

# PrEP use in young African women in HPTN 082: Effect of drug level feedback

Connie Celum, Nyaradzo Mgodzi, Linda-Gail Bekker, Sybil Hosek, Deborah Donnell, Pete Anderson, Bonnie Dye, Subash Pathak, Yaw Agyei, Jessica Fogel, Mark Marzinke, Keo Makgamathe, Sheetal Kassim, Shorai Mukaka, Heather Noble, Adeola Adeyeye, Sinead Delany-Moretlwe  
on behalf of the HPTN 082 Study Team

## Background

- 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 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
- $\leq 200$  women who decline PrEP at enrollment

Eligibility criteria: Sexually active in past month; VOICE risk score  $\geq 5$ ; 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  $\geq 4$  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

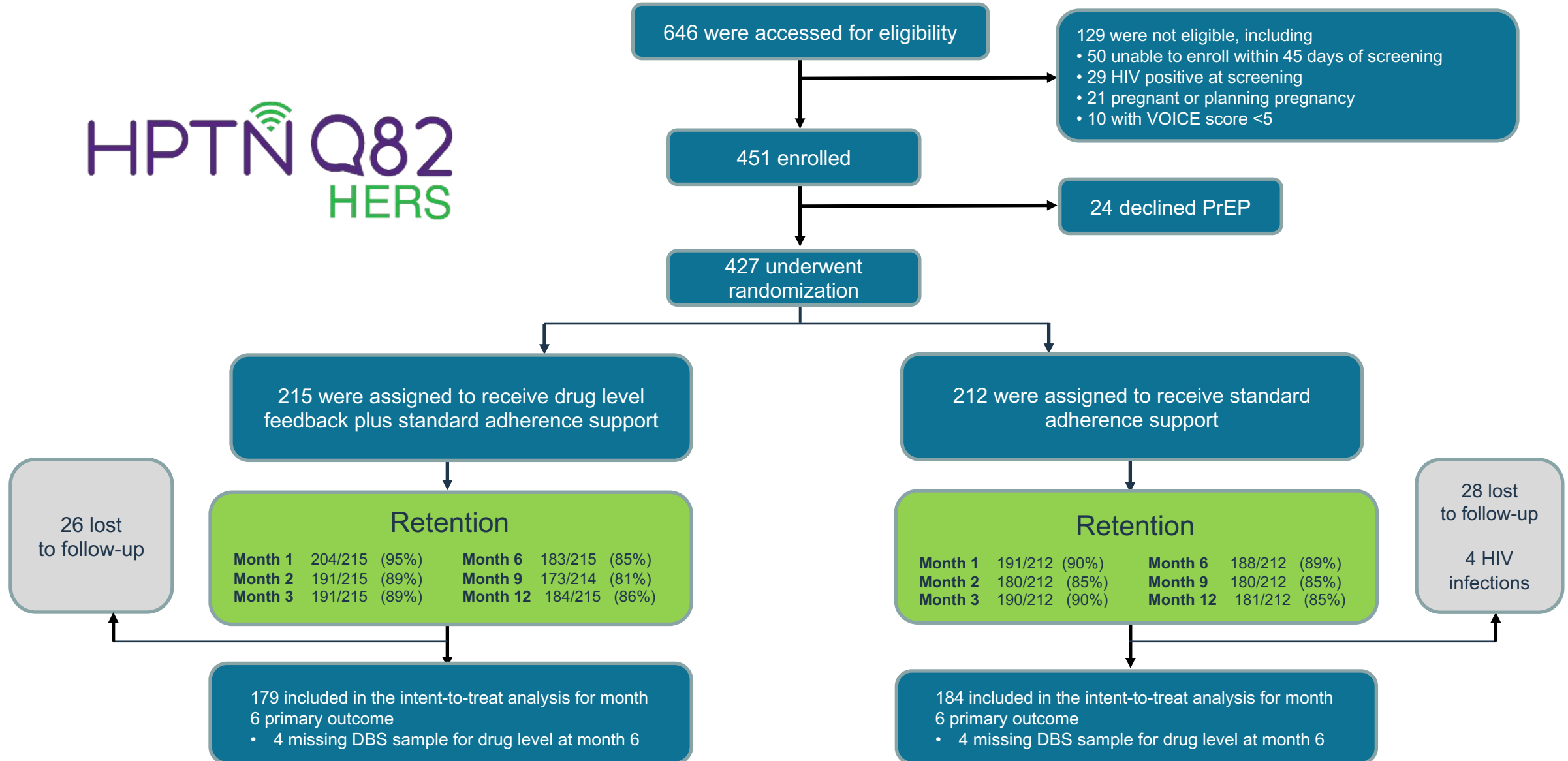
| Sample Month | Results Month | Threshold              |  | Counseling Message   |
|--------------|---------------|------------------------|--|--|
| Month 1      | Month 2       | $>500$ fmol/punch      |   | <p><i>4 or more doses per week (&gt;500 fmol/punch at wk 4 and &gt;700 fmol/punch at wk 8)</i></p> <p><b>Key message:</b> 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.</p>   |
| Month 2      | Month 3       | $\geq 700$ fmol/punch  |  |  |
| Month 1      | Month 2       | 16.6 – 499 fmol/punch  |   | <p><i>~1-3 doses per week (between detectable – 499 fmol/punch at wk 4 and detectable to 699 fmol/punch at wk 8)</i></p> <p><b>Key message:</b> 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?</p> |
| Month 2      | Month 3       | 16.6 – 699 fmol/punch  |  |  |
| Month 1      | Month 2       | BLQ (<16.6 fmol/punch) |  | <p><i>No TFV-DP detected (below quantification of 16.6 fmol/punch)</i></p> <p><b>Key message:</b> 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?</p>  |
| 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

## Analysis: Definitions and methods

- Primary adherence outcome: TFV-DP  $\geq 700$  fmol/punch at 6 months
- Predictors of high adherence at 6 months (TFV-DP  $\geq 700$  fmol/punch)
  - Logistic regression, adjusted for site
- Persistence: Detectable TFV-DP at 3, 6 & 12 months

HPTN Q82  
HERS





# Demographics & Sexual Partner Characteristics

| Baseline characteristic                            | Standard Adherence Support*<br>N=212 | Enhanced Adherence Support*<br>N=215 |
|--|--------------------------------------|--------------------------------------|
| Age (years) median (IQR)                           | 21 (19, 23)                          | 21 (19, 22)                          |
| <b>Education</b>                                   |                                      |                                      |
| Secondary school or higher                         | 184 (98%)                            | 187 (98%)                            |
| <b>CES-D depression score <math>\geq 10</math></b> | 126 (59%)                            | 133 (62%)                            |
| <b>Any intimate partner violence, past year</b>    | 100 (48%)                            | 116 (54%)                            |
| <b>Trauma symptoms</b>                             | 137 (65%)                            | 152 (71%)                            |
| <b>Primary sex partner in past 3 months</b>        | 174 (83%)                            | 182 (85%)                            |
| <b>HIV status of primary partner</b>               |                                      |                                      |
| 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*<br>N=212 | Enhanced Adherence Support*<br>N=215 |
|---|--------------------------------------|--------------------------------------|
| <b>Thinks partner has other partners</b>            |                                      |                                      |
| Yes   | 54 (31%)                             | 62 (34%)                             |
| Don't know  | 74 (43%)                             | 94 (52%)                             |
| <b>Vaginal sex past month (median, IQR)</b>         | 4 (2,8)                              | 4 (2,8)                              |
| <b>Condoms with vaginal sex, past mo</b>            |                                      |                                      |
| Always or often                                     | 60 (36%)                             | 36 (28%)                             |
| <b>Curable STI</b><br>CT, GC, trichomonas, syphilis | 80 (38%)                             | 87 (40%)                             |
| <b>Perceived risk of HIV, next year</b>             |                                      |                                      |
| None  | 50%                                  | 44%                                  |
| Small   | 27%                                  | 35%                                  |
| Moderate  | 9%                                   | 8%                                   |
| Great   | 9%                                   | 7%                                   |
| <b>Plan to disclose PrEP use</b>                    | 80 (38%)                             | 87 (40%)                             |

# Tenofovir levels at 3, 6, & 12 months

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

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

## Tenofovir levels at 3, 6, & 12 months

|   | 3 months     | 6 months     | 12 months    |
|---|--------------|--------------|--------------|
| <b>Tenofovir diphosphate (TFV-DP), DBS</b>                | <b>N=371</b> | <b>N=363</b> | <b>N=347</b> |
| Detectable  | 83.6%        | 56.5%        | 31.4%        |
| $\geq 700$ fmol/punch* among those with detectable TFV-DP | 24.8%        | 20.9%        | 8.6%         |
| <b>Plasma tenofovir</b>                                   | <b>N=380</b> | <b>N=370</b> | <b>N=363</b> |
| Detectable  | 64.8%        | 46.8%        | 25.3%        |
| $>40$ ng/ml**   | 48.4%        | 38.4%        | 17.4%        |

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

\*\* Plasma tenofovir  $>40$  ng/ml associated with daily use and efficacy among women in Partners PrEP (Donnell JAIDS 2014)

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

|                        | <b>Standard adherence support</b><br>TFV-DP $\geq$ 700 fmol/punch) | <b>Enhanced adherence support</b><br>TFV-DP $\geq$ 700 fmol/punch) | <b>Difference in proportion with TFV-DP <math>\geq</math>700 fmol/punch</b> | <b>95% CI</b> | <b>P-value</b> |
|------------------------|--|--|---|---------------|----------------|
| <i>Intent to treat</i> | 40/184 (21.7%)   | 36/179 (20.1%)   | -1.6%   | -9.9%, 6.7%   | 0.7            |

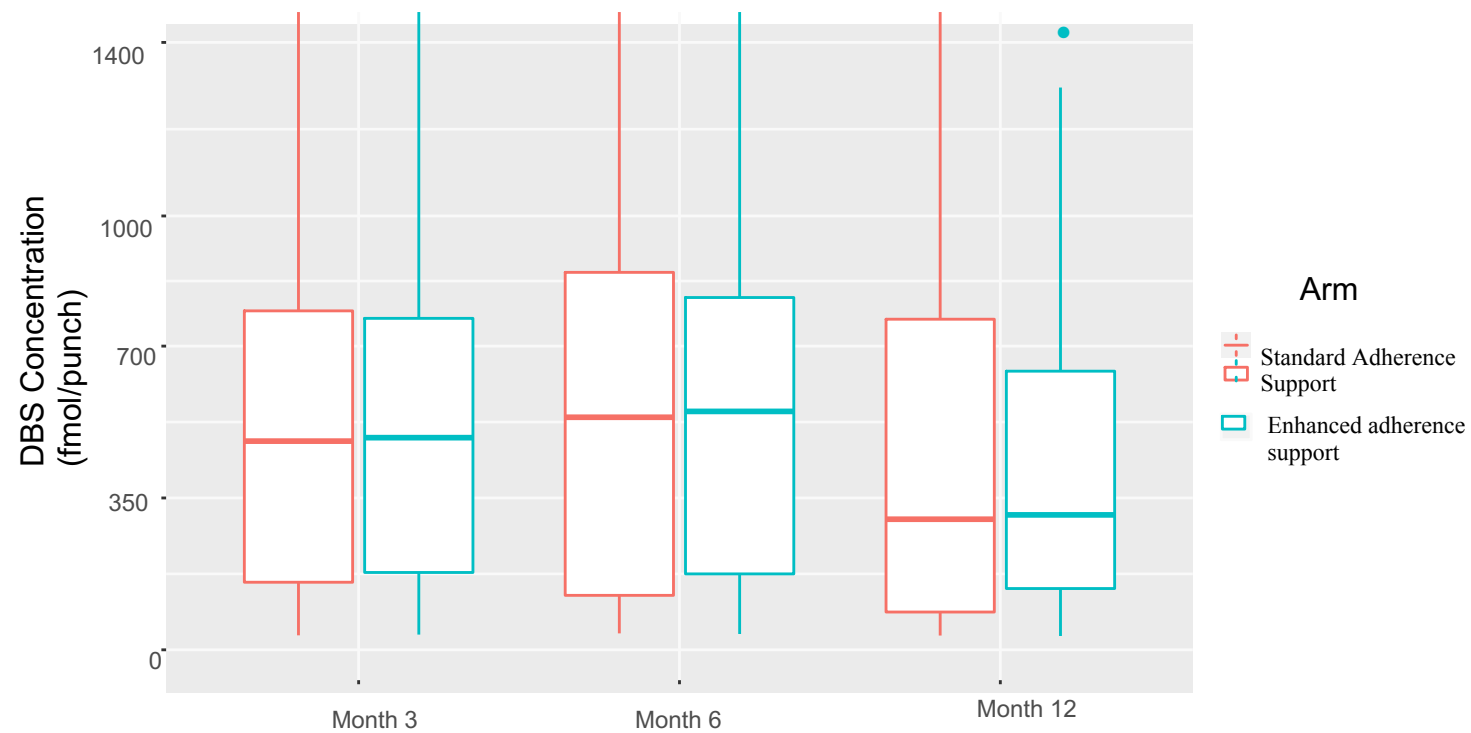
# Effect of drug level feedback on adherence (TFV-DP $\geq 700$ fmol/p) at 6 months

|                               | <b>Standard<br/>adherence support</b><br>TFV-DP $\geq 700$<br>fmol/punch | <b>Enhanced<br/>adherence support</b><br>TFV-DP $\geq 700$<br>fmol/punch | <b>Difference in<br/>proportion with<br/>TFV-DP <math>\geq 700</math><br/>fmol/punch</b> | <b>95% CI</b> | <b>P-value</b> |
|-------------------------------|--|--|--|---------------|----------------|
| <i>Intent to treat</i>        | 40/184 (21.7%)   | 36/179 (20.1%)   | -1.6%  | -9.9%, 6.7%   | 0.7            |
| <i>Per protocol analysis*</i> | 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

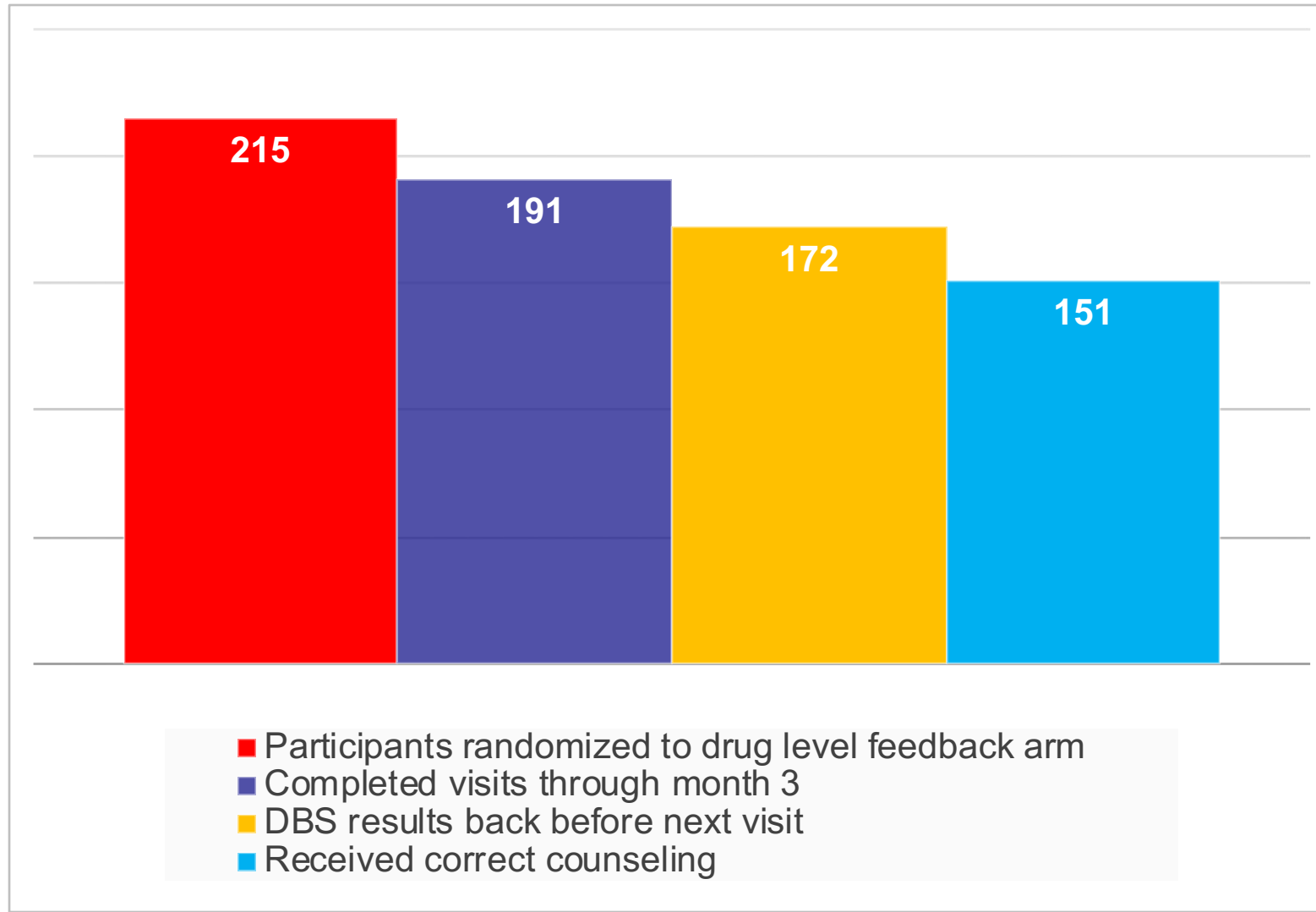
# PrEP adherence & persistence, by arm



| DBS results                              | N=371     | N=363       | N=347      |
|--|-----------|-------------|------------|
| Drug hold or stopped PrEP in prior month | N=7       | N=21        | N= 26      |
| Detectable TFV-DP among those on PrEP    | 305 (84%) | 202 (59%) * | 109 (34%)* |

\*p<0.001 for months 6 and 12 compared to month 3

# Challenges of retrospective drug level feedback





# Correlates of high adherence at 6 months

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

## HPTN 082: Summary

- Very high PrEP uptake (95%) among young women who were at risk for HIV, a majority of whom took PrEP in the first 6 months
- No effect of drug level feedback on proportions with detectable TFV-DP or high adherence by arm at 6 months
  - Challenges in operationalizing DBS drug level feedback and counseling about adherence levels 1-2 months ago
  - Research is needed to determine effective adherence support to sustain use including POC adherence assays (eg., urine TFV)
- Women who perceived themselves to be at risk of HIV and were motivated to use PrEP (HPRM score) had higher adherence at 6 months

## HPTN 082 Summary (2)

- Adherence declined significantly after month 3
  - Associated with change to quarterly visits, similar to other PrEP studies in youth (ATN 110/113, PlusPills)
- Low HIV incidence (1%) given risk profile of this cohort;
  - Counterfactual HIV incidence of 3.7% based on modeling (Moore CROI 2019)
  - Will assess whether low incidence was due to higher adherence during periods of risk (“prevention-effective adherence”)
- Longer-acting PrEP & choice of options will likely increase uptake, adherence & persistence (i.e., effective coverage)

## ACKNOWLEDGEMENTS

- The youth CABs for their engagement, ideas and feedback
- The young women who participated in HPTN082
- HPTN 082 team with special thanks to the site teams at Emavundleni (Cape Town), Spilhaus (Harare) and Ward 21 (Johannesburg)

# ACKNOWLEDGEMENTS

Youth community advisory boards, participants, and HPTN 082 team



## ACKNOWLEDGEMENTS

The HIV Prevention Trials Network is funded by the National Institute of Allergy and Infectious Diseases (UM1AI068619, UM1AI068613, UM1AI1068617), with co-funding from the National Institute of Mental Health, and the National Institute on Drug Abuse, all components of the U.S. National Institutes of Health.

Gilead Sciences for donation of Truvada for the study

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.