Clarification Memo # 1 to:

HPTN 082: Uptake and adherence to daily oral PrEP as a primary prevention strategy for young African women: A Vanguard Study

DAIDS Protocol #: 12068

Clarification Memo Version: 7 March 2016

Summary of Revisions and Rationale

Summary of Revisions
The HPTN 082 protocol v1.0, 8 December 2015 has been updated to reflect the changes listed in this Summary of Revisions and Rationale. All changes made are clearly indicated in the next section, Implementation of the Protocol Modifications.

1) That the determination to use plasma versus DBS for drug level concentrations for the drug level feedback counseling will be based on the best available assay at the time of study implementation.
2) Further, because of the difference in assay used and also as new pharmacokinetic information continues to change we have clarified the protocol to note that the precise thresholds for drug level feedback counseling will be included in the SSP.
3) To fix the oversight that Gilead was left off the cover page of the protocol as a Co-Sponsor.
4) To revise affiliation information for one Protocol Team member.

Implementation of the Protocol Modifications

The procedures clarified in this memorandum have been approved by the Division of AIDS (DAIDS) Medical Officer and are to be implemented immediately upon issuance. IRB approval of HPTN 082 Protocol Clarification Memo #1 to HPTN 082 Version 1.0 is not required by the sponsor; however, sites may submit the Clarification Memo to the responsible IRBs for their information.

No change in the informed consent forms is necessitated by or included in this Clarification Memo.

The modifications included in this Clarification Memo will be incorporated into the next full protocol amendment. Text noted below by strikethrough will be deleted; text appearing below in **bold** will be added. Edited text is also highlighted in grey for ease of review.

Revision 1 &2- Related Changes: Assay for drug level feedback and thresholds for drug level feedback

1.2.2. Adherence to open-label PrEP

In summary, for the HPTN 082 intervention, we will support the formation of effective PrEP adherence habits among all women who accept PrEP through: 1) brief adherence counseling based on CBT for women who accept PrEP at enrollment with monthly visits in the first three months to support adherence habit formation; 2) two-way weekly SMS text messaging to provide cognitive reminders about visits and support for PrEP adherence, using an existing platform for SMS reminders, and 3) peer support through HPTN 082 adherence support clubs;.

All of these will be described in more detail in Section 4.3. In addition, we will randomize women in a 1:1 ratio to have counseling about their early ~~plasma~~ TFV **or TFV-DP** levels to assess whether this intervention affects adherence.

4.3. Adherence Support for PrEP Acceptors

Counseling based on drug levels

Women who are randomized to enhanced counselling will have adherence monitoring based on plasma **or DBS** TFV**/TFV-DP** levels obtained 4 and 8 weeks after PrEP acceptance as described in Section 4.6.4. Adherence counseling based on drug levels will be provided at the next visit (i.e., for participants who accept PrEP at enrollment Week 4 levels will be provided at the Week 8 visit, Week 8 levels will be provided at the Week 13 visit). Pictorial tools will be developed in conjunction with the youth CABs in order to provide youth-relevant representations of drug levels (e.g., cell phone bars or wireless signal strength symbols).

4.6.4. Counseling based on feedback from drug level data

Participants who are randomized to enhanced counseling will have measurements of plasma TFV **or DBS TFV-DP** levels on samples taken 4 and 8 weeks after PrEP acceptance. These will be "convenience" or "untimed" samples with respect to the previous dose. ~~A plasma TFV threshold of >40 ng/mL Plasma t~~**T**hresholds **will be developed and included in the SSP and counseling manuals. T**hese will be used for counseling women about their adherence. ~~;For example, 40 ng/mL represents the lower 95th confidence interval for the TFV trough for daily dosing at steady-state, and it has been associated with PrEP efficacy in the Partner's PrEP study.53 Additional TFV plasma thresholds (described below) were will be determined through extensive knowledge of TFV pharmacokinetics from numerous studies including HPTN 066.~~ The adherence counseling based on TFV **or TFV-DP** levels will be provided at the next visit (i.e., Week 4 level will be provided at the Week 8 visit, and Week 8 drug levels will be provided at the Week 13 visit). A semi structured feedback guide will be included for site adaption in the SSP. Women will receive the following counseling during their cognitive behavioral counseling sessions:

- For those with TFV ~~>40 ng/mL~~ **or TFV-DP** levels **consistent with a dose within 24 hours or consistent dosing (for example, at least 6 doses per week) in the preceding month:** Positive re-enforcement with continued encouragement to maintain adherence.
- For those with TFV ~~5-40 ng/mL:~~ **or TFV-DP** levels **that are quantifiable but consistent with less frequent dosing**: Discuss details about their dosing patterns in the past ~~week~~ **month** and encourage greater adherence in order to get optimal protection from PrEP.
- For those with TFV ~~<5ng/mL~~ **or TFV-DP** levels **which are undetectable**: **Discuss willingness and/or need to continue PrEP use and if willing and in need of PrEP,** emphasize the need for greater adherence and explore barriers to taking PrEP, avoiding punitive language.

4.6.5. Primary Adherence Assessment

For the primary adherence outcome measurement (adherence in the cohort by randomization arm) drug levels will be measured retrospectively. The main adherence assessment will be performed using plasma and/or DBS samples. The testing plan will be determined at a later

date, based on evaluations of plasma TFV levels and DBS TFV-DP levels in women that are currently underway.

We will utilize plasma TFV levels to assess recent dosing within the last 5 days and DBS TFV-DP levels to assess cumulative dosing in the prior month. DBS has been used to detect intracellular levels of TFV-DP in red blood cells, providing a measure of cumulative adherence behavior over the prior one-two months. A threshold of 700 fmol/punch predicted 100% efficacy among MSM in iPrEX OLE.[24] Given the long half-life for TFV-DP, gradients of cumulative adherence can also be estimated, such as those described in iPrEX OLE as follows: Below limit of quantitation (BLQ, no doses), BLQ to 349 fmol/punch (fewer than two tablets per week), 350–699 fmol/punch (two or three tablets per week), 700–1249 fmol/punch (four to six tablets per week), and ≥1250 fmol/punch (daily dosing). Women may respond to TDF/FTC differently compared with men due to differences in mucosal drug distribution, and ongoing analyses of HPTN 066 and DOT-DBS will be used to compare plasma tenofovir and intracellular TFV-DP in DBS to identify the appropriate thresholds indicating high, intermediate, and no recent adherence based on plasma TFV and cumulative dosing based on intracellular TFV-DP in women.

~~A plasma TFV level of >40 ng/mL will be interpreted to indicate dosing within the last 24 hours. DBS can be used to detect intracellular levels of TFV-DP, providing a measure of cumulative adherence behavior over the prior 2 months. A threshold of 700 fmol/punch predicted 100% efficacy in iPrEX OLE.24 Given the long half-life for TFV-DP, gradients of cumulative adherence can also be estimated, such as those described in iPrEX OLE as follows: Below limit of quantitation (BLQ, no doses), BLQ to 349 fmol/punch (fewer than two tablets per week), 350–699 fmol/punch (two or three tablets per week), 700–1249 fmol/punch (four to six tablets per week), and ≥1250 fmol/punch (daily dosing). Although women may respond to TDF/FTC differently compared with men due to differences in mucosal drug distribution, there are no in vivo data to support a specific TFV-DP threshold in women. In the absence of such data, we will use the 700 fmol/punch threshold that suggests consistent dosing and was associated with full efficacy in iPrEx OLE, unless new data become available. Finally, FTC-triphosphate levels in DBS serve as a surrogate for quantifiable plasma TFV (at ≥ 10ng/mL), which informs dosing within the last 48 to 72 hours.24~~

5.14. Qualitative data collection

The use of qualitative methods that give young women the opportunity to discuss their decision-making, adherence barriers, and facilitators in their own words will result in a more culturally-sensitive approach to the study of PrEP uptake and adherence among young women in Africa.

In-depth qualitative interviews will be conducted with three distinct groups of women including:

1. Young women who accept and adhere to PrEP (**when possible** these women will be selected ~~from those who have TFV levels >40 ng/mL~~ **based on drug levels** at Week 4).
2. Young women who accept but do not initiate, **do not** adhere to PrEP, or discontinue **PrEP** (**when possible** these women will be selected **based on drug levels** ~~among those with TFV levels <40 ng/mL~~ at Week 4), and

3. Young women who do not accept PrEP during the first 3 months.

7.2.2 Secondary Endpoints

Consistent with the secondary study objective to assess correlates of PrEP adherence at Weeks 13, 26, and 52, after adjusting for study arm, such as adherence at prior study visits, sociodemographic factors, individual-level and partner-level characteristics, exposure to study-based adherence support, and risk practices, the following endpoint(s) will be assessed:

- TFV levels in plasma or DBS at Week 13, 26 and 52 amongst those women who accept (based on CRFs) and remain on PrEP (based on drug dispensed)
- Drug not dispensed among those who accept but do not remain on PrEP

Covariates assessed at baseline and follow-up visits will include:

- TFV/**TFV-DP** levels in plasma **or DBS**
- Sexual risk
- Alcohol use
- Number of partners
- Age of partner
- Transactional sex
- Intimate partner violence

7.4. Data Analysis

7.4.1. Primary Analyses

Amongst those who accepted PrEP and were randomized, we will report average adherence to daily PrEP as ~~the proportion with plasma TFV >40 ng/mL at any visit using TFV levels at~~ **described previously based on ongoing analysis from relevant studies** at Weeks 13, 26 and 52 after accepting PrEP. The difference in proportion adherent at weeks 13, 26 and 52 will be compared between arms using a t-test (assuming the normal approximation to the binomial) at each visit. Women who are missing drug level assessment but did not have drug dispensed at their most recent visit will be defined as non-adherent. Among all women who accept PrEP, the primary assessment will compare the proportion with **TFV levels or TFV-DP levels consistent with a dose within 24 hours or consistent dosing (for example, at least 6 doses per week) in the preceding month** ~~TFV levels in plasma >40 ng/mL~~ across all visits between arms using logistic regression accounting for repeated measures. If DBS is used~~, the above TDF levels will be replaced with~~ a TFV-DP threshold ~~for~~ **consistent with** high adherence ~~of 700 fmol/punch, or~~ **as** determined from ongoing studies **will be used** when available.

Secondary Analyses

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- In PrEP users, the risk of acquisition will be compared between visits with and without ~~plasma~~ TFV~~>40 ng/mL~~ **or TFV-DP above thresholds defined in the SSP** using time-dependent survival analysis methods. ~~For the same analysis, the value for TFV-DP in DBS will be determined from ongoing studies, or 700 fmol/punch will be used if no additional data are available.~~

Appendix IA: Schedule of Study Visits and Procedures for PrEP Acceptors

Laboratory Evaluations/Procedures						
HIV testing (see SSP Manual)[4]	X	X	X	X	X	X
Hepatitis B serology[7]	X					
Serum creatinine (for creatinine clearance, Schwartz Equation)	X				X[5]	X
Pregnancy testing [3, 4]	X	X	X	X	X	X
STI testing (TV[6], GC/CT, syphilis)	X				X[5]	X
~~Plasma TFV~~ **Drug level** concentration (per randomization)[8]			X			
Plasma storage	X	X	X	X	X	X
DBS storage			X	X	X	X

[8]Sample will be plasma and/or DBS to be determined at study implementation.

Revision 3- Related Changes: Addition of Gilead to cover page

Sponsored by:
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Non-IND Study

Revision 4- Related Changes: Protocol Team Roster

Adeola Adeyeye MD, MPA **(c)**
Medical Officer, ~~HJF-DAIDS~~
Prevention Science Program, DAIDS, NIAID, NIH
Room 8B36 MSC 9831, 5601 Fishers Lane
Rockville, MD 20852, USA
Phone: 240 669 5005
Email: adeyeyeao@niaid.nih.gov