Will young women take oral PrEP?

Lessons from HPTN 082, 3P and POWER

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Background to HPTN 082/HERS

- HIV incidence of 4-6% among young African women in recent HIV prevention trials
- PrEP is highly effective when taken with good, but not, perfect adherence
- PrEP use was low (20-25%) in FEM-PrEP and VOICE trials
- Qualitative research among former VOICE participants indicated drug level feedback could foster more honest discussion about PrEP adherence
- Given the need for primary HIV prevention among young African women and the high effectiveness of PrEP, it is important to assess the effectiveness of PrEP adherence support strategies

Primary Objectives of HPTN 082

- To assess the proportion and characteristics of young HIV-uninfected women who accept versus decline PrEP.
- To assess the difference in PrEP adherence in young women randomized to enhanced adherence support (using drug level feedback) versus standard of care adherence support.

HPTN
HIV Prevention Trials Network

HPTN Q82 HERS

HPTN 082: Evaluation of daily oral PrEP as a primary prevention strategy for young African women

Study Population

Uninfected women
Ages 16-25 yrs

Johannesburg & Cape Town, South Africa
Harare, Zimbabwe

Target Enrollment

- **400 women who accept PrEP at enrollment**
- **≤ 200 women who decline PrEP at enrollment**

Standard adherence support

Standard adherence support *plus* drug level feedback

Eligibility criteria: Sexually active in past month; VOICE risk score ≥5; interest in PrEP; access to mobile phone; hepatitis B seronegative

Standard adherence support in HPTN 082

- Weekly two way SMS in first 3 months
- Monthly adherence clubs
  - Peer support
  - Address concerns & share experiences about PrEP
  - Problem-solve adherence challenges
- Brief counseling at visits: Months 1,2, 3, 6, 9 and 12
- Discrete pill containers

Drug level feedback at months 2 and 3

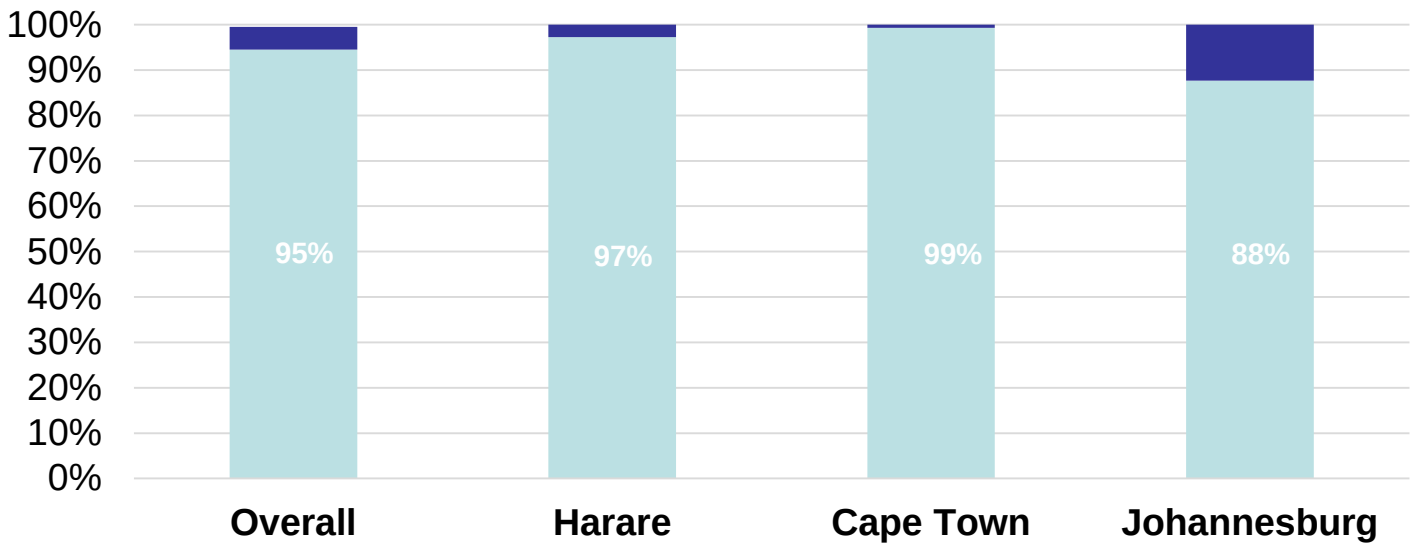
- Women randomized to enhanced counseling have DBS TFV-DP levels obtained at months 1 and 2.
  - Results given at next visit (month 2 and 3)
- DBS are a measure of average adherence in prior month
- Counseling messages for ≥4 doses/week (green), 1-3 doses/week (yellow) and below detection (red)
  - Lower thresholds used at month 1 before TDF-DP levels reached steady-state

Sample Month	Results Month	Threshold		Counseling Message
Month 1	Month 2	≥500 fmol/punch		4 or more doses per week (*>500 fmol/punch at wk 4 and >700 fmol/punch at wk 8*) Key message: You are doing great! Keep up the good work and remember that taking one PrEP pill every day is needed for strong protection against HIV.
Month 2	Month 3	≥700 fmol/punch		
Month 1	Month 2	16.6 – 499 fmol/punch		~1-3 doses per week (*between detectable – 499 fmol/punch at wk 4 and detectable to 699 fmol/punch at wk 8*) Key message: It looks like you are trying to take the PrEP medication, but are having some difficulties. Remember that taking one pill every day is needed for strong protection against HIV. How can we help you do even better?
Month 2	Month 3	16.6 – 699 fmol/punch		
Month 1	Month 2	BLQ (<16.6 fmol/punch)		*No TFV-DP detected (below quantification of 16.6 fmol/punch)* Key message: It looks like you haven't been able to take the PrEP medication. Is PrEP something that you are still interested in? If yes, how can we help you?
Month 2	Month 3	BLQ (<16.6 fmol/punch)		

Anderson P et al. TFV-DP in DBS: DOT-DBS Study. CROI 2017
Anderson P et al Sci Transl Med 2012
Grant R et al Lancet Infect Dis 2014

HPTN 082: PrEP uptake

Figure 1: PrEP uptake overall and by site



Analysis: Definitions and methods

- Primary adherence outcome: TFV-DP ≥700 fmol/punch at 6 months

- Predictors of high adherence at 6 months (TFV-DP ≥700 fmol/punch)
  - Logistic regression, adjusted for site

- Persistence: Detectable TFV-DP or plasma TFV at 3, 6 & 12 months

Demographics & Sexual Partner Characteristics

Baseline characteristic	Standard Adherence Support* N=212	Enhanced Adherence Support* N=215
Age (years) median (IQR)	21 (19, 23)	21 (19, 22)
Education		
Secondary school or higher	184 (98%)	187 (98%)
CES-D depression score ≥10	126 (59%)	133 (62%)
Any intimate partner violence, past year	100 (48%)	116 (54%)
Trauma symptoms	137 (65%)	152 (71%)
Primary sex partner in past 3 months	174 (83%)	182 (85%)
HIV status of primary partner		
HIV negative	112 (79%)	97 (68%)
HIV positive	1 (1%)	2 (1%)
Does not know	27 (19%)	42 (30%)

Sexual behavior, risk perception, & PrEP

Baseline characteristic	Standard Adherence Support* N=212	Enhanced Adherence Support* N=215
Thinks partner has other partners		
Yes	54 (31%)	62 (34%)
Don't know	74 (43%)	94 (52%)
Vaginal sex past month (median, IQR)	4 (2,8)	4 (2,8)
Condoms with vaginal sex, past month		
Always or often	60 (36%)	36 (28%)
Curable STI CT, GC, trichomonas, syphilis	**80 (38%)**	**87 (40%)**

Tenofovir levels at 3, 6, & 12 months

	3 months	6 months	12 months
Tenofovir diphosphate (TFV-DP), DBS	**N=371**	**N=363**	**N=347**
Detectable	83.6%	56.5%	31.4%
≥700 fmol/punch* (among those with detectable TFV-DP)	24.8%	20.9%	8.6%

* TFV-DP ≥700 fmol/punch was associated with 100% efficacy among MSM in the iPrEX OLE study & the 25th percentile of 4 doses/week on average (Grant Lancet HIV 2014)

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Effect of drug level feedback on adherence (TFV-DP >700 fmol/p) at 6 months

	Standard adherence support TFV-DP≥700 fmol/punch	**Enhanced adherence support** TFV-DP≥700 fmol/punch	**Difference in proportion with TFV-DP ≥700 fmol/punch**	**95% CI**	**P-value**
Intent to treat	40/184 (21.7%)	36/179 (20.1%)	-1.6%	-9.9%, 6.7%	0.7
*Per protocol analysis**	40/181 (22.1%)	17/115 (14.8%)	-7.3%	-15.7%, 2.5%	0.2

* Per protocol analysis excluded women who:
- were not receiving PrEP due to a clinical or laboratory hold
- did not receive drug level feedback because DBS results were not available at next visit, or
- received drug level counselling that did not correspond to the appropriate category based on actual DBS drug levels

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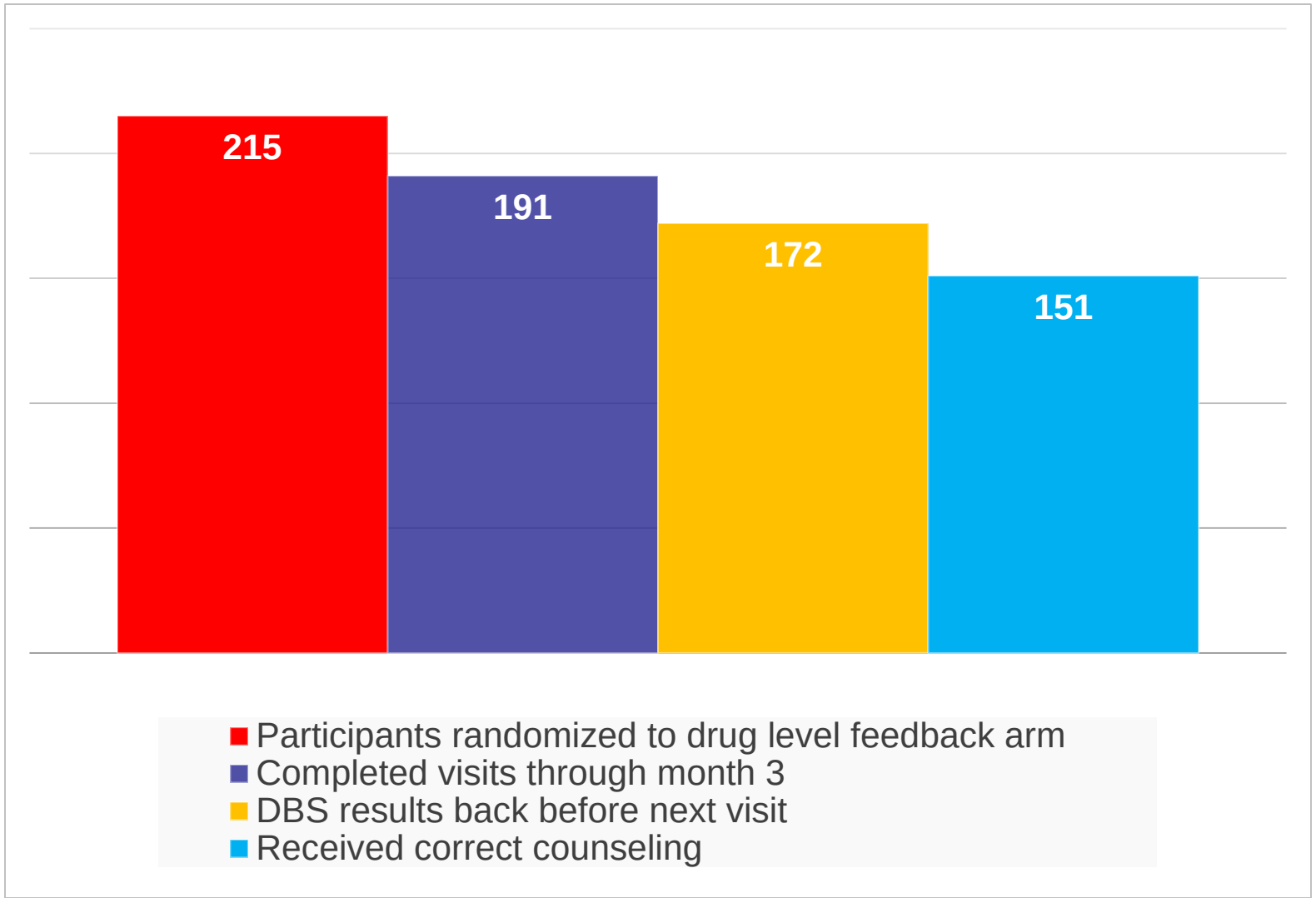
Challenges of retrospective drug level feedback



HPTN Q82
HERS

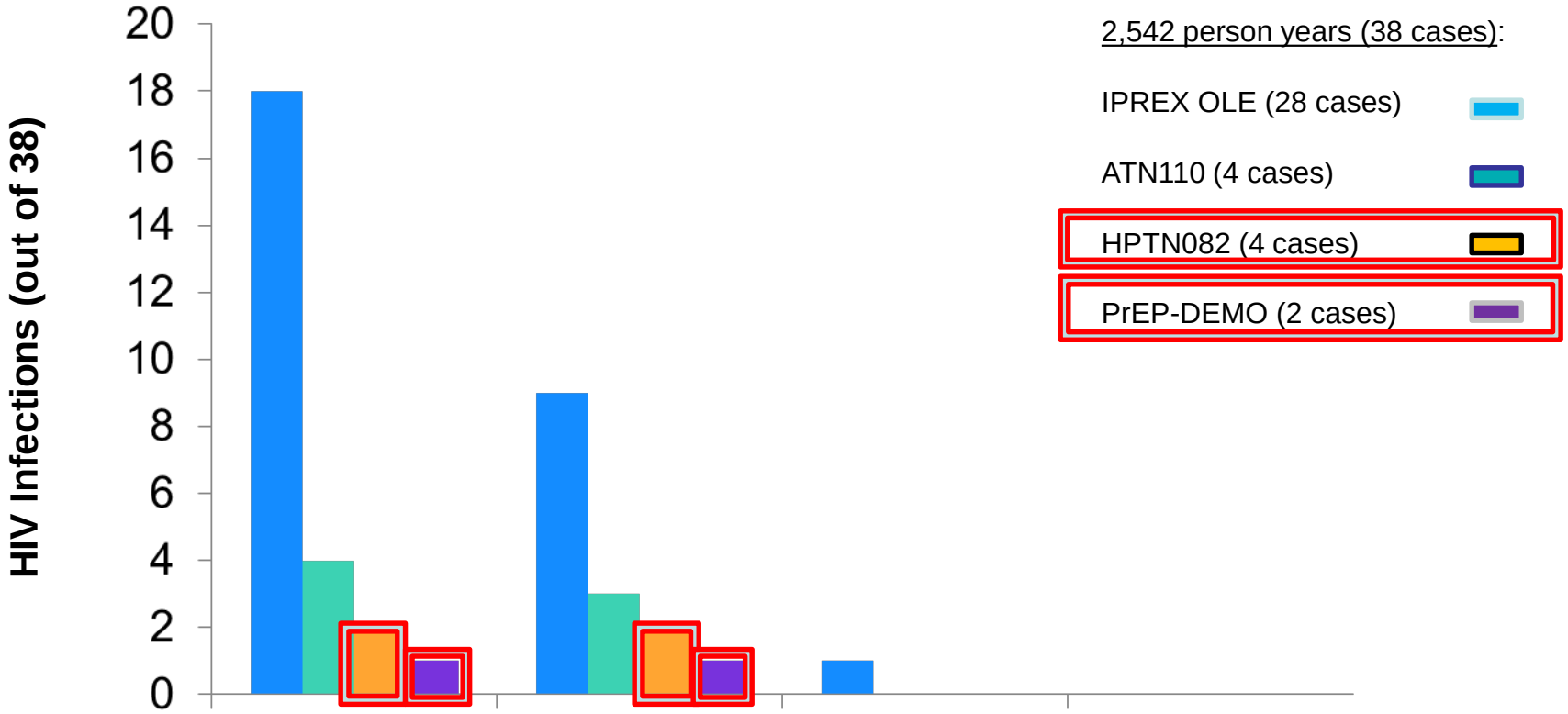
Correlates of high adherence at 6 months

Covariate	Univariate Odds Ratio (95% CI)	Multivariate Odds Ratio (95% CI)	Multivariate P-values
Perceived risk of HIV (any vs none)	1.9 (1.1, 3.2)	2.4 (1.2, 4.5)	0.008
PrEP readiness score (per unit increase)	1.0 (1.0, 1.1)	1.0 (1.0, 1.1)	0.004
Disclosed to someone about PrEP use	3.3 (1.2, 8.8)	3.0 (1.0, 9.1)	0.06
Number of sexual partners, past 3 months	1.2 (1.0, 1.5)	1.3 (1.0, 1.6)	0.07
Participant ever dropped out of school	1.8 (1.0, 13.1)	2.0 (1.0, 14.1)	0.07
Adherence club participation (per club attendance)	1.7 (1.2, 2.3)	1.3 (1.0, 1.8)	0.10

HIV seroconversions

- Four HIV seroconverters (at months 3, 6, and two at 9) observed in 404 person-years of follow-up
- HIV incidence of 1.0/100 person-years (95% CI 0.3-2.5)
- 2 had undetectable DBS TFV-DP concentrations and 2 detectable but low concentrations (74 and 243 fmol/punch) in the visit at or prior to when they were first detected HIV seropositive
- Three had no resistance mutations & one had D67N (NRTI mutation) and four NNRTI mutations (K101E, K103N, E138A, and G109A)
  - No resistance mutations associated with TDF or FTC

Consistent PrEP adherence-response in men & women



DBS (fmol/punch)	BLQ	BLQ - 349	350-699	≥700
Adherence	No dosing	< 2 doses/wk	2-3 doses/wk	≥4 doses/wk
HIV risk reduction (OLE) (95% CI)		44% (-31,77)	84% (21,99)	100% (86, 100)

Pete Anderson MTN 2019

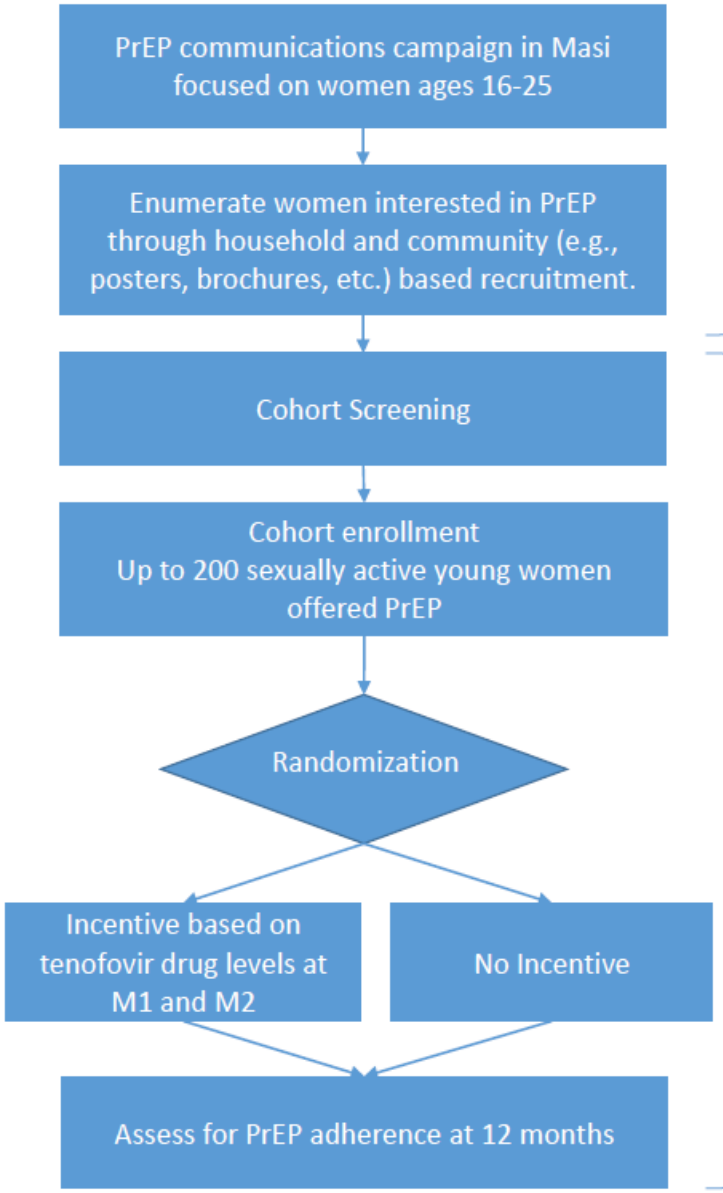
Grant. Lancet Infect Dis. 2014 Sep;14(9):820-9. AY Liu JAMA Intern Med. 2016 Jan 1;176(1):75-84.
Hosek. JAIDS 2016 Sep 13; Molina. NEJM 2015 Dec 3;373(23):2237-46. Anderson, STM 2012 (PMID 22972843); Celum C et al. IAS 2019; 21-24 July 2019, Mexico City, Mexico.

HPTN 082: Summary

- Very high PrEP uptake (95%) among young women at risk for HIV, a majority of whom took PrEP in the first 6 months
- No effect of drug level feedback on proportions with high adherence by arm at 6 months
  - Challenges in operationalizing DBS drug level feedback
  - Research needed on effective adherence support including POC urine TFV assays
- Women who perceived themselves to be at risk of HIV and were motivated to use PrEP had higher adherence at 6 months
- Low HIV incidence (1%) given risk profile of this cohort
  - Counterfactual HIV incidence of 3.7% based on modeling (Moore CROI 2019)
  - Was low incidence due to higher adherence during periods of risk (“prevention-effective adherence”)?

The 3P study:

Social marketing & conditional incentives to increase PrEP adherence



Phase I: Evaluation of PrEP demand creation strategy in Masi.

Phase II: Evaluation of PrEP initiation and adherence with incentives conditioned on early drug levels.

PrEP demand creation video & brochures

Developed in collaboration with McCann Global Health

Incentives conditioned on tenofovir levels to increase adherence among young women on PrEP in Cape Town

Celum, C[1], Gill, K[2], Morton, J[1], Stein, G[1], Myers L[2], Thomas, K[1], McConnell, M[3], van der Straten, A[4], Baeten, J[1], Duyver, M[2], Mendel, E[2], Naidoo, K[2], Dallimore, J[2], Wiesner, L[5], Bekker, LG[2]

[1]University of Washington, Seattle, WA, USA, [2]Desmond Tutu HIV Foundation, University of Cape Town, Cape Town, South Africa, [3]Harvard University, Boston, MA, USA, [4]Women's Global Health Imperative, RTI and UCSF San Francisco, CA, USA, [5]University of Cape Town, Cape Town, South Africae

Demographics (N= 200 women)

- Median age was 19 (IQR 17-21)
- 78% had secondary education or higher

Behavioral Characteristics at baseline

- 86% had a primary partner; median relationship duration of 12 months
- 17% said their primary partner had other partners and 55% were not sure
- Condom use was low: 32% always or often used a condom; 22% never used a condom
- 19% reported interpersonal violence in the past year
- 13% reported weekly alcohol use

Curable STIs at baseline

- 32% had a curable STI : 25% with chlamydia and 11% with gonorrhea

Table 1: PrEP adherence, as assessed by TFV-DP levels at 3 months by study arm

Tenofovir diphosphate in DBSat month 3	Total	Incentive Arm	Control Arm
Concentration in fmol/ pumch			
Median (IQR)	694.5 (397.5, 1020.5)	758.0 (446.0, 1140.0)	606.0 (268.0, 969.0)
N Undetectable (BLQ)	4	1	3
N Detectable	160	80	80

Table 4: Effect of conditional incentive on 3 month TFV-DP concentration a continuous outcomes

	Incentive Arm		Control Arm			
	N	Mean (SD)	N	Mean (SD)	Difference Mean (95% CL)	p-value*
Month 3 tenofovir concentration by arm	81	822.0 (522.0)	85	689.1 (546.3)	132.8 (-30.8, 296.5)	0.1111

- There was a nonsignificant trend of higher mean TFV-DP levels at 3 months in the conditional incentive arm

Bekker & Celum, IAS 2019

POWER PrEP delivery locations

Where We Work

Objective

Develop cost-effective and scalable models for implementation of ARV-based HIV prevention products for young women in Cape Town and Johannesburg (South Africa) and Kisumu (Kenya).

Consortium Partners

UNIVERSITY OF WASHINGTON
INTERNATIONAL CLINICAL RESEARCH CENTER

DESMOND TUTU HIV FOUNDATION

KENYA MEDICAL RESEARCH INSTITUTE
KEMRI

WITS RHI

Carnegie Mellon University

MASSACHUSETTS GENERAL HOSPITAL

RTI INTERNATIONAL

POWER Objectives

Evaluate PrEP use:

- Assess and understand persistence and patterns of use

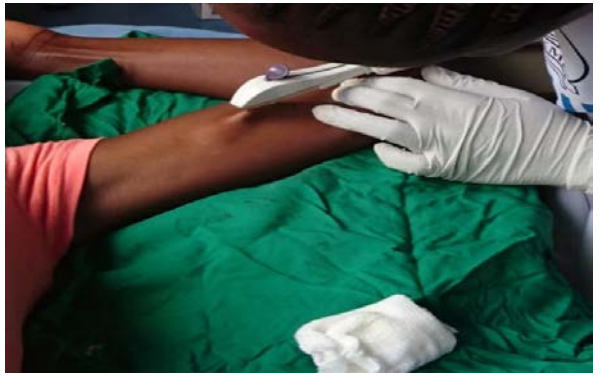
Demonstrate effective delivery models:

- Test 3 different PrEP delivery models
- Assess cost and cost effectiveness

Cape Town:
Mobile delivery services

Johannesburg:
Youth-friendly clinics

Kisumu:
Family planning clinics



POWER: PrEP uptake and interruptions

Enrolled
N-1738

PrEP Uptake
N-1582(91%)

Interruptions
N-1331/1423(94%)

Reasons-missed visits, decline and protocol hold

PrEP Restarts
224/1094(20%)

After PrEP initiation at month 0 the clinics expected clients back at M1,M3,M6…

Time of PrEP restart
91/204 (45%) between 1st and 2nd months

POWER Key findings

- Women enrolling in POWER and initiating PrEP are at high risk for HIV acquisition: Unknown partner HIV status, low condom use
- High proportions of risky behavior leading to high prevalence of STI
- High PrEP uptake (91%)
- Common PrEP interruptions (94%)
- 20% restarted PrEP, most of which were due to missed visits
- 46% re-initiated within a month of interruption.

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POWER Prevention Options for Women Evaluation Research

What we have learned so far

- High PrEP interest & motivation among African AGYW
- Drug level feedback did not increase adherence (HPTN 082)
  - Trend towards higher adherence with drug level feedback and incentives (3P)
- Persistence is challenging; frequent ‘restarts’
  - Simplify PrEP refills to avoid unintended discontinuations, counseling messages about avoiding interruptions, & minimize barriers to restarting PrEP
- Adherence does not have to be perfect to have prevention benefit
- Chlamydia & gonorrhea very common & usually asymptomatic
  - Need better STI control strategies than syndromic STI management

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HPTN 082 HERS

BE THE GENERATION TO END HIV 3P PREP - POWER - PRIDE

POWER Prevention Options for Women Evaluation Research