, and resources for public health. That must give pause for thought.

Reuters

In the end, health professionals are left with a difficult challenge with regard to the new health security paradigm. Yes, marrying health issues to security concerns can do much in terms of harnessing political leadership and resources for various international health issues. But playing the security card also has a range of unintended side-effects in terms of orienting the global health agenda around a fairly narrow set of diseases, and ones that tend to reflect the current priorities of western governments. The deeper challenge for the health security paradigm is, I would suggest, how best to ensure that a sound balance between all three versions of security is maintained. How, in a time of increased pressure on budgets, can the merging of global health and security maintain high levels of resources and leadership for global health, without encouraging the neglect of those health concerns that predominantly affect developing countries? To stick with the metaphor at hand, health security advocates will have to play with a full deck if the notion of health security is to remain a meaningful framework for improving global health in the 21st century.

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Peter John Iliff

Paediatrician and defender of human rights in Zimbabwe. He was born on Oct 29, 1951, in Lahore, Pakistan, and died from renal cancer on Feb 1, 2011, in Harare, Zimbabwe.

Zimbabwe in its current state is not the most convivial setting in which to practise paediatrics. When Peter Iliff went there in 1988, along with his obstetrician wife Virginia, circumstances were very different. "When they arrived the health system was functioning well by the standards of many developing countries", according to Sunandra Ray, then a public health specialist in Harare. But during the latter half of Iliff's two decades in the country, things went downhill. Yet throughout his time working in Zimbabwe he remained committed to working to improve the health of its people.

Although Iliff did his medical training at the University of Cambridge and the London Hospital, life outside the UK was hardly a new experience. Born to medical missionary parents based in Lahore he spent his early childhood in Pakistan. The year before he went up to Cambridge found him travelling and teaching English in Afghanistan. And after various jobs in paediatrics in London, Swindon, and Oxford he spent a couple of years working at the King Abdul Aziz Military Hospital in Saudi Arabia. From there he went to his final destination, Harare, as a lecturer with a special interest in neonatology at the University of Zimbabwe. But what was it about Africa that held him?

Jonathan Green, professor of child and adolescent psychiatry at Manchester University in the UK and a friend since Cambridge days, thinks that Iliff had become disaffected with the prospect of the career he'd embarked upon in the UK. "I remember him saying to me once that he looked at the consultants who were heading up the firms he was in and feeling he didn't want to be like them." He became demoralised—not with paediatrics but with National Health Service medicine, thinking that much of the spark had been ground out of many of the people he saw in more senior positions. When the couple first got to Zimbabwe Iliff was severely injured in a car accident. It was then, Green thinks, that he realised he was in a place where he wanted to stay. "It was something about how he was looked after there, and finding himself recovering in this culture." Another friend from his student days, neonatologist Sandy Calvert of St George's Hospital, London, says "Peter was very passionate about what he did, and very committed to his work."

The increasing malevolence of the Mugabe regime put that commitment to the test. Iliff's response was not to pack up and go, but to stay and fight. In 2002 he and Virginia were part of a small group who founded the Zimbabwe Association of Doctors for Human Rights (ZADHR), of which he was still Secretary when he died. "At one point there was some pretty serious intimidation going on", Ray recalls. "It included having our names on the front page of the newspaper accusing us of being British spies." Primrose Matambanadzo, ZADHR's Coordinator, describes Iliff's contribution as one of the main reasons that the organisation is still functioning. "With great integrity and bravery", she says, "he contributed to ZADHR's advocacy efforts against organised violence and torture". Green describes Iliff as "a very modest guy and didn't shout about this achievements. But he could be stubborn. He could be extremely outspoken."

Although reluctant to part company with the neonatology unit he'd built up at the University of Zimbabwe, Iliff's talents were well used in the research project of which he became Medical Director, and which occupied the last 10 years of his working life with a focus on HIV. ZVITAMBO, an acronymic shortening of Zimbabwe Vitamin A for Mothers and Babies, was set up in 1997 under the directorship of Jean Humphrey of Johns Hopkins Bloomberg School of Public Health. Its original aim had been to investigate the effect of a postpartum dose of vitamin A on mothers and infants; it found no significant effect. But the detailed information that had been collected showed several other findings, including the vital observation that exclusive breastfeeding helps reduce the risk of mother-to-child transmission of HIV. Illiff led ZVITAMBO's HIV research and programme support work in rural areas. He was also involved with helping an HIV orphan outreach programme. Zvitambo is, appropriately, a word in the Shona language meaning precious—which is pretty much how Iliff viewed his adopted country. Besides his wife Virginia, he leaves a son and a daughter.

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Response to Correspondence on Great Ormond Street Hospital

I read with some surprise the letter from Barbara Buckley and Martin Elliott (published online June 28),[1] co-medical directors of Great Ormond Street Hospital (GOSH), on your Offline piece.[2] As someone directly connected to events that led to the collapse of the paediatric service based at St Ann's, Haringey, in 2007, I believe that it is imperative that I respond.

As Buckley and Elliott note, GOSH was indeed employing all medical staff at St Ann's in Haringey from 2003 onwards. As such, when we raised concerns about the clinical risks within the department, it was the clinical unit lead at the GOSH Trust, David Elliman, who was professionally accountable. We raised our concerns with him many times in meetings, and I personally did so in my appraisal, particularly with regard to difficulty with being on site to supervise paediatric trainees with child protection cases.

In the NHS London report[3] investigating my concerns about the management of the department and the failure of whistleblowing policy, the authors concluded: "The Consultants' concerns were over potential risks to patients and so related to patient safety. Insofar as Dr DE [David Elliman] considers that issues of increased waiting times through excessive workload, lack of follow-up appointments and the unavailability of notes did not affect patient safety, that is a conclusion with which we would not agree."

In addition, they agreed with my assertions that "The issue of excessive workload for Dr KH [Kim Holt] had not, however, been dealt with prior to the commencement of her absence through sickness in February 2007, and it does not appear that the issue of communication between management and clinical staff was specifically addressed in the action plan drawn up in response to the concerns."[3]

The paediatric service at St Ann's collapsed after two resignations in the summer of 2006. These followed our numerous raising of concerns and the financial cuts being imposed at the time, which led to the loss of the named doctor post in child protection—a key role in the effective development of systems and support for staff working in child protection. Subsequently, in a confidential report in 2008, Jo Sibert and Deborah Hodes criticised the lack of the named doctor post as one of the concerns that they had about the department.

This case demonstrates how short-term decisions to meet budgetary constraints can have far-reaching consequences if the implications are not thought through. There is a very important lesson here, that frontline clinical staff who are observing whether a service is clinically safe have important views that need to be respected. In a letter colleagues and I wrote to senior management in 2006, we noted that we neither felt respected nor listened to.

In the final paragraph of their letter,[1] Buckley and Elliott comment that "it does not matter whether the death of a child occurs in Westminster or Wigan, agencies and individuals need to own up to their faults and draw lessons for the future". Fine words. I think now is the time for that to happen, and I hope that the senior management team and Board of GOSH will stop trying to ignore the fact that whistleblowing policy failed. Attempts were made to force me to accept a severance payment, but I could not accept the terms of the proposed agreement. Those who fail to learn lessons are likely to repeat their mistakes.

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Great Ormond Street Hospital and its management team

We are perplexed by the campaign that *The Lancet* is waging against Great Ormond Street Hospital (GOSH) and its management team.[1,2] It is easy to claim the moral high ground in tragic or emotive cases, such as the absolutely tragic death of a child; sadly, it seems that it is also all too easy to ignore facts in order to develop a case that does not hold water.

We wonder why *The Lancet* has decided to repeat, unchallenged, the personal views of a small minority of consultants. All other articles in *The Lancet* focus on providing an evidence base for health care. So why is the Editor prepared to repeat allegations about GOSH in the complete absence of evidence? Like every organisation, we have individual members of staff who are unhappy, either because they have a personal agenda, or because they are being challenged by change necessary for continuous improvement. The managerial, financial, and clinical governance of this Trust is continually the subject of extensive external scrutiny; rightly so. No concerns have been raised in that process. We have a long tradition of welcoming external peer review, and there exist several recent examples.

The Trust is engaged in a process of modernisation and transformation, and has invested heavily in this programme. GOSH has become a leader in paediatric patient safety and its Zero Harm programme, initiated and led by our Chief Executive Officer and supported by the Board, is recognised as innovative and

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progressive. Yet *The Lancet* fails to acknowledge this in its pursuit of a resignation based on innuendo and presumed truths.

This Trust has many staff whose views are not represented by the quotes presented in your journal. Indeed, *The Lancet* admits that the disaffected are a minority among the consultants.[2] Moreover, consultants represent less than 7% of the GOSH workforce, every member of which is expected to be committed to high-quality care for children.

We do not dismiss the anxieties of this small minority and indeed there has been a meeting with those who raised the issues, which was described by both sides as "useful". We have invited every member of staff to raise any concerns they have by either the recognised management structure, directly with us, via a dedicated electronic reporting system, or via an independent non-executive director. What is clear is that the vast majority of our staff remains mystified by the allegations made. If *The Lancet* took the trouble of coming to speak to staff and patients then perhaps a different story would emerge. *The Lancet*'s Editor appears only to have selective evidence.

We invite *The Lancet*'s editorial team to visit GOSH to hear directly from the full range of staff and to see the way we are transforming health care for children. We aim at continuous improvement, clinical excellence, and the safety of children, in an atmosphere of openness and transparency.

We are all members of the GOSH Trust Board, as follows: Chair (TB), Non-Executive Director (YB), Co-Medical Director (BB), Chief Executive (JC), Non-Executive Director (AC), Deputy Chief Executive (FD), Co-Medical Director (ME), Non-Executive Director (AF), Non-Executive Director (MM), Chief Nurse (LM), Chief Finance Officer (CN), and Non-Executive Director (CT).

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1 Horton R. Offline: "The depth of the deception"? *Lancet* 2011; **377:** 2068.
2 Horton R. Offline: "A singular lack of foresight". *Lancet* 2011; **378:** 14.

Radiology service at Great Ormond Street Hospital

We are responding to your Offline comment (July 2, p 14)[1] and would like to make statements of fact regarding the musculoskeletal radiology service at Great Ormond Street Hospital.

In March, 2010, a radiology consultant with an interest in musculoskeletal radiology left the Trust to return to her native country (this was a sudden unexpected resignation). We immediately appointed a locum and the permanent post was appointed in the autumn of 2010.

With regard to the specific issue of skeletal dysplasia studies, since the spring of 2010 we have reported these challenging studies in-house but also sent them out for second review by acknowledged experts. This benchmarking process has been audited over the past year and showed a high concordance with external review.

As a result, and in partnership with the acknowledged experts who assisted with this benchmarking exercise, we are now only sending selected cases for second review. We consider this to represent the best clinical practice and good governance. It is hard to see what more would be needed and we believe that our practice at least matches that of any other children's hospital. We believe you have been misinformed.

KC is Specialty Lead for Radiology at Great Ormond Street Hospital; all other authors are consultant radiologists there.

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HPTN 052 and the future of HIV treatment and prevention

The HPTN 052 trial, as discussed in your May 21 Editorial (p 1719),[1] provides more optimism about the use of antiretroviral drugs (ARVs) for prevention of HIV transmission. Focusing on the HIV-infected partner of discordant couples, the HPTN 052 results were striking, and validated findings from seven previous observational studies.

According to WHO guidelines, at least 9 million people worldwide—half again the number of those currently on ARVs—could benefit from being treated. Another 20 million will need ARV drugs in the future as their HIV disease progresses and the guidelines for starting ARV treatment get changed to reflect the HPTN 052 findings. An estimated US$35 billion will be needed to support HIV services by 2031 in low-resource settings.[2]

The above calculation indicates that some form of implicit rationing of antiretroviral drugs is already occurring. Given the current economic outlook, even more rationing will be necessary as the people who are currently HIV-infected become eligible for ARV treatment. Despite our utopian calls for universal access to ARVs for all HIV-infected people, we are faced with the grim realities of present-day clinical care.

How can we ramp up access to ARV treatment for everyone in the world who needs it? How will we make rational decisions to allow the greatest public health effect for an unavoidable limited supply of drugs? At first glance,

HPTN 052 could help: individuals who qualify clinically for ARV drugs and who are most likely to spread HIV infection become the highest priority for treatment. However, this approach raises problems. Those most likely to spread HIV infection are frequently the most stigmatised populations in our society—sex workers with many partners, men having sex with men in high-risk settings, migrant workers with multiple concurrent partners, injecting drug users in high-prevalence HIV injecting networks, and so on. Conversely, those whom society frequently perceives as "innocent" victims—HIV-positive monogamous sex partners or HIV-positive young children—are not likely to transmit HIV infection to others. Thus, under a public health model, these groups become a lower priority for HIV treatment as prevention.

Application of prevention criteria to target ARV access means that we must proactively reach out to the HIV-infected people most likely to transmit. We need better means to diagnose acute HIV infection,[3] better systems to help those who are unaware of their infection status get tested, and better protections for stigmatised, vulnerable HIV-infected populations so that they can have a more active role in prevention.

HPTN 052 has encouraged the HIV prevention world to focus on HIV-infected people, just as the other three studies of pre-exposure prophylaxis have focused on HIV-uninfected populations. Our future challenge is how we choose to distribute a limited resource—antiretroviral drugs: for treatment, for prevention, or for both.[4] Clearly it would be wonderful if we could find the US$35 billion necessary to treat all-infected people by 2031. In addition to financial resources, we also need more human capacity and stronger health systems to manage all these patients. However, if we cannot treat everyone, we must make hard choices with explicit criteria to determine who gets treatment.

I was Principal Investigator of the HIV Prevention Trials Network (HPTN) from 1995 to 2006. The HPTN sponsored the HPTN 052 trial. Additionally, I am President, Research at FHI, which helped facilitate the CAPRISA 004 study and conducted FEM-PrEP. I was funded by NIH HIV Prevention Trials Network Coordinating and Operations Center Grants 1 U01 A1068619-01 and 1 U01 A146749-0 and by USAID Contraceptive and Reproductive Health Technologies Research and Utilization Cooperative Agreement AID/CCP-A-00-05-000022 and Preventive Technologies Agreement GHO-A-00-09-00016-00.

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1 The Lancet. HIV treatment as prevention—it works. *Lancet* 2011; **377:** 1719.
2 Anglemyer A, Rutherford GW, Egger M, Siegfried N. Antiretroviral therapy for prevention of HIV transmission in HIV-discordant couples. *Cochrane Database Syst Rev* 2011; **5:** CD009153.
3 Cohen MS, Shaw GM, McMichael AJ, Haynes BF. Acute HIV-1 infection. *N Engl J Med* 2011; **364:** 1943–54.
4 Schwartlander B, Stover J, Hallett T, et al. Towards an improved investment approach for an effective response to HIV. *Lancet* 2011; **377:** 2031–41.

The findings of the HIV Treatment for Prevention Trial HPTN 052—ie, a 96% reduction in HIV transmission within discordant couples[1]—confirms that early treatment is a potent intervention for clearly defined couples. But its implementation on a population scale might not be so successful, and we are concerned about calls such as that in your May 21 Editorial[2] to dispense with behavioural HIV prevention programmes in favour of this approach.

In high-prevalence African countries, where half of all new infections globally now occur, early treatment will not prevent the roughly 40% of infections estimated to occur during acute infection,[3] or the 30–60% of new infections in "stable" couples that originate outside the couple.[4] Indeed, it did not prevent the seven to 11 infections (of a total of 40) that seem to have originated from outside the couples in the HPTN 052 trial.[1] Of course, this risk would be eliminated if absolutely every HIV-positive person were treated, but this seems a utopian goal, given the state of African health systems. In reality, attempts at mass treatment would almost certainly accelerate drug resistance, increasing the already overwhelming costs and logistical challenges of treating those who need it most urgently.

Behavioural prevention has saved millions of lives around the world, the best documented cases being the national campaigns of Uganda and Thailand and the internally designed awareness-raising within the gay communities of western countries during the 1980s and early 1990s. When behaviour-change programmes succeed, they tend to involve collective changes in norms and behaviour, preceded by the development of some sort of community consensus.[5] International development agencies' programmes could be greatly improved if they informed people about the dangers of long-term concurrent sexual partnerships—in addition to casual sex[4]—and worked more closely with people at risk to develop their own responses to this threat. The Tostan programme has used such an approach to reduce the practice of female genital mutilation, and others could used it to fight HIV as well.


AFP/Getty Images

We declare that we have no conflicts of interest.

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1 National Institute of Allergy and Infectious Diseases. Treating HIV-infected people with antiretrovirals protects partners from infection. http://www.niaid.nih.gov/news/newsreleases/2011/Pages/HPTN052.aspx (accessed May 27, 2011).
2 The Lancet. HIV treatment as prevention—it works. *Lancet* 2011; **377:** 1719.
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4 Epstein H, Morris M. Concurrent partnerships and HIV: an inconvenient truth. *J Int AIDS Soc* 2011; **14:** 13.
5 Mackie G. Ending footbinding and infibulation: a convention account. *Am Sociol Rev* 1996; **61:** 999–1017.

The HPTN 052 trial results on the effect of treatment on the sexual transmission of HIV[1] should help transform the fight against HIV. They should pave the way for the development of normative guidance by international technical agencies to inform investments. The Global Fund is finalising its 5-year strategy for 2012–16, with an ambitious target to accelerate the scale-up of antiretroviral treatment (ART). At present, more than half of the 6 million people who receive ART in low-income and middle-income countries do so through programmes supported by the Global Fund.[2]

As suggested in the new HIV investment framework proposed by experts from UNAIDS and other key institutions,[3] ART needs to be combined with targeted behaviour-change programmes to develop an integrated response to the HIV epidemic that will support change at the individual and community levels, develop community responses, reduce stigma, and ensure the optimum uptake of biomedical and other services.[4] These basic programme activities need to be underpinned by crucial programme enablers such as targeted communication interventions[5] to achieve an optimum comprehensive response.

As we celebrate the game-changing results from the HPTN 052 trial about the effects of treatment on HIV transmission, we should not hastily abandon non-biomedical elements of HIV prevention but support a comprehensive and integrated response guided by the new proposed investment framework to ensure an effective response.

We declare that we have no conflicts of interest.

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1 The Lancet. HIV treatment as prevention—it works. *Lancet* 2011; **377:** 1719.
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3 Schwartländer B, Stover J, Hallett T, et al. Towards an improved investment approach for an effective response to HIV/AIDS. *Lancet* 2011; **377:** 2031–41.
4 WHO, UNAIDS, UNICEF. Towards universal access: scaling up priority HIV/AIDS interventions in the health sector. Geneva: World Health Organization, 2010.
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A strategic revolution in HIV and global health

Your Editorial (June 18, p 2055)[1] sees a new leadership role for UNAIDS in global health, with AIDS at the leading edge of a new movement for integrating health responses to disease. This Editorial is obviously based on the self-serving press releases and reports of UNAIDS. The UNAIDS Strategic Plan[2] on which these are based was itself prepared by consultants charged with saving UNAIDS in the light of rapidly increasing awareness of its irrelevance to global health. Only when the writing was so clearly on the wall for UNAIDS did the organisation commission this work to try to reposition UNAIDS given that international funding is shifting from HIV to health systems development.

This play for leadership based on strengthening health systems and integrating vertical programmes now being promoted by UNAIDS is, of course, an admission that the organisation was ill-founded in the first place: it has been the main promoter of the biggest vertical programme in history. So UNAIDS is now to assume "a potentially new leadership role in global health"?[1] The idea is farcical. It should be closed and *The Lancet*'s Editor has said as much in an earlier Comment.[3]

UNAIDS tops a significant list of self-serving UN organisations existing mainly to keep international bureaucrats and their technocrats in jobs—an aim *The Lancet* seems keen to support in this case. If *The Lancet* does not have the time to critique properly this UNAIDS spin on reality, then it should at least decline to promote it. If more integrated and efficient health systems are to materialise, they will be achieved at country level by those who for a decade have been fighting the disease-dedicated funding fads of international agencies—led of course by funding for HIV. That this is now changing is good. That it needs global leadership is debatable. That this leadership could be provided by UNAIDS is ridiculous.

I declare that I have no conflicts of interest.

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1 The Lancet. A strategic revolution in HIV and global health. *Lancet* 2011; **377:** 2055.
2 UNAIDS. Getting to zero: 2011–2015 UNAIDS strategy. http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2010/20101221_JC2034E_UNAIDS-Strategy_en.pdf (accessed June 29, 2011).
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Body-mass index, abdominal adiposity, and cardiovascular risk

The conclusion of the Emerging Risk Factors Collaboration (March 26, p 1085),[1] that measures of abdominal obesity do not add to the association of body-mass index (BMI) with cardiovascular disease, is not supported by the data in the paper or those from several independent studies.

First, after adjustment for systolic blood pressure, diabetes, and total and HDL cholesterol, the waist-to-hip ratio had a hazard ratio that was significantly greater (1·12, 95% CI 1·08–1·15) than that of BMI (1·07, 1·03–1·11; p for heterogeneity=0·028; assuming the two regression coefficients are correlated at ≥0·4,

which is the lower confidence limit of the univariate correlation).

Second, regression dilution bias will affect the hazard ratio of waist-to-hip ratio to a greater degree than for BMI. The regression dilution ratio is 0·95 for BMI, indicating that the adjusted hazard ratio will be very close to the unadjusted value of 1·07, whereas with a regression dilution ratio for waist-to-hip ratio of 0·63, its relation with cardiovascular events will be about 50% steeper on a logarithmic scale, after adjusting for this bias.

Third, in data provided in figure 1 of the Collaboration's paper, the hazard ratio associated with waist-to-hip ratio is stronger than that with BMI for coronary heart disease and ischaemic stroke, after adjustment for intermediate risk factors.

Fourth, data provided in figure 3 indicate that waist-to-hip ratio and waist circumference are associated with higher risk of cardiovascular disease within the lowest, middle, or upper third of BMI.

Fifth, large case-control studies[2,3] and large cohort studies[4] have shown a clear incremental association with abdominal obesity over BMI for non-fatal myocardial infarction, non-fatal ischaemic strokes, and for total mortality or death from circulatory causes. The data presented by the Emerging Risk Factors Collaboration are directionally consistent with these findings.

Finally, both INTERHEART[2] and the Emerging Risk Factors Collaboration[1] are consistent in showing that adjustment for blood pressure, lipids, and glucose substantially attenuates the association between obesity and cardiovascular disease.

We declare that we have no conflicts of interest.

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1 Emerging Risk Factors Collaboration. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. *Lancet* 2011; **377:** 1085–95.

2 Yusuf S, Hawken S, Ounpuu S, et al. INTERHEART Study Investigators. Obesity and the risk of myocardial infarction in 27 000 participants from 52 countries: a case-control study. *Lancet* 2005; **366:** 1640–49.

3 O'Donnell MJ, Xavier D, Liu L, et al, for the INTERSTROKE investigators. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet* 2010; **376:** 112–23.

4 Pischon T, Boeing H, Hoffman K, et al. General and abdominal adiposity and risk of death in Europe. *N Engl J Med* 2008; **359:** 2105–20.

The Emerging Risk Factors Collaboration[1] present impressive pooled data from more than 220 000 patients, correlating indirect measurements of adiposity with first-onset cardiovascular events. They show no significant improvement in risk prediction, compared with traditional assessment.

Aside from energy storage, adipose tissue affects glucose metabolism and vascular biology. Visceral adiposity has greater endocrine activity than does subcutaneous fat, modulating tissue concentrations of adipokines such as adiponectine and resistine (markers of insulin resistance), or transforming growth factor α and interleukin 6 (inflammatory mediators).[2] However, indirect measures might not truthfully characterise visceral adiposity in individuals.[3]

To demonstrate this poor representation, we used multidetector CT to calculate the entire volume of abdominal visceral and subcutaneous fat in a cohort of 400 patients with abdominal aortic aneurysm. The volume of visceral adipose tissue correlated imperfectly with body-mass index and waist circumference (r=0·718 and r=0·808, respectively), with greater discrepancy between higher ranges (figure). Gender conferred large differences in visceral adipose tissue: mean 5·4 L (SD 2·1) in men versus 3·4 L (1·8) in women (p<0·0001). Correlation of visceral adipose tissue with metabolic syndrome was strong for men, but absent in women (p<0·0001 and p=0·52, respectively). Testing for individual criteria for metabolic syndrome revealed significant correlations with triglycerides and HDL cholesterol only.

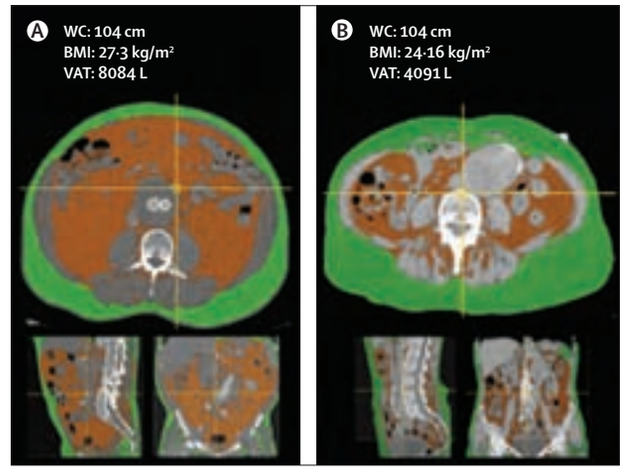

Figure: **Volumetric measurement of abdominal fat by use of multidetector CT**
Patients A and B present with the same waist circumference (WC), but the visceral fat volume is nearly twice as high in patient A as in patient B. BMI=body-mass index. VAT=visceral adipose tissue.

In conclusion, use of indirect measures to assess central adiposity could underestimate its contribution to cardiovascular risk. Moreover, gender should be considered when interpreting different methods. Accurate volumetric measurements to distinguish between visceral and subcutaneous compartments, although impractical for screening, provide valuable insight into the relation between adiposity and atherosclerosis.

We declare that we have no conflicts of interest.

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1 Emerging Risk Factors Collaboration. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. *Lancet* 2011; **377:** 1085–95.

2 Hajer GR, van Haeften TW, Visseren FL. Adipose tissue dysfunction in obesity, diabetes, and vascular diseases. *Eur Heart J* 2008; **29:** 2959–71.

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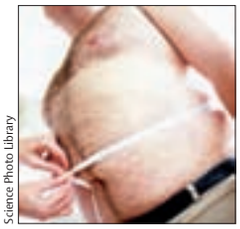
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Authors' reply

The Emerging Risk Factors Collaboration (ERFC)[1] analysed individual data from 58 prospective studies involving 221 934 people to assess body-mass index (BMI), waist circumference, and waist-to-hip ratio in the prediction of cardiovascular disease. The hazard ratio—adjusted for age, sex, and smoking—for coronary disease was 1·32 (95% CI 1·24–1·41) per 5 kg/m² higher baseline BMI, similar to findings in other large-scale prospective analyses, such as corresponding hazard ratios of 1·3–1·4 reported in the Prospective Studies Collaboration[2] and in the pan-European EPIC study.[3]

By contrast, INTERHEART,[4] a retrospective case-control study, noted a corresponding odds ratio for myocardial infarction of only 1·12 (1·08–1·16) per 5 kg/m² higher baseline BMI. As stated in the ERFC report, this discrepancy might be related to the greater susceptibility of retrospective studies to bias (eg, selection biases, reverse causality), which could explain INTERHEART's finding that waist-to-hip ratio is three times more strongly related to coronary disease than is BMI. Prospective data from the ERFC have shown that BMI, waist circumference, and waist-to-hip ratio each have broadly similar associations with coronary disease—ie, hazard ratios adjusted for age, sex, and smoking per 1 SD higher baseline values of 1·29 (1·22–1·37), 1·32 (1·24–1·40), and 1·30 (1·22–1·38), respectively.

Most cardiovascular risk scores involve a single "baseline" measurement of several conventional risk factors at the outset of a 5–10-year period. The ERFC has shown that baseline BMI, waist circumference, and waist-to-hip ratio—whether assessed singly or in combination—did not importantly improve cardiovascular risk prediction in people when additional information was available for systolic blood pressure, history of diabetes, and lipids. This conclusion was based on measures of risk discrimination and reclassification, which are more informative for assessment of incremental predictive value than are measures of risk association (eg, adjusted hazard ratios).[5] The ERFC also showed that the year-to-year consistency of BMI assessment within individuals is superior to that of waist circumference or waist-to-hip ratio. This finding implies that BMI assessment is more reproducible in clinical settings than is assessment of waist circumference or waist-to-hip ratio. However, as suggested by Salim Yusuf and Sonia Anand's comment on regression dilution bias, this finding also implies that serial assessment of abdominal adiposity could enhance risk prediction.

Whereas the ERFC report studied simple adiposity measures for population-wide risk prediction, Frederico Gonçalves and colleagues rightly point out that causal assessment of the role of adiposity should benefit from use of more detailed methods (such as imaging).

We declare that we have no conflicts of interest.

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1 Emerging Risk Factors Collaboration. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. *Lancet* 2011; **377:** 1085–95.

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Department of Error

White PD, Goldsmith KA, Johnson AL, et al. The PACE trial in chronic fatigue syndrome—Authors' reply. Lancet *2011;* ***377:*** *1834–35*—In this Correspondence (May 28), references 2 and 3 in the reference list should have been transposed. This correction has been made to the online version as of July 15, 2011.

Chan FKL, Lanas A, Scheiman J, Berger MF, Nguyen H, Goldstein JL. Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): a randomised trial. Lancet *2010;* ***376:*** *173–79*—In this Article (July 17, 2010), the third sentence of the fourth paragraph in the Results section should have read: "The number of patients with moderate-to-severe abdominal symptoms at month 6 was 132 (6%) for the celecoxib group and 162 (7%) for the diclofenac plus omeprazole group (p=0·0495)". These corrections have been made to the online version as of July 15, 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

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Summary

Background The non-nucleoside reverse transcriptase inhibitor (NNRTI), rilpivirine (TMC278; Tibotec Pharmaceuticals, County Cork, Ireland), had equivalent sustained efficacy to efavirenz in a phase 2b trial in treatment-naive patients infected with HIV-1, but fewer adverse events. We aimed to assess non-inferiority of rilpivirine to efavirenz in a phase 3 trial with common background nucleoside or nucleotide reverse transcriptase inhibitors (N[t]RTIs).

Methods We undertook a 96-week, phase 3, randomised, double-blind, double-dummy, non-inferiority trial in 98 hospitals or medical centres in 21 countries. We enrolled adults (≥18 years) not previously given antiretroviral therapy and with a screening plasma viral load of 5000 copies per mL or more and viral sensitivity to background N(t)RTIs. We randomly allocated patients (1:1) using a computer-generated interactive web-response system to receive oral rilpivirine 25 mg once daily or efavirenz 600 mg once daily; all patients received an investigator-selected regimen of background N(t)RTIs (tenofovir-disoproxil-fumarate plus emtricitabine, zidovudine plus lamivudine, or abacavir plus lamivudine). The primary outcome was non-inferiority (12% margin on logistic regression analysis) at 48 weeks in terms of confirmed response (viral load <50 copies per mL, defined by the intent-to-treat time to loss of virologic response [TLOVR] algorithm) in all patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, number NCT00543725.

Findings From May 22, 2008, we screened 947 patients and enrolled 340 to each group. 86% of patients (291 of 340) who received at least one dose of rilpivirine responded, compared with 82% of patients (276 of 338) who received at least one dose of efavirenz (difference 3·5% [95% CI −1·7 to 8·8]; $p_{non\text{-}inferiority}<0·0001$). Increases in CD4 cell counts were much the same between groups. 7% of patients (24 of 340) receiving rilpivirine had a virological failure compared with 5% of patients (18 of 338) receiving efavirenz. 4% of patients (15) in the rilpivirine group and 7% (25) in the efavirenz group discontinued treatment due to adverse events. Grade 2–4 treatment-related adverse events were less common with rilpivirine (16% [54 patients]) than they were with efavirenz (31% [104]; p<0·0001), as were rash and dizziness (p<0·0001 for both) and increases in lipid levels were significantly lower with rilpivirine than they were with efavirenz (p<0·0001).

Interpretation Despite a slightly increased incidence of virological failures, a favourable safety profile and non-inferior efficacy compared with efavirenz means that rilpivirine could be a new treatment option for treatment-naive patients infected with HIV-1.

Funding Tibotec.

Lancet 2011; 378: 229–37

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Introduction

Recent changes in treatment guidelines[1,2] for HIV-1 recommend early initiation of highly active antiretroviral therapy. For first-line treatment in particular, short-term and long-term tolerability are very important for initiation and staying on treatment. Efavirenz-based regimens are recommended for individuals infected with HIV-1 who are treatment naive.[1,2] However, efavirenz is associated with neurological and psychiatric adverse events, rash, teratogenicity, and increases in concentrations of LDL cholesterol and triglycerides.[3,4]

Rilpivirine (TMC278 [Edurant]; Tibotec Pharmaceuticals, County Cork, Ireland) is a US FDA-approved non-nucleoside reverse transcriptase inhibitor (NNRTI),[5] which can be given once per day.[6] In a phase 2b dose-ranging trial[7] of treatment-naive patients with HIV-1, once-daily rilpivirine showed much the same efficacy to once-daily efavirenz for 96 weeks, both given with a background regimen of two nucleoside or nucleotide reverse transcriptase inhibitors (N[t]RTIs). Equivalent efficacy of rilpivirine and efavirenz was sustained for 192 weeks.[8] Rilpivirine had a better neurological, rash, and lipid profile than did efavirenz,[7,8] and did not show teratogenic potential in preclinical studies.[9]

TMC278 against HIV, in a once-daily regimen versus efavirenz (THRIVE) was a 96-week trial that aimed to

assess the efficacy, safety, and tolerability of rilpivirine versus efavirenz, with two investigator-chosen background N(t)RTIs in treatment-naive patients with HIV-1 infection. We aimed to show non-inferiority of rilpivirine compared with efavirenz in terms of the percentage of patients with confirmed response (viral load <50 copies per mL defined by the time-to-loss of virological response [TLOVR] algorithm). Because choice of N(t)RTI is often made in clinical practice on the basis of characteristics of patients and local availability, THRIVE was designed to assess rilpivirine with one of three combination N(t)RTI regimens. In this analysis, we report data from the primary analysis at 48 weeks. The results of a companion phase 3 trial (ECHO),[10] which compared rilpivirine with efavirenz with a background regimen of tenofovir-disoproxil-fumarate and emtricitabine, are reported separately.

Methods

Trial design and patients

We undertook our phase 3, randomised, double-blind, double-dummy, active-controlled trial in 98 academic medical centres, independent non-profit centres, or hospitals in 21 countries (USA and Puerto Rico, Canada, Australia, Europe [seven countries], South Africa, Asia [four countries], and Latin America [6 countries]). The trial had a 6-week screening period, a 96-week treatment period, and a 4-week follow-up period.

Eligible patients were adults (≥18 years) who were naive to antiretroviral therapy, with a screening plasma viral load of 5000 copies per mL or more and viral sensitivity to the background N(t)RTIs, as assessed with the vircoTYPE HIV-1 assay. Main exclusion criteria were HIV-2 infection, documented presence of at least one of 39 NNRTI resistance-associated mutations (RAMs)[11] active clinically significant disease (eg, pancreatitis, cardiac dysfunction, active and significant psychiatric disorder, adrenal insufficiency, or hepatic impairment), renal impairment, and for women, pregnancy or breastfeeding.

The protocol was reviewed and approved by independent ethics committees and institutional review boards at participating sites or at a central institutional review board for some sites (eg, in the USA), and the trial was undertaken in accordance with the principles of good clinical practice and the Declaration of Helsinki. All patients provided written consent.

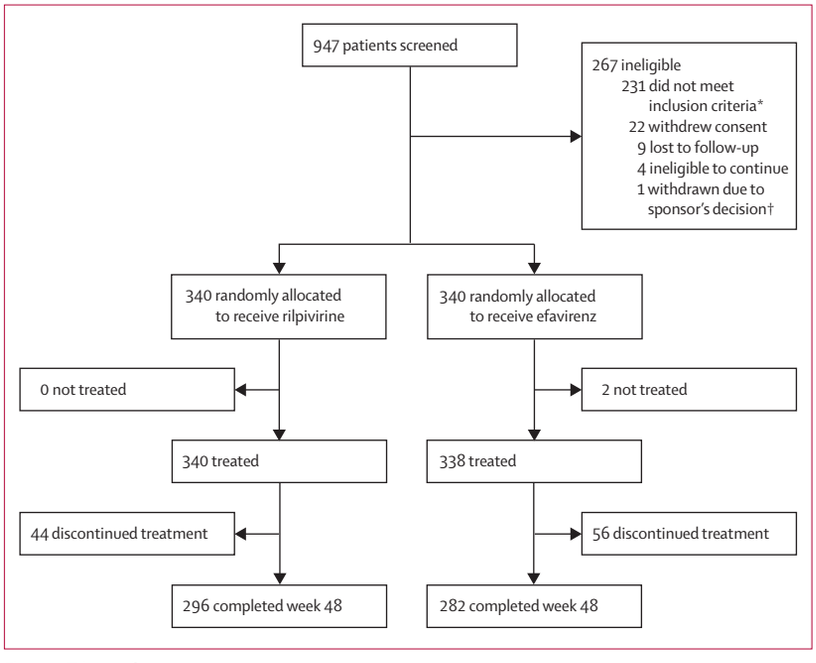

Figure 1: **Trial profile**
*Eg, presence of non-nucleoside reverse transcriptase inhibitor resistance-associated mutations and viral load fewer than 5000 copies per mL. †Discontinued because time between screening and baseline was more than 6 weeks.

Randomisation and masking

We randomly allocated patients with a computer-generated interactive web-response system in a one-to-one ratio to receive oral rilpivirine 25 mg once daily or efavirenz 600 mg once daily after investigator selection of the background N(t)RTI regimen, which included tenofovir-disoproxil-fumarate plus emtricitabine, zidovudine plus lamivudine, or abacavir plus lamivudine. Randomisation was stratified by background regimen and screening viral load (≤100 000 copies per mL, 100 001–500 000 copies per mL, and >500 000 copies per mL). Investigators, the sponsor, and patients were masked to NNRTI treatment assignment.

Procedures

We used a double-dummy regimen in which rilpivirine (or matching placebo) was taken with a meal, whereas efavirenz (or matching placebo) was taken on an empty stomach in the evening. N(t)RTIs were taken according to the locally applicable procedures and package inserts, but preferably at the same time as rilpivirine or efavirenz for abacavir plus lamivudine and tenofovir-disoproxil-fumarate plus emtricitabine. For zidovudine plus lamivudine (taken twice daily), the first dose was preferably taken in the morning with rilpivirine (or placebo), and the second dose was preferably taken in the evening with efavirenz (or placebo).

Disallowed drugs were all investigational drugs, drugs that could reduce rilpivirine exposure (eg, 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. Antacids (≥2 h before or ≥4 h after) and histamine H_2-receptor antagonists (≥12 h before or ≥4 h after) after rilpivirine were allowed. Switches between N(t)RTIs were allowed only if intolerance occurred and were guided by resistance testing.

Our primary outcome was non-inferiority of rilpivirine to efavirenz in terms of percentage of all patients 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 weeks. We used a non-inferiority margin of 12% (lower limit of two-sided 95% CI) to establish non-inferiority of rilpivirine from efavirenz, which is in accordance with the margin of 10–12% suggested by the FDA for HIV drug development.[12] Secondary outcomes were 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 Self-Report Inventory), pharmacokinetics, and pharmacokinetic and pharmacodynamic relations.

We followed-up patients at weeks 2, 4, 8, 12, and 16, and every 8 weeks thereafter. We collected urine and blood samples for haematology and biochemistry, urinalysis, immunology, plasma viral load, and viral genotype and phenotype assessments. We assessed plasma viral load (concentration of *HIV-1* RNA) with the Amplicor HIV-1 monitor test version 1.5 (Roche, Basel, Switzerland).

In the primary analysis, patients were regarded as non-responders if they discontinued treatment prematurely for any reason or if they had virological failure. Patients with virological failure were classified as never suppressed (never achieving viral load <50 copies per mL before week 48) or as rebounder (after achievement of two consecutive viral load values of <50 copies per mL but then having viral load ≥50 copies per mL at two consecutive assessments).

Virological failure in the resistance analysis was assessed in all patients who had received at least one dose of study drug and included all failures of treatment in the database, irrespective of time of failure (at, before, or after week 48), treatment status or reason for discontinuation, provided the following criteria were met: never achieved two consecutive viral load values of fewer than 50 copies per mL and had an increase in viral load 0·5 $\log_{10}$ copies per mL or more above the nadir (never suppressed) or first achieved two consecutive viral load values <50 copies per mL followed by two consecutive (or single, when last available) viral load values of 50 copies per mL or more (rebounder).

Virco (Mechelen, Belgium) did the viral phenotypic assessments with the Antivirogram assay and genotypic assessments with the VircoTYPE HIV-1 assay. We coded adverse events with MedDRA (version 11.0), and established severity of adverse events according to the division of AIDS grading scale.[13] An independent international data and safety monitoring board monitored safety and efficacy throughout the trial.

We estimated glomerular filtration rate at baseline, weeks 2, and 24 on the basis of serum creatinine ($eGFR_{creat}$) with the modification of diet in renal disease trial formula[14] and serum cystatin C concentrations ($eGFR_{cyst}$) with the Hoek formula.[15] We did an electrocardiograph at screening and weeks 2, 12, 24, and 48.

Statistical analysis

We assessed non-inferiority of rilpivirine to efavirenz in patients who received at least one dose of rilpivirine or efavirenz, irrespective of protocol adherence, and in a per-protocol population of all randomly allocated patients who received study drugs, excluding those with major protocol violations.

Assuming a response rate of 75% at week 48 for both treatment groups,[16–22] we needed to enrol 340 patients in each group to establish non-inferiority of rilpivirine to efavirenz, with a maximum allowable difference of 12% at 95% power. We assessed the primary efficacy endpoint with a predicted-response analysis by use of a logistic regression analysis adjusted for the stratification factors (baseline $\log_{10}$ plasma viral load and background N[t]RTIs). We also did a sensitivity analysis for the subpopulation, excluding patients who discontinued for reasons other than virological failure according to the resistance analysis criteria.

In the analysis of mean change in absolute CD4 cell count from baseline, for premature discontinuations, we

	Rilpivirine group (n=340)	Efavirenz group (n=338)
Women	90 (26%)	94 (28%)
Median age, years	36 (19–62, 29–42)	36 (19–69, 29–43)
Race		
White	206/338 (61%)	204/338 (60%)
Black	76/338 (22%)	76/338 (22%)
Asian	45/338 (13%)	49/338 (14%)
Other races/unable to ask	11/337 (3%)	9/338 (3%)
Median viral load, $\log_{10}$ copies per mL	5 (3–7, 4·5–5·3)	5 (3–7, 4·5–5·4)
Categorised viral load, copies per mL		
≤100 000	187 (55%)	167 (49%)
100 001–500 000	118 (35%)	136 (40%)
>500 000	35 (10%)	35 (10%)
Median CD4 cell count, cells per μL	263 (2–744, 177–342)	263 (1–1137, 171–353)
US Centers for Disease Control and Prevention category		
A	237 (70%)	232 (69%)
B	82 (24%)	90 (27%)
C	21 (6%)	16 (5%)
Clade B	238 (70%)	219 (65%)
Active co-infection*		
Hepatitis B	12/338 (4%)	13/336 (4%)
Hepatitis C	18/336 (5%)	20/333 (6%)
Combination of N(t)RTIs in background regimen		
Tenofovir-disoproxil-fumarate plus emtricitabine	204 (60%)	202 (60%)
Zidovudine plus lamivudine	101 (30%)	103 (30%)
Abacavir plus lamivudine†	35 (10%)	33 (10%)

Data are n (%), median (range, IQR), or n/n assessed (%). N(t)RTI=nucleoside or nucleotide reverse transcriptase inhibitor. *Hepatitis B infection status was confirmed by hepatitis B surface antigen; hepatitis C virus infection status was determined by hepatitis C virus antibody and qualitative *HCV* RNA if the test for hepatitis C viral antibodies was positive or if patients were immunocompromised (CD4 cell count <100 cells per μL). †HLAB57*01 or HLAB57*01 hypersensitivity testing was required for abacavir selection.

Table 1: **Baseline demographics of patients and disease characteristics**

	Rilpivirine group (n=340)	Efavirenz group (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*	8 (2%)	7 (2%)	..
Never suppressed†	16 (5%)	11 (3%)	..
Discontinuation due to adverse event or death‡	9 (3%)	24 (7%)	..
Other discontinuation§	16 (5%)	20 (6%)	..
Predicted response (%)¶	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)

Data are n (%), n/n assessed (%), unless otherwise stated. *Confirmed response before week 48 with confirmed rebound at or before week 48. †No confirmed response before week 48. ‡Investigator adjudicated, irrespective of viral load value at time of discontinuation. §Lost to follow-up, non-compliance, withdrew consent, ineligible to continue, or sponsor's decision. ¶Primary analysis adjusted for baseline viral load and background nucleoside or nucleotide reverse transcriptase inhibitors.

Table 2: **Treatment outcomes (defined by the TLOVR algorithm) at week 48**

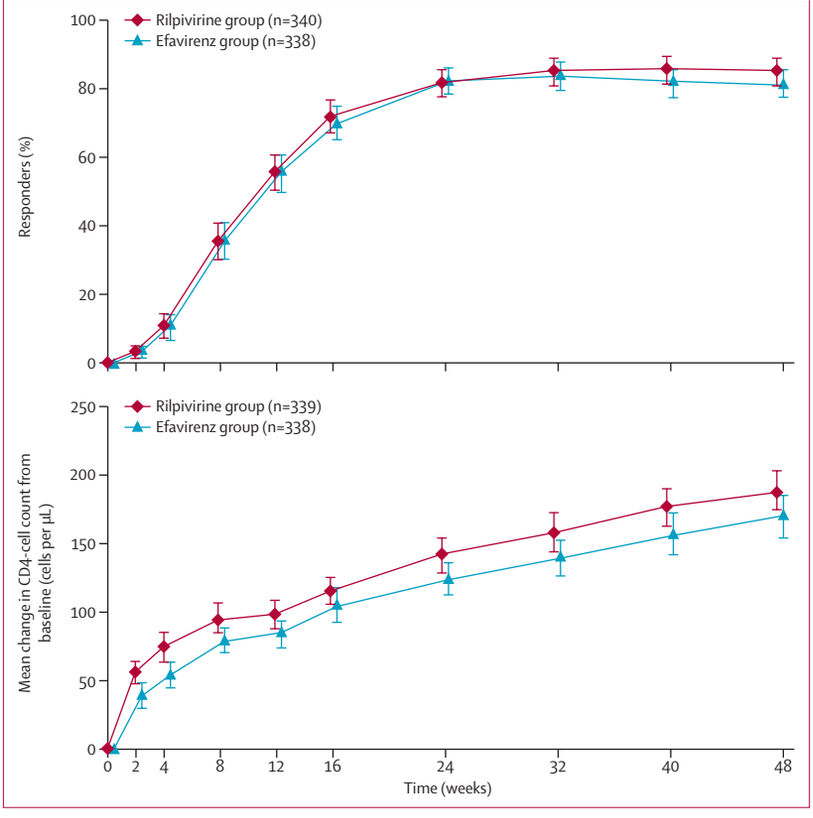

Figure 2: **Outcomes for all patients who received at least one dose of rilpivirine or efavirenz**
(A) Patients with a viral load of fewer than 50 copies per mL (defined by the intent-to-treat TLOVR algorithm) from baseline to 48 weeks (B). Mean change in absolute CD4 cell count from baseline. For premature discontinuations, data were imputed with baseline value (non-completer was failure). For other missing values we used the last observation carried forward method. Error bars are 95% CI.

imputed data with baseline values (non-completer was classified as failure). For other missing values, we used the last observation carried forward method.

We undertook preplanned statistical analyses with Fisher's exact test (5% significance level) for prespecified adverse events that reported a significant difference in the phase 2b trial.[7] For adverse events, we made no adjustment for multiple comparisons between groups. We used a non-parametric Wilcoxon rank-sum test to compare changes in lipid concentrations between treatment groups.

This study is registered with ClinicalTrials.gov, number NCT00543725.

Role of the funding source

The study sponsor was involved in the design and conduct of the trial, and in data collection and analysis. All authors had full access to the 48-week clinical trial report. The corresponding author had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile and table 1 shows the baseline characteristics of patients. The study started on May 22, 2008. The cut-off date for the 48-week analysis was Jan 28, 2010, and for the 96-week analysis was Jan 7, 2011. 326 patients (48%) were from the USA, Canada, Europe, and Australia. As reported by the investigators, discontinuations were mainly due to adverse events (15 of 340 [4%] in the rilpivirine group compared with 25 of 338 [7%] in the efavirenz group), virological failure (investigator-reported virological failure; 13 [4%] *vs* 8 [2%]), loss to follow-up (10 [3%] *vs* 6 [2%]), and withdrawn consent (2 [1%] *vs* 11 [3%]). Six patients (2%) in each group had major protocol violations, which included use of a disallowed drug (5 [1%] *vs* 4 [1%]), use of disallowed background therapy (1 [<1%] in both groups), or selection criteria not met (0 *vs* 1 [<1%]).

One of 204 (<1%) patients in the rilpivirine group switched from the initial background regimen of tenofovir-disoproxil-fumarate plus emtricitabine, five of 101 (5%) switched from zidovudine plus lamivudine, and one of 35 (3%) switched from abacavir plus lamivudine; the corresponding values in the efavirenz group were one of 202 (<1%) patients, five of 103 (5%) patients, and one of 33 (3%) patients.

In the primary analysis, 86% of patients (291 of 340) assigned to receive rilpivirine had a confirmed viral load of fewer than 50 copies per mL at 48 weeks, compared with 82% (276 of 338) for efavirenz (table 2). The lower 95% CI of estimated difference in confirmed response at 48 weeks in the logistic regression model was greater than –12% and –10%, confirming non-inferiority at the 12% (primary endpoint) and 10% margins ($p<0·0001$). However, we did not note superiority. 7% (24 of 340) of patients in the rilpivirine group had virological failure compared with 5% (18 of 338) in the efavirenz group. Results from the predicted-response analysis that adjusted for stratification factors were equivalent to those for the main analysis (table 2). Rilpivirine remained non-inferior

to efavirenz in the per-protocol analysis (table 2). Figure 2 shows percentages of responders in both groups from baseline to 48 weeks (primary analysis).

In a sensitivity analysis excluding patients who discontinued for reasons other than virological failure (defined as in the resistance analysis), 91% (291 of 319) patients in the rilpivirine group responded, compared with 93% (276 of 296) in the efavirenz group (difference –2·0%, 95% CI –6·3 to 2·2).

Mean CD4 cell counts continuously increased from baseline to 48 weeks for rilpivirine and efavirenz (figure 2). At week 48, the mean change from baseline in CD4 cell count was 189 cells per µL (95% CI 174–203) with rilpivirine and 171 cells per µL (155–187) with efavirenz (p=0·09).

The Modified Medication Adherence Self-Report Inventory data were not available for all patients. 89% (243 of 272) of patients who self-reported better than 95% adherence responded to treatment in the rilpivirine group as did 90% (206 of 230) in the efavirenz group. 64% (23 of 36) of patients who were less than or equal to 95% adherent responded in the rilpivirine group (median adherence 92·2%), compared with 62% (24 of 39) in the efavirenz group (median adherence 91·5%). In the rilpivirine group, 91% (170 of 187) of patients with a baseline viral load of 100 000 copies per mL or fewer responded, compared with 80% (94 of 118) for 100 001–500 000 copies per mL, and 77% (27 of 35) for more than 500 000 copies per mL; the corresponding numbers for the efavirenz group were 84% (140 of 167), 82% (112 of 136), and 69% (24 of 35). The background N(t)RTI regimen had no significant effect on response. However, given the small numbers of patients with low (≤95%) adherence as assessed by the Modified Medication Adherence Self-Report Inventory and high baseline viral loads, findings from such patients should be interpreted with caution.

8% of patients (27 of 340) in the rilpivirine group had virological failure according to the resistance analysis (including those without emerging mutation at failure) compared with 6% (20 of 338) in the efavirenz group (table 3).

We did safety analyses with all available data, including those for patients treated beyond 48 weeks. Adverse events were generally mild-to-moderate (grade 1 or 2). Prevelance of any grade 2–4 adverse events at least possibly related to treatment was lower in the rilpivirine group than it was in the efavirenz group (table 4). Rash was the main adverse event leading to discontinuation in the efavirenz group (five patients), but no discontinuations related to rash occurred in the rilpivirine group. All other adverse events that caused discontinuation from various system organ classes occurred in less than 1% of patients in either group.

Neurological events of interest (cluster headache, cranial neuropathy, disturbance in attention, dizziness, facial palsy, headache, lethargy, memory impairment, mononeuropathy, paraesthesia circumoral, photophobia, restlessness, sensation of pressure in ear, somnolence, uveitis, vertigo, or blurred vision) possibly related to treatment (any grade) occurred in 18% of patients (62 of 340) in the rilpivirine group compared with 39% (132 of 338) in the efavirenz group (p<0·0001). Individual neurological adverse events occurring in 2% or more of patients included dizziness (10% of patients [33 of 340] in the rilpivirine group *vs* 28% [94 of 338] in the efavirenz group; p<0·0001), headache (6% [20] *vs* 8% [27]), somnolence (4% [13] *vs* 8% [28]), and disturbance in attention (1% [three] *vs* 2% [seven]). Psychiatric events of interest (abnormal dreams, affective disorder, aggression, agitation, anxiety, confusional state, depressed mood, depression, euphoric mood, homicidal ideation, insomnia, irritability, libido decreased, major depression, mood swings, nervousness, nightmare, panic attack, phobia, post-traumatic stress disorder, sleep disorder, social phobia, sopor, stress symptoms, or suicide attempt) at least possibly related to treatment (any grade) occurred in 15% of patients (52 of 340) in the rilpivirine group compared with 20% (69 of 338) in the efavirenz group (p=0·09). Psychiatric adverse events occurring in 2% of

	Rilpivirine group (n=340)	Efavirenz group (n=338)
Virological failure (resistance analysis)	27 (8%)	20 (6%)
Virological failure (resistance analysis) with resistance data at time of failure		
With any treatment-emergent NNRTI RAM	13/22 (59%)	7/15 (47%)
With any treatment-emergent IAS–USA N(t)RTI RAM[23]	14/22 (64%)	5/15 (33%)
With any treatment-emergent NNRTI and/or IAS–USA N(t)RTI RAM[23]	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
K65R	0	2/5 (40)

Data are n (%) or n/n assessed (%). Virological failure (resistance analysis) was defined as any patient 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 fewer than 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 fewer than 50 copies per mL followed by two consecutive (or single, when last available) viral load values 50 copies per mL or more (rebounder). NNRTI=non-nucleoside reverse transcriptase inhibitor. RAM=resistance-associated mutation. IAS=international AIDS society. N(t)RTI=nucleoside or nucleotide reverse transcriptase inhibitor.

Table 3: **Treatment-emergent NNRTI and N(t)RTI RAMs (occurring in two or more patients with available resistance data in either treatment group) at 48 weeks**

	Rilpivirine group (n=340)	Efavirenz group (n=338)	p value*
Median treatment duration, weeks	55 (2–83, 53–64)	55 (0–84, 53–63)	..
Adverse events			
Any	313 (92%)	312 (92%)	..
Treatment-related adverse events (≥ grade 2)	54 (16%)	104 (31%)	<0·0001
Adverse events leading to permanent discontinuation	15 (4%)	25 (7%)	..
Serious adverse events (including death)	22 (7%)	24 (7%)	..
Death	1 (<1%)	3 (1%)	..
Most common treatment-related adverse events (≥grade 2)†‡			
Insomnia	7 (2%)	6 (2%)	..
Headache	5 (1%)	9 (3%)	..
Nausea	2 (1%)	9 (3%)	..
Dizziness	0	20 (6%)	..
Rash§	1 (<1%)	30 (9%)	<0·0001
Treatment-emergent grade 3 or 4 laboratory abnormalities†			
Any grade 3 or 4 laboratory abnormality	41/340 (12%)	63/330 (19%)	..
Increased pancreatic amylase¶	9/340 (3%)	11/330 (3%)	..
Increased alanine aminotransferase||	6/340 (2%)	11/330 (3%)	..
Increased aspartate aminotransferase||	6/340 (2%)	7/330 (2%)	..
Reduced white blood cell count**	7/340 (2%)	5/329 (2%)	..
Increased LDL-C††	2/340 (1%)	19/327 (6%)	..
Increased lipase (fasting)‡‡	2/340 (1%)	5/330 (2%)	..
Increased triglycerides (fasting)§§	1/340 (<1%)	10/329 (3%)	..
Increased total cholesterol (fasting)¶¶	0/340	11/329 (3%)	..

Data are median (range, IQR), n (%), or n/n assessed (%). ULN=upper limit of normal. *Rilpivirine versus efavirenz, Fisher's exact test, preplanned analysis. †Occurring in ≥2% of patients in either group. ‡Not including laboratory abnormalities reported as an adverse event. §Rash, erythema, allergic dermatitis, macular rash, urticaria, maculopapular rash, papular rash, pustular rash, drug eruption, exanthem, scaly rash, toxic skin eruption, or urticaria papular. ¶>2·0–5·0 × ULN. ||>5·0–10·0 × ULN. **1·000 × 10^9–1·499 × 10^9 cells per L. ††≥4·91 mmol/L; a combination of calculated values and directly measured values were used if the triglyceride concentration was too high for LDL-C to be calculated. ‡‡>3·0–5·0 × ULN. §§8·49–13·56 mmol/L. ¶¶>7·77 mmol/L.

Table 4: **Treatment-emergent adverse events and laboratory abnormalities at 48 weeks**

	Rilpivirine group	Efavirenz group	p value
Total cholesterol (mmol/L)	0·08 (–0·01 to 0·16)	0·79 (0·69 to 0·90)	<0·0001
HDL-C (mmol/L)	0·11 (0·08 to 0·13)	0·27(0·24 to 0·30)	<0·0001
Total cholesterol/HDL-C	–0·36 (–0·48 to –0·25)	–0·28 (–0·38 to –0·17)	0·25
LDL-C (mmol/L)	–0·02 (–0·09 to 0·05)	0·44 (0·34 to 0·53)	<0·0001
Triglycerides (mmol/L)	–0·07 (–0·17 to 0·04)	0·14 (0·01 to 0·26)	<0·0001

Analyses were done with the Wilcoxon rank-sum test in a preplanned analysis.

Table 5: **Mean change in fasting lipid parameters from baseline to 48 weeks**

patients or more were abnormal dreams or nightmares (7% [24 of 340] patients in the rilpivirine group *vs* 11% [38 of 338] in the efavirenz group; p=0·06), insomnia (6% [20] *vs* 5% [16]), and sleep disorder (2% [seven] *vs* 3% [nine]). Most neurological (98%) and psychiatric (96%) adverse events of interest were grade 1 or 2.

3% of patients (nine of 340) in the rilpivirine group had rash at least possibly related to treatment (any grade), compared with 13% (43 of 338) in the efavirenz group (p<0·0001). Of all treatment-related rashes (grouped term), 100% were grade 1–2 in the riplivirine group, with 99% grade 1–2 and 1% grade 3 in the efavirenz group. Rash resolved with continued dosing in both treatment groups, apart from for five patients who discontinued because of rash in the efavirenz group.

Table 4 shows rates of serious adverse events and treatment-emergent grade 3–4 laboratory abnormalities. There was one death in the rilpivirine group (bronchopneumonia) and three in the efavirenz group (one cerebral toxoplasmosis and dysentery, one cerebrovascular accident, and one respiratory failure). All four deaths were unrelated to treatment. With the exception of increased LDL-cholesterol (6% with efavirenz), individual grade 3–4 laboratory abnormalities occurred in 3% or less of patients.

Mean increases in total cholesterol, LDL-cholesterol, and triglyceride concentrations from baseline to week 48 were significantly lower with rilpivirine than they were with efavirenz (p<0·0001; table 5). The mean increase in HDL-cholesterol was significantly lower with rilpivirine than it was with efavirenz (p<0·0001). The ratio of total cholesterol to HDL-C did not differ between groups.

We noted a small increase from baseline in mean serum creatinine at the first on-treatment assessment, which remained stable over 48 weeks with rilpivirine (range 4·11–7·16 µmol/L), but no change with efavirenz. Treatment-associated changes in glomerular filtration rate differed according to the estimation used. There was a maximum mean decrease in $eGFR_{creat}$ of 5–9 mL/min per 1·73 m² from baseline during treatment with rilpivirine, corresponding to the change in creatinine concentration, with glomerular filtration rate remaining in the healthy range for all patients. $eGFR_{cyst}$ increased in both groups at week 2 (3 mL/min for rilpivirine *vs* 5 mL/min for efavirenz) and at week 24 (22 mL/min *vs* 31 mL/min). There were no grade 3–4 creatinine abnormalities, abnormalities reported as adverse events, or renal-related trial discontinuations.

Overall, QT-intervals corrected according to Fridericia's formula (QTcF) increased from baseline to week 48 in both groups, with no notable differences between groups; mean increases were 12·0 ms (95% CI 10·1–13·8) for rilpivirine and 14·1 ms (12·3–16·0) for efavirenz. There were few adverse events potentially related to conduction abnormalities or to rate and rhythm disturbances (two patients in the rilpivirine group and six in the efavirenz group). One patient in the rilpivirine group discontinued because of a grade 3 QT prolongation (QTcF increased >60 ms [77 ms] at week 48), which was reported by the investigator as an asymptomatic adverse event. No concomitant medications were regarded as having caused the increase in QTcF.

Discussion

We showed that oral rilpivirine once daily is non-inferior in terms of efficacy to efavirenz at 48 weeks when given in combination with background N(t)RTIs. Both rilpivirine and efavirenz had high response rates. In our

study, response rates to efavirenz were among the highest reported when compared with earlier studies in treatment-naive patients (panel).[25–29] For both groups, the proportion of patients with virological failure was low. Within these virological failures, the rate of rebound after suppression was also low and much the same between groups with less than 5% of patients never suppressed in either group. The proportion of patients who discontinued due to adverse events and other reasons was lower for rilpivirine than it was for efavirenz, resulting in similar response rates.

Although our study was not powered to assess within-group significance, response rates seemed highest in the rilpivirine group for patients with lowest baseline viral loads, and background N(t)RTI regimen seemed to have no significant effect on responses. The slightly higher virological failure rate noted with rilpivirine than with efavirenz might be explained by a greater effect of suboptimum adherence on virological failure with rilpivirine than with efavirenz. Because of statistical power limitations in the separate ECHO and THRIVE studies, however, results of additional exploratory analyses of effects of factors on response and virological failure will be reported separately for pooled data analyses. Furthermore, pharmacokinetic and pharmacodynamic relationships will be reported elsewhere for the pooled data.

The proportion of virological failures (according to the resistance analysis criteria) with at least one treatment-emergent NNRTI RAM was much the same in both groups, whereas the proportion with at least one treatment-emergent international AIDS society–USA N(t)RTI RAM[23] was higher in the rilpivirine group than it was in the efavirenz group. Consistent with reports from the phase 2b TMC278-C204 trial,[7,8] E138K was the most prevalent NNRTI RAM in the rilpivirine group and K103N was in the efavirenz group, whereas M184I/V were the most prevalent N(t)RTI RAMs in both groups. Phenotypic testing in the pooled analysis showed that 28 of 31 (90%) patients who had virological failure in the rilpivirine group and were phenotypically resistant to rilpivirine were cross-resistant to etravirine.[30] A pooled analysis of sensitivity to NNRTIs will be presented separately.

Rilpivirine was well tolerated, with a more favourable overall profile than efavirenz considering grade 2–4 adverse events at least possibly related to treatment, rash, dizziness, and smaller increases in some proatherogenic lipid parameters, but there was no significant difference in the ratio of total cholesterol to HDL-cholesterol between groups. These data support the more favourable safety profile for rilpivirine compared with efavirenz that was reported in the phase 2b TMC278-C204 trial[7,8] and in the phase 3 ECHO trial.[10] By use of cystatin C, which is an alternative indication of renal function,[31] rilpivirine did not have a clinically relevant effect.

One limitation of our trial was that it was not powered to assess comparisons of efficacy in the various subsets of patients. Moreover, a comprehensive NNRTI RAM list was used to screen out patients potentially resistant to NNRTIs because the trial was double-blinded. Response rates might have been higher in this trial than they would be in the

Panel: Research in context

Systematic review

Before approval of rilpivirine, two main non-nucleoside reverse transcriptase inhibitors (NNRTIs) were available for the first-line treatment of patients with HIV-1 infections in combination with reverse transcriptase inhibitors: efavirenz and nevirapine. Both drugs are equally effective in suppression of HIV infection[24] but cause different side-effects that can restrict their use. Treatment with efavirenz can lead to rash, impaired mental function, vertigo, abnormal dreams, and fetal malformations, whereas nevirapine treatment is associated with severe rash and liver damage due to hypersensitivity reactions. These adverse effects emphasise the unmet need for additional first-line NNRTI treatment options with a good safety profile.

We searched the PubMed database to May, 2011, for randomised controlled trials and clinical trials published in English with the search term "rilpivirine". Rilpivirine has only been assessed in one phase 2b study.[7,8] This randomised, controlled, dose-finding study of 368 patients showed that rilpivirine provided long-term (96 weeks) efficacy and tolerability in treatment-naive adults with HIV-1 infections, with comparable response rates with efavirenz. In this study, all daily rilpivirine doses (25 mg, 75 mg, and 150 mg) resulted in much the same response rates. Grade 2–4 adverse events at least possibly related to study medication, including nausea, dizziness, abnormal dreams or nightmares, rash, somnolence, and vertigo were less frequent with TMC278 than they were with efavirenz in the context of an open-label trial (only the dose of rilpivirine was masked).[7]

Interpretation

The phase 3 ECHO[10] and THRIVE trials were independently undertaken and powered to investigate the non-inferior efficacy of rilpivirine 25 mg once daily in combination with different reverse transcriptase inhibitors backbones for first-line therapy in adults with HIV-1 infection, compared with efavirenz, the preferred NNRTI for treatment-naive patients. Both studies met the primary objective of non-inferiority and also showed rilpivirine to have a more favourable side-effect profile versus efavirenz, with a reduced incidence of rash and central nervous system adverse reactions. However, the virological failure rate was slightly higher with rilpivirine than it was with efavirenz, and exploratory analyses are ongoing to examine the reasons for this difference in more detail.

Rilpivirine was better tolerated than was efavirenz in terms of lower incidences of discontinuations due to adverse events, especially due to central nervous system side-effects such as insomnia, depression, dizziness, or due to rash, when compared with patients taking efavirenz. Consequently, rilpivirine might be suitable for use in some treatment-naive patients, which efavirenz is not, such as women of child bearing age or potential and patients with certain pre-existing psychiatric conditions.

The ECHO trial[10] examined rilpivirine with emtricitabine and tenofovir-disoproxil-fumarate, a combination that has been submitted for marketing approval as a fixed-dose combination for antiretroviral-naive patients with HIV-1 infection. If this fixed-dose single-tablet is approved, it would be an alternative to the currently licensed once-daily single tablet, ATRIPLA combining emtricitabine and tenofovir-disoproxil-fumarate to efavirenz.

THRIVE assessed the safety and efficacy of rilpivirine with three different background regimens (tenofovir-disoproxil-fumarate plus emtricitabine, zidovudine plus lamivudine, or abacavir plus lamivudine) versus efavirenz. Based on these data and the findings in ECHO, rilpivirine 25 mg tablets have been approved in the USA in combination with other antiretroviral drugs for the first-line treatment of HIV infection.

Taken together, these data suggest that once-daily rilpivirine is likely to be a valuable treatment option for antiretroviral-naive patients with HIV-1 infection.

clinic where patients might harbour transmitted resistance. However, E138K has a low prevalence in routine clinical resistance testing (<1%).[32] Our trial had a double-blind, double-dummy design, meaning that patients had to take study treatment twice daily, rather than once daily, although the effect of this design feature on response rates is not known. A further limitation of the study was that, in common with most clinical HIV studies,[33] some populations of patients were under-represented (eg, women). Nevertheless, subgroup analyses of the combined ECHO and THRIVE populations by sex, region, race, clade, and co-infection with hepatitis B and C,[30,34,35] show that the efficacy of rilpivirine and efavirenz are equivalent, suggesting broader applicability of our data.

Thus, on the basis of our data and those from the companion phase 3 trial, ECHO,[10] rilpivirine is expected to be a valuable treatment option for antiretroviral-naive patients infected with HIV-1.

Contributors

All authors contributed substantially to the study's conception, design, and undertaking. CJC, JA-V, BC, JF, MAJ, KR, HW, and CZ all participated in recruiting patients to the trial and reported data for those patients. HC, LTR, SV, and KB all had a substantial involvement in the data analyses. All authors were involved in the development of the first manuscript, interpretation of data, have read and approved the final version, and have met the criteria for authorship as established by the International Committee of Medical Journal Editors.

Conflicts of interest

CJC has received research funding from Tibotec, Gilead, Bristol-Myers Squibb, Merck, Sharp & Dohme, Tobira, and ViiV Healthcare; has received speakers' honoraria from Tibotec, Gilead, Bristol-Myers Squibb, and Merck, Sharp & Dohme; and is on advisory boards for Gilead, Tibotec, Merck, Sharp & Dohme, Abbott, Tobira, and Bristol-Myers Squibb. JA-V has received research grants or honoraria for participation in advisory boards or conferences from Boehringer Ingelheim, Bristol-Myers Squibb, Tibotec Therapeutics, Abbott, Merck, Sharp & Dohme, and ViiV Healthcare. BC has received research funding, consultancy fees, lecture sponsorships from, or has served on advisory boards for Abbott, Boehringer Ingelheim, Gilead, GlaxoSmithKline, ViiV Healthcare, Janssen-Cilag, Merck, Sharp & Dohme, and Pfizer. JF and HW declare no conflicts of interest. MAJ has received honoraria from Bristol-Myers Squibb, GlaxoSmithKline, Tibotec, ViiV Healthcare, Abbott, and Merck, Sharp & Dohme. KR has received consultancy fees, or honoraria, travel grants, or research grants from Tibotec, F Hoffmann-La Roche, Merck, Sharp & Dohme, Bristol-Myers Squibb, Gilead, Abbott, and GlaxoSmithKline; has received the Professional Researcher Strengthen Grant from the National Science and Technology Development Agency, BIOTEC, Ministry of Science and Technology, Thailand, the National Research University Project of CHE, and the Ratchadaphiseksomphot Endowment Fund (HR1161A). CZ has received grants or research support from Pfizer, Tibotec, Bristol-Myers Squibb, Avexa, and Advent, and received consultancy fees from Tibotec. HC, LTR, SV, and KB are all full time employees of Tibotec.

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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

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Summary

Background Efavirenz with tenofovir-disoproxil-fumarate and emtricitabine is a preferred antiretroviral regimen for treatment-naive patients infected with HIV-1. Rilpivirine, a new non-nucleoside reverse transcriptase inhibitor, has shown similar antiviral efficacy to efavirenz in a phase 2b trial with two nucleoside/nucleotide reverse transcriptase inhibitors. We aimed to assess the efficacy, safety, and tolerability of rilpivirine versus efavirenz, each combined with tenofovir-disoproxil-fumarate and emtricitabine.

Methods We did a phase 3, randomised, double-blind, double-dummy, active-controlled trial, in patients infected with HIV-1 who were treatment-naive. The patients were aged 18 years or older with a plasma viral load at screening of 5000 copies per mL or greater, and viral sensitivity to all study drugs. Our trial was done at 112 sites across 21 countries. Patients were randomly assigned by a computer-generated interactive web response system to receive either once-daily 25 mg rilpivirine or once-daily 600 mg efavirenz, each with tenofovir-disoproxil-fumarate and emtricitabine. Our primary objective was to show non-inferiority (12% margin) of rilpivirine to efavirenz in terms of the percentage of patients with confirmed response (viral load <50 copies per mL intention-to-treat time-to-loss-of-virological-response [ITT-TLOVR] algorithm) at week 48. Our primary analysis was by intention-to-treat. We also used logistic regression to adjust for baseline viral load. This trial is registered with ClinicalTrials.gov, number NCT00540449.

Findings 346 patients were randomly assigned to receive rilpivirine and 344 to receive efavirenz and received at least one dose of study drug, with 287 (83%) and 285 (83%) in the respective groups having a confirmed response at week 48. The point estimate from a logistic regression model for the percentage difference in response was –0·4 (95% CI –5·9 to 5·2), confirming non-inferiority with a 12% margin (primary endpoint). The incidence of virological failures was 13% (rilpivirine) versus 6% (efavirenz; 11% *vs* 4% by ITT-TLOVR). Grade 2–4 adverse events (55 [16%] on rilpivirine *vs* 108 [31%] on efavirenz, p<0·0001), discontinuations due to adverse events (eight [2%] on rilpivirine *vs* 27 [8%] on efavirenz), rash, dizziness, and abnormal dreams or nightmares were more common with efavirenz. Increases in plasma lipids were significantly lower with rilpivirine.

Interpretation Rilpivirine showed non-inferior efficacy compared with efavirenz, with a higher virological-failure rate, but a more favourable safety and tolerability profile.

Funding Tibotec.

Introduction

Many antiretroviral regimens with similar antiviral activity are available for treatment-naive individuals infected with HIV-1.[1–4] Treatment selection is increasingly based on the tolerability profile and convenience of the regimen. Several treatment guidelines recommend the non-nucleoside reverse transcriptase inhibitor (NNRTI), efavirenz, in combination with tenofovir-disoproxil-fumarate and emtricitabine.[1–4] However, efavirenz is associated with several adverse events.[5,6] Furthermore, efavirenz is contraindicated for pregnant women because of concerns over potential teratogenicity.[1,5,6]

Rilpivirine (Tibotec Pharmaceuticals, Co Cork, Ireland) is an NNRTI that has been approved for use in the USA.[7] It is a potential alternative to efavirenz for treatment-naive patients infected with HIV-1. This drug does not seem teratogenic in non-primate animals.[8] In a large, phase 2b, randomised trial (TMC278-C204)[9] in 368 treatment-naive patients, all once-daily doses of rilpivirine (25 mg, 75 mg, and 150 mg) showed antiviral efficacy similar to that recorded with once-daily 600 mg efavirenz, when either drug was given in combination with two nucleoside/nucleotide reverse transcriptase inhibitors (N[t]RTIs). Both rilpivirine and efavirenz had similar, sustained efficacy over 192 weeks.[10] Rash and neurological and psychiatric adverse events were reported less commonly with rilpivirine than with efavirenz, and lipid increases were smaller. The once-daily 25 mg dose of rilpivirine was selected for further development, because it had the best benefit–risk balance, with the lowest incidence of discontinuations due to adverse events and rashes.[9] Further, once-daily 25 mg rilpivirine had no effect on QTc interval in a thorough QT trial.[11,12] In our trial, Efficacy Comparison in Treatment-naive,

HIV-infected Subjects of TMC278 and Efavirenz (ECHO), our aim was to assess the efficacy, safety, and tolerability of rilpivirine versus efavirenz, each combined with a background regimen of tenofovir-disoproxil-fumarate and emtricitabine. We present data from our primary 48-week analysis.

Methods

Participants

We did a 96-week (April 21, 2008, to Jan 4, 2011), phase 3, double-blind, double-dummy, active-controlled randomised trial, to assess the efficacy, safety, and tolerability of once-daily 25 mg rilpivirine versus once-daily 600 mg efavirenz with a background regimen of tenofovir-disoproxil-fumarate and emtricitabine. Our trial was done at 112 sites across 21 countries (USA, Canada, Australia, South Africa, ten countries in Europe, three in Asia, and four in Latin America).

Our main inclusion criteria were patients aged 18 years or older, who had not been previously treated with antiretroviral drugs, a plasma viral load at screening of 5000 copies per mL or greater, and viral sensitivity to tenofovir-disoproxil-fumarate and emtricitabine (assessed with the resistance genotype virco TYPE HIV-1 assay; Virco BVBA, Beerse, Belgium). Further exclusion criteria included 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, 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),[13] any active clinically significant disease (eg, pancreatitis, cardiac dysfunction, active and significant psychiatric disorder, adrenal insufficiency, hepatic impairment), renal impairment (estimated glomerular filtration rate based on creatinine <50 mL per min), and, for women, pregnancy or breastfeeding.

All patients gave written consent before any trial-related procedure. Our protocol was reviewed and approved by independent ethics committees and institutional review boards, and our trial was done in accordance with the principles of good clinical practice and the Declaration of Helsinki.

Randomisation and masking

Patients infected with HIV-1 were randomly assigned (1:1) by a computer-generated interactive web response system to receive either once-daily 25 mg rilpivirine or once-daily 600 mg efavirenz, both given in combination with a fixed-dose background regimen of once-daily 300 mg tenofovir-disoproxil-fumarate and once-daily 200 mg emtricitabine. The investigator, sponsor, and patient did not know which NNRTI treatment the patient was assigned to receive. Randomisation was stratified by screening viral load (≤100 000 copies per mL, >100 000 to ≤500 000 copies per mL, and >500 000 copies per mL). Our double-dummy design required that rilpivirine (or matching placebo) be taken with a meal, whereas efavirenz (or matching placebo) was required to be taken on an empty stomach in the evening.

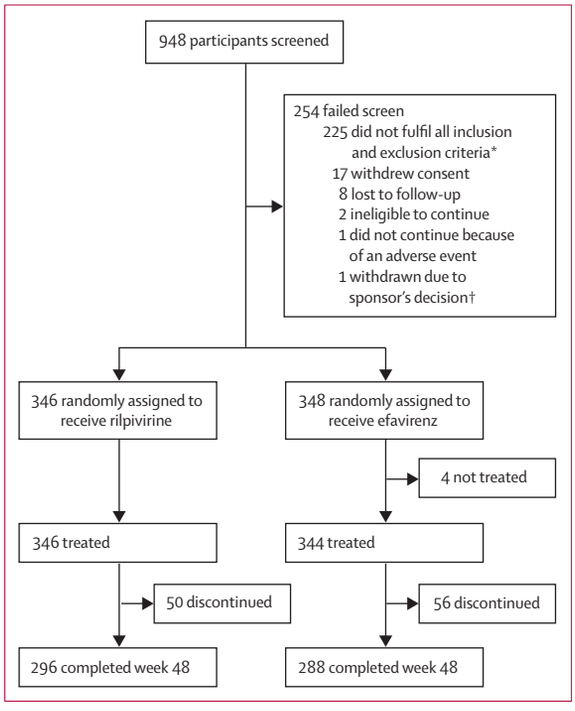

Figure 1: **Trial profile**
*The primary reasons screened patients did not meet our inclusion or exclusion criteria were the presence of non-nucleoside reverse transcriptase inhibitor resistance-associated mutations and a viral load of less than 5000 copies per mL. †Discontinued because more than 6 weeks elapsed between screening and baseline.

Procedures

Our trial consisted of a 6-week screening period, a 96-week treatment period, and a 4-week follow-up period. The results of a companion phase 3 trial, TMC278 against HIV, in a once-daily regimen versus efavirenz (THRIVE),[14] are reported separately.

Disallowed drugs included those which could reduce exposure to rilpivirine (ie, 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. Antacids (given at least 2 h before or at least 4 h after rilpivirine) and histamine H_2-receptor antagonists (given at least 12 h before or at least 4 h after rilpivirine) were permitted. Switches of N(t)RTIs were only allowed if there was N(t)RTI intolerance, and in accordance with the drug susceptibility profile; treatment was judged to have not failed in these patients.

Our primary objective was to show non-inferiority of treatment with once-daily 25 mg rilpivirine compared

	Rilpivirine group N=346	Efavirenz group N=344
Number of women	78 (23%)	69 (20%)
Median age (years; range)	36 (18–78)	36 (19–67)
Race		
White	214 (62%)	206 (60%)
Black	89 (26%)	80 (23%)
Asian	33 (10%)	48 (14%)
Other or not allowed to ask	10 (3%)	10 (3%)
Median viral load (log_{10} copies per mL; range)	5 (2–7)	5 (3–7)
Categorised viral load (copies per mL)		
≤100 000	181 (52%)	163 (47%)
>100 000 to ≤500 000	131 (38%)	134 (39%)
>500 000	34 (10%)	47 (14%)
Median CD4 cell count (cells per μL; range)	240 (1–888)	257 (1–757)
Centers for Disease Control and Prevention category		
A	249 (72%)	242 (70%)
B	83 (24%)	79 (23%)
C	14 (4%)	23 (7%)
Clade B	247 (71%)	243 (71%)
Active co-infection*		
Hepatitis B	11/341 (3%)	19/342 (6%)
Hepatitis C	8/332 (2%)	11/332 (3%)

Data are n (%) unless otherwise stated. *Hepatitis B infection status was confirmed by positive hepatitis B surface antigen. The hepatitis C virus (HCV) infection status was established by HCV antibody and qualitative HCV RNA if the test for HCV antibodies was positive or if patients were immunocompromised (CD4 cell count <100 cells per μL).

Table 1: **Baseline demographics and disease characteristics**

	Rilpivirine group	Efavirenz group	Percentage difference (95% CI)
ITT-TLOVR outcome	N=346	N=344	..
Viral load less than 50 copies per mL	287 (83%)	285 (83%)	0·1 (–5·5 to 5·7)
VF_{eff}	38 (11%)	15 (4%)	..
Rebounders	16 (5%)	8 (2%)	..
Never suppressed	22 (6%)	7 (2%)	..
Discontinuation due to adverse events*	6 (2%)	25 (7%)	..
Discontinuation due to reason other than an adverse event†	15 (4%)	19 (6%)	..
Model-predicted response‡	83%	84%	–0·4 (–5·9 to 5·2)
Per-protocol–TLOVR outcome	N′=335	N′=330	..
Viral load less than 50 copies per mL	282 (84%)	275 (83%)	0·8 (–4·8 to 6·5)

Data are n (%) unless otherwise stated. N=number of patients. TLOVR=time-to-loss of virological response. VF_{eff}=virological failure for the efficacy (ITT-TLOVR) endpoint (never suppressed [no confirmed response before week 48] or rebounders [confirmed response before week 48 with confirmed rebound at or before week 48]). N′=number of assessable patients in each treatment group. ITT=intention-to-treat. *As per investigator, irrespective of viral-load value at time of discontinuation. †Lost to follow-up, non-compliance, withdrew consent, ineligible to continue, or sponsor's decision. ‡Logistic regression (ITT-TLOVR outcome <50 copies per mL) adjusted for baseline viral load.

Table 2: **Treatment outcome at week 48**

with once-daily 600 mg efavirenz in terms of the percentage of patients with confirmed response (according to the intention-to-treat time-to-loss-of-virological-response [ITT-TLOVR] algorithm) at week 48, with a non-inferiority margin of rilpivirine versus efavirenz of 12% (based on the lower limit of the two-sided 95% CI). Our selected non-inferiority margin was chosen in accordance with US Food and Drug Administration guidelines for HIV drug development that suggest a margin ranging from 10% to 12%.[15]

Our secondary endpoints were non-inferiority at a 10% margin, superiority (if non-inferiority was shown), durability of 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.

Patients attended scheduled trial visits at weeks 2 and 4, every 4 weeks until week 16, and then every 8 weeks. We collected urine and blood samples for urinalysis, haematology and biochemistry, immunology, plasma viral load, and viral genotype and phenotype determinations. We established plasma viral load (HIV-1 RNA concentration) with the Amplicor HIV-1 Monitor Test version 1·5 (Roche, Basel, Switzerland).

In our ITT-TLOVR analysis, non-responders were patients who discontinued the trial prematurely for any reason, or who had virological failure. We categorised patients with virological failure as either never suppressed (never achieving viral load <50 copies per mL before week 48) or as a rebounder (after having achieved two consecutive viral load values of <50 copies per mL but then having viral load ≥50 copies per mL at two consecutive timepoints).

We established virological failure according to our resistance analysis in our intention-to-treat (ITT) population and included all treatment failures in the database, irrespective of time of failure (whether at, before, or after week 48), treatment status, or reason for discontinuation, provided these criteria were met: never achieved two consecutive viral-load values less than 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 less than 50 copies per mL with two subsequent consecutive (or single, when last available) viral-load values of 50 copies per mL or greater (rebounder). Viral phenotypic and genotypic assessments were done by Virco BVBA (Mechelen, Belgium), with Antivirogram and Virco TYPE HIV-1 assays, respectively.

An independent data and safety monitoring board monitored the safety of patients during the trial. The Medical Dictionary for Regulatory Activities (version 11·0) was used to code adverse events, and adverse-event severity was assessed with the Division of Acquired Immunodeficiency Syndrome grading scale.[16] Included in our assessment of adverse events were those whose association with NNRTIs are well described: neurological events of interest and psychiatric events of interest. Neurological events of interest are defined as cluster headache, cranial neuropathy, disturbance in attention,

dizziness, facial palsy, headache, lethargy, memory impairment, mononeuropathy, paraesthesia circumoral, photophobia, restlessness, sensation of pressure in ear, somnolence, uveitis, vertigo, or blurred vision. Psychiatric events of interest are defined as abnormal dreams, affective disorder, aggression, agitation, anxiety, confusional state, depressed mood, depression, euphoric mood, homicidal ideation, insomnia, irritability, libido decreased, major depression, mood swings, nervousness, nightmare, panic attack, phobia, post-traumatic stress disorder, sleep disorder, social phobia, sopor, stress symptoms, or suicide attempt.

We estimated glomerular filtration rate (GFR), based on serum creatinine, with the Modification of Diet in Renal Disease trial formula ($eGFR_{creat}$).[17] An electrocardiograph was recorded at screening and at weeks 2, 12, 24, and 48.

Statistical analysis

The population for primary analysis was our ITT population (ie, all who had received a study drug). We did an additional analysis on our per-protocol population (ie, as ITT but excluding major protocol violations). Our sample-size calculations took into account response rates in previous trials with efavirenz.[18–24] Given an expected response rate of 75% at week 48, we needed 340 patients in each treatment group to establish non-inferiority of rilpivirine to efavirenz with a maximum allowable difference of 12% at 95% power. We also did a logistic-regression analysis for our primary efficacy endpoint adjusted for the stratification factor, baseline $\log_{10}$ plasma viral load (≤100 000, >100 000 to ≤500 000, and >500 000 copies per mL). We did a sensitivity analysis on the subpopulation censored for non-virological failure according to our resistance analysis, excluding patients who discontinued for reasons other than virological failure according to our resistance analysis.

In our analysis of mean change in absolute CD4 cell count from baseline, for premature discontinuations data were assigned the baseline value (non-completer equalled failure). For other missing values, our last observation was carried forward.

We preplanned all presented statistical analyses. We used Fisher's exact test (5% significance level) to compare prespecified adverse events for which a significant difference had been recorded in the phase 2b trial.[9] We applied no adjustment for multiple comparisons between groups. We did a non-parametric Wilcoxon rank-sum test to compare lipid changes between our two treatment groups.

Role of the funding source

The study sponsor was involved in the design and conduct of the trial, and in the collection and analysis of the data. All authors had full access to the 48-week clinical trial report. The corresponding author had final responsibility to submit the manuscript for publication.

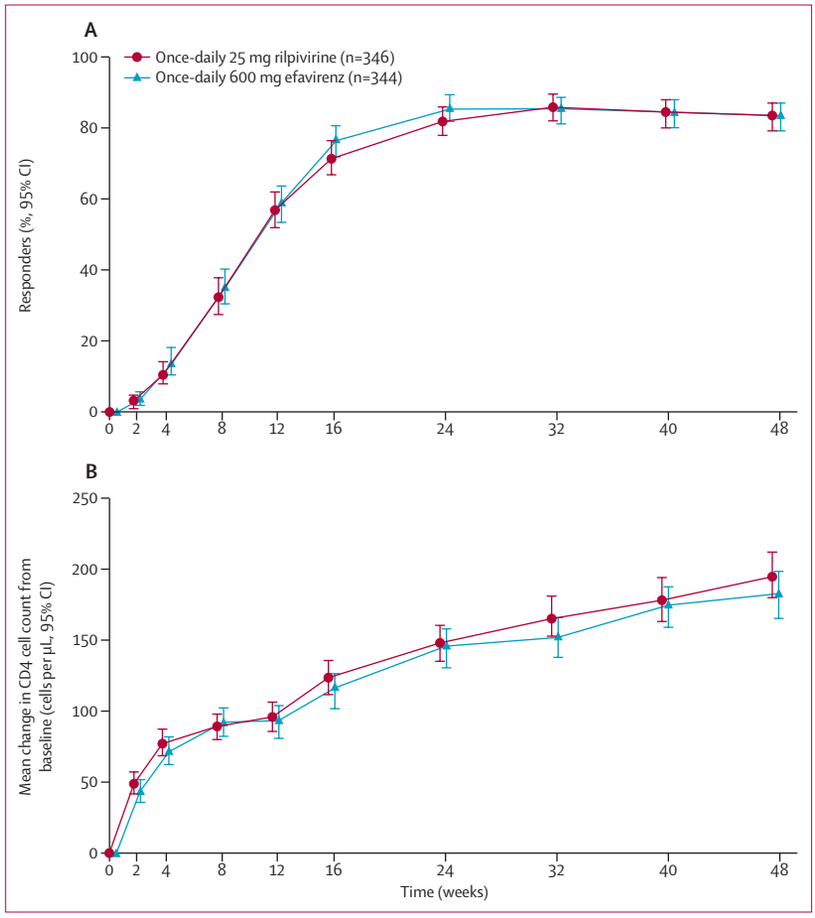

Figure 2: **Percentage of patients with a viral load of less than 50 copies per mL from baseline to week 48 (A) and mean change in absolute CD4 cell count from baseline (B)**
(A) Intention-to-treat time-to-loss-of-virological-response algorithm. (B) At week 48, mean change in absolute CD4 cell count from baseline was 196 cells per µL (95% CI 179–212) for rilpivirine and 182 cells per µL (165–198) for efavirenz (p=0·13).

Results

Figure 1 shows the trial profile. Our ITT analyses included the 690 patients who received at least one dose of study drug. 106 patients (15%) discontinued treatment before week 48, and reasons for discontinuations, as reported by the investigators, were balanced between groups, with the exception of adverse events (eight in the rilpivirine group *vs* 28 in the efavirenz group) and investigator-reported virological failure (23 *vs* six, respectively). The incidence of major protocol violations was similar in each group (11 of 346 patients in the rilpivirine group *vs* 14 of 344 in the efavirenz group) and included use of a disallowed drug in the treatment period (six *vs* nine), deviation of background treatment (three *vs* five), selection criteria not met (two *vs* none), and non-compliance with study drug intake (one *vs* two). One patient assigned to receive efavirenz switched background regimen to abacavir plus lamivudine because of renal impairment.

Overall, demographic and baseline characteristics were balanced between the two groups (table 1). Most

	Rilpivirine group N=346	Efavirenz group N=344
VF_{res}	45 (13%)	19 (6%)
VF_{res} with resistance data at time of failure	40	13
VF_{res} with any treatment-emergent NNRTI RAM	26/40 (65%)	8/13 (62%)
VF_{res} with any treatment-emergent IAS-USA N(t)RTI RAM[25]	28/40 (70%)	4/13 (31%)
VF_{res} with any treatment-emergent NNRTI or IAS-USA N(t)RTI RAM[25]	29/40 (73%)	8/13 (62%)
NNRTI RAM incidence in patients who failed with NNRTI mutations*	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 patients who failed with N(t)RTI mutations†	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

Data are n (%). VF_{res}=virological failure established with the resistance analysis defined as any patient in the intention-to-treat 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 less than 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 less than 50 copies per mL with two subsequent consecutive (or single, when last available) viral load values of 50 copies per mL or greater (rebounder). N=number of patients in each treatment group. n=number of observations. NNRTI=non-nucleoside reverse transcriptase inhibitor. RAM=resistance-associated mutation. IAS-USA=International AIDS Society-USA. N(t)RTI=nucleoside/nucleotide reverse transcriptase inhibitor. *One patient receiving efavirenz had V108I (8%), as did one patient receiving rilpivirine (3%). †K70E was reported in one patient in the rilpivirine group versus no patients in the efavirenz group.

***Table 3*: Most prevalent treatment-emergent NNRTI and N(t)RTI RAMs (in two or more patients with available resistance data) at the time of week 48 analysis**

patients (400; 58%) were from the USA, Canada, Europe, and Australia.

At week 48, 83% of patients from both groups had confirmed response (ITT-TLOVR algorithm; table 2). There were proportionally more virological failures in the rilpivirine group than in the efavirenz group (table 2). Our model-predicted responses, with the covariate log_{10} baseline plasma viral load, were similar to the ITT-TLOVR responses (table 2). The estimated difference in ITT-TLOVR response from our logistic-regression model was –0·4% (95% CI –5·9% to 5·2%). Since the lower limit of the 95% CI for the difference between rilpivirine and efavirenz was greater than both –12% (p<0·0001) and –10% (p=0·0007), we established non-inferiority at the 12% (primary endpoint) and 10% margins. However, we did not show superiority at the 5% significance level. Analysis of our per-protocol population confirmed that rilpivirine was non-inferior to efavirenz in confirmed response (table 2). In a sensitivity analysis excluding patients who discontinued for reasons other than virological failure according to our resistance analysis (ITT-TLOVR, population censored for non-virological failure), response rates were 86% (287 of 333) in our rilpivirine group and 94% (285 of 303) in our efavirenz group (difference –7·9%, 95% CI –12·5% to –3·2%). The percentage of responders for the two treatments increased over time, with no notable differences between the two groups (figure 2). Figure 2 also shows a steady increase from baseline in mean CD4 cell count.

The proportion of responders in the group of patients who self-reported greater than 95% adherence (M-MASRI; although data were not available for all patients) was 86% (236 of 275) for rilpivirine and 87% (229 of 262) for efavirenz. For patients who were 95% adherent or less, the proportion of responders was 68% (30 of 44) versus 73% (41 of 56), respectively. The median adherence of patients in the 95% adherent or less category who were treated with rilpivirine was 91% (n=44) and in patients treated with efavirenz was 92% (n=56).

The proportion of responders for patients with baseline viral load of 100 000 copies per mL or less was 90% (162 of 181) for rilpivirine versus 83% (136 of 163) for efavirenz. The proportion of responders for baseline viral load of 100 000 copies per mL to 500 000 or less copies per mL, was 79% (104 of 131) versus 83% (111 of 134), respectively. For baseline viral load of greater than 500 000 copies per mL, the proportion of responders was 62% (21 of 34) versus 81% (38 of 47). However, since some of the numbers of patients in these categories are small, the results in patients with 95% or less M-MASRI adherence and high baseline viral load should be interpreted with caution.

There was a greater proportion of virological failures according to our resistance analysis in the rilpivirine group versus the efavirenz group (table 3). At the time of failure, a similar high proportion of virological failures in each treatment group developed at least one treatment-emergent NNRTI RAM, whereas the proportion of virological failures with one or more treatment-emergent International AIDS Society-USA (IAS-USA) N(t)RTI RAM[25] was higher in the rilpivirine group (table 3). The most common treatment-emergent NNRTI RAM in the rilpivirine group was E138K; in the efavirenz group K103N was the principal NNRTI RAM. M184I, V, or both were the most common IAS-USA N(t)RTI RAMs in both groups.

Our safety analysis included data from patients treated beyond week 48 (table 4). Adverse events were generally mild-to-moderate (grade 1 or 2). The incidence of grade 2 or greater adverse events possibly related to treatment was greater for efavirenz (p<0·0001 rilpivirine *vs* efavirenz; Fisher's exact test, preplanned analysis). The most commonly reported grade 2 or greater adverse events possibly related to treatment in 2% or greater of patients in either group were dizziness, abnormal dreams

and nightmares, insomnia, nausea, and any rash (table 4). The incidences of serious adverse events, irrespective of relatedness, were similar between groups. There was one death in the efavirenz group due to Burkitt's lymphoma, which was unrelated to treatment (table 4). The incidence of discontinuations due to adverse events was greater for efavirenz (table 4).

Neurological events of interest (55 [16%] of 346 patients in the rilpivirine group *vs* 126 [37%] of 344 in the efavirenz group; p<0·0001) and psychiatric events of interest (50 [15%] *vs* 86 [25%], respectively; p=0·0006) possibly related to treatment (any grade) were at a significantly lower incidence with rilpivirine than with efavirenz. Individual neurological adverse events in 2% or greater of patients were dizziness (22 of 346 *vs* 85 of 344; p<0·0001), headache (22 *vs* 15), somnolence (12 *vs* 21), and disturbance in attention (two *vs* ten). Psychiatric adverse events in 2% or greater of patients were abnormal dreams and nightmares (32 of 346 *vs* 49 of 344; p=0·045), insomnia (14 *vs* 23), depression (six *vs* nine), anxiety (two *vs* eight), and sleep disorder (two *vs* 11). Most neurological and psychiatric adverse events of interest were grade 1 or 2 in severity, and the prevalence of these adverse events declined after the first 4–8 weeks of treatment in both groups.

The incidence of any rash possibly related to treatment (any grade) was lower (p<0·0001) for rilpivirine (4%; 12 of 346) than for efavirenz (15%; 50 of 344); most rashes were grade 1 or 2. Grade 3 rash was reported in one patient treated with rilpivirine and two patients treated with efavirenz, and no grade 4 rash was reported. One patient on rilpivirine discontinued because of a treatment-related rash versus three on efavirenz. Rash resolved with continuous dosing in both treatment groups in those who remained on study treatment.

Treatment-emergent grade 3 or 4 laboratory abnormalities happened at an incidence of 10% with rilpivirine compared with 16% for efavirenz. With the exception of hypophosphataemia, individual grade 3 or 4 laboratory abnormalities happened in a lower proportion of patients treated with rilpivirine versus those treated with efavirenz (table 4).

There were no relevant increases from baseline at week 48 in mean low-density lipoprotein-cholesterol (LDL-C) and triglyceride concentrations for rilpivirine (table 5). However, LDL-C and triglycerides increased with efavirenz (table 5). Rilpivirine was associated with lower increases than efavirenz in total cholesterol and high-density lipoprotein-cholesterol (HDL-C; table 5). There was no difference in the change from baseline at week 48 in the total cholesterol over HDL-C between groups.

There was a small increase from baseline in mean serum creatinine concentration for rilpivirine at our first on-treatment assessment, but then the concentration remained stable over the 48-week treatment period (range 5·69–9·07 µmol/L), whereas values remained around baseline for efavirenz (range 0·10–2·38 µmol/L). Consequently, $eGFR_{creat}$ remained slightly below baseline levels with rilpivirine, but within normal limits (mean decreases were 8–11 mL/min per 1·73 m²), and at about baseline levels with efavirenz. We did not record grade 3 or 4 abnormalities in creatinine, and no abnormalities

	Rilpivirine group N=346	Efavirenz group N=344	p value*
Median treatment duration (weeks; range)	56 (0–87)	56 (1–88)	..
Adverse events			
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% or greater of patients in either group†			
Dizziness	4 (1%)	23 (7%)	..
Abnormal dreams or nightmares	5 (1%)	18 (5%)	..
Insomnia	5 (1%)	10 (3%)	..
Nausea	3 (1%)	8 (2%)	..
Rash‡	6 (2%)	26 (8%)	0·0002
Treatment-emergent grade 3§ or 4 laboratory abnormalities in greater than 2% of patients in either group	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%)	..

Data are n (%) unless otherwise stated. N=number of patients in each treatment group. N′=number of assessable patients in each treatment group. LDL-C=low-density lipoprotein-cholesterol. *Rilpivirine versus efavirenz, Fisher's exact test, preplanned analysis. †Not including laboratory abnormalities reported as an adverse event. ‡Defined as rash, erythema, allergic dermatitis, macular rash, urticaria, maculopapular rash, papular rash, pustular rash, drug eruption, exanthem, scaly rash, toxic skin eruption, or urticaria papular. §The grade 3 cutoff values for each term were >2·0 to ≤5·0 × upper limit of normal for pancreatic amylase, >5·0 to ≤10·0 × upper limit of normal for aspartate aminotransferase and alanine aminotransferase, 0·32–0·64 mmol/L for serum phosphate, ≥4·91 mmol/L for LDL-C (fasting), 8·49–13·56 mmol/L for triglycerides (fasting), and >7·77 mmol/L for total cholesterol (fasting). ¶Combined total of calculated values and directly measured values (if the triglyceride level was too high for LDL-C to be calculated).

Table 4: **Overview of treatment-emergent adverse events and laboratory abnormalities at the time of week 48 analysis**

	Rilpivirine group	Efavirenz group	p value*
Total cholesterol (mmol/L)	0·03 (–0·06 to 0·11)	0·63 (0·53 to 0·73)	<0·0001
HDL-C (mmol/L)	0·07 (0·04 to 0·10)	0·24 (0·21 to 0·27)	<0·0001
Total cholesterol/HDL-C	–0·14 (–0·33 to 0·05)	–0·24 (–0·40 to –0·09)	0·25
LDL-C (mmol/L)	–0·04 (–0·10 to 0·03)	0·31 (0·23–0·39)	<0·0001
Triglycerides (mmol/L)	–0·10 (–0·19 to –0·01)	0·16 (–0·07 to 0·38)	0·01

Data are mean (95% CI). Lipid samples were taken fasting. HDL-C=high-density lipoprotein-cholesterol. LDL-C=low-density lipoprotein-cholesterol. *Rilpivirine versus efavirenz, Wilcoxon rank-sum test, preplanned analysis.

Table 5: **Change in lipid variables from baseline to 48 weeks**

Panel: **Research in context**

Systematic review

A recent Cochrane review[30] stated that the non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz and nevirapine are equally effective in suppressing infection with HIV but cause side-effects that can limit their use, highlighting a need for additional first-line NNRTIs with a better safety profile. We searched PubMed for supporting evidence up to May, 2011, with the search term "rilpivirine"; we selected randomised controlled trials and clinical trials published in English. Rilpivirine has only been assessed in one phase 2b study (NCT NCT00110305; TMC278-C204). This study showed that rilpivirine provided long-term (longer than 96 weeks) efficacy and tolerability in treatment-naive adults infected with HIV-1, with response rates similar to efavirenz. In this study, all rilpivirine doses resulted in similar response rates. Grade 2–4 adverse events at least possibly related to study medication, including nausea, dizziness, abnormal dreams/nightmare, rash, somnolence, and vertigo, were less common with TMC278 than with efavirenz in the context of an open-label trial (only the dose of rilpivirine was blinded).[9]

Interpretation

In combination with the THRIVE trial,[14] which assessed the safety and efficacy of rilpivirine with three different background regimens (tenofovir-disoproxil-fumarate plus emtricitabine, zidovudine plus lamivudine, or abacavir plus lamivudine) versus efavirenz, our data suggest that once-daily rilpivirine is probably a valuable treatment option for antiretroviral-naive patients infected with HIV-1.

were reported as adverse events. There were no discontinuations due to renal adverse events.

Overall, QT interval corrected according to Fridericia's formula (QTcF) increased over time up to week 48 for both rilpivirine and efavirenz, with no relevant difference between groups. The mean changes from baseline were 10·9 ms (95% CI 9·0–12·8) versus 12·0 ms (10·1–13·7), respectively. There were few adverse events potentially related to conduction abnormalities or to rate and rhythm disturbances (one of 346 *vs* two of 344; these were grade 1 in severity).

Discussion

Once-daily oral 25 mg rilpivirine showed non-inferior efficacy compared with once-daily 600 mg efavirenz at 48 weeks in our trial. Both study drugs achieved response rates (table 2) that are among the highest compared with earlier studies of efavirenz in combination with tenofovir-disoproxil-fumarate and emtricitabine in treatment-naive patients.[24,26] More patients discontinued treatment because of intolerability with efavirenz, although more discontinued because of virological failure with rilpivirine. The CD4 cell count increased to a similar extent in both groups. These efficacy results are consistent with those reported in the companion phase 3 trial, THRIVE,[14] although virological failure rates for rilpivirine were lower in THRIVE, and the difference in virological failures with efavirenz was smaller.

Our finding of more virological failures in the rilpivirine group than in the efavirenz group differs from the phase 2b study.[9] Although self-reported, suboptimum adherence (<95% by M-MASRI) was associated with lower responses in both treatment groups, this alone might not fully explain the difference in virological failure rates between patients on the two study drugs. The lower response in patients on rilpivirine with baseline viral load greater than 500 000 copies per mL compared with efavirenz probably contributed to these findings. Analyses are ongoing to better understand the role of factors such as adherence, drug exposure, and baseline viral load in virological failure. Because of the statistical power limitations for the individual trials, results of additional exploratory analyses of response factors will be reported in pooled analyses of data from ECHO and THRIVE. Additionally, pharmacokinetics and pharmacokinetic and pharmacodynamic relations will be presented elsewhere for the pooled data.

Consistent with other NNRTI regimens,[27] at the time of failure, the proportion of patients with at least one NNRTI RAM was high and similar in both groups. The most prevalent treatment-emergent NNRTI RAMs were consistent with data from TMC278-C204[9,10] and THRIVE.[14] Consequently, cross-resistance exists between rilpivirine and etravirine—initial findings from the pooled ECHO and THRIVE resistance analysis have shown that, of the 31 patients on rilpivirine who experienced virological failure and were phenotypically resistant to rilpivirine, 28 (90%) were cross-resistant to etravirine, 27 (87%) to efavirenz, and 14 (45%) to nevirapine.[28] Studies are in progress to further characterise the effect of specific combinations of NNRTI RAMs that are found in viruses emerging from selection with rilpivirine, on the antiviral activity of etravirine. Of the 12 patients on efavirenz who experienced virological failure and were phenotypically resistant to efavirenz, all were resistant to nevirapine but remained sensitive to etravirine.

Treatment-emergent IAS-USA N(t)RTI RAMs were more common in the rilpivirine group than in the efavirenz group among virological failures. The most common treatment-emergent N(t)RTI RAMs in both groups were M184I and V, which are associated with reduced susceptibility to emtricitabine and lamivudine.[29] An analysis of phenotypic sensitivity to NNRTIs will be presented separately for the pooled data.

As we anticipated from the phase 2b data (panel),[9,10] the safety and tolerability profile of rilpivirine was better than that of efavirenz. Discontinuations due to adverse events were less common with rilpivirine than with efavirenz (table 4). The incidence of any grade 2 or higher adverse events possibly related to treatment in the rilpivirine group was lower than in the efavirenz

group (table 4). Additionally, incidences of rash, neurological adverse events of interest and psychiatric adverse events of interest were lower for rilpivirine than efavirenz. Increases in some proatherogenic lipid variables were also smaller with rilpivirine, but the difference was not substantial in the total cholesterol to HDL-C ratio. Increases in creatinine for rilpivirine were small, and might be related to a rilpivirine effect on the disposition of creatinine, rather than to renal toxicity. Indeed, with the use of cystatin C, thought to be a better indicator of GFR than creatinine,[31] rilpivirine did not decrease GFR in THRIVE.[14] Rilpivirine might increase the exposure to tenofovir after tenofovir-disoproxil-fumarate, but this increase is not thought clinically relevant.[32] Long-term follow-up and assessment is available from the phase 2b trial and will be provided by the week-96 analysis of these phase 3 trials.

There are several limitations to our trial. First, our study used only one N(t)RTI background regimen (tenofovir-disoproxil-fumarate and emtricitabine). However, the THRIVE trial also assessed zidovudine with lamivudine or abacavir with lamivudine, as well as tenofovir-disoproxil-fumarate and emtricitabine selected by the investigator. The consistent findings, irrespective of N(t)RTI background, show the possibility of combining rilpivirine with other antiretroviral drugs. Second, our trial was not powered to assess comparisons of efficacy in various subsets of patients, and therefore it is difficult to generalise our findings to the overall population of patients. However, subgroup analyses of the combined ECHO and THRIVE populations by sex, region, ethnic origin, clade, and hepatitis B and C co-infection[28,33,34] show that the efficacy of rilpivirine and efavirenz are similar, suggesting broader applicability of these data. Furthermore, in routine clinical practice, patients might harbour transmitted resistance, which could reduce response rates. For our trial, we used a comprehensive NNRTI RAM list to screen out patients potentially resistant to NNRTIs. The present prevalence of E138K in routine clinical resistance testing is low (<1%).[35] Finally, since our trial had a double-dummy design, patients had to take their study medication twice daily, rather than the normal once-daily dosing for both NNRTIs, although we did not know what effect this design feature had on response rates. Also, patients were required to take rilpivirine (or matching placebo) with a meal. This recommendation might have been overlooked in our double-blind trial, resulting in some patients taking rilpivirine on an empty stomach and a lower rilpivirine exposure than expected in some cases.

The selection of rilpivirine will rely on assessing individual benefits and risks for individual patients. These data suggest that once-daily rilpivirine, perhaps as a single-tablet regimen in combination with tenofovir-disoproxil-fumarate and emtricitabine,[36] is expected to be a valuable treatment option for patients infected with HIV who have not been previously treated with antiretroviral drugs.

Contributors

All authors substantially contributed to the study's conception, design, and performance. J-MM, PC, BG, AL, AM, MS, KS, and SW all participated in recruiting substantial numbers of patients to the trial and reported data for those patients. HC, LT, SV, and KB were involved in the data analyses. All authors were involved in the development of the primary manuscript, interpretation of data, and have read and approved the final version.

Conflict of interest

J-MM has acted as a consultant, participated in advisory boards, has received speaker fees and has been an investigator for clinical trials for Tibotec, ViiV Healthcare, Gilead, Bristol-Myers Squibb (BMS), Abbott, Boehringer Ingelheim (BI), and Merck, Sharp & Dohme (MSD). PC has received grant research support, advisory and speaker fees from Abbott, Avexa, BI, Gilead, MSD, Tibotec, Janssen, GlaxoSmithKline (GSK), and ViiV Healthcare. BG has participated in advisory boards, has received speaker fees and has been an investigator for clinical trials for Tibotec, BMS, ViiV Healthcare, and MSD. AL has acted as a consultant, participated in advisory boards, speaker bureaus and has been an investigator in for clinical trials for Abbott, BMS, BI, Gilead, MSD, Tibotec, Pfizer, ViiV Healthcare, GSK, and Roche. AM has served on advisory boards and speaker bureaus for Tibotec, GSK, BMS, Gilead, BI, MSD, and ViiV Healthcare, and has received research funding from Tibotec. MS has received consulting fees, research support, or both from BMS, BI, GSK, MSD, Pfizer, Pain Therapeutics, Tibotec/J&J, Vertex, and ViiV Healthcare. SW has received consultancy fees or lecture sponsorships from Abbott, BI, Gilead, MSD, ViiV Healthcare, and Tibotec. HC, LTR, SV, and KB are all full-time employees of Tibotec. KS declares no conflicts of interest.

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Effect of concurrent sexual partnerships on rate of new HIV infections in a high-prevalence, rural South African population: a cohort study

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Summary

Background Concurrent sexual partnerships are widely believed to be one of the main drivers of the HIV epidemic in sub-Saharan Africa. This view is supported by theoretical models predicting that increases in prevalence of concurrent partnerships could substantially increase the rate of spread of the disease. However, the effect of concurrent partnerships on HIV incidence has not been appropriately tested in a sub-Saharan African setting.

Methods For this population-based cohort study, we used data from the Africa Centre demographic surveillance site in KwaZulu-Natal, South Africa, to try to find support for the concurrency hypothesis. We used a moving-window approach to construct estimates of the geographical variation in reported concurrent and lifetime partners in sexually active men aged 15–55 years (n=2153) across the study area. We then followed up 7284 HIV-negative women (≥15 years of age) in the population and quantified the effect of the sexual behaviour profiles of men in the surrounding local community on a woman's hazard of HIV acquisition.

Findings During 5 years' follow-up, 693 new female HIV infections occurred (incidence 3·60 cases per 100 person-years). We identified substantial intercommunity heterogeneity in the estimated point-prevalence of partnership concurrency (range 4·0–76·3%; mean 31·5%) and mean number of lifetime sexual partners (3·4–12·9; mean 6·3) in sexually active men in this population. After adjustment for individual-level sexual behaviour and demographic, socioeconomic, and environmental factors associated with HIV acquisition, mean lifetime number of partners of men in the immediate local community was predictive of hazard of HIV acquisition in women (adjusted hazard ratio [HR] 1·08, 95% CI 1·03–1·14, p=0·004), whereas a high prevalence of partnership concurrency in the same local community was not associated with any increase in risk of HIV acquisition (adjusted HR 1·02, 95% CI 0·95–1·09, p=0·556).

Interpretation We find no evidence to suggest that concurrent partnerships are an important driver of HIV incidence in this typical high-prevalence rural African population. Our findings suggest that in similar hyperendemic sub-Saharan African settings, there is a need for straightforward, unambiguous messages aimed at the reduction of multiple partnerships, irrespective of whether those partnerships overlap in time.

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Introduction

Concurrent sexual partnerships are widely held to be one of the primary drivers of the HIV epidemic, especially in sub-Saharan Africa,[1–3] where about two-thirds of the world's HIV-positive population live and more than 70% of all new HIV infections occurred in 2008.[4] This view is supported by theoretical mathematical models predicting that under specific conditions, small increases in the prevalence of concurrent partnerships could substantially increase the rate of spread of HIV.[5–7] Consequently, researchers have argued that reduction of concurrent partnerships should be a major focus of global HIV prevention strategies.[8–11] In contrast to serially monogamous sexual partnerships, concurrent partnerships are thought to allow an increased rate of spread of HIV by linking up what would otherwise be discrete sexual networks in time and space. Additionally, being in a concurrent relationship could increase the probability of an infected individual having sex with a susceptible partner during the acute HIV infection stage, when there is higher potential for onward transmission of the virus. However, to date there is no clear empirical evidence to show the effect of concurrent partnerships on the rate of new HIV infections.[12,13]

Measurement of any effect of concurrency on risk of new infection poses a challenge for standard individual-focused epidemiological methods, in which populations are usually viewed as collections of individuals, rather than as meaningful entities with inherent properties related to the likelihood that individuals within them acquire disease.[14] Having concurrent partners is not expected to change an individual's risk of acquiring HIV, provided that partner concurrency does not increase an individual's cumulative number of unprotected sex acts. However, for the two reasons described above, concurrency could increase the rate of HIV spread through a population.[2,6] Consequently, studies that test the association between partnership concurrency and infection status at an individual level have been labelled

as "theoretically misguided and empirically irrelevant" by proponents of the theory.[15] Hence, to test the concurrency hypothesis appropriately, the focus has to be shifted away from an individual's own sexual behaviour patterns and onto the behaviours of the individuals in the network of people from whom an HIV-negative person is likely to choose a sexual partner.

To test this transmission dimension of the concurrency theory and try to find empirical support for the hypothesis, we followed up a large, population-based cohort of HIV-negative women in a rural South African population over 5 years and quantified the effect of the sexual behaviour profiles of men in the surrounding local community (from which an HIV-negative individual most often chooses a sexual partner) on their individual risk of acquiring an infection. We used detailed geographical data and a novel spatial statistical method to create unique virtual communities around each woman to derive sensitive and realistic community-level sexual behaviour estimates of men in the surrounding community. We then used a multivariable statistical model to contrast the increased risk of infection in an HIV-negative woman living in a community with high numbers of reported lifetime sexual partners in men (a widely accepted and robust index of risky sexual behaviour) against that of a woman living in a community with a high prevalence of male concurrent sexual partnerships.

Methods

Setting

This population-based cohort study used data from one of the most comprehensive demographic surveillance sites in Africa—the Africa Centre Demographic Information System.[16] The site has collected sociodemographic information on a population of 87 000 individuals within a circumscribed geographic area (434 km²) in rural KwaZulu-Natal, South Africa, for more than a decade. All individuals under surveillance are geolocated to their respective homesteads (accuracy <2 m).[17] With the exception of the township, the homesteads in the study area are scattered across the landscape and are not concentrated into villages or compounds as they are in other parts of Africa.

Nested within the demographic information system are the population-based HIV surveillance and sexual behaviour surveys, which take place annually in all consenting resident individuals aged 15 years or older. After written informed consent was given, fieldworkers obtained blood by finger prick and prepared dried blood spots for HIV testing according to Joint UN Programme on HIV/AIDS and WHO guidelines.[18] The Africa Centre's HIV cohort is open—ie, individuals continually enter the cohort when they reach the age of 15 years or migrate into the area and leave it because of death or out-migration. 60% of individuals contacted agreed to be tested at least once. More than 24% of the adult population are infected with HIV and infection peaks at more than 50% in women aged 25–29 years and 44% in men aged 30–34 years.[19] The rate of new infections remains high and fairly constant over time at around 3·2 new infections per 100 person-years[20] and peaks in women at 7·5 per 100 person-years (at age 24 years) and in men at 5·0 per 100 person-years (at age 29 years). These longitudinal HIV incidence estimates have been independently confirmed using a locally calibrated test of recent HIV infection in a cross-sectional sample of individuals.[21] The population is characterised by low rates of marriage with only 31% of women and 23% of men ever having been married and 14% of those marriages being polygamous for men.[22]

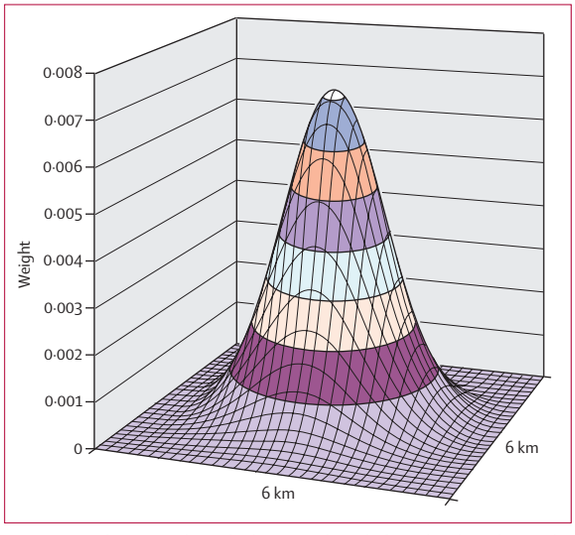

Figure 1: **Two-dimensional standard Gaussian kernel of search radius 3 km used to map geographical variations in mean lifetime partners and point-prevalence of concurrency in sexually active men across the surveillance area**
The Z axis shows the weights given to each cell. The greater the distance from the centre of the kernel, the lower the weight assigned to that cell in the community-level calculation.

Sexual behaviour survey

We used data from a questionnaire about sexual partnership patterns undertaken in 2004 from 2699 men (of whom 2153 were sexually active) who were aged 15–55 years and were resident in the surveillance area.[16] 63% of men contacted agreed to participate in the survey. Men's sexual behaviour data was used because of the well documented greater reluctance of women compared with men to report on multiple sexual partnerships.[23] Participants were asked how many sexual relationships they were currently in and how many lifetime sexual partners they had had. Men were coded as having concurrent partners if they reported currently being in more than one sexual relationship.

Construction of community-level variables

To produce robust estimates of the sexual behaviour variables that vary across continuous geographical

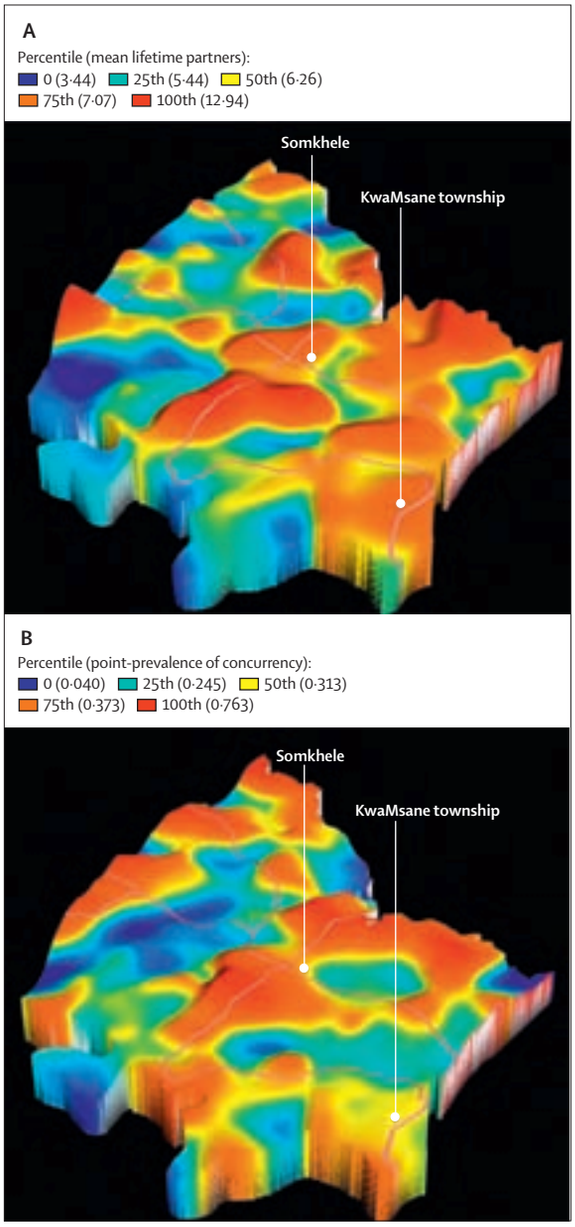

Figure 2: **Age-standardised geographical variations in mean lifetime partners (A) and point-prevalence of concurrency (B) in sexually active men across the surveillance area**
Obtained by a standard Gaussian kernel of radius 3 km (main roads are superimposed). The Z axis is proportional to the value of the community-level sexual behaviour covariate for any given geographical location.

space, we used a Gaussian kernel method.[17,24] The method does not impose any static geographical boundaries on the data and resulted in community-level estimates that were both sensitive to local variations and robust. Data from 2153 sexually active men were plotted on a map of the study area consisting of a grid of 30 m×30 m cells in Idrisi Taiga (Clark University, Worcester, MA, USA). We then passed a standard Gaussian kernel of search radius 3 km (total

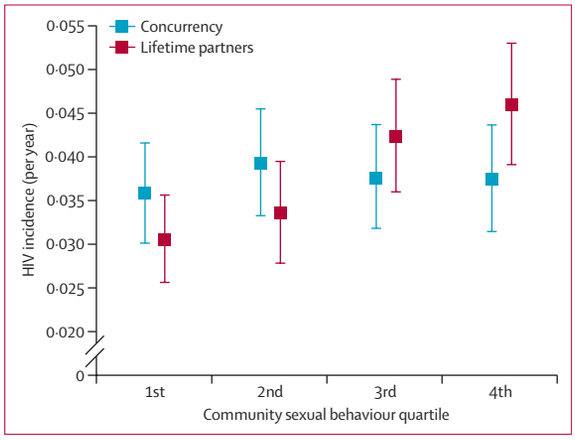

Figure 3: **A comparison of female age-standardised HIV incidence by mean lifetime partners and point-prevalence of concurrency among sexually active men in the surrounding local community (as shown in figure 2)**
Error bars show 95% CIs.

area 28 km²) across the map to derive community-specific measures of the point-prevalence of partnership concurrency (a robust population-level indicator of concurrency[25,26]) and mean numbers of lifetime partners. The kernel moved systematically across the map and for each cell calculated a Gaussian-weighted estimate of mean lifetime partners and concurrency prevalence within a search radius of 3 km (figure 1). A median of 285 (IQR 104–491) men were included in each community-level calculation. The resulting estimate was then placed onto a new map at the same location as the central cell. The kernel was moved one cell to the right (and then down one row at the end of the row) and the process was repeated. We then standardised the resulting community measures of sexual behaviour against the eligible population of the sexual behaviour survey using 10-year age-bands to adjust for differences in age distribution across the surveillance area. Additionally, we derived male HIV prevalence (n=4982) across the study area for the 2004 HIV survey using the same method.

In this population, partner choice is strongly affected by geography and 61% of women reported at least one partnership with a man in the same immediate *isigodi* (a Zulu term for a small community headed by a local chief, which have a median area of 16·9 km²) during the observation period. However, in view of the scattered distribution of the population and because the optimum size of the individual's community was not precisely known, we investigated the potential effect of the size and shape of the kernel, producing estimates with kernels of 2·5 km, 3·0 km, and 3·8 km radii, which evaluated an area of between 19·6 km² and 45·4 km². We also checked the potential effect of the weighting in the kernel by deriving estimates from kernels of SD 1 and 3. The smaller the search radius used in the kernel, the greater the range in community-level estimates

	Person-years*	Events	Crude HIV incidence rate (per 100 person-years of observation)
Community level (men)†			
Concurrency, quartiles			
1st (4·0–24·3%)	4737·19	161	3·40 (2·89–3·97)
2nd (24·4–31·2%)	4917·73	194	3·94 (3·41–4·54)
3rd (31·3–37·3%)	4824·77	170	3·52 (3·01–4·09)
4th (37·4–76·3%)	4795·89	168	3·50 (2·99–4·07)
Lifetime partners, quartiles			
1st (3·4–5·4)	4919·32	154	3·13 (2·66–3·67)
2nd (5·5–6·2)	4816·34	151	3·14 (2·66–3·68)
3rd (6·2–7·1)	4746·17	188	3·96 (3·42–4·57)
4th (7·1–12·9)	4793·75	200	4·17 (3·61–4·79)
HIV prevalence, quartiles			
1st (0·0–8·8%)	4898·92	155	3·16 (2·67–3·70)
2nd (8·9–13·1%)	4918·61	168	3·42 (2·92–3·97)
3rd (13·2–17·6%)	4788·25	166	3·47 (2·96–4·04)
4th (17·6–31·1%)	4669·80	204	4·37 (3·79–5·01)
Individual level			
Age (years)			
15–19	6701·51	342	5·10 (4·58–5·67)
20–24	2033·72	152	7·47 (6·33–8·76)
25–29	1023·38	53	5·18 (3·88–6·77)
30–34	1203·61	38	3·16 (2·23–4·33)
35–39	1584·07	43	2·71 (1·96–3·66)
40–44	2086·71	30	1·44 (0·97–2·05)
≥45	4642·58	35	0·75 (0·53–1·05)
Years of education, quartiles (years)			
1st (0–5)	4205·94	93	2·21 (1·78–2·71)
2nd (6–9)	4369·76	206	4·71 (4·09–5·40)
3rd (10–11)	4718·77	231	4·89 (4·28–5·57)
4th (12)	2452·75	95	3·87 (3·13–4·73)
Wealth, tertiles			
Wealthiest	3711·45	139	3·75 (3·15–4·42)
Intermediary wealth	7729·53	272	3·52 (3·11–3·96)
Poorest	7313·06	251	3·43 (3·02–3·88)
Marital status			
Single	14945·57	633	4·24 (3·91–4·58)
Married, monogamous	3635·14	51	1·40 (1·04–1·84)
Married, polygamous	689·83	9	1·30 (0·60–2·48)
Residence			
Rural	13723·76	457	3·33 (3·03–3·65)
Peri-urban	5242·55	230	4·39 (3·84–4·99)
Urban	309·27	6	1·94 (0·71–4·22)
Partners in previous 12 months			
0	1389·22	13	0·94 (0·50–1·60)
1	13331·53	595	4·46 (4·11–4·84)
>1	312·56	37	11·84 (8·33–16·32)

*Person-years are based on midpoint imputation of the date of the last negative and first positive test for HIV seroconverters and on the date of the last negative test for those who are censored. †Derived from men in the surrounding local community with a standard Gaussian kernel (radius 3 km) around each woman in the cohort (figure 2).

Table 1: **Descriptive characteristics of women in the HIV incidence cohort (N=7284)**

obtained and the greater the sensitivity to local variation in the resulting estimates. The use of a large kernel will result in smoothing towards the mean and important geographical variation in the outcome variable might be lost.

Statistical analysis

We followed up 7284 women who were HIV negative at baseline, were tested at least twice during the study period (2004–09), and were resident in the surveillance area at least 50% of the time (only 273 did not meet the latter criterion). Each woman was geolocated to her homestead of residence and the estimated mean number of lifetime partners and point-prevalence of concurrency of men in the surrounding unique local community (as calculated with the Gaussian kernel of search radius 3 km) was extracted. We then used an interval-censored parametric survival analysis of time to HIV seroconversion to investigate the effect of mean number of lifetime partners and point-prevalence of concurrency of men in each woman's virtual community on her hazard of HIV acquisition. The survival model assumed that time to seroconversion followed a Weibull distribution and accounted for the fact that few individuals were tested every year (on average 1·8 years) and therefore precise seroconversion times were not known[27] (a detailed description of statistical methods is shown in the webappendix pp 1–2). The resulting estimates from the survival analysis were adjusted for other important individual-level determinants of HIV incidence in the study population (age, number of years in education, wealth tertile, urban locale, marital status, and reporting more than one partner in the previous 12 months over the duration of the study[28]) and male community-level HIV prevalence. Survey participants were not required to answer all questions, and thus data were missing for the covariates age, marital status, wealth, years of education, and sexual behaviour. A complete case analysis of these covariates would include 5364 of the 7284 eligible women in the cohort. Coverage was lowest for women's sexual behaviour data (75%). To account for missing covariate information in the incidence cohort, we used a multiple imputation procedure with five imputed datasets.[29] Hazard ratios, standard errors, and test statistics were adjusted appropriately to account for the imputation procedure. All analyses were done with Stata (version 11.0).

To assess the potential role of the size and shape of the community on the results of the statistical analysis, we did a full set of parallel statistical analyses for kernels of different sizes and shapes. Additionally, we ran the analysis using an alternative community-level index of partnership concurrency—mean numbers of concurrent partners. Furthermore, we ran a secondary analysis to assess the effect of combined community-level male and female sexual behaviour (derived from 2153 men and 4815 women) on the hazard of HIV acquisition in

11 861 participants of both sexes who had undergone repeat testing.

Role of the funding source

The funders had no role in the design and conduct of the study, interpretation of the data, or approval of the report. The corresponding author had access to all study data and made the final decision to submit for publication.

Results

Over the duration of the study (2004–09), we measured an incidence of 3·60 cases (95% CI 3·33–3·87) per 100 person-years (693 new female infections in 19 275·58 person-years of follow-up). The overall point-prevalence of men reporting concurrent partners in the 2004 sexual behaviour survey was 23·2% (95% CI 21·8–24·7). Among men who reported being sexually active, 28·9% (95% CI 27·0–30·8) reported having two or more concurrent partners and the median number of reported lifetime partners was five (IQR three to eight).

The geographical analysis revealed substantial variation in men's sexual behaviour across the different communities of the study area (figure 2). The estimated age-standardised point-prevalence of sexually active men in concurrent relationships varied between 4·0% and 76·3% (mean 31·5%) and standardised mean number of reported lifetime sexual partners varied between 3·4 and 12·9 (mean 6·3) in communities across the surveillance area. There were clear disparities between the two indices in many areas. For example, on the eastern side of the study area around the township (characterised by the highest HIV prevalence[17]) communities are characterised by high numbers of reported lifetime partners, but low prevalence of partnership concurrency. Substantial differences also occurred along the western boundary of the study area,

	Mean lifetime partners*		Concurrency*		Both†	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Unadjusted models						
Mean lifetime partners	1·09 (1·03–1·14)	0·001	..	..	1·10 (1·04–1·16)	0·001
Concurrency (10% increase)	..	..	1·00 (0·94–1·07)	0·981	0·96 (0·90–1·03)	0·307
Adjusted models						
Community level (male)						
Mean lifetime partners	1·08 (1·03–1·14)	0·004	..	..	1·09 (1·03–1·15)	0·004
Concurrency (10% increase)	..	..	1·02 (0·95–1·09)	0·556	0·99 (0·91–1·06)	0·730
Prevalence (10% increase)*‡	1·17 (0·98–1·39)	0·074	1·20 (1·01–1·42)	0·042	1·17 (0·99–1·39)	0·072
Individual level						
Partners in previous 12 months (*vs* 0)						
One	2·58 (1·43–4·64)	0·002	2·56 (1·42–4·62)	0·002	2·58 (1·43–4·64)	0·002
More than one	4·84 (2·45–9·56)	<0·0001	4·84 (2·45–9·56)	<0·0001	4·83 (2·45–9·54)	<0·0001
Marital status (*vs* single)						
Married, monogamous	0·60 (0·43–0·83)	0·002	0·60 (0·44–0·84)	0·002	0·60 (0·44–0·84)	0·002
Married, polygamous	0·67 (0·34–1·33)	0·250	0·67 (0·34–1·34)	0·257	0·67 (0·34–1·33)	0·250
Urban (*vs* rural)						
Peri-urban	1·17 (0·95–1·45)	0·147	1·19 (0·96–1·47)	0·118	1·16 (0·94–1·44)	0·166
Urban	0·71 (0·31–1·63)	0·418	0·72 (0·31–1·66)	0·444	0·71 (0·31–1·63)	0·415
Wealth tertile (*vs* wealthiest)						
Intermediary wealth	0·94 (0·76–1·15)	0·553	0·94 (0·77–1·16)	0·581	0·94 (0·76–1·15)	0·551
Poorest	0·87 (0·70–1·09)	0·220	0·89 (0·71–1·10)	0·283	0·87 (0·70–1·08)	0·217
Years of education	0·96 (0·93–0·98)	0·001	0·96 (0·93–0·98)	0·001	0·96 (0·93–0·98)	0·001
Age (*vs* 15–19 years)						
20–24 years	1·52 (1·25–1·84)	<0·0001	1·50 (1·24–1·82)	<0·0001	1·52 (1·25–1·84)	<0·0001
25–29 years	1·11 (0·82–1·49)	0·498	1·10 (0·82–1·47)	0·539	1·11 (0·82–1·49)	0·499
30–34 years	0·72 (0·50–1·03)	0·069	0·71 (0·49–1·01)	0·057	0·72 (0·50–1·03)	0·069
35–39 years	0·55 (0·39–0·79)	0·001	0·55 (0·38–0·79)	0·001	0·55 (0·39–0·79)	0·001
40–44 years	0·29 (0·19–0·44)	<0·0001	0·29 (0·19–0·44)	<0·0001	0·29 (0·19–0·44)	<0·0001
≥45 years	0·19 (0·12–0·28)	<0·0001	0·19 (0·12–0·28)	<0·0001	0·19 (0·12–0·28)	<0·0001

HR=hazard ratio. *Derived from male sexual behaviour in the surrounding local community with a standard Gaussian kernel (radius 3 km) around each woman in the cohort (figure 2). †Includes both male community-level mean lifetime partners and prevalence of concurrent partnerships covariates. ‡Unadjusted hazard ratio, 1·26 (p<0·0001).

Table 2: **Full output from interval-censored parametric survival analysis showing the effect of community-level mean lifetime partners and prevalence of partnership concurrency in men on a woman's hazard of acquiring HIV infection (N=7284)**

See Online for webappendix

	HR (95% CI)	p value
Gaussian 3·8 km radius (SD 1)		
Mean lifetime partners		
Unadjusted	1·12 (1·06–1·20)	0·0002
Adjusted A	1·11 (1·04–1·18)	0·002
Adjusted A+B	1·12 (1·04–1·20)	0·002
Prevalence of concurrency, 10% increase		
Unadjusted	1·00 (0·93–1·08)	0·967
Adjusted A	1·02 (0·94–1·11)	0·568
Adjusted A+B	0·97 (0·89–1·06)	0·567
Gaussian 3 km radius (SD 3)		
Mean lifetime partners		
Unadjusted	1·17 (1·08–1·28)	0·0003
Adjusted A	1·11 (1·01–1·23)	0·035
Adjusted A+B	1·14 (1·02–1·27)	0·019
Prevalence of concurrency, 10% increase		
Unadjusted	0·96 (0·87–1·07)	0·501
Adjusted A	0·99 (0·88–1·10)	0·831
Adjusted A+B	0·94 (0·83–1·06)	0·291
Gaussian 2·5 km radius (SD 1)		
Mean lifetime partners		
Unadjusted	1·07 (1·02–1·12)	0·003
Adjusted A	1·07 (1·02–1·12)	0·006
Adjusted A+B	1·07 (1·02–1·13)	0·007
Prevalence of concurrency, 10% increase		
Unadjusted	0·99 (0·93–1·05)	0·888
Adjusted A	1·02 (0·96–1·08)	0·628
Adjusted A+B	1·00 (0·94–1·06)	0·718
Gaussian 3 km radius (SD 1), mean number of concurrent partners*		
Unadjusted	1·06 (0·87–1·29)	0·553
Adjusted A	1·10 (0·90–1·35)	0·329
Adjusted A+B	0·88 (0·69–1·14)	0·332

HR=hazard ratio. The unadjusted model includes only the male community-level sexual behaviour covariate. The adjusted A model includes one of the community-level sexual behaviour covariates and community level HIV prevalence (male), partners in past 12 months, marital status, years of education, urban locale, wealth tertile, and age. The adjusted A + B model included all the independent variables included in model A (in the row immediately above) and the community-level sexual behaviour covariate not included in model A. *An alternative community-level indicator of partnership concurrency.

Table 3: **Sensitivity analysis of the effect of size and shape of the kernel (used to derive the male community-level sexual behaviour variables) and an alternative community-level concurrency measure on a woman's hazard of HIV acquisition (N=7284)**

where partnership concurrency was highly prevalent, but where numbers of lifetime partners were generally low.

At an ecological level, female HIV incidence did not differ by prevalence of male concurrency in the surrounding local community (figure 3). With respect to reported lifetime partners, a clear exposure-response relation was evident. Communities with the highest number of lifetime partners in men had the highest HIV incidence in women.

Table 1 shows the characteristics of women in the cohort and number of HIV seroconversions reported. At an individual level, age, place of residence (urban or rural), marital status, years of education, and reporting of more than one partner in the previous 12 months (at least once during follow-up) were all significantly associated with a woman's hazard of HIV acquisition (table 2). Being in a polygamous marriage was not associated with hazard of HIV acquisition in our analyses, but only 242 women (3%) in the cohort reported being married to a polygamous man. For every 10% increase in community-level HIV prevalence in men, the hazard of HIV acquisition in women increased by 26% ($p<0·0001$). After adjustment for individual risk factors and sexual behaviour profiles of men in the surrounding community, the hazard ratios decreased to 1·17–1·20 in the three models shown in table 2.

The mean number of reported lifetime sexual partners in men in the surrounding local community strongly predicted risk of HIV acquisition in HIV-negative women (both before and after adjustment for individual-level sexual behaviour, demographic, socioeconomic, and environmental factors associated with HIV acquisition; table 2). For every unit increase in mean number of lifetime partners for men at a community level, the corresponding hazard of HIV acquisition in women increased by 8% ($p=0·004$). In other words, an HIV-negative woman living in a community with high numbers of reported lifetime partners in men (>12) has nearly double the hazard of HIV acquisition, after adjustment for other factors, compared with a woman living in a community with low numbers of reported lifetime sexual partners (fewer than four). By contrast, living in a community with high levels of male concurrent partnerships was not associated with an increased risk of HIV acquisition to the woman even after adjustment for individual-level factors and reported numbers of lifetime partners in the surrounding community ($p=0·730$).

The results were robust to the size and shape of the virtual community (kernel) and an alternative population-level indicator of partnership concurrency—mean numbers of concurrent partners (table 3). Restriction of the analysis only to women who had been resident in the study area for the full period of follow-up (n=6534) similarly had no effect on the findings (for mean lifetime partners, $p=0·001$; for concurrency prevalence, $p=0·644$). The results also remained consistent in a secondary analysis that assessed the effect of standardised community-level male and female sexual behaviour on the hazard of HIV acquisition of 11 861 repeat HIV-testers of both sexes (webappendix pp 3–4).

Discussion

Our work constitutes a formal test of the effect of concurrent partnerships on HIV incidence in this setting (panel). By shifting the focus away from an individual's own sexual behaviour patterns and onto the sexual behaviour profiles of the surrounding local community, we have tested the transmission dimension of the concurrency theory. The study took place in an area with one of the highest population-based prevalences of HIV

documented worldwide[19] and where there are large variations in the level of male partnership concurrency across the population. However, these differences in the prevalence of male concurrency did not translate into detectable differences in prospective incidence of HIV in women. The results were robust to differing definitions of community and held after we controlled for demographic, socioeconomic, behavioural, and environmental factors. Furthermore, the results also held at an ecological level and for the secondary analysis that quantified the effect of combined male and female sexual behaviour at a community level on the incidence of all participants (male and female) in the cohort. We were therefore unable to find any evidence to support the belief that concurrent partnerships are an important driver of the rate of spread of HIV infection in this hyperendemic setting. At the same time, the relation between numbers of lifetime partners in the community and risk of new infection provides strong and robust evidence of the effect of multiple partnering on HIV transmission and emphasises the importance of the characteristics of local community on spread of the virus (over and above an individual's characteristics and behaviours). This strong independent association is indicative of the fact that mean number of lifetime partners proxies for rate of partner turnover during the study period and thus men living in communities with high numbers of lifetime partners (relative to the age-profile of the community) continue to have (on average) higher numbers of sexual partnerships.

As in any observational study involving collection of data for sexual behaviour and HIV acquisition, the possibility of bias affecting the results must be considered and discussed. Importantly, selection on the independent variables in the multivariable survival analysis would not have biased the hazard coefficient estimates. Thus, the hazard coefficients will not be affected by selection on age, education, wealth, urban versus rural residence, marital status, HIV prevalence, community-level concurrency, and partners reported in the last 12 months. Of course, a randomised controlled trial could further improve the strength of the evidence for concurrency effects, because it would allow us to control for selection on both known or unknown factors, but such a study is not feasible. By using a community-level estimate of concurrency as a surrogate measure for the concurrency practices of a participant's partner or partners in our analyses, we would naturally expect some attenuation of any concurrency effect. However, this attenuation would also apply to the community lifetime partners covariate, which is a significant predictor of HIV acquisition in our analysis, and thus attenuation would be unlikely to account for the null finding on the effect of concurrency on HIV acquisition.

A limitation of the study is that data for concurrency and lifetime partners were obtained only at the beginning of the study in 2004. We therefore assumed that no large systematic shifts in patterns of male sexual behaviour at a community level have taken place during the study. Such systematic shifts are unlikely, but nevertheless the theoretical possibility remains. Another limitation is that we were unable to control for all exposures outside an individual's geographically defined community—for example, women with migrant partners who return home periodically. However, since partner choice has a strong local geographical dimension, we would still expect to be able to show an effect (at an ecological or individual level) if concurrent partnerships were playing an important part in transmission.

The evidence for the concurrency hypothesis has been reviewed extensively elsewhere.[13] However, our findings using individual-level longitudinal data for HIV seroconversion are in agreement with those of other studies that have not shown any association between partnership concurrency and HIV prevalence at a city or a country level.[30,31] Similarly, a study in South Africa[32] on intimate partner violence and HIV incidence in women found no relation between respondents' reports of the likelihood that their partner had other partners and risk of HIV acquisition. A small study in Malawi[33] that attempted to investigate the association between

***Panel:* Research in context**

Systematic review

Although theoretical mathematical models suggest that concurrent sexual partnerships could account for the rapid spread of HIV in sub-Saharan Africa, a recent systematic review[13] concluded that there is no empirical evidence to show that the kinds of concurrent partnerships found in Africa produce more rapid spread of HIV than do other forms of sexual behaviour. Provision of such evidence is not straightforward, however, because partnership concurrency is a risk factor for disease transmission and spread through a population and not of individual risk of disease acquisition (provided that having concurrent partners does not increase an individual's cumulative number of sex partners or unprotected sex acts).

Interpretation

Our study is the first to examine the effect of prevalence of concurrency in the surrounding local community on an individual's risk of HIV acquisition. By shifting the focus away from an individual's own sexual behaviour patterns and onto the sexual behaviour profiles of the surrounding local community, our study has tested the transmission dimension of the concurrency theory in a typical rural South African population with high HIV prevalence. Although the mean number of lifetime partners of men in the immediate local community was independently predictive of hazard of HIV infection in women, a high prevalence of partnership concurrency in the same local community was not associated with any increase in risk of HIV acquisition. Our data therefore provide no evidence to suggest that the high rate of new HIV infections is being driven by the segment of the sexually active population reporting concurrent sexual partners (29% of men and 2% of women). Our findings suggest that in similar hyperendemic sub-Saharan African settings, there is a need for clear messages aimed at the reduction of multiple partnerships, irrespective of whether those partnerships overlap in time. However, the absence of an effect of concurrency on HIV incidence in this setting should not be taken to necessarily mean that high levels of concurrent partnerships could not have played an important part in the initial stages of the HIV epidemic in this population or continue to play a part in other specific epidemic settings.

partnership measured the correlation between HIV serodiscordance and concurrency in couples in Likoma Island. The results suggested that concurrent partnerships increased exposure to HIV infection. However, the use of prevalent (as opposed to incident) infection, the small sample size (142 couples), and the possibility of selection bias (in only 23% of concurrent partnerships were both partners tested for HIV) make it difficult to draw any robust inferences.

To spread widely, HIV infection has to have a high basic reproductive number, which will depend on the likelihood of transmission and the contact pattern throughout the population.[34] Theoretically, concurrency along with high rates of partner turnover in key individuals can increase the spread of infection, as can factors such as high viral loads[35] and the presence of other sexually transmitted infections.[36] The present high incidence of infection in this population is possible because of the high prevalence of infectious individuals and the number of partners they have over time. What initially drove the rapid spread of infection is uncertain, but it has to have been a function of contacts and transmission patterns to which concurrency might have contributed. Hence, the absence of a positive concurrency finding in this hyperendemic setting should not be taken to necessarily mean that high levels of concurrent partnerships could not have played an important part in the initial stages of the HIV epidemic in this area or indeed continue to play a part in other specific epidemic settings. Additionally, as noted previously, formal polygamous marriages (a form of partnership concurrency that could be protective for acquisition of HIV[37]) occur in the study area although fairly rare (3% of women in the cohort). Therefore, application of our methods to other study sites where the local epidemiology of HIV differs will be important. In the early stages of the HIV epidemic, when the disease is concentrated mainly in high-risk populations, it seems plausible that partnership concurrency could increase the rate at which HIV spreads outside these groups to the general population.

There is a growing debate about the relative merits of, and empirical evidence for, the effect of concurrent partnerships on the HIV epidemic in Africa.[2,10,12,13,15] A systematic review of the empirical evidence for the concurrency theory concludes, "promoters of the concurrency hypothesis have failed to establish that concurrency is unusually prevalent in Africa or that the kinds of concurrent partnerships found in Africa produce more rapid spread of HIV than other forms of sexual behaviour."[13] Currently, several countries are planning or implementing HIV prevention strategies that specifically target the reduction of concurrent sexual partnerships.[25] The dwindling funds available for HIV programmes worldwide[38] and the difficulties of design and implementation of culturally sensitive messages around partnership concurrency, combined with the absence of empirical evidence for an effect, make these interventions a difficult investment to justify. Furthermore, there is a danger of such messages inadvertently giving the impression that having many serially monogamous partnerships does not place an individual (and his or her partners) at significant risk of infection. Thus, rather than "developing a hierarchy of messages beneath the core theme of concurrent partners reduction",[11] messages should be limited to specific behaviours and biological factors with proven effect on HIV acquisition or transmission as part of a combination prevention approach. Even where campaigns refer to both multiple and concurrent partnerships, the unnecessary appeal to reduction of concurrent partnerships is likely to dilute the message. Conversely, simplifying the public health message to reduction in multiple partnerships alone is likely to improve message clarity and effectiveness.[39]

Our results provide clear evidence of the effect of multiple partnering on HIV transmission in this typical rural, high-prevalence African population. However, we find no evidence to suggest that the high rate of new infections is being driven by the segment of the sexually active population reporting concurrent sexual partners (29% of men and 2% of women). Our findings suggest that in similar hyperendemic sub-Saharan African settings, there is a need for straightforward, unambiguous messages aimed at the reduction of multiple partnerships, irrespective of whether those partnerships overlap in time.

Contributors

FT and TB designed the study. NM designed the sexual behaviour survey. FT did the spatial analyses and took primary responsibility for writing the report. LH, FT, and TB did the statistical analyses; LH drafted the statistical methods section. All authors contributed to data analysis and interpretation and writing and critiquing of the report.

Conflicts of interest

We declare that we have no conflicts of interest.

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The role of acute and early HIV infection in the spread of HIV and implications for transmission prevention strategies in Lilongwe, Malawi: a modelling study

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Summary

Background HIV transmission risk is higher during acute and early HIV infection than it is during chronic infection, but the contribution of early infection to the spread of HIV is controversial. We estimated the contribution of early infection to HIV incidence in Lilongwe, Malawi, and predict the future effect of hypothetical prevention interventions targeted at early infection only, chronic infection only, or both stages.

Methods We developed a deterministic mathematical model describing heterosexual HIV transmission, informed by detailed behavioural and viral-load data collected in Lilongwe. We included sexual contact within and outside of steady pairs and divided the infectious period into intervals to allow for changes in transmissibility by infection stage. We used a Bayesian melding approach to fit the model to HIV prevalence data collected between 1987 and 2005 at Lilongwe antenatal clinics. We assessed interventions that reduced the per-contact transmission probability to 0·00003 in people receiving them, and varied the proportion of individuals receiving the intervention in each stage.

Findings We estimated that 38·4% (95% credible interval 18·6–52·3) of HIV transmissions in Lilongwe are attributable to sexual contact with individuals with early infection. Interventions targeted at only early infection substantially reduced HIV prevalence, but did not lead to elimination, even with 100% coverage. Interventions targeted at only chronic infections also reduced HIV prevalence, but coverage levels of 95–99% were needed for the elimination of HIV. In scenarios with less than 95% coverage of interventions targeted at chronic infections, additional interventions reaching 25–75% of individuals with early infection reduced HIV prevalence substantially.

Interpretation Our results suggest that early infection plays an important part in HIV transmission in this sub-Saharan African setting. Without near-complete coverage, interventions during chronic infection will probably have incomplete effectiveness unless complemented by strategies targeting individuals with early HIV infection.

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Introduction

Acute HIV infection is the period between HIV acquisition and the development of detectable antibodies against the virus. Early HIV infection, including acute infection, is characterised by rapid viral replication, intense immune response and immune destruction, and viral diversification.[1] Phenotypic factors unique to the founder virus or viruses causing infection,[2] along with high viral loads,[3,4] result in greater transmission risk during early infection than during chronic stages of infection.[5–8]

The population-level effect of transmission prevention efforts during early infection will vary across settings, dependent on the contribution of individuals with early infection to epidemic spread. Estimates of this contribution have varied widely,[6,9–18] dependent on site-specific factors such as risk behaviour patterns and the local epidemic stage. In the past 2 years, a strategy to use mass antiretroviral treatment to stop the spread of HIV-1 has gained much attention.[19] This test-and-treat strategy advocates regular, widespread HIV testing and immediate initiation of antiretroviral treatment for infected people and is based on the premise that reductions in viral load caused by antiretroviral treatment will decrease an individual's infectiousness. However, the population-level effectiveness of this approach will depend partly on the role of early infection in continuing virus transmission: when it has a major role, the effectiveness of test-and-treat strategies will probably be restricted, unless patients with early infection can be detected and included. The findings from a mathematical modelling study[19] that have prompted much controversy[20–29] suggest that a yearly test-and-treat strategy could eliminate HIV, but concerns have been expressed that the importance of early infection was underestimated in this model.[22,24,25]

In this study, we estimated the contribution of early infection to HIV spread in Lilongwe, Malawi, where HIV-1 is hyperendemic and transmission is almost entirely through heterosexual contact. We also examined the population-level effect of prevention interventions affecting only early infection, only chronic infection, or both, with an emphasis on estimation of the effect of a yearly test-and-treat strategy.[19] To address these aims, we used empirical data from our studies in Lilongwe[3,30] to develop a mathematical model describing heterosexual HIV transmission.

Methods

Modelling analysis

Modelling analysis was done in five steps (figure 1): defining the model structure and equations (step one); doing a Bayesian melding procedure to identify model parameter values most compatible with recorded epidemic dynamics, with prior estimates for biological and behavioural parameters from our studies in Lilongwe (steps two to four);[3,30] and estimating the contribution of early HIV infection and predicted intervention effects (step five). We describe our methods briefly below, with additional details given in the webappendix (pp 2–10).

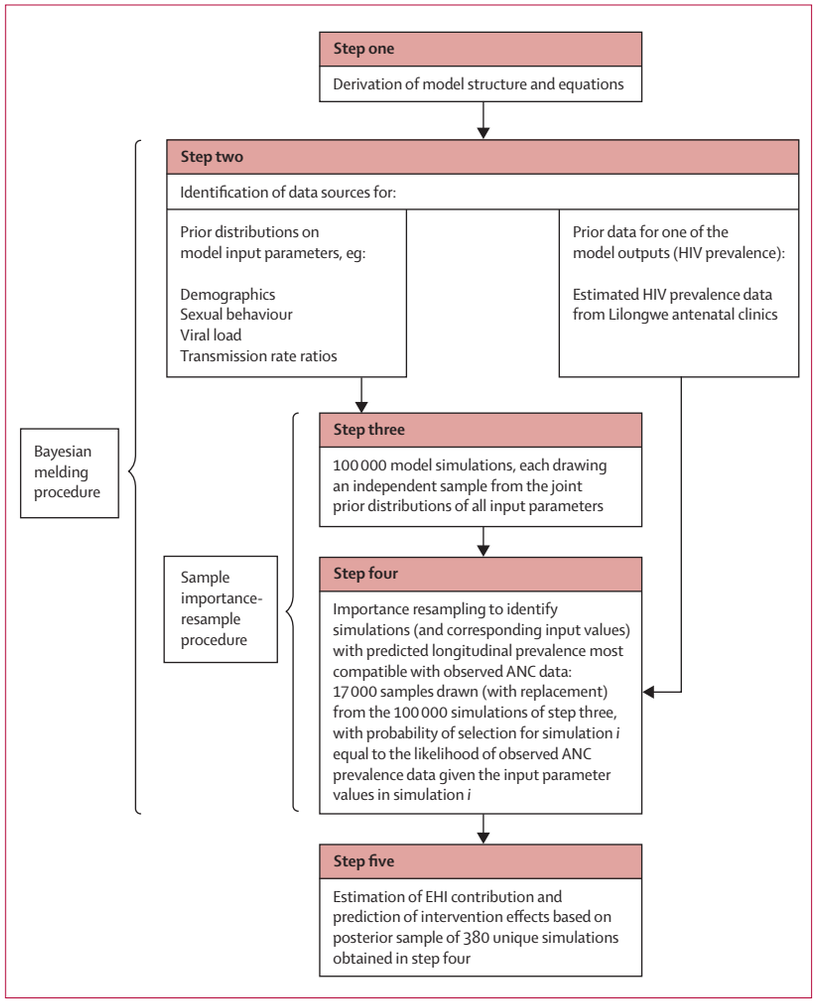

Figure 1: **Modelling analysis**
ANC=antenatal clinic. EHI=early HIV infection.

Model structure

We constructed a compartmental, deterministic model describing heterosexual partnership formation and dissolution (figure 2). According to previous modifications[15] on the classic pair-formation model,[31] sexual contact was assumed to occur at a constant frequency in steady partnerships; as casual, one-off contacts by paired individuals outside of steady partnerships; and as casual, one-off contacts by unpaired individuals (single people). This structure captures occurrences that are important in the context of time-varying HIV infectivity. For instance, if at least one member of a partnership is HIV positive, then an individual outside of that partnership will not get infected (by one of the two individuals in the partnership) while both partners are monogamous, but might become infected on partnership dissolution or sexual contact outside the pair. Additionally, pairs of uninfected individuals will not become infected with HIV while both partners are monogamous, but they might become infected through sexual contact outside of their partnership. Long-term concurrency is not captured, but the model allows for consecutive partnerships and sporadic concurrency. Our data suggest that long-term monogamy predominates in Lilongwe, with a small proportion of the population engaging in consecutive partnerships in quick succession, sporadic concurrency, or long-term concurrency.[30] Individuals entered the model as single people, and exited after an assumed sexual lifespan of 35 years, with additional AIDS-related mortality in the final infection stage.

To capture temporal variation in transmission probabilities, we divided HIV into early infection, asymptomatic HIV, early AIDS, and late AIDS. We defined early HIV infection as the initial 1 month to 6 months of raised infectivity, on the basis of the best available estimates of transmission rates by infection stage,[6] calculated in HIV-serodiscordant couples in Rakai, Uganda.[5] We divided this period into five intervals to allow for changes in transmission probabilities related to changing viral loads. Intervals one to four were each 1 week in duration to capture the initial viral load changes.[3] We sampled interval five from a uniform distribution of 1·4 weeks to 5 months, corresponding to the total assumed early infection duration of about 1 month to about 6 months.[6] We represented the asymptomatic period as three equal intervals (intervals six to eight) of 1·8 years to 3·2 years each to approximate previously described survival time distributions in untreated individuals.[32] We based the durations of early AIDS (interval nine) and late AIDS (interval ten) on the Rakai analyses, specifying normal distributions with mean 0·75 years in early AIDS and 0·83 years in late AIDS.[6]

As an additional extension, we stratified the model population into two groups to accommodate heterogeneity of sexual behaviour. The prior distributions that we specified corresponded to longer partnerships and lower rates of sexual contact when not in a relationship in the lower-risk group than in the higher-risk group. Individuals remained in one risk group and steady pairs were formed within groups. However, one-off contacts

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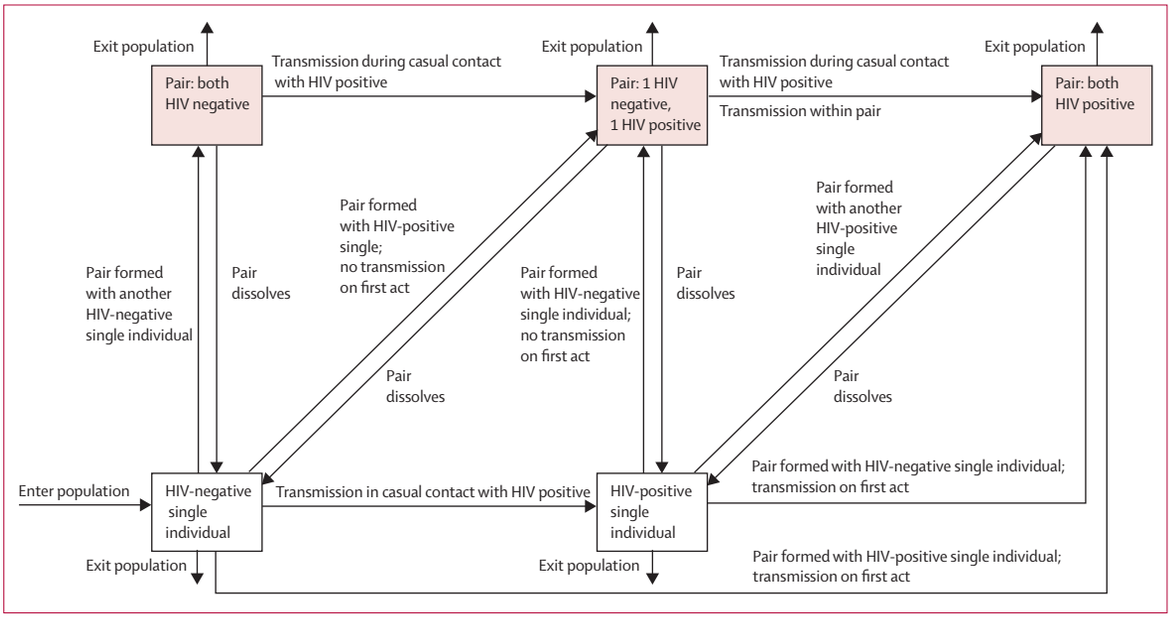

***Figure 2*: Simplified model structure**
Separate risk groups and multiple stages of infection are excluded to simplify the figure. Unshaded boxes represent single (unpaired) individuals. Shaded boxes represent steady partnerships.

with casual partners were chosen without risk-group restrictions. The model allowed for increased HIV transmission probabilities for contacts with higher-risk partners, representing an assumed greater likelihood of transmission-amplifying cofactors, such as ulcerative sexually transmitted infections (STIs) or anal intercourse. Sexual behaviour parameters were held constant across infection status and infection stage categories.

Statistical analysis

We used a Bayesian melding approach[32,33] to fit the model to empirical HIV prevalence data and to account for uncertainty in model inputs and outputs (figure 1). This approach combines prior information about inputs (eg, sexual behaviour and transmission probabilities) with data about a primary output (HIV prevalence). Sources of prior information for inputs are described under Parameter values below. For data on model output, we used HIV prevalence estimates from Lilongwe antenatal clinics (ANC) from between 1987 and 2005.[34] We implemented a sample–importance–resample algorithm to identify the input parameter values producing epidemic curves most closely matching ANC data. Briefly, we ran 100 000 model simulations, sampling randomly from the prior distributions of all input parameters in each simulation. Next, we weighted each simulation according to its likelihood-based compatibility with ANC data, and then we resampled (with replacement) from the simulations, with probability of selection proportional to the assigned weight. With this approach, the simulation resampled most frequently (the mode) is the best-fitting simulation (ie, the most compatible with empirical HIV prevalence data). The 2·5th and 97·5th percentiles were used to obtain 95% credible intervals for model parameters and outputs.

We used the Runge-Kutta 4 algorithm in Berkeley Madonna 8.0.1 to solve the model numerically. We did statistical and graphical analyses with SAS 9.1, Stata 9, and R 2.10.1.

Parameter values

We based the initial size of the adult population (aged 15–49 years) on census data (table),[35] and sampled uniformly in the range 1960–85 for the year of the first HIV case in Lilongwe (because the exact year is not known).

We based the per-contact transmission probability for asymptomatic HIV infection, along with transmission cofactor effects, on meta-analysis estimates.[7,8] We allowed the transmission cofactor effect to range from one (no transmission amplification) to six (per-contact transmission probability six times as high in the higher-risk group than in the lower-risk group). The upper bound was set on the basis of estimates for the cofactor effect of concomitant STIs[7,8] but could also broadly represent other cofactors, such as the possibility of some sexual contacts being anal rather than vaginal. To calculate per-contact transmission probabilities for early infection and early AIDS, we multiplied the asymptomatic-period estimate by the transmission rate ratios comparing early infection and early AIDS to asymptomatic infection in Rakai (table).[6] We then used longitudinal viral load data from acute infection cases in Lilongwe,[3] along with transmission rates calculated

according to viral load,[36] to estimate separate transmission probabilities within each early infection interval, subject to the constraint that the weighted average transmission probability across intervals equalled the overall average transmission probability for the early infection period. To match the absence of transmission events recorded during late AIDS in the Rakai data (probably attributable to the ceasing of sexual activity because of illness),[6] we set the per-contact transmission probability for this period to zero.

	Definition	Input value or prior distribution*	Posterior distribution (mode [95% credible intervals])
Demographic parameters			
μ	Rate of leaving sexually active population	0·029 per year	NA
n	Initial size of entire Lilongwe population (n)	976 625	NA
θ	Proportion of initial population aged 15–49 years	Uniform (0·43–0·48)	0·44 (0·43–0·48)
τ	Year of first HIV infection in Lilongwe	Uniform (1960–1985)	1969 (1964–1978)
Sexual behaviour parameters†			
π_0	Proportion of initial population in low-risk group	Uniform (0·1–0·9)	0·60 (0·54–0·71)
Parameters specific to lower-risk group			
Q_0	Proportion of low-risk individuals in a steady partnership	Uniform (0·6–0·9)	0·60 (0·60–0·89)
ρ_0	Rate of steady pair formation by single individuals in low-risk group (steady pairs formed per year)	NA‡	0·66 (0·35–4·01)§
σ_0	Rate of steady pair separation in low-risk group (separations per year)	Uniform (0·05–0·47)	0·38 (0·06–0·45)§
ϕ_0	Unprotected contact frequency in low-risk pairs (contacts per year)	Normal (65·1, 18·6)	33·1 (26·1–88·6)
s_0	Rate of low-risk single individuals having one-off, casual contacts (casual partners per year)	Uniform (0–6)	3·0 (0·2–5·2)
χ_0	Rate of low-risk paired individuals having one-off, casual contacts (casual partners per year)	Normal (2·1, 0·97)	2·4 (0·3–3·0)
Parameters specific to higher-risk group			
Q_1	Proportion of high-risk individuals in a steady partnership	Uniform (0·1–0·9)	0·79 (0·41–0·88)
ρ_1	Rate of steady pair formation by single individuals in high-risk group (steady pairs formed per year)	NA‡	33·7 (9·9–176·1)¶
σ_1	Rate of steady pair separation in high-risk group (separations per year)	Uniform (0·2–26·1)	9·0 (6·5–25·2) ¶
ϕ_1	Unprotected contact frequency in high-risk pairs (contacts per year)	Uniform (16–45)	33·5 (20·8–44·6)
s_1	Rate of high-risk single individuals having one-off, casual contacts (casual partners per year)	Uniform (0–24)	0·8 (0·6–23·1)
χ_1	Rate of high-risk paired individuals having one-off, casual contacts (casual partners per year)	Uniform (0–24)	2·1 (0·3–23·2)
Parameters related to per-contact HIV transmission probabilities†			
Viral loads during course of early HIV infection			
VL_1	Log_{10} viral load in early HIV, interval one (week 1)	Normal (1·709, 0·5)	1·7 (0·9–2·6)
VL_2	Log_{10} viral load in early HIV, interval two (week 2)	Normal (5·273, 0·5)	5·5 (4·5–6·3)
VL_3	Log_{10} viral load in early HIV, interval three (week 3)	Normal (6·769, 0·5)	6·7 (6·2–7·5)
VL_4	Log_{10} viral load in early HIV, interval four (week 4)	Normal (6·157, 0·5)	6·2 (5·5–7·0)
VL_5	Log_{10} viral load in early HIV, interval five	Normal (5·219, 0·3)	4·5 (4·5–5·7)
Per-contact transmission probabilities during course of infection			
$h_{1,0}$	Per-contact transmission probability in week 1 of EHI (low-risk group)	NA‡	0·003 (0·001–0·004)
$h_{2,0}$	Per-contact transmission probability in week 2 of EHI (low-risk group)	NA‡	0·03 (0·007–0·04)
$h_{3,0}$	Per-contact transmission probability in week 3 of EHI (low-risk group)	NA‡	0·04 (0·01–0·05)
$h_{4,0}$	Per-contact transmission probability in week 4 of EHI (low-risk group)	NA‡	0·03 (0·01–0·05)
$h_{5,0}$	Per-contact transmission probability in final interval of EHI (low-risk group)	NA‡	0·02 (0·01–0·03)
$h_{6,0}$, $h_{7,0}$, $h_{8,0}$	Per-contact transmission probability in asymptomatic HIV (intervals six to eight; low-risk group)	Normal (0·0007, 0·00007)	0·0007 (0·0006–0·0008)
$h_{9,0}$	Per-contact transmission probability in early AIDS (interval nine; low-risk group)	NA‡	0·006 (0·003–0·015)
$h_{10,0}$	Per-contact transmission probability in late AIDS (interval ten; low-risk group)	0	NA
Relative transmission rates/probabilities			
$\ln(r_E)$	Natural log of relative transmission rate (EHI *vs* asymptomatic HIV)	Normal (3·26, 0·37)	3·4 (2·6–3·9)
$\ln(r_L)$	Natural log of relative transmission rate (early AIDS *vs* asymptomatic HIV)	Normal (1·97, 0·32)	2·0 (1·1–2·9)
$\ln(r_v)$	Natural log of relative transmission rate per log_{10} increase in viral load	Normal (0·896, 0·145)	0·9 (0·7–1·1)
r_E	Relative transmission rate (EHI *vs* asymptomatic HIV)	NA‡	30·3 (13·6–47·1)
r_L	Relative transmission rate (early AIDS *vs* asymptomatic HIV)	NA‡	7·1 (3·1–18·8)
r_v	Relative transmission rate per log_{10} increase in viral load	NA‡	2·5 (2·0–3·1)
c	Relative change in transmission probabilities in high-risk group (*vs* low-risk group)	Uniform (1–6)	5·4 (3·1–6·0)

(Continues on next page)

	Definition	Input value or prior distribution*	Posterior distribution (mode [95% credible intervals])
(Continued from previous page)			
HIV infection interval durations (without treatment)†			
Duration of early HIV infection, overall and by interval			
$1/\gamma_1$, $1/\gamma_2$, $1/\gamma_3$, $1/\gamma_4$	Duration of each of first four intervals of early HIV (intervals one to four)	1 week each	NA
$1/\gamma_5$	Duration of early HIV, interval five (weeks)	Uniform (1·4–21·8)	16·6 (3·1–21·3)
$1/\gamma_1 + 1/\gamma_2 + 1/\gamma_3 + 1/\gamma_4 + 1/\gamma_5$	Total duration of EHI (intervals one to five; months)	NA‡	4·8 (1·6–5·8)
Duration of chronic HIV infection, overall and by interval			
$1/\gamma_6$, $1/\gamma_7$, $1/\gamma_8$	Duration of each interval of asymptomatic HIV (intervals six to eight; years)	Uniform (1·83–3·17)	1·9 (1·8–2·8)
$1/\gamma_9$	Duration of early AIDS (interval nine; years)	Normal (0·75, 0·2)	0·9 (0·3–1·0)
$1/\gamma_{10}$	Duration of late AIDS (interval ten; years)	Normal (0·83, 0·12)	1·1 (0·7–1·1)
Duration of entire infectious period			
$1/\gamma_1 + \ldots + 1/\gamma_{10}$	Time from HIV infection to death from AIDS (years)	NA‡	8·0 (7·2–10·5)

EHI=early HIV infection. NA=not applicable. *For parameter values that varied across model runs, distributions are given as: uniform (lower limit–upper limit) or normal (mean, SD)—parameters not specified in this format were held constant at the listed value across runs. †The webappendix (pp 5–9) describes derivation of input values for these parameters in detail. ‡Parameter was not specified directly in this form as an input parameter, but as a function of other parameters. §In the low-risk group, the posterior mode for the pair separation rate (σ_L=0·38 separations per year) corresponds to an average pair duration about 2·5 years (1 / 0·38). The posterior mode for the pair formation rate (ρ_L=0·66 formations per year) corresponds to an average gap between partners of about 1·5 years (1 / 0·66). ¶In the high-risk group, the posterior mode for the pair separation rate (σ_H=9·0 separations per year) corresponds to an average pair duration of about 0·11 years (1 / 9·0) or 1·3 months. The posterior mode for the pair formation rate (ρ_H=33·7 formations per year) corresponds to an average gap between partners of about 0·03 years (1 / 33·7) or 11 days. Together, these durations correspond to an average of about seven steady partners per year for individuals in the high-risk group.

Table: **Input parameter definitions, prior distributions, and posterior distributions**

We estimated sexual behaviour parameters from data we collected at Kamuzu Central Hospital Sexually Transmitted Infections Clinic in Lilongwe.[3,30] These data included detailed information about partnership durations and contact frequency by marital status and partner type (ie, marital or cohabiting partners *vs* non-marital and non-cohabiting partners).

Estimation of the role of early infection and prediction of intervention effects

We calculated the yearly proportion of new infections caused by sexual contact with an individual with early infection from model equations tracking cumulative infections by calendar time and index infection period. We explored the potential effects of an HIV prevention intervention that was assumed to substantially decrease the per-contact transmission probability in all contacts affected by the intervention. Such an intervention could be strictly behavioural (eg, consistent condom use by a male partner), strictly biological (eg, antiretroviral treatment use by infected individuals), or a combination of the two. The per-contact transmission probability in such contacts was reduced to 0·000033. This value is the estimated midpoint of man-to-woman and woman-to-man transmission probabilities, assuming viral suppression with antiretroviral treatment,[37] but can also approximate effective condom use or other highly effective interventions. The intervention was not assumed to affect pair formation or dissolution rates, nor the frequency of sexual contact within or outside of steady partnerships. We varied the intervention coverage for each disease stage—ie, the proportion of infected individuals (0%, 25%, 50%, 75%, 85%, 90%, 95%, 100%) in whom transmission probabilities were successfully reduced—to explore scenarios with intervention effects during early infection only (as a benchmark), chronic infection only, or both early and chronic infection.

To compare the maximum possible benefits of interventions in each disease stage, we assumed that interventions began early in a specific period. Interventions during early infection were assumed to start 3 weeks after infection and to end at the start of chronic infection. This assumption, which is based on our experience with detection of acute infection in Lilongwe,[3] allows for blood collection in the second week of infection and an additional week to report positive HIV RNA or p24 antigen test results. Interventions targeting individuals with chronic infection were assumed to start at the beginning of the earliest chronic infection interval (interval six) and continue through the development of AIDS. In this assumption, HIV diagnoses are made earlier on in disease course than most diagnoses,[38] but it approximates the time at which a highly effective test-and-treat programme with yearly HIV antibody tests would detect cases.[19] With such a strategy, infected individuals would be detected on average about 6 months into infection, roughly the time at which chronic infection starts in our model.

Interventions were assumed to begin in 2010 (at a mature epidemic phase). Our main intervention effect measures were the predicted HIV prevalence and incidence during 2010–40. We also calculated the intervention coverage needed for elimination of HIV during this period, with two separate definitions: the

Granich definition (reduction in yearly incidence to less than one infection per 1000 population),[19] and the Dahlem definition (reduction in yearly incidence to zero infections), which was developed at the WHO-sponsored Dahlem Workshop on the Eradication of Infectious Diseases.[39] As a complementary analysis, we predicted the percentage of new infections averted between 2010 and 2015.

Because intervention effects on the life expectancy of an index case could range from the minimum (with strictly behavioural interventions) to substantial (with antiretroviral treatment), we modelled two extremes of interventions delivered during chronic infection: no effect on infection duration and increased average infection duration by about 10–15 years.[19,40] Life expectancy increase with increased average infection duration is based on survival-time estimates for individuals starting antiretroviral treatment at the beginning of chronic infection.[19,40] Therefore, the intervention targeted at only chronic infection with increased life expectancy approximates an annual test-and-treat strategy.

For base-case analyses, we used the modal input parameters. To explore intervention effects in situations with a greater or lesser importance of early infection, we used the input parameters producing the upper and lower 95% Bayesian credible limits of the proportion of new cases attributable to early infection in 2010.

Additional sensitivity and influence analyses

To consider intervention effects with various alternative conditions, we did analyses with greater assumed life expectancy increases in individuals receiving antiretroviral treatment, and with interventions (targeted at early infection, chronic infection, or both) starting later in a given disease stage. We also explored the individual effect of each input parameter on results, examined epidemic dynamics within the high-risk and low-risk groups separately, and considered a model in which sexual behaviour parameters could change during the course of the epidemic. The webappendix (pp 11–43) describes additional sensitivity and influence analyses in more detail.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

The Bayesian melding procedure yielded a posterior distribution of 380 unique epidemic curves in good agreement with the ANC data used to define HIV prevalence in Lilongwe (figure 3). From the modal simulation, we estimated that HIV prevalence in Lilongwe's general adult population peaked at 24·7% (95% credible intervals 22·7–25·0) in 1996, decreased to 17·3% (17·0–18·8) in 2005, and was 14·3% (14·2–16·6) in 2010 (figure 3). ANC prevalence estimates peaked at 27·0% (95% confidence interval 22·7–31·6%) in 1996 and decreased to 18·6% (16·0–21·3%) in 2005.

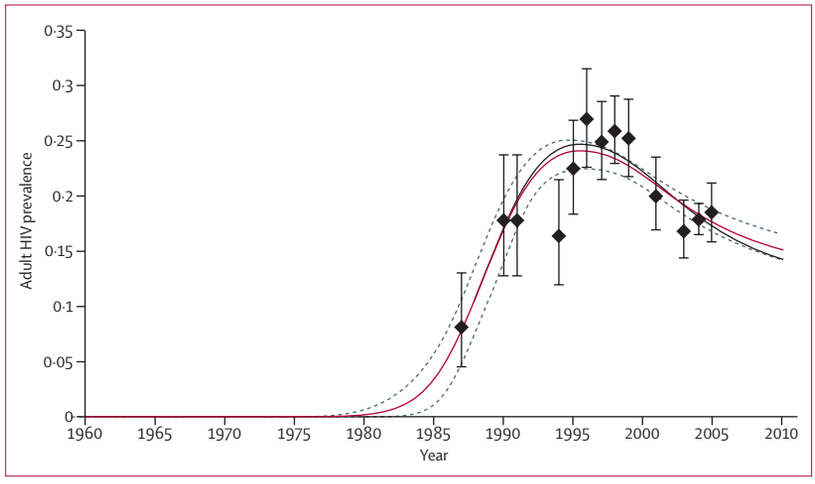

Figure 3: **HIV prevalence in Lilongwe, Malawi**
HIV prevalence data from the sentinel surveillance site in a Lilongwe antenatal clinic are shown as points (error bars are 95% confidence intervals). HIV prevalence output generated from the mode (ie, best-fitting) set of input parameters is shown as the solid black line (dashed lines are the 2·5th and 97·5th percentile values). The red curve is the median value at each timepoint from the model output.

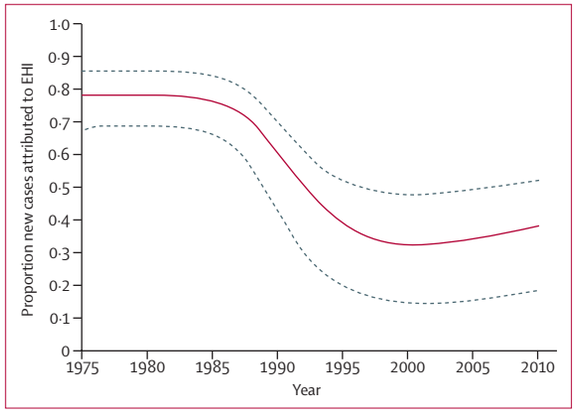

Figure 4: **Estimated proportion of incident HIV infections attributable to contact with individual with early HIV infection**
The solid line is the proportion of incident HIV infections attributable to sexual contact with an individual with early HIV infection (EHI), as estimated by the mode set of input parameters in our model. The dashed lines correspond to the simulations producing the 2·5th and 97·5th percentile values in 2010.

Input parameter definitions and prior distribution and posterior distribution values are given in the table. The estimated proportion of individuals in the high-risk group declined from 40% in the initial population (table) to about 20% in the later stages of the epidemic.

The best-fitting partnership durations were 2·5 years in the low-risk group (with durations of 1·5 years between partnerships) and 1·3 months in the high-risk group (with durations of 11 days between partnerships). For most input parameters (eg, viral load and transmission probabilities),

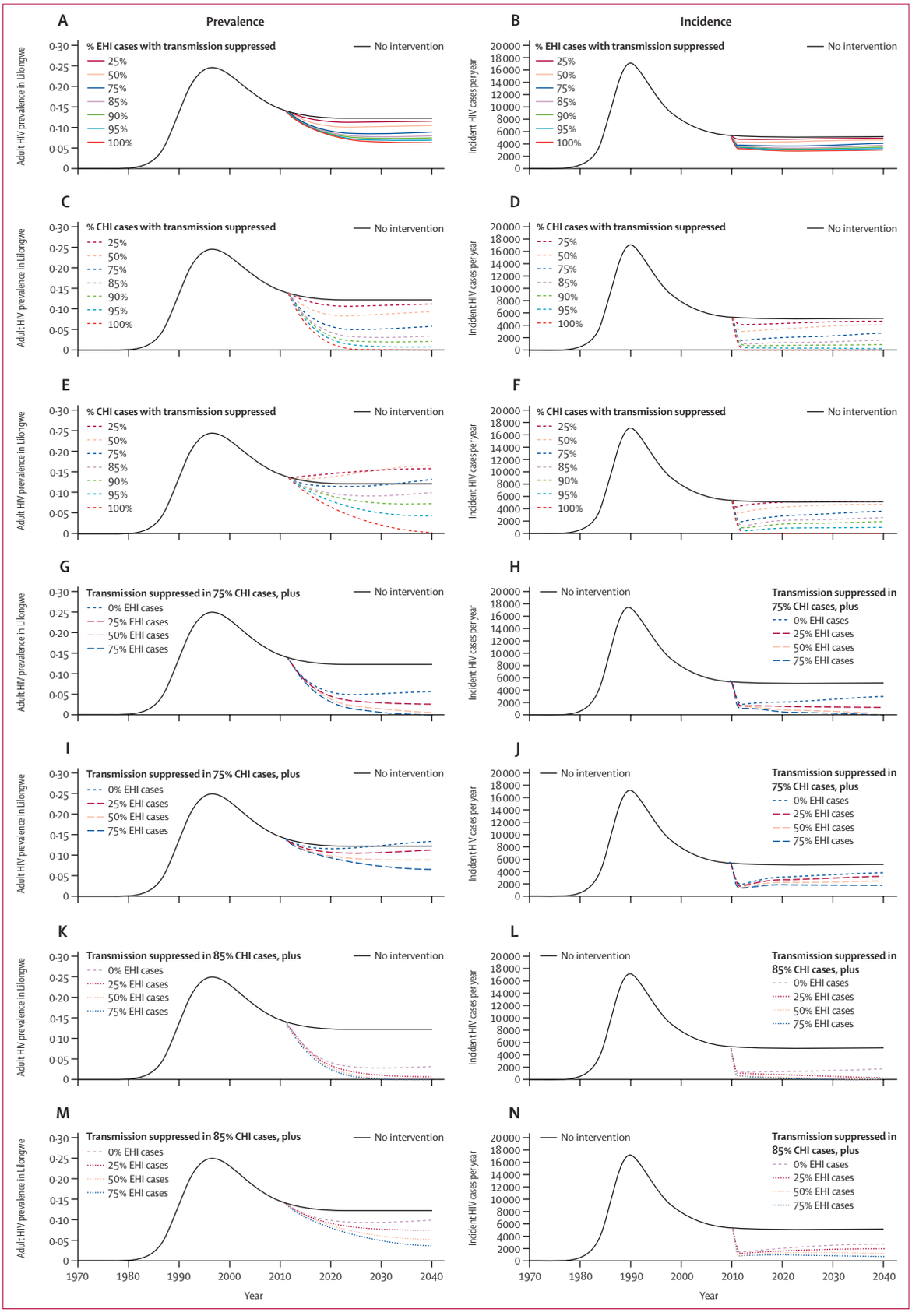

***Figure 5*: Predicted effects on HIV prevalence and incidence of interventions targeted at early HIV infection only, chronic HIV infection only, or both**

Effects on prevalence and incidence are predicted for interventions that target early HIV infection (EHI) only (A and B); chronic HIV infection (CHI) only with no effect on life expectancy (C and D); CHI only with increased life expectancy (E and F); and both EHI and CHI with varying levels of coverage, without (G, H, K, and L) and with (I, J, M, and N) increase in life expectancy associated with the chronic-phase intervention.

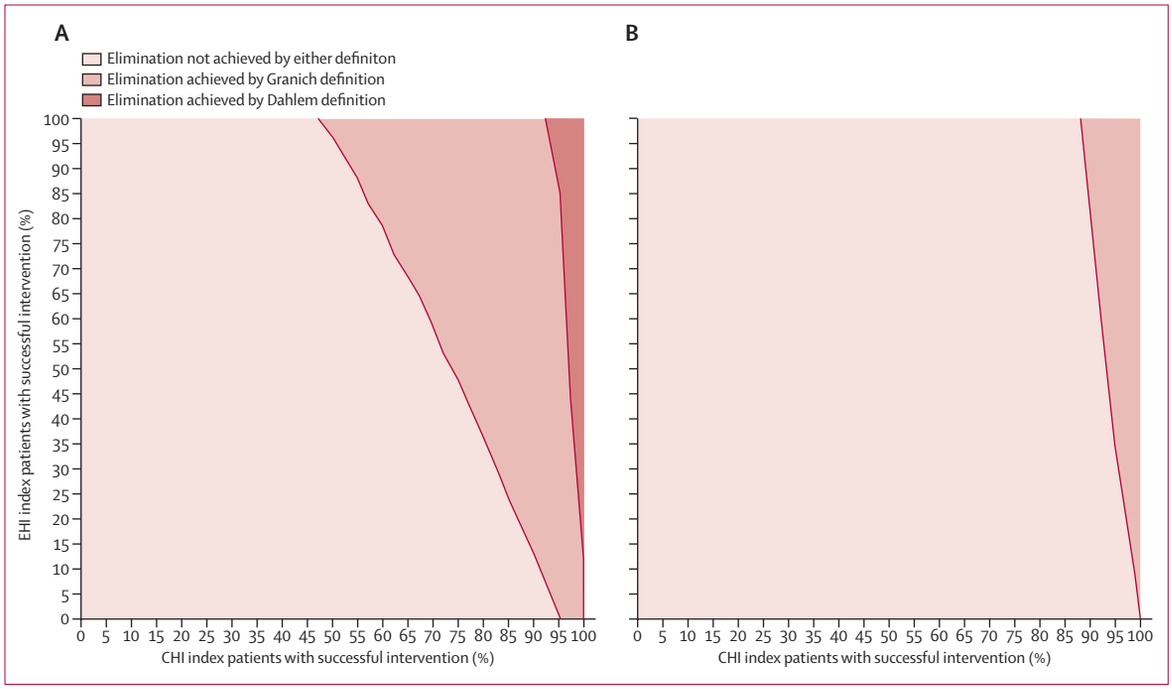

***Figure 6*: Intervention coverage needed for HIV elimination in Lilongwe, Malawi**
Predicted levels of coverage needed for interventions started in 2010 that target early HIV infection (EHI), chronic HIV infection (CHI), or both to result in HIV elimination within 30 years of intervention implementation, with the assumption of no increase in life expectancy associated with CHI-only interventions (A), or increased life expectancy associated with CHI-only interventions (B).

the specified prior distributions were qualitatively similar to the posterior distributions resulting from the fit to empirical prevalence data (webappendix pp 11–19). The model fit was most informative (ie, the prior and posterior distributions differed most substantially) for the proportion of the initial population in the high-risk group, transmission cofactor effects, and high-risk pair formation and dissolution rates.

On the basis of the model results, 38·4% (95% credible interval 18·6–52·3) of incident HIV infections resulted from contact with a partner with early infection in 2010 (figure 4). The best-fitting early infection duration was 4·8 months, with a corresponding transmission rate ratio of 30 comparing early to asymptomatic infection, and per-contact transmission probabilities during early infection ranging from 0·003 to 0·04 in the low-risk group (table). Cumulative transmission probability during early infection in low-risk, HIV-discordant pairs was about 26% (95% credible interval 11–50).

Biological or behavioural interventions assumed to sharply reduce HIV transmission probabilities during early infection (with no residual effect thereafter) were predicted to substantially reduce HIV prevalence in Lilongwe, but not to result in HIV elimination, even when 100% of early infection cases received the intervention (figure 5). Because the intervention for early infection only was not assumed to affect life expectancy, changes in HIV prevalence and incidence were qualitatively similar (figure 5).

In several scenarios, lifelong interventions targeted at chronic infection only initiated about 6 months after infection were predicted to have a greater effect on HIV prevalence and incidence than were interventions for early infection only, but results were sensitive to assumptions about life expectancy (figure 5). HIV elimination within 30 years under the Dahlem definition (reduction in yearly incidence to zero cases[39]) was not possible with interventions for chronic infections only, and elimination under the Granich definition (reduction in annual incidence to less than one infection per 1000 persons[19]) was possible only with 95% coverage of interventions for only chronic infection (with the assumption of no life expectancy increase) or 99% coverage of interventions for only chronic infection (with the assumption of a life expectancy increase of 10–15 years; figure 6). If the intervention was assumed to increase life expectancy (eg, treatment as prevention[19,41]), coverage levels of 75% or less for interventions for only chronic infection were predicted to increase HIV prevalence above the level that would be expected with no intervention (figure 5).

The combination of early-stage and chronic-stage interventions reduced HIV prevalence and incidence substantially, even if intervention coverage for chronic infection was only 75–85% (figure 5). Although the intervention coverage in each stage needed for elimination depends on the definition of elimination and the intervention effects on life expectancy (figure 6), the

combination of results shown in figure 5 and figure 6 suggests that if very high levels of coverage (ie, ≥95%) cannot be attained with an intervention for chronic infection only, then the addition of interventions for early infection will be necessary to sustainably reduce HIV prevalence and incidence in Lilongwe.

Our findings were much the same in sensitivity analyses when 18·6% or 52·3% of transmission (our lower and upper 95% credible limits, respectively) was assumed to be from individuals with early infection. Complementary analyses of infections averted showed similar trends. Sensitivity analyses in which interventions for chronic infection increased life expectancy by 10–20 additional years provided further support for inclusion of interventions targeted at early infection, as did analyses in which interventions for chronic infection were assumed to start about 2 years—rather than about 6 months—into infection. The webappendix (pp 20–43) gives results of sensitivity analyses and other complementary analyses.

Discussion

Our results suggest that early infection plays an important part in the spread of HIV in Malawi, and that the detection of—and prevention of transmission from—people with early infection will be needed for maximum HIV prevention. These findings are likely to be generalisable to similar settings, and the model structure is readily adaptable to other settings with mostly heterosexual or homosexual transmission and with data available for setting model parameters.

The magnitude of the HIV epidemic in sub-Saharan Africa has been difficult to explain. One explanation for the extensive spread of HIV emphasises the importance of people with acute and early infection, who are highly infectious but are rarely aware of their infection status.[42] Increased transmission at early stages of infection has been ascribed to high viral loads[3,4] and an apparent increase in viral infectivity.[43] In rhesus macaques, the ratio of infectious virions to total virions is up to 750 times as high during acute infection as it is during chronic infection.[43] In Ugandan HIV-serodiscordant couples, transmission rates were about 25 times higher during early infection than they were during asymptomatic infection.[6] Phylogenetically defined infection clusters[16–18,44] and documented acute-to-acute transmission events[45,46] lend further support to the potential importance of early infection in the spread of HIV.

We did this study to understand the contribution of early infection to the HIV epidemic in Lilongwe, where we have done studies to identify patients with acute infection,[47–49] characterise their sexual behaviours,[50] and measure viral load changes during early infection.[3] We estimated that sexual contact with individuals with early infection causes 19–52% of HIV transmissions in Lilongwe, with a mode of 38%. Our results suggest that the initial period of raised transmissibility might be about 5 months, and that transmissibility during early infection is 30 times as great as it is during chronic infection.

Mathematical modelling estimates of the importance of early infection in the spread of HIV vary widely,[6,9,10,12–15,31,51] partly because of differing assumptions and a paucity of data for parameter definitions (panel). Endemic-phase estimates of the proportion of new infections in sub-Saharan Africa that arise from an individual with early infection have ranged from 7% to 31% in modelling studies.[6,13] Phylogenetic studies done in developed countries have estimated that 25–49% of incident infections arise from sexual contact with an individual with early infection.[16–18,44]

A strength of our model is the extensive use of local data for setting of the parameters of the model. We used sexual behaviour data from Lilongwe to define contact patterns specific to the setting of interest, viral load data from patients with acute infection in Lilongwe to provide a detailed description of the time-course of transmission probabilities during early infection, and local HIV prevalence data to identify the specific input parameter values most compatible with observed epidemic dynamics in Lilongwe. The close parameterisation of the model, done with data from the setting of interest, allows us to expect results with greater reliability and applicability—at least in Lilongwe and similar settings—than could be expected from a model that used a combination of parameter values derived from disparate populations.

Our model was enhanced in several other ways in comparison with previous models addressing acute and early infection. To model contact patterns relevant to HIV transmission, we incorporated both steady pairs and casual contacts, with consideration of both high-risk and low-risk groups. The Bayesian melding approach allowed us to account for input and result uncertainty. Finally, we did sensitivity analyses to assess intervention effects over a range of predicted early infection contributions.

The idea to use antiretroviral treatment as a transmission prevention strategy has received much attention;[19,41] it emerged after HIV replication was shown to be reduced in the genital tracts of individuals receiving such treatment,[57,58] and HIV transmission was suppressed in serodiscordant couples when the index case received antiretroviral treatment.[59–61] A widely cited mathematical model has concluded that yearly test-and-treat strategies could virtually eliminate the epidemic in South Africa,[19] but the importance of early infection seems to have been underestimated in that model,[22,24,25] and other modelling studies examining the potential benefits of antiretroviral treatment have been less optimistic about the test-and-treat approach.[53,54]

Accordingly, we examined the effects of behavioural or biomedical interventions that might substantially reduce sexual transmission at different stages of HIV. One such intervention was assumed to improve survival and reduce transmissibility from the onset of chronic infection,

approximating a yearly test-and-treat strategy.[19] Our results suggest that even highly effective behavioural or biological interventions—including test-and-treat programmes—are unlikely to eliminate HIV in Lilongwe or similar settings unless people with early infection are included. Even if the contribution of early infection to continuing HIV transmission is as low as about 20% (the lower credible limit in our analysis), intervention during chronic infection only is unlikely to eliminate HIV unless nearly all individuals with chronic infection have lifelong transmission suppression. If coverage for interventions targeted at chronic infections only is not complete, additional early infection interventions can lead to substantial improvement. Our results suggest that strategies to prevent transmission from individuals with chronic and early infection provide the greatest chance for pronounced, long-term reductions in HIV incidence and prevalence. Sensitivity analyses in which interventions targeted at chronic infections were assumed to provide even greater survival benefits, or to start at times more typical of clinical practice, provided even greater support for inclusion of interventions during early infection.

Interventions directed toward individuals with early infection have unique challenges. Although antibody tests can detect some post-acute early infection cases, a test-and-treat approach to identify specifically individuals with early infection would need a very brief interval for repeat testing (about 3–6 months), and reliance on antibody tests would result in missed acute infection cases. Large-scale programmes of HIV testing twice or four times a year would be difficult to implement and sustain. Both biological and behavioural interventions intended for individuals with early infection might need more targeted approaches, such as partner notification or campaigns to encourage HIV testing in individuals who have engaged in recent high-risk behaviour and who have symptoms of acute retroviral infection.[62] These case-finding strategies—in combination with pooling of blood samples,[47] targeted HIV RNA screening,[48,63] or newer HIV detection tests[1,64]—could increase the numbers of individuals with early infection detected, even in resource-limited settings. Encouragingly, our best-fitting value of 4·8 months for the period of increased transmissibility suggests that interventions provided during the first few months of infection, rather than the first few weeks, could have a substantial public health benefit. We have previously shown that HIV concentration in seminal plasma remained raised for more than 2 months after infection,[3] which lends support to this suggestion.

Interventions started during early infection might also have unique benefits that are not captured in our model. Adherence to biological or behavioural interventions initiated during early infection might remain high at least through the most infectious period,[50] potentially maximising cost-effectiveness and minimising the detrimental effect of waning adherence reported with some interventions.[65,66] Additionally, some studies suggest a clinical benefit from initiation of treatment during early infection.[67]

Mathematical models of HIV transmission depend heavily on assumptions about sexual behaviour. The input values for sexual behaviour parameters in our model were based on a cross-sectional study done in patients attending a sexually transmitted infection clinic in Lilongwe[30] that recorded long-term monogamy to be common, with only 14% of individuals reporting long-term concurrency, sporadic concurrency, or consecutive, monogamous partnerships in rapid succession. Although based on a small sample (n=186) with generalisability probably restricted to similar settings, these data are some of the most detailed available on partnership durations and gaps between consecutive partnerships in sub-Saharan Africa. In our best-fitting model simulation, both the duration of partnerships and gaps between consecutive partnerships were much shorter in the high-risk group than they were in the low-risk group. Therefore, the difference between steady partners and casual contacts seems to be substantially less distinct for individuals in the high-risk group than for those in the low-risk group, potentially explaining why some behavioural parameters resulting from the model fit vary in unexpected ways across groups. For example, despite the higher casual contact rate that we initially posited for single people in the high-risk group, the best-fitting parameter set suggests a lower rate,

***Panel:* Research in context**

Systematic review

In a review of mathematical models estimating the contribution of acute and early HIV infection to HIV transmission,[52] we noted that estimates have varied widely, because of differences in epidemic stage, populations studied, model structure, parameter values, and assumptions in the absence of site-specific data. None of these modelling studies compared the potential effect of transmission prevention interventions started in acute and early HIV infection with those started in chronic infection. Previous modelling studies examining treatment-as-prevention strategies for established infection[19,53–55] have had mixed results related to the control of HIV.[56]

Interpretation

Findings from our study suggest that transmission prevention interventions that achieve intermediate levels of coverage during both early and chronic HIV infection will have a far greater effect on the spread of HIV in Malawi than would interventions that focus on chronic HIV alone. As such, the population-level effect of test-and-treat strategies is likely to be optimised only if individuals with early HIV are included or if complementary interventions targeting the earliest phases of infection are incorporated into the overall prevention approach.

possibly because the shorter gap between steady partnerships translates into less time as a single person in the high-risk group. We also note that the partner change rate in our higher-risk group was slower than it was in the highest-risk groups of several previous HIV epidemic models,[13,55] and that none of our behavioural parameters were especially extreme, despite being set from data collected from an STI clinic population. The fact that recorded behaviours in the STI clinic population were not especially extreme could be because of the high prevalence of STIs in Malawi,[68,69] which would result in a substantial overlap between STI clinic populations and the general population.

The importance of sexual partner concurrency in the HIV epidemic of sub-Saharan Africa has been emphasised and debated.[70–74] Intuitively, concurrency seems potentially important for transmission during early infection, because long-term monogamy would limit the high infectiousness of newly infected individuals to just one other person—their steady partner. Our model captured only a simple form of concurrency—one-off encounters outside of pairs—and did not include long-term concurrency. However, our best-fitting parameter set included short gaps between partners (11 days) in a high-risk group that constituted about 20% of the present population. These short gaps in a subset of the population are consistent with (and based on) our data from Malawi,[30] and provide an alternative explanation for rapid HIV spread and the corresponding importance of early infection; however, the potential contribution of long-term concurrency to the spread of HIV cannot be excluded.

All mathematical models have limitations. In our model, individuals and pairs were restricted to a given risk group, and only a very simple form of concurrency was captured. Additionally, our model did not incorporate population age structure or differing HIV risk behaviours between men and women. The inclusion of behavioural heterogeneity across two separate risk groups could capture some age-related behavioural variation, but the results give an average picture for the sexually active population overall. Nevertheless, our division of early infection into intervals, our inclusion of more than one risk group, and our incorporation of both steady and casual contacts probably give a more accurate representation of transmission dynamics than did previous models that assumed only one-off contacts occurring at random within populations. Additional considerations, such as drug resistance, side-effects, behavioural disinhibition, and intervention cost, should also be carefully appraised before implementation of specific treatment-based interventions.

Our analyses suggest that early infection is crucial in the continuing HIV epidemic in Lilongwe. This result suggests that early stages of HIV infection can be important for epidemic spread not only in the earliest phases of HIV epidemics, but also in more mature epidemics. Consequently, prevention approaches directed at all stages of HIV will probably be necessary to ensure a long-term effect on the epidemic in Lilongwe and similar settings. As plans for treatment as prevention are developed, our results suggest that strategies for detection and management of patients with acute and early infection should be included.

Contributors

KAP, ACG, WCM, IFH, and MSC had the idea for and designed the study. KAP, ACG, and WCM participated in model development and analysis. KAP, ACG, WCM, IFH, AEP, FEAM, GK, and MSC contributed to data collection or interpretation. KAP drafted the paper, with critical revision by ACG, WCM, IFH, AEP, and MSC. All authors read and approved the final version of the paper.

Conflicts of interest

We declare that we have no conflicts of interest.

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HIV prevention transformed: the new prevention research agenda

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We have entered a new era in HIV prevention whereby priorities have expanded from biomedical discovery to include implementation, effectiveness, and the effect of combination prevention at the population level. However, gaps in knowledge and implementation challenges remain. In this Review we analyse trends in the rapidly changing landscape of HIV prevention, and chart a new path for HIV prevention research that focuses on the implementation of effective and efficient combination prevention strategies to turn the tide on the HIV pandemic.

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Introduction

Until recently, HIV prevention lacked credibility with data from prevention trials showing little or no decrease in incident HIV.[5] Furthermore, when successes were made public,[6–8] explanations were often conflicting and lessons for application to other settings unclear. However, the past year marked the end of this steady stream of disappointing results, and a concomitant change is evident in public perception and the opinions of policy makers. The discourse on HIV prevention now includes the possibility that the epidemic can be stopped.[9]

Increasingly scarce financial resources also drive this renewed focus on prevention. The global economic crisis has substantially affected funding for HIV, with resources for prevention levelling off in the past decade and future funding commitments unclear.[10] These reductions put many programmes at risk and warrant a sharpened focus on prevention. Fiscal constraints have created pressure on prevention programmes to be more accountable by providing clearer evidence of impact and delivering better value for money.

We review developments in HIV prevention from the past 3 years (since *The Lancet* Series on HIV prevention in 2008[2–4]), with particular emphasis on gaps in knowledge and a focus on what are now the most salient prevention issues: discovery in the continued search for vaccines and a cure; new challenges related to antiretroviral-based prevention; implementation challenges that preclude scale-up of prevention strategies known to be effective—specifically, HIV testing, voluntary medical male circumcision (VMMC), and prevention of mother-to-child transmission (PMTCT); and progress on and challenges for structural and behavioural interventions.

Vaccines and the search for a cure

Strategies for vaccine development include innate, cell-mediated, or antibody-mediated resistance to infection, or all three.[11] Successful modification of HIV in Rhesus macaque monkeys led to increased focus on cell-mediated immunity;[12] however, the STEP trial[13] (using immunogens that worked in macaques) showed neither protection from HIV nor alteration in viral replication in vaccine recipients, but did stimulate an immune response that exerted pressure on the virus acquired.[14] In a trial in Thailand[15] a canarypox vector vaccine (ALVAC-HIV) boosted with a recombinant glycoprotein vaccine (AIDSVAX B/E) led to a 31% reduction of HIV incidence in vaccine recipients. The immune responses that enabled protection are a focus of intensive post-trial studies, including consideration of non-neutralising antibodies that function via antibody-dependent cellular cytotoxic effects (ADCC).[16,17]

Renewed interest[18] in curing HIV was partly stimulated by a report of a bone-marrow transplant of *CCR5*-deleted stem cells to an HIV-positive patient, who seemed to eliminate detectable HIV after engraftment of this tissue.[19] This result confirmed the importance of the *CCR5* receptor for HIV replication, and galvanised experiments focused on gene therapy to modify this receptor, to date conducted ex vivo and in a mouse model.[20] Investigators committed to curing AIDS have further divided this work into immunomodification[21] and the use of antiretroviral drugs to eliminate all HIV-infected cells.[22] For both approaches, the latent reservoir of HIV-infected T cells is the greatest challenge. At the start of HIV infection, the virus is integrated into host DNA, and cells become quiescent and allow HIV replication at a very low rate, even with antiretroviral therapy (ART).[23] However, when ART is discontinued, viral load returns to a level recorded before therapy. A novel class of cancer drugs designed to

Search strategy and selection criteria

We covered several topics in HIV prevention (biomedical, behavioural, structural) that together comprise combination prevention.[1] We focused on randomised trials, rigorous observational studies, and systematic and meta-reviews completed since *The Lancet* Series on HIV prevention in 2008.[2–4] The most recent reviews[5] were used as a starting point. We searched PubMed and Medline for papers published in peer-reviewed journals since 2008, and electronic conference proceedings of recent HIV/AIDS-related conferences up to the end of April, 2011. We also reviewed relevant publications and websites from international organisations, including UNAIDS and WHO, and non-governmental organisations and advocacy groups involved in HIV prevention research. Search terms included "HIV", "prevention", "antiretroviral therapy (ART)", "vaccines", "behavior", "HIV testing", "male circumcision", "microbicides", "mother-to-child transmission (MTCT)", "implementation science", and "operations research". Because the effectiveness of a single intervention was not the objective of the review, systematic review methods were not used. The goal was instead to broadly review existing prevention interventions and identify salient issues, research needs, and gaps in knowledge.

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force replication in each infected cell in the latent pool (so traditional ART can work) is now entering clinical trials.[22]

An alternative to eradication of HIV is a so-called functional cure of infection that is evoked by stimulation of T cells to restrict HIV replication in the absence of antiretroviral drugs. Intensive studies of the HIV response to T cells in acute infection,[24] and of the few patients whose immune systems control HIV,[25] suggest the feasibility of this approach with a combination of immunogenic proteins (a therapeutic vaccine), immunostimulatory cytokines, and other novel forms of immune modification of the virus by reactive T cells.[26] Patients treated very early might have a smaller pool of latent virus, and might therefore be good candidates for such curative therapy.[22]

Product development and proof-of-concept studies are important areas in the search for HIV vaccines and a cure. The next phase of vaccine research will focus on development of immunogens that allow the HIV-negative recipient to form durable neutralising antibodies.[27] Protection of Rhesus macaques from simian immunodeficiency virus (SIV) was possible with the passive infusion of monoclonal antibodies that neutralise SIV.[28] Additionally, Stamatatos and colleagues[29] and Tomaras and colleagues[30] described the detection of very broad and potent neutralising antibodies in a patient with HIV infection. However, such antibodies are generated too late to affect the disease.[27] These findings could facilitate the design of a vaccine that leads to secretion of high concentrations of protective antibodies in the genital tract, whether neutralising or ADCC.[11,16] Another innovative approach is passive immunisation, either by direct administration of broadly neutralising antibodies, or by use of gene transfer technology to achieve sustained production of antibodies. In the search for a cure, experiments using vaccination, maximal ART, and adjunctive cytokines are in progress, and are the subject of the Martin Delaney cure award.[31–33]

Prevention based on antiretroviral drugs

Pre-exposure prophylaxis

Concerted and ongoing efforts aim to understand the penetration of antiretroviral drugs into the male and female genital tract, and the protective effects of oral or topical (ie, microbicide) pre-exposure drugs on HIV acquisition.[34] The first results were reported in 2010, in the CAPRISA 004 study in South Africa.[35] 889 high-risk women used an applicator that delivered 1% tenofovir gel into the vaginal vault up to 12 h before, and within 12 h after, intercourse. Investigators reported a 39% reduction in overall acquisition of HIV, and maximum reduction was 54% in the most adherent women. HIV acquisition was inversely correlated with detection of tenofovir in the vaginal secretions—an indication of the strong association between product adherence and efficacy. An ongoing trial[36] further examines these results by examining daily use of gel and oral pre-exposure prophylaxis, and compares these regimens with placebo. Tenofovir gel also inhibits replication of herpes simplex virus-2 (HSV-2), and reduced acquisition of this virus was noted in CAPRISA.[35]

Eight trials with oral antiretroviral agents for pre-exposure prophylaxis are currently ongoing,[37] using antiviral agents that proved protective in a macaque model.[38] In the iPrEx study in 2010,[39] HIV-negative men who have sex with men were given daily emtricitabine and tenofivir disoproxil fumarate (TDF plus FTC) for up to 2·8 years. This antiretroviral combination was selected because it offered the greatest protection to Rhesus macaques in a model of rectal exposure.[38] The study recorded a 44% reduction in HIV acquisition and, as with CAPRISA,[35] efficacy was strongly associated with concentrations of antiretroviral drug, which is a direct marker of adherence. Some study participants had mild renal dysfunction or decrease in bone mineral density, and two who had unrecognised acute (seronegative) HIV infection on pre-exposure prophylaxis developed a antiretroviral-resistant variant. By contrast, the FEM-PrEP trial of TDF plus FTC offered to high-risk women was discontinued because an equal number of infections occurred in both the placebo and treatment groups.[40] The precise explanation for the difference between the IPrEx and FEM-PrEP results is unknown; however, a strong possibility is that the concentration of tenofovir in the female genital tract is insufficient to prevent HIV acquisition.[41,42] These results do not diminish the potential for oral pre-exposure prophylaxis, but recommendation of wide-scale promotion for women would be premature.

Treatment for prevention

Treatment for prevention describes the public health or community benefits from the use of ART to decrease onward transmission of HIV.[43] The biological mechanism is that treatment reduces viral load and thus reduces infectiousness.[44] Five observational reports noted substantial reduction of HIV transmission to a sexual partner when the HIV-infected index case was given ART.[45] The HPTN 052 study[46] is a randomised controlled trial that directly examines the ability of ART to interrupt HIV transmission from an index patient with HIV to his or her sexual partner. On April 28, 2011, the multinational Data Safety and Monitoring Board overseeing the study reported a substantial difference in prevention and treatment outcomes related to early start of ART, and recommended that the randomisation study be ended. Findings from the study showed a 96% reduction of HIV transmission attributed to the use of antiretroviral drugs.[47]

Some (but not all) results from mathematical modelling analyses lend support to the population-level use of treatment for prevention[48,49] and suggest a greater benefit than that possible with pre-exposure prophylaxis.[50] Guidelines for HIV treatment support early start of ART,[51] which would also favour the public health potential of this approach, and several population-level pilot studies of antiretroviral drugs for prevention are now planned. Importantly, the HPTN 052 trial has bridged a crucial

gap by unequivocally showing that treatment for prevention is efficacious.

Key research areas for prevention with antiretroviral drugs

The extent to which pre-exposure prophylaxis and ART reach individuals with the highest viral load is central to the success of prevention approaches based on antiretroviral drugs. The main challenge is whether the right people have the right drug concentrations of the right drugs at the right time.[17] Hence, an important issue for both pre-exposure prophylaxis and treatment for prevention is to establish eligibility, for which high and frequent uptake of HIV testing is a requisite. In treatment for prevention, the difficulty in detection of people with HIV infection who are asymptomatic has been well documented.[52,53]

Another approach is to emphasise ART access before the rise in viral load that typically occurs in late stages of infection, especially in patients with the highest viral loads[54]—eg, those with early infection who are the most infectious.[17] Patients with acute and primary HIV infection have also been difficult to identify, even though most are symptomatic.[17] Although new diagnostic approaches might overcome some of these challenges,[55] the difficulty of linking asymptomatic people to care has been well documented.[44,43,56]

Another important issue, given challenges related to universal access, is how to prioritise distribution of antiretroviral drugs. Most agree that pregnant women in Africa and discordant couples are high-priority groups, but the need extends far beyond these groups. Moreover, the potential role of pre-exposure prophylaxis in these groups should be tempered by the findings of the FEM-PrEP study.[40] The most crucial issue for distribution is how to ensure that equity considerations are appropriately addressed in resource-poor settings when treatment is not available to all who need it.

The burden of adding antiretroviral-based prevention to already strained health systems remains to be determined. The frail health infrastructure of sub-Saharan Africa, characterised by severe shortages in structural and human resources, is widely recognised as one of the main challenges in addressing the epidemic. To confront this issue, task shifting (ie, redistribution of tasks from highly trained health workers to those with less training, including non-professionals) is becoming more widespread.[57,58] Such reorganisation also decentralises health services (eg, to rural areas), reducing the travel burden to attend hospitals or clincs. Although task shifting is an efficient strategy with many documented successes, it presents many challenges, including the provision of training and supervision that is sufficient to maintain quality and safety, and the need to address resistance from governments and health professionals. However, task shifting is not a substitute for much needed resources and investments in health systems throughout the area.

As is apparent from the CAPRISA[35] and iPrEx[39] trials, adherence is a key issue, and research continues to examine innovative real-time strategies to monitor adherence to ART that could increase the reliability of adherence measures while increasing uptake.[59] Development of interventions that are less dependent on adherence (eg, rings, implants, longacting antiretroviral drugs, and slow-release topical approaches) is one of the crucial challenges.[60] Adherence is also a challenge for treatment for which approaches independent of adherence are needed. Research now aims to assess topical and systemic intervention products that differ from products used for treatment, well tolerated products, and the use of products for postexposure prophylaxis.[61]

Effective prevention strategies dominated by implementation challenges

HIV testing

HIV testing is recognised as a crucial part of almost all programmes for HIV prevention, especially in view of new developments in prevention with antiretroviral drugs. Testing can identify people living with HIV/AIDS for the purpose of HIV prevention and care,[56] and can also identify those who are HIV negative, who can then be prioritised for prevention interventions to help them to maintain their status (eg, pre-exposure prophylaxis, VMMC). This approach, whereby HIV testing is central to the prevention–treatment continuum, moves away from general risk reduction messages for all audiences (eg, condom use, sexually transmitted infection [STI] treatment) towards specifically tailored approaches for individuals based on their serostatus and prevention needs.

Although HIV testing—which has historically been combined with risk reduction counselling—can prevent inadvertent transmission to sexual and needle-sharing partners in people living with HIV/AIDS, this effect is generally not noted in individuals who are HIV negative[62,63] (although the community-level benefit of testing on prevention is being investigated in Project Accept[64]). Research is focused on streamlining the content of the testing process, particularly in response to the diminishing support for pre-test counselling, by moving assessments of individual risk and plans for risk reduction to post-test sessions.[65,66] Hence, we refer to HIV testing alone as part of a large programme of combination prevention, which is intentionally disaggregated from a broad approach to HIV testing and counselling.

Much of the substantial scale-up in HIV testing[67] has been attributable to worldwide recognition of the value of expanding testing from client-initiated testing (eg, voluntary counselling and testing) to routine testing,[65] which could normalise and destigmatise HIV testing.[68] Furthermore, such strategies are cost effective,[69] have individual clinical benefits (via earlier detection),[70] and could potentially greatly reduce new infections when coupled with early start of ART.[49] However, successful implementation of so-called test-and-treat strategies are

challenged by the difficulties of testing of large numbers of healthy people who are not attending health-care services, incomplete engagement in HIV care,[56] and inadequate technology to detect people with acute HIV infection who are the most infectious.[17]

The most crucial questions for HIV testing centre on identification of the best strategies to increase demand for and provision of testing services, in both individuals and couples. Overall coverage of testing is low—a median of 17% of women and 14% of men in the general epidemics in sub-Saharan Africa from 2005 to 2009 had ever been tested for HIV infection and knew their results.[71] Demand for HIV testing is a complex function of access to health care, perception of risk, fear, stigma, and the threat of violence.[72–74] Although onsite rapid testing and provider-initiated testing can overcome some of these obstacles, approaches to mitigate fear and the threat of violence (particularly for women) are being investigated. Similarly, models of service delivery to optimise uptake of testing and linkage to care and treatment, while protecting patient rights and confidentiality, are an active part of operations research. Home-based, door-to-door testing is a promising model,[64,75] as are structural interventions, such as economic incentives,[76] which can play an important enabling part. In this way, both supply-side and demand-side barriers as well as inefficiencies can be addressed to improve access to and delivery of this key entry point to HIV prevention services.

Prevention of mother-to-child transmission

WHO's four-pronged strategy[77] for PMTCT recommends: (1) primary HIV prevention in women of childbearing age; (2) prevention of unintended pregnancies in women with HIV infection; (3) prevention of HIV transmission from women with HIV to their infants via use of antiretroviral drugs; and (4) provision of treatment, care, and support to women with HIV and to their families. To date, most emphasis has been placed on the third prong (perhaps at the expense of the others)—the integrated cascade of services centred on antiretroviral drug use offered in antenatal, perinatal, and postnatal care that together can reduce the risk of mother-to-child transmission to less than 5% in breastfeeding populations and less than 2% in non-breastfeeding populations.[78,79] For maximum effect, pregnant women who are HIV positive should receive a series of interventions, including attending antenatal care; being offered, accepting, and receiving the results of a HIV test; and accepting and adhering to antiretroviral-drug prophylaxis for themselves and their exposed infant: the PMTCT cascade. Thus, the success of PMTCT programmes is highly sensitive to the cumulative impact of attrition of mother–infant pairs at each step. Only 15–30% of pairs in high-burden countries complete the cascade.[80]

In 2010, WHO revised the guidelines for PMTCT treatment in response to increased evidence about the improved effectiveness of combination antiretroviral regimens compared with monotherapy (eg, single-dose nevirapine). The new guidelines recommended that all eligible pregnant women with HIV (ie, CD4 cell count ≤350 cells per μL) receive lifelong antiretroviral therapy for their own health, and that HIV-positive women who are not eligible for this therapy and their exposed infants have one of two prophylactic combination regimens to prevent transmission from mother to child.[79,81] Furthermore, for the first time, antiretroviral drug prophylaxis was recommended during breastfeeding in settings where breastfeeding is the safest feeding option for infants.

Worldwide, progress has been made in scaling up PMTCT in resource-poor settings. About 370 000 children born to mothers with HIV infection were newly infected with HIV in 2009—a decrease of 24% from 2004.[52] Testing coverage of pregnant women also improved from 7% in 2005 to 26% in 2009, and 53% of HIV-positive women in low-income and middle-income countries received antiretroviral drugs to prevent mother-to-child transmission in 2009—an increase from 45% in 2008, and 15% in 2005.[67] However, a recent demographic model showed that even if new HIV infections in women of reproductive age were halved, the unmet need for contraception was eliminated, the new guidelines had 90% coverage, and the duration of breastfeeding was reduced to 12 months, the reduction in new infections in children and the rate of mother-to-child transmission would still fall short of UNAIDS' objectives by 2015.[78] Thus, focus on all four prongs of WHO's PMTCT strategy is essential.

Understanding women's fertility intentions and the expansion of family planning services to HIV-infected non-pregnant and pregnant women is important to address the second prong of WHO's PMTCT strategy. The provision of contraception to women with HIV who do not want to become pregnant can be more cost effective than the provision of PMTCT services.[82] In addition, stimulation of demand and strengthening of delivery of services are a major focus of research attention, with particular emphasis on prevention of leakage at every step in the cascade. Low use of antenatal-care services, poor provider knowledge, low coverage of HIV testing, and poor patient documentation and tracking systems have hindered translation of research findings into routine practice.[83] Of the 25 highest burden countries, only ten had moved from single-dose nevirapine to more effective combination regimens for PMTCT by 2009, although WHO has recommended this approach since 2004.[84] Furthermore, the emphasis on immunological monitoring to establish ART eligibility will need substantial scale-up of CD4 cell testing (in 2008, only 24% of pregnant women with HIV received a CD4 cell count[85]) and complementary implementation research to identify models of service delivery that minimise attrition in view of the added complexity of combination regimens and immunological monitoring.[86]

Male circumcision

In the past 3 years, further studies have confirmed that VMMC reduces risk of HIV acquisition in men.[87–89] By contrast, the question of the protective effect of VMMC

for women has been debated. Although the benefit to women of their male partner not acquiring HIV is obvious, whether voluntary male circumcision has benefit for the woman if her partner is already positive is unclear. Findings from one randomised controlled trial suggested no immediate benefit of VMMC in reduction of transmission from infected men to their female partners,[90] but an older observational study[91] and a recent prospective study[92] showed reductions of up to 46% in male-to-female transmission. These data have led to revised calculations of the potential population-level effect of VMMC, with estimates of infection reductions for men and women as high as 28% in Zimbabwe.[93] These potential benefits are amplified by reductions in the risk of acquisition and transmission of human papillomavirus, the precursor to cervical cancer, in men,[94–96] although research is conflicting about the effect of VMMC on acquisition of *Trichomonas vaginalis*.[97,98]

Since 2008, district-level scale-up efforts in Kenya[99] and Tanzania[100] have shown that VMMC can be delivered at a pace and scale consistent with reaching population-level effect. However, although ecological studies[101,102] of populations in which traditional male circumcision is common provide some evidence for population-level outcomes, no data are available for how great an effect this scale-up will have on the epidemic. Efforts will benefit from implementation research, such as how best to create demand, increase levels of HIV testing, and maximise adherence to the 6-week period of sexual abstinence after surgery. Research into non-surgical methods[103,104] will also provide valuable options in settings where surgical staff are scarce.

Although there are examples of rapid and intensive scale-up, the same has not happened in some high-burden regions and countries. In many countries, policy makers have been slow to support VMMC.[105,106] This reluctance may stem from perceptions that support is biased towards particular religious groups, that its advocation will lead to widespread behavioural disinhibition, and that rollout will strain already overburdened health systems.[105,107] Indeed, although rapid scale-up seems best accomplished by assembly of one-time teams of health-care staff,[99,100] elements of the health system that are weak in many low-resource countries are still heavily relied on, highlighting the need for task shifting and further innovation into issues related to supply-chain, transportation, and financing. These real and perceived barriers have slowed the rollout of VMMC, but indications such as dedicated funding within PEPFAR bilateral budgets show that support is growing.

Structural and behavioural interventions

Structural interventions

Structural interventions can reduce high-risk behaviours, STIs, and known mediators of risk, including gender inequality and intimate partner violence.[108–110] Recently, studies of cash transfer programmes have strengthened the hypothesis that economic instability and poverty drive risk behaviour in young women. A randomised trial in Malawi[111,112] showed that girls receiving a cash transfer (either unconditional or linked to school attendance) had a lower prevalence of HIV and HSV-2 infections than did controls (60% and 75% lower, respectively), because of delayed sexual debut, fewer and younger partners, less sexual activity, and reduced transactional sex. A randomised trial in Tanzania[113] linking cash transfers to remaining free of STIs suggested that men and women receiving incentives had a 25% lower incidence of infection than did controls. By contrast, another programme in Malawi[114] that paid men and women to maintain their HIV-negative status for 1 year, noted no effect, although size and timing of the incentive might have been limiting factors. The preliminary results of these studies suggest that financial security could affect sexual behaviour, and that the promotion of economic empowerment and sustainable livelihoods might be key to reduction of HIV risk.[115]

Legislative reforms, reducing stigma and discrimination, and enhancing social capital are important structural interventions for a range of populations, including sex workers, men who have sex with men, and injecting drug users.[3] A systematic review showed that policy-level support and empowerment strategies for sex workers can improve acceptability, adherence, and coverage of HIV-prevention programmes.[116] Similarly, modelling suggests that approaches designed to mitigate the harmful effects of drug use, such as needle and syringe exchange programmes, medication assisted treatment for substance misuse, and other interventions, could substantially curtail epidemics related to injecting-drug users, particularly when implemented alongside non-discriminatory laws and rights-based interventions.[117,118]

Further research is needed to guide replication and scale-up of promising programmes, and to document how different structural interventions affect patterns and pathways of risk. Although structural interventions are difficult to evaluate in randomised trials,[8] important methodological innovations and lessons are emerging with new support from donors.[3,119,120] Further research should explore key elements of economic interventions such as microfinance (leading to independence and more choice and control over sexual partners and behaviours), including the additional benefits of training or community mobilisation.[109,121] For cash transfer programmes, understanding which behaviours can be incentivised is important, as is the size, frequency, and conditionality of transfers.[122] Finally, the importance of structural interventions that address cultural norms, gender and economic inequalities, migrant labour, and other factors underlying individual behaviour (eg, concurrent partnerships) is a substantial area of exploration.

For more on **PEPFAR bilateral budgets** see http://www.pepfar.gov

Behavioural interventions

Coates and colleagues[4] concluded that behavioural strategies were essential, but not sufficient, components of comprehensive HIV prevention and that "behavioural

strategies themselves need to be combinations of approaches at multiple levels of influence". Although estimates have suggested a decreased incidence of HIV in 33 countries, along with reduced sexual-risk behaviour in young people,[52,123] weaknesses in the availability of both programme evaluation and behavioural and epidemiological data make causal attribution of these reductions to HIV prevention programming difficult. For example, in Zimbabwe, careful analysis has suggested that incidence declines with behaviour change,[7,8] but this finding contrasts with a randomised controlled trial of a multipronged prevention intervention in one region of Zimbabwe that failed to show an effect (potentially because of timing or insufficient power).[124]

In the generalised epidemics of southern Africa, much attention has focused on overlapping or concurrent partnerships; albeit with controversy.[125,126] Although there is no disagreement that multiple concurrent partnerships contribute to risk for HIV transmission, and thus should be subject to HIV prevention programming responses,[127] the normative hold of concurrency makes such partnerships difficult to address directly. Regional media campaigns in South Africa suggest some preliminary effects on some risk behaviours, but no effects (as yet) for multiple partnerships.[128]

Behavioural strategies for prevention in men who have sex with men have shifted from generic strategies to ones that are tailored toward the serostatus of both partners. A review noted increased incidence in men who have sex with men in many high-income countries, and the prevalence of seroadaptive behaviours in these populations.[129] 14–44% of HIV-positive men who have sex with men, and 25–38% of those who are HIV negative, reported restricting unprotected anal intercourse to seroconcordant partners, and 14–35% and 6–15% of men who are HIV positive or negative, respectively, who have sex with men reported selecting insertive or receptive sex on the basis of HIV status. Evidence is available that men who have sex with men use partner viral load as another determinant in behaviours to reduce risk,[130] with added attention to this strategy after the so-called Swiss statement that HIV transmission in the context of fully suppressed viral load and absence of STIs was unlikely.[131]

Behavioural prevention for injecting-drug users continues to focus on strategies aimed at mitigating the harmful impacts of drug use, in order to reduce risk behaviour (needle sharing) and HIV incidence.[117,132] Importantly, most studies have noted that the effect of these programmes is greatly enhanced with combinations of structural (eg, law reform), biomedical (eg, ART), and behavioural (eg, needle and syringe programmes) approaches.[117]

Difficulties in measurement of HIV incidence, together with the well documented problems in self-report of sexual behaviour, mean that the "gold standard" of evidence for behavioural interventions is unlikely to be reached soon.[5] However, large-scale behavioural change is clearly central to reduction of incidence, and behavioural interventions are crucial in amplification and facilitation of other prevention approaches, including driving demand for HIV services such as HIV testing, VMMC, PMTCT, and treatment. Assessment of the effect that these programmes have on service uptake might be useful both alone and as a proxy for effect on HIV incidence. Key questions for implementation of behavioural interventions concern the challenge of bringing community-based programmes to scale while maintaining quality and a better appreciation of the balance between local adaptability and fidelity.

See Online for webappendix

	Effectiveness of prevention intervention			Number of trials
	Positive effect	Adverse effect	No effect	
Behavioural	..	..	7	7
Structural: microfinance, CCTs	1*[111]	..	2[108,114]	3
Diaphragm use	..	..	1	1
Topical agents (microbicides)				
Non-ARV based	..	1	11	12
ARV-based PrEP	1[35]	..	..	1
Systemic, oral PrEP	1[39]	..	2†[133],‡[40]	3
Treatment as prevention	1[47]	..	..	1
Male circumcision	3	..	1	4
STI treament	1	..	8	9
Vaccine	1	..	3	4
Total trials	9	1	35	45

Results of 43 phase 2b or phase 3 randomised trials of 45 interventions to prevent the sexual transmission of HIV. Adapted from Padian and colleagues,[5] and updated with results of six trials since July, 2010 (the period since the last review).[35,39,40,47,111,114] See webappendix for full list of references for each category. Positive effect was when the intervention significantly reduced the risk of HIV in the intervention group compared with the control group; adverse effect was when the intervention significantly increased the risk of HIV in the intervention group compared with the control group; and no effect was when the intervention showed no significant effect (positive or adverse), thus the null hypothesis could not be rejected. CCT=conditional cash transfer. ARV=antiretroviral. PrEP=pre-exposure prophylaxis. STI=sexually transmitted infection. *Study, which has not yet been published in peer-reviewed publications, did not measure HIV incidence but showed differences in HIV prevalence. †Premature closure of the trial substantially reduced study power. ‡FEM-PrEP study prematurely closed because of futility after interim analyses revealed no protection against HIV. Table reproduced with permission from Wolters Kluwer Health.

Table: **Interventions to prevent the sexual transmission of HIV**

Discussion

In the past year, HIV prevention has changed substantially and several efficacious interventions have reinvigorated the preventive science community (table). The value of prevention with antiretroviral drugs for individuals with and without HIV has emphasised the overlap of treatment and prevention, and reinforces the need for integrated strategies for epidemic control. No longer is it acceptable to consider expenditures for treatment and prevention separately; the challenges of sustainably financing epidemic control apply equally to both.[134] New prevention approaches demand increased interdisciplinary approaches within the prevention community. 30 years into the HIV/AIDS epidemic, clearly the separation of biomedical and behavioural prevention is outdated and inefficient. For example, the successes of biomedical interventions, such as pre-exposure prophylaxis and treatment for prevention, will rely as much on the ability

of an intervention to enhance adherence (behavioural), as on the drugs' pharmacokinetics (biomedical).

A significant change in new prevention findings is the promise for more prevention strategies whose initiation and implementation is under the control of women. For example, topical pre-exposure prophylaxis, especially when used as prophylaxis by women, has the potential to change the gender dynamic in the epidemic enormously. A vaccine would be the great equaliser, presumably protecting men and women indistinguishably. Additionally, growing research has shown that structural interventions including conditional cash transfers have the potential to reduce risk behaviours as well as STIs and HIV. Given that HIV in much of Africa disproportionately affects women,[52] this is a significant change in approach and holds substantial promise for future implementation. Until recently, all available prevention technologies, such as male and female condoms and male circumcision, required male initiation or acceptance, or both.

The central role of prevention based on antiretroviral drugs has emphasised the importance of adherence-independent approaches. Perhaps more importantly, the promise of such prevention has indicated that ethical and policy issues are as important as research into effectiveness. In view of scarce resources, the need to prioritise those who get antiretroviral drugs (pre-exposure prophylaxis or treatment for prevention), and consider the burden of distribution in view of frail health systems, calls for a different type of research that focuses on the balance between efficiency and equity and issues related to implementation science. An essential question is how a country's health service could maintain antiretroviral therapy in legions of healthy patients with high CD4 cell counts mainly for prevention benefits to partners, when it is not able to initiate and maintain high retention of those with low CD4 cell counts who need ART for survival.

HIV testing, VMMC, and PMTCT research should focus on implementation science issues related to efficient and effective scale-up, including methods to increase demand, uptake, and adherence, and those to optimise and strengthen elements of the health system, including procurement, supply chain, transportation, and sustained financing.

As we move forward, we cannot fail to assess impact.[135] Although methodological challenges such as the absence of a reliable incidence assay, the lack of naive control groups, and no suitable surrogates for HIV complicate evaluation, the time has come to require that programmes be implemented so that impact can be assessed. Concurrent advances in methods of evaluation have been made to support this effort.[136] This is essential in order to ensure transparent and unequivocal results that can demonstrate the effect of the programme being evaluated and just as importantly, that can inform the global effort to combat HIV/AIDS.

The future of HIV prevention is in operationalisation, implementation, and assessment of combination prevention programmes.[1,137] However, combination interventions have their challenges, including adaptation and replication of complex and multifaceted prevention programmes whose successes might depend on subtle factors of context or programme delivery. For example, the development of one integrative package that sufficiently incorporates local ownership of AIDS responses is unlikely; specifically, the need to tailor the combination to local epidemiology remains paramount. Our challenge is to carefully select a group of effective interventions that together have an increased chance of success by complementing each other to achieve the elusive goal of changing the course of the HIV epidemic.

Contributors

NSP, NH, BS, and SIM constructed the original outline of the manuscript. All authors participated equally to writing, revising, and the final approval.

Conflicts of interest

We declare that we have no conflicts of interest. The findings and conclusions in this paper are those of the authors and do not necessarily represent the views of the US Department of State.

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Drug concentrations after topical and oral antiretroviral pre-exposure prophylaxis: implications for HIV prevention in women

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The early closure of a clinical trial assessing the effectiveness of oral antiretroviral pre-exposure prophylaxis (PrEP) in women, FEM-PrEP,[1] is a substantial setback for HIV prevention. Expectations of this trial were high in view of favourable results from the pre-exposure prophylaxis initiative (iPrEX) trial,[2] which studied the same drug and dosing strategy in men who have sex with men, and the Centre for the AIDS Programme of Research in South Africa (CAPRISA 004) trial,[3] which tested tenofovir gel (a topical PrEP formulation) in heterosexual women. As a result, the interim FEM-PrEP trial results, announced on April 18, 2011, which showed no protection against HIV infection,[1] were disappointing. Using publicly available information[1] and data from other PrEP studies, we offer a potential explanation for the results of the FEM-PrEP trial.

In high HIV prevalence settings, such as sub-Saharan Africa, young women have disproportionately high HIV incidence rates, up to 8-times higher than for men of the same age.[4] Available HIV prevention strategies provide few options for young women who are at high risk of infection but who are unable to convince their partner to be faithful or use condoms, underscoring the urgent need for a women-initiated HIV prevention technology. To this end, several microbicide trials have been undertaken during the past 17 years. Until 2010, none had shown protection against HIV acquisition.[5] A new approach was needed. Antiretroviral drugs, already shown to be effective in treating HIV infection and prevention of mother-to-child transmission, heralded a new option to prevent sexual transmission.

FEM-PrEP was a phase 3, double-blind, randomised, placebo-controlled trial assessing the effectiveness of daily oral tenofovir disoproxil fumarate and emtricitabine for prevention of HIV acquisition in women aged 18–35 years in South Africa, Kenya, and Tanzania. At a scheduled interim analysis, the HIV incidence rate was 5 per 100 person-years in the 1951 women enrolled, and the 56 HIV endpoints were equally distributed between the study groups.[1] Continuation of the study to the planned 72 HIV endpoints in an attempt to show effectiveness was deemed futile, so the decision was made to undertake an orderly closure of the trial.

Why did the FEM-PrEP trial not show protection against HIV infection? To conclude that oral tenofovir disoproxil fumarate and emtricitabine does not prevent HIV infection in women would be overly simplistic and premature; several possible explanations exist for the reported primary HIV outcome in the trial. Such results could have occurred by chance in a trial of a truly effective product, but the chance of observing no effectiveness if the drug is truly 50% protective against HIV is about 3 in 1000. However, two of the most plausible explanations for the trial results are low pill adherence and inadequate drug concentrations at the site of infection—ie, the genital tract.

Adherence and drug distribution are only two of the many components of the pathway that is intended to end with antiretroviral drugs preventing the development of HIV infection after viral exposure in the female genital tract. However, they are both crucial for the desired outcome. Adherence levels are dependent on human behaviour in the context of the user's social environment, whereas the available concentration of the drug is affected by its pharmacological properties and host-cell biology.

Although reported adherence in the FEM-PrEP trial was high,[1] its accuracy cannot be assessed at this time. Blood concentrations of the drugs in women assigned to tenofovir disoproxil fumarate and emtricitabine and analysis of effectiveness, stratified by adherence levels, will provide a more reliable indication of pill adherence during the trial. A comparison of drug concentrations in the women who developed HIV infection with those in appropriately selected controls who remained uninfected during the course of the trial could likewise provide useful clues. In the meantime, exploration of alternate explanations is important, in the event that low adherence does not fully account for the trial's outcome.

Tenofovir and emtricitabine concentrations in genital and rectal tissues have been assessed in previous phase 1 and pharmacokinetic studies of the oral preparation and tenofovir gel. With orally administered drug, the median cervicovaginal fluid concentration of tenofovir and emtricitabine at the end of the 24 h dosing interval was 68 ng/mL (IQR 28–112) and 596 ng/mL (537–644), respectively.[6] Vaginal tissue concentrations of tenofovir and emtricitabine were 7 ng/g and 63 ng/g (ng/g is roughly equivalent to ng/mL), respectively.[7]

These concentrations from oral dosing are substantially lower than vaginal concentrations achieved with topical tenofovir gel or rectal concentrations from oral tenofovir disoproxil fumarate and emtricitabine. The median cervicovaginal fluid concentration of tenofovir at the end of the 24 h gel dosing interval was 100 000 ng/mL and the vaginal tissue concentration was 7000 ng/g.[8] Rectal tissue concentrations of tenofovir and emtricitabine 24 h

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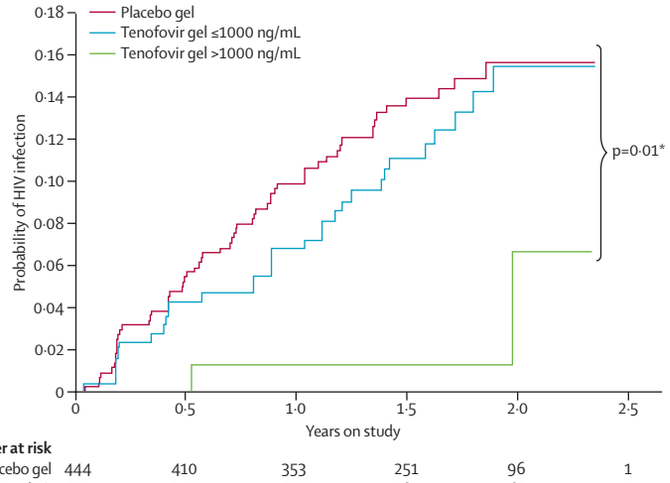
	Vaginally administered 1% tenofovir gel	Orally administered tenofovir disoproxil fumarate
Blood		
Plasma[7,8,10,11]	~1–10 ng/mL	25–50 ng/mL
Peripheral blood mononuclear cell[11]	<10 fmol/10^6 cells	~70 fmol/10^6 cells
Mucosal fluid		
Cervicovaginal[7,8,10]	~10^5–10^6 ng/mL	~70 ng/mL
Tissue		
Vaginal (tenofovir)[7,8,10,11]	~10^3–10^4 ng/g	10 ng/g
Vaginal (tenofovir diphosphate)[7,8,10,11]	~10^3 fmol/mg	1–10 fmol/mg
Cytobrush cells (tenofovir diphosphate)[8,11]	~10^4–10^5 fmol/10^6 cells	~10^3 fmol/10^6 cells
Rectal (tenofovir)[7,11]	NA	2000 ng/g
Rectal (tenofovir diphosphate)[7,11]	NA	100–1000 fmol/mg

PBMC=peripheral blood mononuclear cell. NA=not available.

Table: **Tenofovir concentrations measured in blood, mucosal fluid, and tissue 24 h after topical or oral administration**



Number at risk

Placebo gel	444	410	353	251	96	1
Tenofovir gel ≤1000 ng/mL	253	240	217	162	63	0
Tenofovir gel >1000 ng/mL	82	82	69	49	15	0

Figure: **HIV infection rates in women in the CAPRISA 004 trial[3]**
Women assigned to tenofovir gel are stratified by cervicovaginal fluid concentrations of tenofovir.
*Log rank comparing women with tenofovir concentrations greater than 1000 ng/mL versus placebo.

after a single dose of the oral drug were 1877 ng/g and 124 ng/g, respectively.

Since tenofovir diphosphate and emtricitabine triphosphate are the metabolites of the parent drugs that inhibit viral replication, their intracellular tissue concentrations after oral and topical dosing could be informative. Although threshold concentrations for protection against HIV infection have not yet been established, data from an ex-vivo colorectal biopsy infection model[9] suggest that at least 1000 fmol/mg of tenofovir diphosphate could be needed for near complete protection. The concentrations of this metabolite 24 h after one oral dose of tenofovir disoproxil fumarate and emtricitabine were 206 fmol/mg in rectal tissue and only about 2 fmol/mg in vaginal tissue.[7] By comparison, the tenofovir diphosphate concentrations 24 h after one tenofovir gel dose were about 1000 fmol/mg in vaginal tissue and roughly 10 000 fmol/10^6 cervical cells obtained from cytobrush sampling.[8] In short, tenofovir diphosphate concentrations are about 100-fold higher in rectal than vaginal tissues with oral tenofovir disoproxil fumarate and emtricitabine, and about 1000-fold higher in vaginal tissues with tenofovir gel than with oral tenofovir disoproxil fumarate and emtricitabine (table).

To gain insight into the potential threshold tenofovir concentrations needed to prevent HIV infection in women, we assessed tenofovir concentrations in undiluted aspirated cervicovaginal fluid with a validated ultra performance liquid chromatograph-mass spectrometry method in women assigned to tenofovir gel in the CAPRISA 004 trial.[3] Samples were available from the first study visit post infection from 34 of the 38 HIV seroconverters and from a randomly selected study visit from 301 women assigned to tenofovir gel who remained uninfected during the trial.

With data from this trial,[3] HIV incidence in women with tenofovir concentrations of 1000 ng/mL or less (n=253) and those with tenofovir concentrations of 1000 ng/mL or more (82) was compared with that in the placebo gel group (figure). The HIV incidence rate in women with tenofovir concentrations of 1000 ng/mL or less was close to that in the placebo group (7·8 *vs* 9·1 per 100 women-years; incidence rate ratio [IRR]=0·86, 95% CI 0·54–1·35, p=0·51). However, the HIV incidence rate in women with tenofovir concentrations greater than 1000 ng/mL was significantly lower than that in the placebo group (2·4 *vs* 9·1 per 100 person-years; IRR=0·26, 95% CI 0·05–0·80, p=0·01). Adjustment for age, study site, duration of study participation at the point when tenofovir concentration was measured, sexual frequency, and condom use did not materially change this finding.

These tenofovir concentrations are proxy markers of drug exposure at the actual time of HIV exposure, and some residual systematic differences between the three groups of women could account for some of the variations in HIV risk, despite adjustment for potential confounders. Notwithstanding, our data suggest that cervicovaginal fluid concentrations of tenofovir greater than 1000 ng/mL were required to prevent HIV infection. This value is more than ten times the concentration seen with oral tenofovir disoproxil fumarate and emtricitabine.

What are the implications for HIV prevention research? Detailed analyses of the FEM-PrEP[1] data will undoubtedly enhance our understanding of how antiretrovirals prevent HIV infection in women. In the interim, our suggestions for continuing and proposed PrEP research are: first, the effectiveness trials that are underway (registered with ClincalTrials.gov, numbers NCT00705679, NCT00557245, NCT00448669, NCT00119106) for tenofovir disoproxil fumarate alone and in combination with emtricitabine are crucially needed to corroborate or refute the FEM-PrEP[1] trial results and to provide information about HIV effectiveness in diverse populations, various

formulations, and in different routes of transmission. Researchers need to factor the FEM-PrEP trial outcome into the information provided to participants. Furthermore the data-review plans, especially the rules for futility, might need to be revisited.

Second, investigators need to revise existing or develop new animal-challenge and tissue models for PrEP to be able to assess varying drug dosages. Specifically, further animal models with which to assess vaginal challenge after oral dosing are needed. Additonally, the models might need an infectious virus inoculum that is closer to physiological values. Third, until there is improved clarity about the threshold concentration of tenofovir that is likely to protect against HIV, the goal in future clinical trials of this drug should be to attain the highest tolerable drug concentrations in the vagina. Options such as combinations of oral and topical formulations could be worth investigation, especially in settings in which anal sex is common in women. Fourth, efforts to enhance adherence in PrEP trials are crucial. Finally, new PrEP formulations, such as intravaginal rings and injectables, will need to be carefully assessed to work out whether the drug concentrations achieved at the site of viral exposure are likely to be high enough to prevent HIV infection.

The FEM-PrEP trial is a sharp reminder of the uncertainty of the scientific endeavour. Success needs an iterative approach to identify the most appropriate drugs, drug concentrations, adherence support, formulations, and dosing regimen for each route of HIV transmission. The proof of principle that antiretroviral drugs can prevent sexual transmission of HIV has reinvigorated HIV prevention. It has created new hope that antiretroviral-based PrEP strategies, especially those that are women-initiated, could in combination with other prevention interventions, finally stem the tide of the HIV pandemic.

Contributors

QAK and SSAK as Co-Principal Investigators conceived and designed the CAPRISA 004 trial. ADMK analysed the tenofovir concentrations in the cervicovaginal fluid. LW undertook the statistical analysis. SSAK prepared the first draft of the report and all authors contributed important edits and revisions.

Conflicts of interest

We declare that we have no conflicts of interest.

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Prevention of mother-to-child transmission of HIV and the health-related Millennium Development Goals: time for a public health approach

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Like many other countries in Africa, Malawi is preparing to revise its policies for prevention of mother-to-child transmission (PMTCT) of HIV and for antiretroviral therapy (ART) in response to WHO's 2010 guidelines.[1,2] This guidance is timely in view of the limited efficacy of single-dose nevirapine used in many PMTCT programmes[3] and the challenges facing the effective expansion of health service delivery.[4] The drive from the Global Fund to Fight AIDS, Tuberculosis and Malaria to increase coverage of PMTCT services is increasing, particularly in countries with high burdens of HIV infection; high coverage is essential to reduce transmission to infants, to provide treatment for HIV-infected women, and to meet the relevant 2015 Millennium Development Goals of reducing child mortality, improving maternal health, and combating HIV infection and AIDS, malaria, and other diseases.

The WHO guidelines specify that a CD4 cell count is crucial to decisions on the eligibility of HIV-infected pregnant women for lifelong ART. In Malawi, however, access to CD4 cell count analysis is minimal (panel)[5] and is unlikely to improve anytime soon. Thus, to make this test a prerequisite for increasing the coverage of PMTCT services and early access to ART would hinder rapid expansion in countries with heavily constrained health systems. Malawi, therefore, proposes a strategy that does not rely solely on CD4 cell counts but is based on the WHO guidelines and the public health approach outlined in the current Ministry of Health ART guidelines.[6] This strategy takes into account the weaknesses in the Malawi health system[7] yet should increase the coverage notably from the current 35%. It should also narrow the gap among the estimated 950 000 people living with HIV infection between the 225 000 currently receiving ART and the 440 000 who are eligible.[5,8]

In HIV-infected pregnant women ART use is recommended when CD4 cell counts are 350 cells per μL or less, irrespective of WHO clinical stage, or in women with disease in clinical stage 3 or 4. For pregnant women with CD4 cell counts higher than 350 cells per μL or with disease at clinical stage 1 or 2 who do not yet need ART for their own health, WHO proposes two time-limited options for antiretroviral prophylaxis (table). The Ministry of Health in Malawi chose to use a regimen of tenofovir, lamuvidine, and efavirenz in these women. This regimen is simple, it avoids zidovudine-induced side-effects, particularly anaemia, which is a common feature of pregnancy in Malawi, and it will be used as the first-line regimen in adolescents and adults. The logistics of delivery will be improved, the risks of running out of stocks lessened, the need for multiple guidelines and training eliminated, and the likelihood of successful implementation increased. Moreover, the proposed regimen is available in a fixed-dose combination of one tablet per day, can be safely used with antituberculosis drugs, is effective against hepatitis B virus, and can be used without routine laboratory monitoring of toxic effects.[9]

We propose to offer all HIV-infected pregnant women lifelong ART. This approach is not completely new, but rather is a more feasible alternative to WHO's proposed option B, which we call option B+. The proposed change is akin to the test and treat mathematical model elucidated by Granich and colleagues.[10] In view of the regimen's good safety profile, the difficulties involved in expansion of CD4 cell count testing, and the urgent need to increase the coverage of the PMTCT programme, we argue that waiting 2–3 years for the results of a pilot study would not be ethical. We therefore propose immediate implementation of this approach. If CD4 counts did become more accessible in Malawi, the guidelines could be adapted.

The expansion of the PMTCT programme in Malawi through implementation of option B+ would have various other benefits. The total fertility rate in Malawi is high, around 5·6 births per woman,[11] which is unlikely to be much lower in HIV-infected women.[12] Soon after the breastfeeding period (median duration 23 months[13]) many women become pregnant again. Thus, a stop-start approach to ART administration is almost redundant. Many women present for antenatal care late in pregnancy—an estimated 50% are thought to attend after 28 weeks of gestation—and continuing prophylaxis with antiretroviral drugs would mean that the next pregnancy could be protected from conception. The stopping of ART after cessation of breastfeeding might lead to viral rebound, with the risk of transmission to a sexual partner or fetus being notably raised. Scheduled stopping is also difficult to implement, as it requires tapering of doses to prevent drug resistance, owing to the different half-lives of the antiretroviral drugs. Additionally, the risks of opportunistic disease or death might be raised.[14] Tenofovir and lamuvidine are active against hepatitis B virus; 10–15% of people living with HIV infection in Malawi are also infected with

hepatitis B virus,[15] and reactivation of this virus is a risk if ART is stopped.

Universal, lifelong ART for HIV-infected pregnant women will achieve maximum coverage and could potentially lead to elimination of paediatric HIV/AIDS.

In women in Zimbabwe even those with CD4 cell counts higher than 350 cells per μL had a risk of death around six times higher than that in non-infected women within 24 months post partum, and early ART could reduce mortality by 50–90%.[16] Prevention of maternal deaths has a striking effect on child survival, independent of any effect gained from the prevention of HIV transmission.

The risk of developing tuberculosis increases with declining CD4 cell counts, from 500 cells per μL;[17] the majority of pregnant women have CD4 cells counts in this range. Early initiation of ART, therefore, reduces the risk of tuberculosis.[18] Observational cohort studies in the USA and Europe also suggest that the early starting of ART significantly lowers mortality related to HIV infection and AIDS.[19]

In Malawi, most HIV-infected women starting prophylaxis with zidovudine do so without the CD4 cell count being known. As about 50% of these women will have counts of 350 cells per μL or lower, all receive zidovudine monotherapy de facto. Although there is no evidence that exposure to zidovudine prophylaxis in women with advanced HIV disease increases the risk of drug resistance, this possibility is of concern.

HIV-transmission in couples is an important contributor to overall transmission rates, and the use of ART greatly reduces the risk of HIV-transmission to non-HIV-infected partners.[20]

HIV status and pregnancy can be confirmed in virtually all health centres in Malawi that provide maternal health services. The message that triple therapy must be taken for life and on a daily basis from the start is simple. Both these features mean the option B+ policy could be rapidly rolled out to and implemented by all centres.

In the first 3 years of the implementation of the option B+ policy we estimate that ART would be started in 25 000 more pregnant women per year than at present; of note, these women would have required ART at some point, and are merely starting treatment earlier. To hit this target, the number of health facilities providing ART would have to increase from 377 to all 650 with mother and child health services. Current constraints on health systems and human resources will need to be addressed to accommodate additional burdens, such as extended intervals between appointments, task-shifting, and expansion of the health staff.

The chosen ART regimen is more expensive than a regimen of stavudine, lamivudine, and nevirapine (US$176 per person per year[21] *vs* $65), but we believe that the advantages justify the initial added cost. In addition, drug prices are expected to lower over time, and reductions in the number of infections, morbidity, and mortality in children and adults will contribute to a decline in overall treatment cost. Moreover, the management costs of option B+ are likely to be similar to those for option A or B, since the frequency of follow-up for mothers and infants is similar in all three. A full economic analysis, however, is needed.

Efavirenz is potentially teratogenic in the first trimester, but the risk seems to be lower than previously thought.[22] In the absence of conclusive evidence, women who desire pregnancy could be offered an alternative ART regimen in which nevirapine replaces efavirenz, until the second trimester of the pregnancy. Other women receiving ART should be offered contraceptives

***Panel*: Factors hampering universal coverage for CD4 cell count testing in Malawi**

Technology

- No easy-to-use, rapid, and reliable test (eg, dipstick technology) is currently available for use by health-care workers at the point of care in all health facilities
- Reliable stocks of reagents and regular maintenance and supervision of existing CD4 cell count equipment are difficult to provide
- Most equipment is currently based in tertiary and district hospitals
- Most machines available at peripheral health facilities are still bench-top machines that require skilled laboratory staff to operate them
- Various quality assurance issues remain unresolved

Health facilities

- The numbers of health-care workers able to do CD4 cell counts within facilities or to do the related administration for remote testing are limited
- Transport of blood samples in a timely manner from all 650 health facilities in Malawi is cumbersome and impracticable, and samples may become unusable
- Blood collection in tubes for transport is associated with the risk of mixing up labelling and results
- Stocks of reagents frequently run out

Patients

- The need for repeat visits to the health centre to collect results implies additional indirect journey costs
- Referral of patients to different clinics where CD4 cell counts can be done leads to loss to follow up, low uptake of referrals, or both, especially among pregnant women

	WHO option A	WHO option B	Malawi Ministry of Health option B+
Mother	Antepartum zidovudine from 14 weeks' gestation, single-dose nevirapine at onset of labour, and zidovudine plus lamivudine during labour and delivery and for 7 days' postpartum	Triple ART regimen from 14 weeks' gestation until 1 week after all exposure to breastmilk has ended	Triple ART regimen started from 14 weeks' gestation and taken for life
Breastfeeding baby	Daily nevirapine from birth to 1 week after all exposure to breastmilk has ended	Daily nevirapine syrup from birth to 6 weeks	Daily nevirapine from birth to 6 weeks

ART=antiretroviral therapy.

***Table*: Antiretroviral prophylaxis options recommended for HIV-infected pregnant women who do not need treatment for their own health**

in line with a comprehensive PMTCT strategy. We recognise that exposure to efavirenz cannot be completely avoided in the first trimester, but this risk seems outweighed by increased coverage and much-reduced overall mortality.

Our approach offers a real opportunity to integrate HIV treatment into mother and child health services and make tangible progress towards achieving the relevant Millennium Development Goals. Option B+ favours women rather than men in terms of ART accessibility, although we feel this inequality is acceptable in view of the policy's potential contribution to the elimination of paediatric HIV infection.

The public health model outlined in this Viewpoint is so far untried and untested, but we are confident that it can work. Concerns about the acceptability to the general population of HIV testing and ART when that programme was scaled up in 2004 proved unfounded. Community acceptability for this approach would, however, have to be assessed from the start and human rights would have to be protected at all times. In the meantime, community leaders and health-care workers would have to be careful not to coerce people into being tested. National guidelines clearly state that everyone has the right to decline HIV testing without any consequences. We would expect community members and people living with HIV and AIDS to play important parts in the delivery strategy. We propose that sentinel sites are set up to improve human resources, infrastructure, and monitoring and reporting of drug tolerability. The people who would be responsible for administration of ART should be specified before implementation.

Increasing the uptake of PMTCT linked with access to CD4 cell count testing has been a major challenge. Progress towards the relevant Millennium Development Goals will, therefore, depend on additional strategies to substantially increase PMTCT coverage. We need to bridge the implementation gap with a bold PMTCT public health approach.[6]

Contributors

EJS, AJ, ABS, and ADH wrote the article. EJS, AJ, DM, SDM, AM, ZC, ADH, JJvO, TM, AB-S, RZ, LL, MZ, WVD, CFG, RA, MS, and FC contributed to the concept of the article. All co-authors were involved in revising drafts and writing and approving the final paper.

Conflicts of interest

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Can further placebo-controlled trials of antiretroviral drugs to prevent sexual transmission of HIV be justified?

Louise Kuhn, Ida Susser, Zena Stein

The Centre for the AIDS Programme of Research in South Africa (CAPRISA) 004 trial[1] that was reported in July, 2010, assessed the efficacy of a gel containing the antiretroviral drug tenofovir, which can be used intravaginally to reduce the risk of sexual transmission of HIV from men to women. In 889 women at community sites in South Africa, the gel was associated with a 39% reduction in HIV incidence in women. After adjustment for reported adherence the reduction was 54%. The randomised, double-blind, placebo-controlled Prexposure Prophylaxis Initiative (iPrEx) study,[2] which was published soon afterwards, assessed the efficacy of daily oral antiretroviral drugs (tenofovir plus emtricitabine) in reducing the risk of sexual transmission of HIV between men. In 2499 high-risk men who have sex with men and transgender women at sites in Peru, Brazil, Ecuador, Thailand, South Africa, and the USA, this drug combination was associated with a 44% reduction in HIV incidence. After adjustment for estimated adherence the reduction was 73%. Despite the clear results from these two trials of the efficacy and safety of antiretroviral drugs to prevent sexual transmission of HIV, further placebo-controlled trials in women are planned or underway.[3] On the basis of fundamental concepts of public health, we believe that to undertake more placebo-controlled trials would be short-sighted and surely unethical, and to delay implementation would cost the lives of the very women whom the drugs are intended to benefit.[4]

A rationale for further placebo-controlled trials is that they are required by regulatory agencies, such as the US Food and Drug Administration, before antiretroviral drugs are approved for prophylactic use. If this claim is true, these agencies are putting researchers in an untenable position and expecting them to violate clinical equipoise—a principle that is central to the ethical use of a placebo. Researchers in this specialty are deeply committed to making these interventions immediately available to the high-risk populations who need them; therefore, further placebo-controlled trials raise a profound ethical dilemma. To enable high-risk men and women to access these interventions in the long term, researchers might feel compelled to act in a compromised way in the short term. Investigators who undertake further placebo-controlled trials will need to make the case to their study participants, and to the Institutional Review Boards that oversee them, that there is genuine uncertainty about whether antiretroviral prophylaxis will reduce the risk of HIV transmission. However, the positive results of the CAPRISA and iPrEx trials and expansion of the scientific evidence-base make such a case increasingly impossible to make.[5]

Our argument against placebo-controlled trials does not mean that further research is not needed. Many important issues do need further research, but they can be best addressed with study designs that do not use placebos. For example, one important question is how best to use antiretroviral drug products. Is oral administration easier and more effective than mucosal administration or vice versa? Is use targeted around anticipated sexual intercourse? And is use of the product before and after intercourse (ie, the original study of tenofavir gel) better or worse than daily consumption (ie, iPrEx and oral contraceptive pills)? Randomised trials comparing different antiretroviral drug strategies are the optimum designs to address these issues, and such comparisons render the use of placebo unnecessary. Safety is another relevant question for which further research is needed. Because the completed trials were large and closely monitored, common and important safety concerns have already been ruled out. The remaining rare and serious side-effects are best addressed through systematic, planned, and transparent data collection with programme roll-out, similar to post-marketing surveillance.

Behavioural factors, including short-term and long-term adherence to antiretroviral prophylaxis, are crucial for whether an intervention can be successfully introduced in the communities that are most affected. However, these factors cannot be satisfactorily addressed by a study in which participants do not know whether they have received an effective intervention or an inert placebo. Furthermore, doubt among participants might undermine adherence in ways that cannot be adequately measured or controlled. Another argument for further placebo-controlled trials is to confirm results that could be wrong. In science, initially positive results can, on further investigation, be not so positive. Randomisation does not guarantee the elimination of confounding and, even in the most rigorously undertaken trial, chance might produce spurious associations. However, the likelihood of chance producing consistent results in two disparate populations is extremely low. The reduction reported in the intention-to-treat analyses of the CAPRISA and iPrEx trials was moderate and did not reach the 50% efficacy that would be equivalent to halving the risk of infection. Nevertheless, for costly and potentially life-limiting infections such as HIV, even small reductions can translate into substantial numbers of lives saved and suffering averted. Additionally, the results of both trials indicate that improved adherence would increase this intervention's efficacy—a result that is consistent with a true biological

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effect. In each trial there is direct biological evidence (cervical specimens with the microbicide, blood with the oral combination) that the presence of the drug relates to protection.

The call for confirmation also neglects the fact that the two trials were not done in the absence of other evidence. They were undertaken after primate studies that supported the effectiveness of this approach.[6] Biological plausibility is further strengthened by the success of post-exposure antiretroviral prophylaxis for sexual and occupational exposures in adults.[7,8] Antiretroviral drugs are routinely made available for health-care workers with needle-stick injuries and other invasive exposures to HIV. A case-control study based on passive surveillance was the basis for these recommendations.[9] The antiretroviral drugs studied are also components of standard HIV treatment for both men and women.[10]

A powerful body of scientific evidence, including placebo-controlled and comparative randomised trials and many years of programmatic experience, has established the use of antiretroviral drugs for preventing HIV transmission to human infants.[11] HIV transmission from mother to child is a pertinent example because infants are typically the most vulnerable population (regarding safety), and transmission occurs through mucosal routes after extensive and repeated exposure, as does sexual transmission (for extrapolation to efficacy).[12] The first ground-breaking trial[13] providing proof-of-principle that antiretroviral drugs can be used before, at the time of, and after exposure to prevent HIV transmission in infants with HIV-infected mothers was 16 years ago. These results set in motion a scientific programme of coordinated and interlinked clinical trials that simplified and refined the use of antiretroviral agents to prevent mother-to-child transmission so successfully that the eradication of paediatric HIV infection has been proposed as a public health goal.[14] Hundreds of thousands, perhaps millions, of infants born to HIV-infected mothers have now been exposed to antiretroviral drugs, and tens of thousands who would otherwise have acquired infection have been spared. Trials of antiretrovirals as prophylaxis in adults have a similar revolutionary potential. A few trials that were done in the years after the first proof-of-concept trial included placebos, which sparked a divisive controversy about ethics.[15] At that time, effective treatment with combination drugs was not yet established and almost nothing was known about the use of antiretroviral drugs for prophylaxis. Despite the merits of the arguments about strategies to prevent perinatal HIV transmission, a proposal of similar placebo-controlled trials in pregnant women and infants would today be unthinkable.

Decisions made about further research after the results of the CAPRISA and iPrEx trials became available raise uncomfortable questions about gender inequity. The level of protection offered in these two trials is almost identical; however, subsequent requirements have differed substantially. The iPrEx study offered open-labelled antiretroviral prophylaxis to the former placebo group of participants, and discussion about how to implement programmes among men who have sex with men in the USA has begun. By contrast, for CAPRISA, before the product can be made available, further placebo trials have been required.[3] The announcement in April, 2011,[16] of the closure of the (FEM-PrEP) placebo trial among women (testing the same pill as that used in iPrEx) on the grounds of statistical futility warns that identical repetition of placebo-controlled trials in women is not necessarily appropriate. In fact, focused clinical studies of differences in the distribution of the drug in vagina and anus could have provided preliminary information that is especially relevant to dosage, which could, and perhaps should, have usefully preceded such trials. Although the differences in pill-taking behaviours and blood concentrations between men and women might be important, adherence could also differ, and both need unblinded testing, as opposed to in the context of placebo-controlled trials. Men and women might differ, but women's needs are of equal importance to men's.

A related issue is the inequity between developed and developing countries. Heterosexual transmission affecting both men and women is the overwhelming mode of HIV transmission in sub-Saharan Africa where rates of HIV incidence are several times higher than in developed countries. Thus, delays in undertaking studies of how to begin implementation of this new intervention carry a human cost. A mathematical model of the possible effect of tenofovir gel on the HIV epidemic in South Africa estimated that between 271 000 and 602 000 new HIV infections could be prevented in 10 years dependent on coverage.[4] Inappropriate reliance on the placebo-controlled trial seems to be the main culprit of this ethical impasse. Even without ethical considerations, these trials are expensive and of long duration. In many settings they are not the most scientifically appropriate way to answer questions about policy or about biological mechanisms. A broader perspective of study design, and of the assessment of scientific evidence than presently exists, would provide a constructive way forward to learn how best to implement these new interventions to improve public health.

Conflicts of interest

We declare that we have no conflicts of interest.

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Uncommon reaction to a common prescription

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In May, 2010, a 50 year-old man presented to us with a 10 day history of abdominal pain, fever, and shivering with elevated C reactive protein and leucocytes. He had a past history of congestive subvalvular aortic stenosis which had not required surgical treatment. He weighed 85 kg, had normal renal and hepatic function, and was not on any regular medication. CT of the abdomen suggested an abscess of the appendix. He was treated with intravenous cefotaxime 1 g three times a day and metronidazole 1 g daily for 2 days and discharged with oral metronidazole 400 mg three times a day and ciprofloxacin 500 mg twice a day. 5 days later, he returned with a complete loss of hearing, fatigue, dizziness, vomiting, impaired balance, ataxia and dysarthria. He was afebrile and CT of the brain was normal. We suspected an encephalopathy caused by an adverse effect of metronidazole and/or ciprofloxacin, and both drugs were discontinued. Within one hour after admission he became unconscious. He was transferred to the intensive care unit and was intubated. MRI of the brain showed bilateral and symmetric swellings of the cerebellar dentate nuclei, dorsal medulla, dorsal pons, midbrain, corpus callosum and increased signal intensity in the supratentorial periventricular white matter (figure A), which was in accordance with previously described cases of metronidazole induced encephalopathy.[1] Meropenem, aciclovir and betamethasone were started to cover possible meningitis and encephalitis.

See Online for webappendix

The electroencephalogram, lumbar puncture, inflammatory markers, microbiological and viral testing, autoimmune markers, and thyroid function tests were all normal. Although the metronidazole concentration in plasma was not measured, an overdose was unlikely because our patient had only been prescribed one box containing 30 pills of 400 mg, and had followed the prescription accordingly. His symptoms and MRI findings were not found to correlate with earlier described cases of ciprofloxacin-induced encephalopathy. Wernicke's encephalopathy may produce similar clinical symptoms, however without MRI lesions of cerebellar dentate nuclei.[2] Furthermore, thiamine was not administered to our patient. Viral encephalitis and bacterial meningitis were ruled out. According to the Naranjo probability scale[3] our patient's symptoms were classified as probably caused by metronidazole (Naranjo Score 5/13). The case was reported to and confirmed by the Swedish adverse effect register institute "SWEDIS" as a probable case of metronidazole-induced encephalopathy. His symptoms gradually resolved and an MRI two months later, showed a clear resolution of the earlier described signal changes (figure B and webappendix). At final follow-up in September, 2010, he was well with only residual hearing impairment.

Metronidazole has been used clinically for more than 30 years and is regarded as a safe antibiotic with few adverse reactions[1,4] Encephalopathy is an extremely rare but serious, neurological side-effect.[1,2] The pathophysiology of metronidazole encephalopathy is unknown, but an acute toxic insult producing axonal swelling may be responsible[2] and the encephalopathy may be completely reversible. There are only twenty cases of metronidazole-induced encephalopathy currently reported in English medical literature.[1] In these cases, neurological adverse effects of metronidazole occurred particularly with doses exceeding 2 g daily or when used for prolonged periods.[2,5] Although MRI findings are typical for this condition, ignorance of metronidazole-induced encephalopathy may result in clinical misjudgment and delay of the diagnosis.

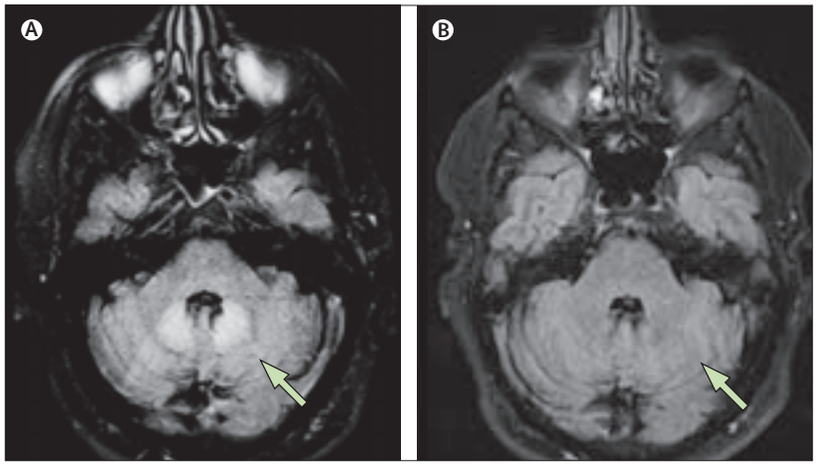

Figure: **MRI of brain in May, 2010 (A) compared to follow up in July, 2010 (B)**
Showing symmetric swelling and increased signal intensity of (A) the cerebellar dentate nuclei (arrow), and (B) complete resolution of signal changes in the dentate nuclei (arrow).

Contributors
KK and NB looked after the patient and wrote the report. Written consent to publish was obtained.

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Further particulars and application forms (152/708) can be obtained at http://www.hku.hk/apptunit/; or from the Appointments Unit (Senior), Human Resource Section, Registry, The University of Hong Kong, Hong Kong (**fax:** (852) 2540 6735 or 2559 2058; **e-mail:** senrappt@hku.hk). **Closes November 30, 2011. Candidates who are not contacted within 6 months of the closing date may consider their applications unsuccessful.** (311393)

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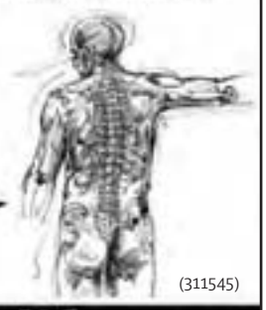
GRANTS

€ 70,000
GRANTS AVAILABLE

The **Wings for Life Spinal Cord Research Foundation** is a grant giving charity funding research aimed at resolving spinal cord injury–induced impairments. We invite applications for project grants in basic sciences, applied basic sciences, and clinical sciences. Proposals should have a view to translation from the laboratory to the clinical setting and have the likelihood of providing real benefits to human patients.

Proposal submission deadlines
Summary deadline: ***1st Sept 2011***
Full Application deadline: ***1st Nov 2011***



WINGS for LIFE

(311545)

www.wingsforlife.com

GRANTS

Call for Applications

Arthritis Research UK

Experimental Arthritis Treatment Centres – submission date Wednesday 19 October 2011

Arthritis Research UK proposes to establish a network of experimental arthritis treatment centres (EATCs) to facilitate early development of novel interventions in the treatment of arthritis and related conditions. Infrastructure funding is available to support an existing experimental treatment resource to yield an enhanced platform for the delivery of 'first in man'/'first in disease' studies of novel arthritis therapies. Each five year EATC award allows up to £75,000 per annum and is subject to midterm review.

Experimental Osteoarthritis Treatment Centre for Biomechanical Interventions – submission date Wednesday 2 November 2011

Arthritis Research UK proposes to establish an experimental osteoarthritis treatment centre (EOTC) to test the role of novel biomechanical interventions for the prevention of osteoarthritis. This initiative is supported by a donation from Össur. Infrastructure funding is available to support existing expertise in conducting clinical studies of osteoarthritis interventions and patient characterisation to assess mechanisms of action and phenotypes for intervention. The five year EOTC award allows up to £50,000 per annum and is subject to midterm review.

Further details are available at **http://www.arthritisresearchuk.org/research/eatcs.aspx**

(311617)

GRANTS

Global health trials:
second call for outline proposals

Maximising impact, *improving* health

£12 million is now available to fund late-stage (phase III/IV) efficacy and effectiveness trials of interventions that will address major causes of mortality and morbidity in low- and middle-income countries.

Proposals are now invited from academic groups based either in the countries where the studies will take place or in the UK.

The submission deadline for outline applications is 12 September 2011.

For more information visit:
www.mrc.ac.uk/jointghtrials or email
jointglobalhealthtrials@headoffice.mrc.ac.uk.

MRC Medical Research Council

UKaid from the Department for International Development

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Celebrating 75 Extraordinary Years

(311269)

GRANTS

THE BREAST CANCER RESEARCH TRUST
President: Dame Vera Lynn, DBE LLD M Mus
Registered Charity: 272214

Applications are invited for grants for clinical and laboratory research projects undertaken in recognised cancer centres and universities in the United Kingdom directly aimed at improving the prevention, early diagnosis and treatment of primary breast cancers. Grants given are in the range £50,000 per annum for one year in the first instance renewable for up to a maximum of two further years (three years in all).

Application forms are available on the website and should be downloaded from: WEBSITE: WWW.BREASTCANCERRESEARCHTRUST.ORG.UK.

The completed application form with a further eight photocopies should be sent to:
The Honorary Administrator, Breast Cancer Research Trust, 48 Wayneflete Tower Avenue, Esher, Surrey KT10 8QG.

It should be noted that email applications are not acceptable.

The deadline for grant applications for consideration in October 2011 is : 20th August 2011.

(311298)

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The role Lead and expand research and teaching developments in Infectious Disease Public Health Programmes within the School.
Remuneration AUD$113,263 – $124,782 p.a., plus 17% superannuation and a clinical loading of AUD$24,284 p.a. (for eligible candidates). Full-time, fixed-term appointment for five years.
Applications close 27 July 2011
Reference No. 492102

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THE UNIVERSITY OF QUEENSLAND
AUSTRALIA

(311297)

NURSING

SENIOR LECTURERS/LECTURERS IN NURSING EDUCATION

The Nursing Division at the Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore, Pakistan requires senior lecturers/lecturers to assist with a Post R/N Diploma in Oncology Nursing and a 4 year BScN Programme, and to supervise and teach in a busy In-service Programme.
The candidate will assist our team in the planning and implementation of this programme. A Competitive Salary Package (Tax Free), Secure accommodation within the Hospital, Comprehensive Health Care Benefit and a 3 year contract are available.
The candidate must be RN, BScN, MScN/MA with a minimum of 4 years teaching experience, and Current Nursing Registration
For more details please send your inquiry and CV by email or mail to: Dr N K Burki, 195 Farmington Avenue, Farmington, CT 06032; shkm2@sbcglobal.net

(310754)

NURSING

DIRECTOR OF NURSING

The Nursing Division at the Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore, Pakistan requires a Director of Nursing to continue the development of this clinical nursing and education department in this state-of-the-art cancer institution. The department offers a direct entry, 4 year BScN Programme and a Post R/N Diploma in Oncology Nursing. There is a busy in-service Programme, with training for nursing managers in all areas.
The candidate will oversee the planning and implementation of this programme. A Competitive Salary Package (Tax Free), travel, Secure accommodation within the Hospital, Comprehensive Health Care Benefit and a 3 year contract are available.
The candidate must be RN, BScN, MScN/MA with administrative and teaching experience, and Current Nursing Registration.
For more details please send your inquiry and CV by email or mail to: Dr N K Burki, 195 Farmington Avenue, Farmington, CT 06032; shkm2@sbcglobal.net

(310756)

PROFESSORSHIPS

University of Zurich[UZH]

Medical Faculty

The Faculty of Medicine of the University of Zurich offers the following academic position:

Professorship for Pulmonology

The University of Zurich is seeking a faculty member for a Full Professorship at the University Hospital Zurich including the position of Director of the Clinic for Pulmonary Medicine. The Clinic of Pulmonary Medicine is known locally, nationally and internationally for outstanding achievements in patient care, research and education. The physicians of the clinic are engaged in all aspects of Pulmonary Medicine, particularly Sleep Disorders, and Lung Transplantation. The Clinic works collaboratively with Thoracic Surgery in the lung transplantation program. Academic and research start-up resources are available for outstanding candidates.

Responsibilities of this professorship include:
- Diagnosis and treatment of lung diseases in adults
- Further development of the existing clinical service according to state-of-the-art scientific and technological innovation
- Close collaboration with thoracic surgery, oncology, neurology, internal medicine, critical care and pathology
- Strengthening and expansion of clinical and basic research on causes, prevention and treatment of lung diseases
- Development or support of the existing research programs in disease areas including asthma, COPD, cystic fibrosis, lung transplantation and immunology, lung cell and vascular biology
- Coordination of the medical student, resident, and fellows training program

The applicant must meet the following **requirements:**
- Outstanding expertise within a field of pulmonary medicine complementary to the locally well established programs in sleep medicine and lung transplantation
- Outstanding scientific accomplishments in pulmonology and successful acquisition of competitive research grants
- Support of the lung transplant program and the program of sleep disorders
- Board certification in pulmonary medicine (FMH or equivalent)
- Documented commitment to clinical and academic teaching as well as to the promotion of young scientists and postgraduate education (CME)
- Dynamic personality with integrative skills, strategic leadership and high ethical standards

Women are encouraged to apply. Please forward (two hard copies and one CD) of your application for this position to the Dean's Office, Medical Faculty, Zurich University, Pestalozzistrasse 3, CH-8091 Zurich, Division for Academic Appointments, by August 15, 2011. Interested candidates should forward his/her curriculum vitae, bibliography, and a statement of research interest and clinical experience. For additional information, please contact the president of the search committee, Prof. Dr. med. Holger Moch, UniversitätsSpital Zürich, Institut für Klinische Pathologie, Schmelzbergstrasse 12, 8091 Zürich,
E-Mail: holger.moch@usz.ch

The application must contain the information outlined in the instructions for submitting applications available at the Dean's Office, Medical Faculty (Fax +41-44-634 10 79), or via Internet at http://www.med.uzh.ch/FormulareundRichtlinien/Bewerbung.html

(311394)

SPECIAL NOTES

DIABETES RESEARCH WELLNESS FOUNDATION

DRWF Clinical Open Funding 2012
Call for Applications

The Diabetes Research & Wellness Foundation invites the submission of research projects and proposals requiring funding in the field of diabetes.Types of application currently considered suitable (with a budget of up to £20,000) would be:

- **Research Projects - clinical, of one year's duration (though extensions may be considered);**
- **Investigators looking to achieve translational clinical pilot study data**
- **Exchange Fellowships (especially between the UK and the USA).**

Applications must be received on or before **Friday, 26 August 2011**. Applicants will be notified end of November/early December and, if successful, expected to take up the grants early in 2012.

Applications should be a maximum 4 sides A4, single line spaced with an 11 or 12 point, clearly readable, font. They should include (as appropriate):
Page 1 - Applicant's name, qualifications, present post and contact details; Name and address of the Institution(s) where the work will be carried out, Head of Department/ Institution and major participants in the project; Signed verification of funding application by Head of Department and department/institution authorities stating "I confirm that this application has been read and that, if granted, the work will be accommodated and administered in the department/institution";
Page 2 - Outline of the proposed research comprising Title, Research question, Relevance to diabetes;
Page 3 - Lay summary, Methodology, Expected outcome;
Page 4 - Any additional information to support the application (references can be included); Amount requested, with a general breakdown of costs;

PLUS: Separate single sheet of A4: (Brief) Curriculum Vitae of main applicant. Eleven hardcopies are required and an electronic copy should be sent as a single word document.

Send by post to: **Clinical Open Funding 2012**, Diabetes Research & Wellness Foundation, 101-102 Northney Marina, Hayling Island, Hampshire PO11 0NH
Telephone **02392 636135** or visit:**www.drwf.org.uk**

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(309664)

TRANSFUSION

(309823)

August 2011

15–Sept 2
Erasmus Summer Programme 2011
Erasmus University Rotterdam, the Netherlands

27 courses, 4 lectures, and 2 masterclasses in 3 weeks
The Erasmus Summer Programme focuses on key principles and methods of quantitative medical research. Open to all students and health professionals, it provides essential updates in a range of applied medical and healthcare disciplines. The first week provides introductory courses, the second week is devoted to methodology courses and the third week offers advanced courses. It is possible to enrol for 1, 2 or 3 weeks in a single discipline or to mix and match courses from different disciplines in order to design your own individual programme.

Contact:
More information and registration:
www.erasmussummerprogramme.nl, www.nihes.nl (305555)

November 2011

10
Blue pill pink pill? Does gender matter?
Royal Pharmaceutical Society, SE1 7JN London

The conference will examine the extent to which gender should be a factor in the development, regulation and use of medicines and discuss gender considerations in clinical practice. This is a joined event between the Royal Pharmaceutical Society (RPS), the Medical Women's Federation (MWF), the National Association of Women Pharmacists (NAWP).

Who should attend?
Women doctors, juniors and consultants involved in therapeutic prescribing and those involved in research. Pharmacists practising in all areas of the profession, anyone working in clinical research in the pharmaceutical industry, hospitals, and academia, healthcare policy makers, regulators, anyone interested in the development of personalised medicine.

Contact: Events team
T: +44 845 257 2570
events@rpharms.com

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Source Subscribers' survey 2002

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THE LANCET

Two Day Conference

Health and Wellbeing – the 21st Century Agenda

Thursday 8th – Friday 9th September 2011, Friends House, 173-177 Euston Road, London, NW1 2BJ

Sexual health nutrition and food **Wellbeing** Community development
Environment Ageing Physical activity Health literacy climate change
Obesity Creative arts Sustainability **Health inequalities**
Sustainability Social care Child health Cancer prevention
Occupational health Epidemiology **International**

The journal *Public Health* is proud to present its second international conference which will take place in London on 8th–9th September 2011.

The programme will be full of exciting, educational and thought provoking sessions, all relevant to those working in the area of health and wellbeing.

Key note speakers include

- **Professor Sir Michael Marmot**, Professor and Director of the International Institute for Society, UCL
- **Jonathon Porritt**, Founder Director of Forum for the Future and former Chairman of the Sustainable Development Commission
- **Professor Sir Andy Haines**, Professor of Public and Primary Care, London School of Hygiene and Tropical Medicine, Chief of Climate Change and Health Protection, Health Protection Agency.
- **Professor Dame Carol Black**, Chair of the Nuffield Trust and Chair of the Governance Board of the Centre for Workforce Intelligence
- **Lord Hunt of Kings Heath**, Deputy Leader of the Opposition in the House of Lords, President of the Royal Society for Public Health and former Minister of State at the Department of Energy and Climate

Plus master classes from

- **Dr Ian Banks**, official spokesman on men's health issues for the BMA and President of the Men's Health Forum
- **Dr Steve Boorman**, Director of Health and Safety, Chief Medical Advisor Royal Mail Group
- **Professor Tim Lang**, Professor of Food Policy, City University, London
- **Dr John Beard**, Director of the Department of Ageing and Life Course at the World Health Organization

There will also be opportunities for networking and participation in health and wellbeing activities, including organised tours of the 2012 Olympic Village, an active poster session, selected moderated posters, plus a master class for aspiring authors on How to Get Published in peer reviewed journals.

EARLY BIRD SPECIAL – *book by March 31st 2011 to receive a 10% discount*

For more information, please visit www.rsph.org.uk or contact Claire Robins, crobins@rsph.org.uk

STUDENT PLACES AVAILABLE

For students undertaking a full time undergraduate or postgraduate qualification in public health or a related discipline, we have a number of reduced rate student places (£50) provided by our sponsors. These will be allocated on a first-come, first-served basis.

CALL FOR POSTERS

Abstracts are invited for oral speed and poster presentations
www.rsph.org.uk/healthandwellbeing
Deadline for submissions Friday April 1st 2011

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Editorial Consultants at *The Lancet*

For further information, contact
david.mcnamee@lancet.com

In April, 2005, *The Lancet*'s editors announced the creation of a new role at the journal—Editorial Consultant. Where did these consultants come from? Most of those appointed had applied to an advertisement we had placed in the journal. Some were invited, because of their previous associations with the journal. We welcome further applications from low-income or middle-income countries, especially from those not represented.

What is an Editorial Consultant? This role has many parts. Editorial Consultants will act as peer reviewers of papers sent to *The Lancet*, and suggest the names of other such reviewers. They will also suggest topics we should cover, or even write themselves. They will act as ambassadors for the journal, telling colleagues about what we do and particularly about our fast-track and protocol-review services.

We have aimed for an international panel of consultants. Perhaps unsurprisingly, most applicants came from Europe or North America. We hope to broaden our range.

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November 17-19, 2011

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