GLADSTONE INSTITUTES

Review of Non-Daily PrEP Clinical Research and Experience

Robert M. Grant, M.D., M.P.H.

IAS 2017, July 2017, Paris

SAN FRANCISCO AIDS FOUNDATION

UCSF

Disclosures

- Gilead Sciences donated study medication to US NIH for trials that I have led, including iPrEx, iPrEx OLE, and HPTN 067.
- VIIV contracted with Gladstone to support research on long-acting injectable PrEP.
- Gilead contracted with San Francisco AIDS Foundation for a trial comparing FTC/TDF with FTC/TAF for PrEP.

PrEP Usage Recommendations: 2017

US FDA[1] and US CDC[1]	Daily.
EMA[1]	Daily.
Health Canada[1]	Daily.
EACS[2] and France[2]	Daily, and may use on demand for MSM.
WHO[3]	Daily is the current recommendation, on demand is safe/effective for MSM and has not been evaluated for others.

1. The reviewed trials were only iPrEx and Partners PrEP (daily studies);
2. European AIDS Clinical Society (EACS) and the French MOH also reviewed Ipergay data;
3. WHO recommendation does not specify daily vs on-demand; The WHO PrEP Implementation Tools, Clinicians Module, 2017 indicates that daily is the current WHO recommendation for all at substantial risk for HIV, although on-demand is safe and effective for MSM.

WHO Meta-Analysis: PrEP Effectiveness (MITT)

Analysis	No. of studies	N	Risk Ratio (95% CI)	p-value	I^2	P-value (meta-regression)
RCTs comparing PrEP to placebo						
Overall	10	17424	0.49 (0.33-0.73)	0.001	70.9	--
Adherence						
High (>70%)	3	6150	0.30 (0.21-0.45)	<0.0001	0.0	<0.0001
Moderate (41-70%)	2	4912	0.55 (0.39-0.76)	<0.0001	0.0	0.009
Low (≤40%)	2	5033	0.95 (0.74-1.23)	0.70	0.0	*ref*
Mode of Acquisition						
Rectal	4	3167	0.34 (0.15-0.80)	0.01	29.1	0.36
Vaginal/penile	6	14252	0.54 (0.32-0.90)	0.02	80.1	
Biological sex[1]						
Male	7	8706	0.38 (0.25-0.60)	<0.0001	34.5	0.19
Female	6	8716	0.57 (0.34-0.94)	0.03	68.3	
Age[2]						
18 to 24 years	3	2997	0.71 (0.47-1.06)	0.09	20.5	0.29
≥25 years	3	5129	0.45 (0.22-0.91)	0.03	72.4	
Drug Regimen						
TDF	5	4303 active	0.49 (0.28-0.86)	0.001	63.9	0.88
FTC/TDF	7	5693 active	0.51 (0.31-0.83)	0.007	77.2	
Drug Dosing						
Daily	8	17024	0.54 (0.36-0.81)	0.003	73.6	0.14
Intermittent	1	400	0.14 (0.03-0.63)	0.01	0.0	
RCTs comparing PrEP to no PrEP						
Overall	2	720	0.15 (0.05-0.46)	0.001	0.0	--

[1] The iPrEx trial included 313 (13%) transgender women.

[2] Includes only studies that stratified age by <25 and ≥25.

Fonner *AIDS* 2016

Clinical Experience with On-Demand PrEP in MSM

	Number (%) choosing On-Demand	Number of Infections on PrEP	Infection Rate (95% CI)
France[1]	1581 (57%)	0	0 (0 to 0.0030)
Montreal[2]	225 (22%)	0	0 (0 to 0.020)
Combined observed	1806 (47%)	0	0 (0 to 0.0026)
Expected if not effective[3]	1806 (47%)	119	6.6 (0.05 to 0.08)

1. Molina IAS 2017 (WEPE0939) Paris, 35% had STIs in the past 12 months; Also new efficacy analysis stratified by sex frequency (Antoni IAS 2017 Tuesday 11:15).
2. Greenwald Adherence 2017 Miami;
3. Assumes incidence 6.6/100 PY as observed in Ipergay, and that patients were followed for an average of 12 months, CI by Wilson method with continuity corrections.

Baseline Characteristics Among Daily and On-Demand PrEP Users in the Montreal L'Actuel Study

VARIABLES		DAILY	ON-DEMAND	P-value
Age, mean (CI)		36.7 (10.3)	39.2 (10.9)	**<0.001**
Education, N (%)	Primary	6 (0.8%)	1 (0.5%)	0.44
	Secondary	110 (14.9%)	24 (11.4%)	
	College	161 (21.8%)	42 (20%)	
	University	461 (62.5%)	143 (68.1%)	
Annual revenue, N (%)	< $10 000	66 (8.8%)	15 (6.8%)	0.09
	$10 001-20 000	73 (9.7%)	18 (8.1%)	
	$20 001-35 000	102 (13.6%)	21 (9.5%)	
	$35 001-55 000	178 (23.7%)	50 (22.6%)	
	$55 001-75 000	144 (19.1%)	40 (18.1%)	
	> $75 000	189 (25.1%)	77 (34.8%)	
Primary reason for seeking PrEP, N (%)*	CAI	625 (73.9%)	202 (83.1%)	0.664
	Multiple PEPs	47 (5.5%)	13 (5.3%)	0.732
	Serodifferent couple	76 (9%)	10 (4.1%)	0.01
# contacts in the last year, Mean (CI)	Regular partners	3.2 (2.3-4.0)	2.2 (1.8-2.6)	0.23
	Occasional partners	22.3 (17.7-26.8)	14.2 (12.2-16.3)	**<0.001**
	TOTAL	**848 (78%)**	**243 (22%)**	

Greenwald *Adherence 2017* Miami

Cost effectiveness of 'on demand' HIV pre-exposure prophylaxis for non-injection drug-using men who have sex with men in Canada

Estelle Ouellet MPA MD(c), Madeleine Durand MD MSc FRCPC, Jason R Guertin MSc PhD(c), Jacques LeLorier MD PhD FRCPC FISPE, Cécile L Tremblay MD FRCPC

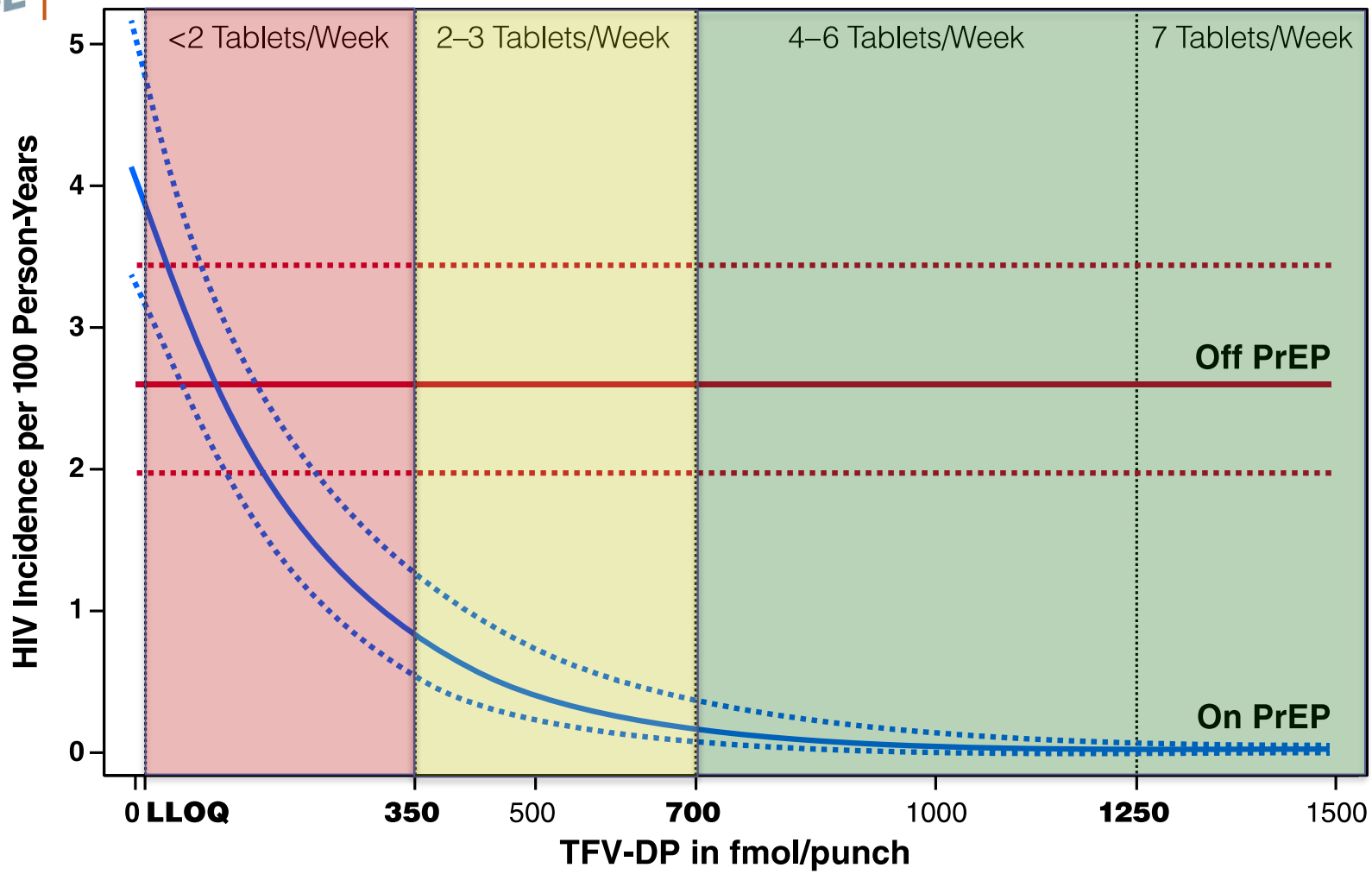
	Undiscounted lifetime		Discounted at 3%	
	Least Expensive	Most Expensive	Lease Expensive	Most Expensive
PrEP (cost per infection averted)	$621,390	$621,390	$621,390	$621,390
HIV (lifetime cost)	$1,439,984	$1,482,502	$662,295	$690,075
Cost Savings	**$818,594**	**$861,112**	**$40,905**	**$68,694**

Assumptions/Approach

- *infection at age 30.*
- *empirically derived direct and indirect costs.*
- *daily use of "on-demand" PrEP.*
- *non-PrEP incidence 3.9/100PY.*

Can J Infect Dis Med Microbiol Vol 26 No 1 January/February 2015

HIV Incidence and Drug Concentrations



Follow-up %	**26%**	**12%**	**21%**	**12%**
Risk Reduction	**44%**	**84%**	**100%**	**100%**
95% CI	**-31 to 77%**	**21 to 99%**	**86 to 100% (combined)**	

Grant WAC Melbourne 2014;
Grant et al, *Lancet Infectious Diseases*, published online July 22, 2014

PrEP Drug Concentrations and HIV Infection in Cis-women.

- No infections if drug concentrations suggested used of 6 or 7 tablets per week.[1]
- Unlike MSM/TGW, there were some infections with 4 to 5 tablets per week.
- PK modeling suggests that about 7 tablets per week are needed for full protection from vaginal exposure.[2]

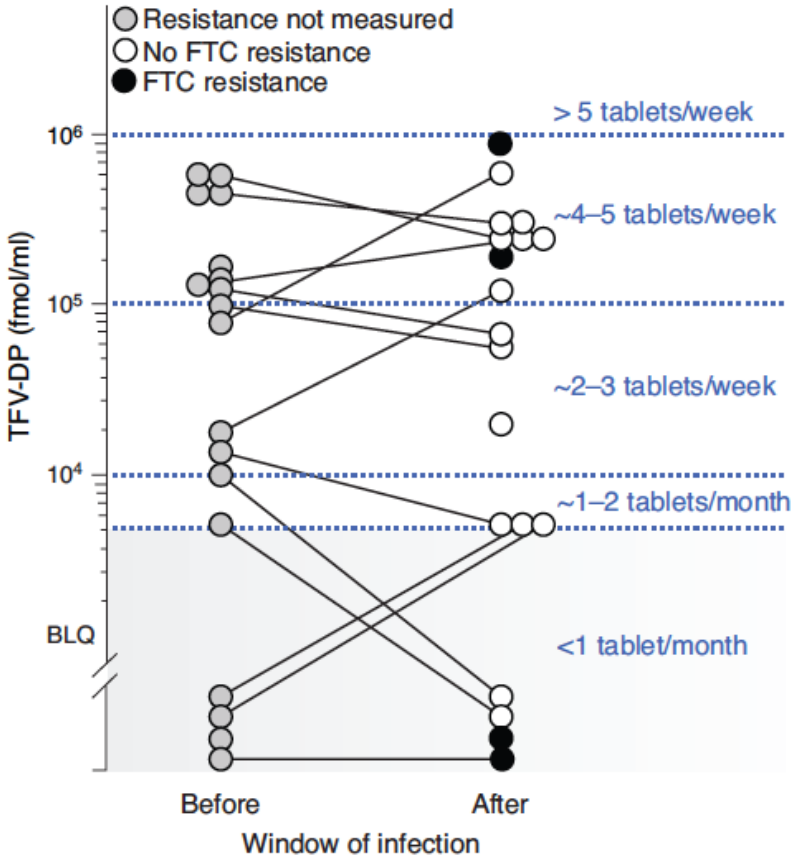


Fig. 2. Intracellular TFV-DP concentrations and clinical drug resistance. Values from active arm seroconverters with drug detected before and/or after the infection window period are plotted, and from all seroconverters with evidence of FTC resistance. Information from seroconverters with no detectable drug or drug resistance is not shown. There was no TFV resistance detected. Values below the limit of detection (5000 fmol) are plotted in the grey area. Black dots represent cases in which FTC resistance was detected using clinical assays. White dots are cases with no evidence of resistance. Resistance could not be measured before the infection window because there was no detectable virus at that visit. FTC, emtricitabine; TDF, tenofovir disoproxil fumarate; TFV-DP, tenofovir diphosphate.

1. Grant *AIDS* 2015
2. Cottrell *JID* 2016

Safety and Adherence to Intermittent Pre-Exposure Prophylaxis (PrEP) for HIV-1 in African Men Who Have Sex with Men and Female Sex Workers

Gaudensia Mutua[1], Eduard Sanders[2,3], Peter Mugo[2], Omu Anzala[1], Jessica E. Haberer[4], David Bangsberg[4], Burc Barin[5], James F. Rooney[6], David Mark[7], Paramesh Chetty[8], Patricia Fast[7], Frances H. Priddy[7]*

PLoS One April 2012 7(4):e33103

Safety, Adherence and Acceptability of Intermittent Tenofovir/Emtricitabine as HIV Pre-Exposure Prophylaxis (PrEP) among HIV-Uninfected Ugandan Volunteers Living in HIV-Serodiscordant Relationships: A Randomized, Clinical Trial

Freddie M. Kibengo[1], Eugene Ruzagira[1], David Katende[1], Agnes N. Bwanika[1], Ubaldo Bahemuka[1], Jessica E. Haberer[2], David R. Bangsberg[2], Burc Barin[3], James F. Rooney[4], David Mark[5], Paramesh Chetty[6], Patricia Fast[7], Anatoli Kamali[1], Frances H. Priddy[7]*

PLoS One Sept 2013 8(9):e74314

- Uganda and Kenya
- Randomized
  - 2:1 to oral FTC/TDF vs placebo
  - 1:1 to daily vs twice weekly and post-intercourse
- 4 months of follow-up
- Sex events monitored by SMS and interview
- Dosing monitored by MEMS

East African iPrEP Results

	Sex acts per week	Daily Adherence (IQR)	Adherence to Fixed twice weekly doses (IQR)	Adherence to Post-Sex Dose (IQR)
MSM (N=67) FSW (N=5)[1]	0.7 to 1.4	83% (63 to 92%)	55% (28 t 78)	26%* (14 to 50%)
Heterosexual SDC (N=36)[2]	1.4 to 1.6	97% (92 to 100)	91% (73 to 97%)	45%* (20 to 63%)

*Adherence to post-sex dose was ~100% by self report

Reasons for missing a dose

- Being away from home (12% for MSM/FSW, 5% for SDC),
- Not having pills with them (11% for MSM/FSW, 6% for SDC),
- Forgetting (8% for MSM, 5% for SDC),
- A change in daily routine (7% for MSM/FSW),
- Using alcohol or drugs (3% for MSM/FSW).

1. Mutua PLOS ONE 2012; 2. Kibengo PLOS ONE 2013

HPTN
HIV Prevention Trials Network

HPTN 067 Design

FTC/TDF

Daily- One tablet/day
Time driven- 1 tablet/2x week with a post sex boost
Event driven- 1 tablet pre-sex and 1 tablet post-sex
No more than 2 tablets daily or 7 tablets/week

Women (incl. TGW) & MSM

6 weeks DOT period

Randomized

D

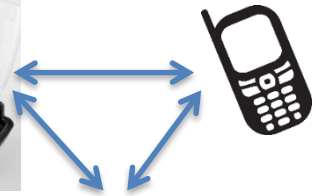
T

E

24 weeks self-administered dosing

4 weeks off drug

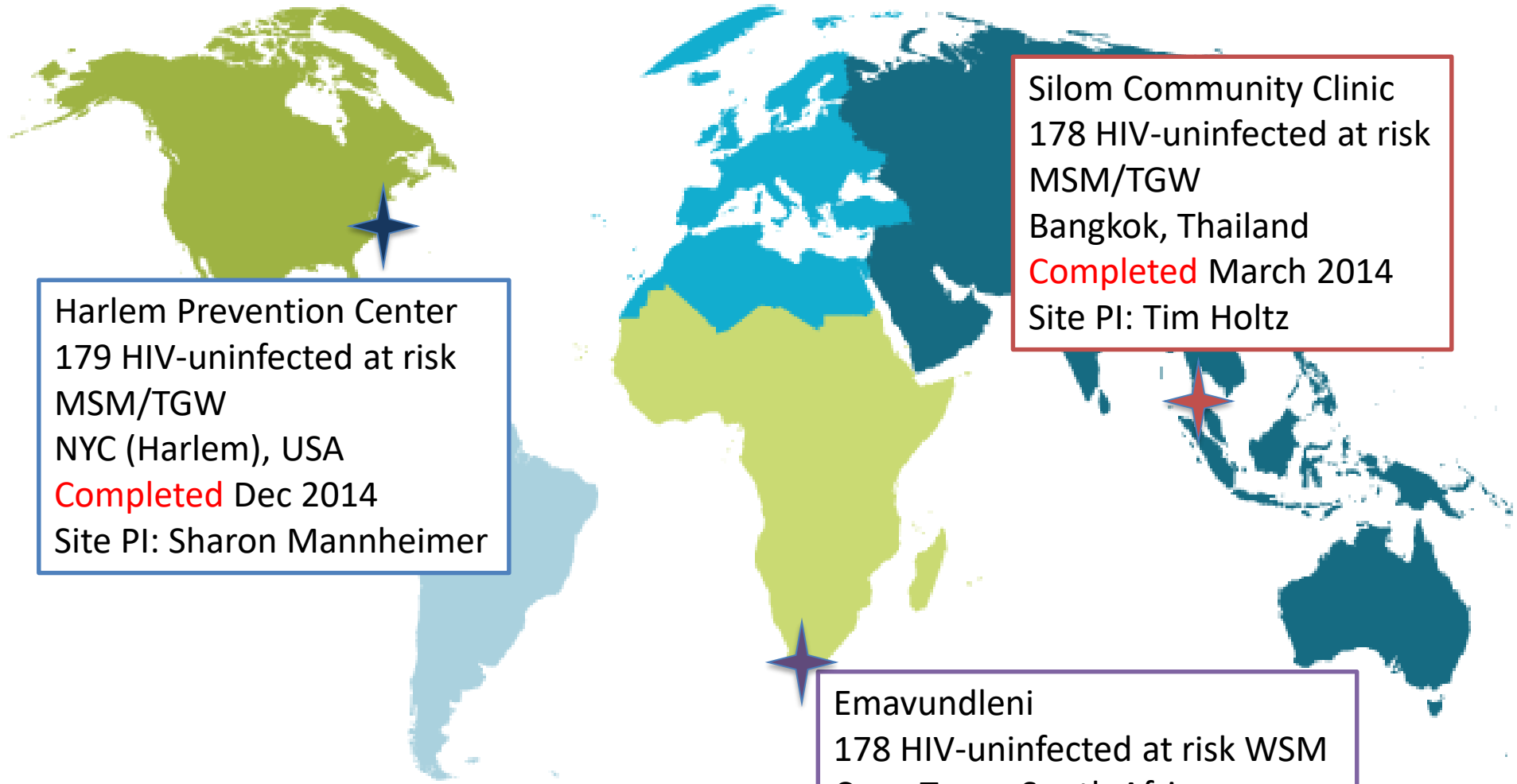
Final Study Visit Week 34



PrEP use and sex

Key informant interviews and focus groups

HPTN
HIV Prevention
Trials Network



Harlem Prevention Center
179 HIV-uninfected at risk
MSM/TGW
NYC (Harlem), USA
Completed Dec 2014
Site PI: Sharon Mannheimer

Silom Community Clinic
178 HIV-uninfected at risk
MSM/TGW
Bangkok, Thailand
Completed March 2014
Site PI: Tim Holtz

Emavundleni
178 HIV-uninfected at risk WSM
Cape Town, South Africa
Completed June 2013
Site PI: Linda Gail Bekker

HPTN
HIV Prevention
Trials Network

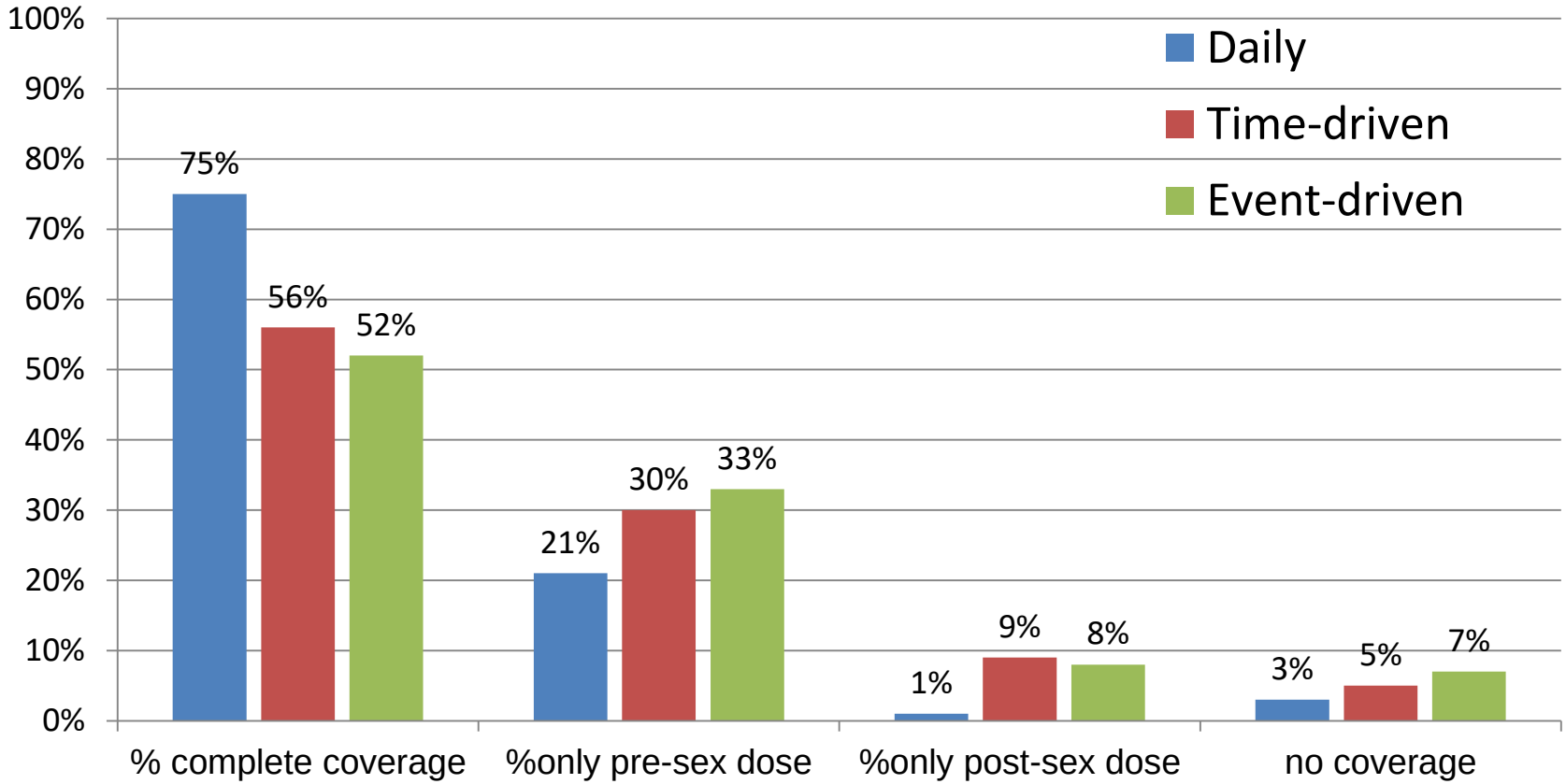
Definition of Primary Outcome: Coverage

Coverage of sex events for all arms:
≥1 pill taken in the 4 days before sex
≥1 pill taken in the 24 hours after sex

Bekker IAS2015, Vancouver, 2015

HPTN
HIV Prevention
Trials Network

Coverage of Sex Events – Women in Cape Town



Reasons of missed post-sex doses: Not at home, concern about disclosing PrEP use to partner, pills not with me, change in routine, not in the mood to worry.

Sex event defined as vaginal or anal intercourse

Time/Daily p = 0.0007, Event/Daily p < 0.0001, Time/Event p = 0.43

Bekker IAS2015, Vancouver, 2015

HPTN
HIV Prevention Trials Network

TFVDF in PBMCs:

% with TFVDP >= 5.2 fmol/10^6 cells PBMC* - Cape Town Women

Participants who report sex in last 7 days with detectable TFV-DP in PBMC (>=5.2 fmol/10^6 cells)	Daily (D)	Time-driven (T)	Event-driven (E)
Week 10	33/40 (82.5%)	16/23 (69.6%)	25/37 (67.6%)
Week 18	29/39 (74.4%)	16/25 (64.0%)	10/30 (33.3%)
Week 30	19/29 (65.5%)	13/24 (54.2%)	12/31 (38.7%)

*Indicative of at least 2 tablets per week.

Time/Daily p = 0.16, Event/Daily p = 0.002, Time/Event p=0.13

Conclusions

- On-Demand FTC/TDF dosing among MSM:
  - Safe, effective, and cost saving.
  - Accumulated clinical experience adds confidence, and still shows no on-demand PrEP failure.
  - Supported by PK modeling and concentration-effect analysis and animal modeling.
  - Provides integrated guidance for how to start and stop around parties, changes in relationships, and drug use.
  - 22 to 57% prefer on-demand if both are offered.
  - Use of the post-sex dose can be challenging; On-demand regimen involving 2 post-sex doses helps.
- On-Demand FTC/TDF Dosing for Women:
  - Coverage was higher in the daily arms of HPTN 067.
  - PK and concentration-effect analysis suggests that 6 to 7 tablets per week are needed for FULL protection for vaginal exposure to HIV.

PrEP was **made possible** by mostly **young study participants who believed** that research could **improve their lives**