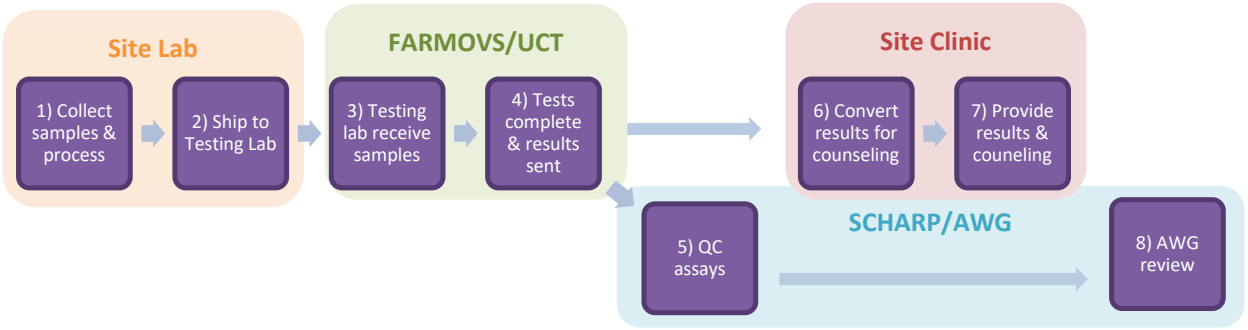
MTN-034/REACH Residual Drug Feedback Process

This document outlines the process for the shipment, testing, and provision of dapivirine ring residual drug and Truvada drug level results to study participants, as well as a brief overview of how the management team will monitor adherence across the study. The goal of this process is to allow for results of used rings and dried blood spots (DBS) collected at a participant's visit to be available for adherence counseling with the participant as soon as possible (i.e., specimens collected at the Month 1 visit would be available for counseling at the Month 2 study visit) and to support teams to encourage adherence at each site.

PROCESS FLOW



PROCESS STEPS

STEP 1: Sites collect participants' used rings and DBS samples from the clinic

Timeframe: after each monthly visit

- All used rings and DBS samples will be temporarily stored at the site, then shipped to the applicable lab on a weekly basis utilizing Laboratory Center (LC) approved carriers.
- Site lab may assign a new, separate, LDMS container each week and "mark to ship" that container when creating a shipping batch.

STEP 2: Sites ship all rings to FARMOVS and ship all DBS samples to UCT weekly

Timeframe: 1-7 days after sample collection.

- SCHARP will not provide specimen shipping lists to sites – sites will ship samples as they are collected.
- Site labs will send an LDMS manifest to the applicable testing lab along with the specimen shipment.

STEP 3: FARMOVS and UCT receives sample shipments

Timeframe: 1-2 days

- FARMOVS and UCT are LDMS labs
- FARMOVS and UCT to test samples as they are received
- FARMOVS and UCT testing runs will not be sorted or randomized by site
- FARMOVS and UCT perform QC on tested samples
  - If discrepancies/outliers are identified, additional testing may be required on a sample

STEP 4: FARMOVS and UCT complete testing and email results to sites via PTID-specific reports

Timeframe: UCT 21 days/FARMOVS: 14 days

- FARMOVS and UCT will send PTID-specific LDMS lab test report PDFs to sites' primary contacts (generally Investigator of Records (IoRs) and clinicians).
- Reports include the following: site name, PTID, Global Specimen ID (LDMS) for each sample tested, visit code when sample was collected, specimen collection date, specimen name, drug level (xx.x mg or x.xx fmol/punch), limits of quantification, Censor Code (if applicable), testing lab name, and type of test performed.

STEP 5: FARMOVS and /UCT upload assay results to SCHARP

Timeframe: weekly

- SCHARP will QC these data for the real time review of adherence data by the study management team REACH Adherence Working Group (see Step 8).

STEP 6: Sites use MTN-034 Drug Feedback Tool to categorize value into a drug level category

Timeframe: 1-2 days

Dapivirine adherence calculation from used rings:

- The site clinician or designee will use the *MTN-034 Drug Feedback tool* as follows:
  1. Enter the visit # that the product was dispensed, the product that the participant was on at time of specimen collection (ring), and ring concentration.
  2. Enter the 'Date Ring Dispensed' and the 'Date Ring Returned'. The tool will auto-calculate the number of days the participant had ring.
  1. Enter the "Ring Manufacturer Load Level"
     - The lot of rings in use as of 1FEB2020 (UL536) has a mean dapivirine load content of 25.0 mg. This lot will be used through study closeout.
  2. The tool will calculate the Adherence Category as listed below
- **Dapivirine qualitative cutoffs:** The ring protection levels are based on a ring use rate (RUR) calculated from the amount of drug released from the ring divided by the time in days (or expected time) from ring dispensation to ring return. Translation from the rates to the protection levels in Table 1 below.

Truvada adherence calculation from DBS:

- The site clinician or designee will use the *MTN-034 Drug Feedback tool* as follows:
  1. Enter the visit # that the product was dispensed, the product that the participant was on at the time of specimen collection (Truvada), and the DBS lab value.
  2. The tool will calculate the Adherence Category as listed in Table 1 below.

Table 1. Drug Level Qualitive Conversion Categories		
DPV Cut-offs	**Adherence Category**	**Truvada Cut-Offs**
If rate >= 0.1071 mg/day	 **High Levels**	4 or more doses per week (>500 fmol/punch if participant did not have access* to Truvada in the previous month, otherwise >700 fmol/punch)
0.0321 mg/day < rate < 0.1071 mg/day	 **Medium Levels**	~1-3 doses per week (16.6 – 499 fmol/punch if participant did not have access* to Truvada in the previous month, otherwise 16.6 to 699 fmol/punch)
If rate <= 0.0321 mg/day	 **Low Levels**	No TFV-DP detected (Less than 16.6 fmol/punch)
**Having access to Truvada in the previous month means that the participant was in the Truvada product use period, or chose to use Truvada during period 3, in the previous month*		

The **MTN-034 Drug Feedback Tool** is available for download at:
https://mtnstopshiv.org/research/studies/mtn-034/mtn-034-study-implementation-materials

Total approximate testing timeline:

→ Site Collection to shipment: 7 days
→ Site shipment to FARMOVS/UCT receipt: 2 days
→ Specimen testing and provision of results to site: UCT 21 days/FARMOVS 14 days
→ Site processing of results before visit: 1-2 days
Total: ~25-32 days

STEP 7: Adherence counseling sessions

Timeframe: during all monthly follow-up visits

The site counselor will use the Drug Feedback tool to inform adherence counseling with participants and will transcribe both the drug level and the qualitative color category onto the Adherence Counseling CRF. The Adherence Counseling CRF will be completed at all follow-up visits. Starting at Visit 5 (month 2), participants will be provided with feedback on residual drug or DBS data.

The study team expects that drug level results will be available on the schedule indicated in Table 2 below. At counselor discretion, results may be provided to the participant at the visit immediately following

availability of results. In the event results are not available, the visit should proceed as originally scheduled and the participant should be counseled that she would be contacted when this information is available (either as part of an interim visit or at the next scheduled study visit). All available results at the time of the visit should be provided to participants during their adherence counseling session. The Adherence Counseling CRF will record the drug levels and the associate qualitative categories for each result available. Sites will be able to enter more than one DBS and/or residual drug result at any given visit (this portion of the form will include log lines).

Table 2. Counseling Sessions with Required Drug Level Feedback

Product Use Period	Counseling Session	Study Visit	Drug Data Available
1	Visit 5	Month 2	Product dispensed at Enrollment (first month of use in Period 1)
	Visit 8	Month 5	Product dispensed at Months 1-3
2	Visit 12	Month 8	Product dispensed at Month 6 (first month of use in Period 2)
	Visit 15	Month 11	Product dispensed at Months 7-9
3 (Choice)	Visit 19	Month 14	Product dispensed at Month 12 (first month of use in Period 3)
	Visit 22	Month 17	Product dispensed at Months 13-15

The Adherence Counseling CRF will ask whether the results were available at the visit. This will allow the REACH team to determine the proportion of results that were available for counseling of the participants at the given visit.

The CRF should reflect the drug results for which the participant was counseled at the time. Sites will not update/correct drug result data entered on the Adherence Counseling CRF data if it is discrepant with assay data from the testing lab.

STEP 8: Real-time review of adherence data by the REACH Adherence Working Group (AWG)
Timeframe: monthly

- Review to occur as part of monthly AWG review of adherence data
- Drug Summary Information for site IoRs: REACH team to provide blinded drug summary information tables, if needed
- Tables of trajectory of drug levels over time

MTN-034/REACH Residual Drug Feedback Process Approvals

Name	Role	Steps Approved	Signature	Date
Edward Livant	MTN LC Study POC	31JAN20 Lot Load Level Change in Step 6 added to version 1.0	Digitally signed by Edward Livant DN: cn=Edward Livant, o=MWRI, ou=IDI, email=livantew@upmc.edu, c=US Date: 2020.02.04 12:26:22 -05'00'	04FEB20
Sybil Hosek	Protocol team	31JAN20 Lot Load Level Change in Step 6 added to version 1.0		11 FEB 20
Elizabeth Brown	Protocol Statistician	31JAN20 Lot Load Level Change in Step 6 added to version 1.0		11 Feb 20
Daniel Szydlo	Statistical Research Associate	31JAN20 Lot Load Level Change in Step 6 added to version 1.0		04 FEB 2020