Welcome to IMPAACT Social Behavioral Scientific Core

SpotLight Series

Adherence in Clinical Trials: Part II - Concepts, Challenges, & Support

Panelists: Jessica Haberer MD, MS and Kenneth Ngure, PhD

The session will begin shortly

Virtual Attendee Logistics:

Please remain muted when not speaking.

Please enter your questions into the chat.

Adherence in Clinical Trials: Concepts, Challenges, and Support- Part II

Jessica Haberer, MD, MS
December 1, 2022

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Outline

- Pharmacokinetic adherence measures
- Electronic adherence monitoring
- SMS as an adherence measure
- Comparison of adherence measures

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Pharmacokinetic Measures- The Basics

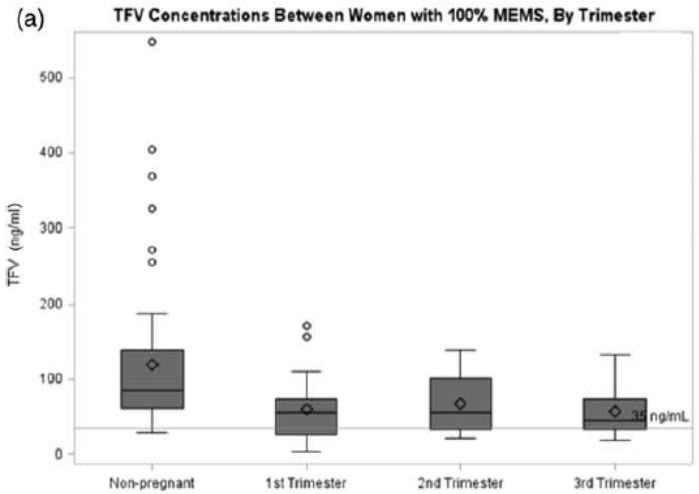
- Objective information about medication use
- Used for both PrEP and ART
- Periodic measurements provide various “lookback periods”
- Best characterized for tenofovir
  - Whole blood/dried blood spots (8 weeks)
  - Plasma (1 week)
  - Peripheral blood mononuclear cells (7-14 days)
  - Hair (variable by length)
  - Urine (1 week)
- More exploration of other drugs in hair (e.g., lopinavir, INH) and urine (INH)

Pharmacokinetic Measures- The Challenges

- Presence = some degree of adherence, but interpretation isn't always clear
- Summary measures
- Cost and processing
- Thresholds are not clearly established in all scenarios
  - 700 fmol/punch equates to protective dosing of tenofovir PrEP among men who have sex with men (Anderson, Sci Transl Med 2012)
  - An equivalent has not yet been established for women

Pharmacokinetic Measures- The Challenges

- Relevant factors for tenofovir in DBS
  - Hemoglobin
  - Pregnancy
  - Weight
  - Population (?)
  - Drug interactions (?)



(Pyra, AIDS, 2018)

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Pharmacokinetics- Areas of Research

Little data in pediatrics

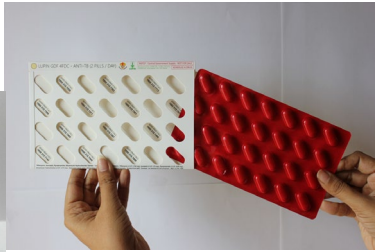
- IMPAACT 2019 (PK, Safety, and Tolerability of ABC/3TC/DTG Dispersible and Immediate Release Tablets)- DBS for abacavir and 3TC

Assessment of adolescent girls and young women

- Pharmacology of TDF-FTC Pre-exposure Prophylaxis in Kenyan Cisgender Women (Mugwanya/Anderson; NCT05057858)
- Targets for PrEP

Electronic Monitoring- The Basics

- Objective adherence data
- “Smart” pill boxes
- Record a time-and-date stamp
- Standard vs real-time
- Provide patterns of adherence



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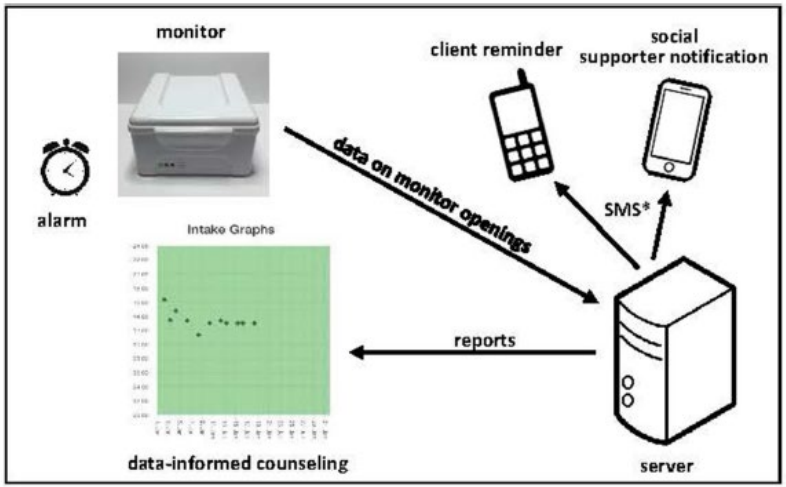
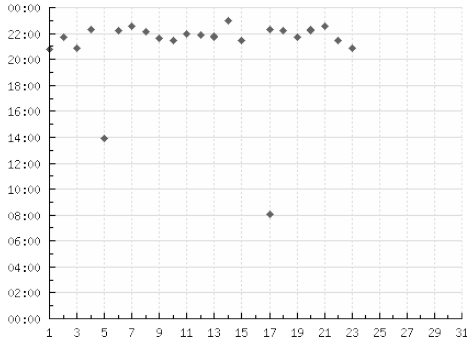
Electronic Monitoring- The Challenges

- Measure of engagement with the monitor, which may differ from adherence
- Devise non-use can falsely lower adherence measurement
- “Curiosity openings” can falsely elevate adherence measurement
- “White coat adherence” may occur due to social desirability
- Cost

Electronic Monitoring- Interventions

- Monitoring itself can be an intervention
- Graphical displays provide feedback and opportunity for counseling
- Real-time devices can be paired with SMS and other outreach





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Protecting Households On Exposure to Newly Diagnosed Index Multidrug-Resistant Tuberculosis Patients (PHOENIx MDR-TB)

- Phase III, open-label, cluster-randomized superiority trial of delamanid vs isoniazid
  - HIV/immunosuppression
  - Children <5 years
- 28 sites in 13 countries (currently)
- HHCs= 901/3,452

- Added value
  - Real-time knowledge of adherence challenges
  - Coupled with outreach and counseling
  - Household-based approach

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SMS- Adherence Measurement

- SMS widely used as an adherence intervention to variable success
- Also used as an adherence measure (i.e., self-report)
- Provides opportunity for ecological momentary assessment
  - Behaviors
  - Beliefs
  - Location

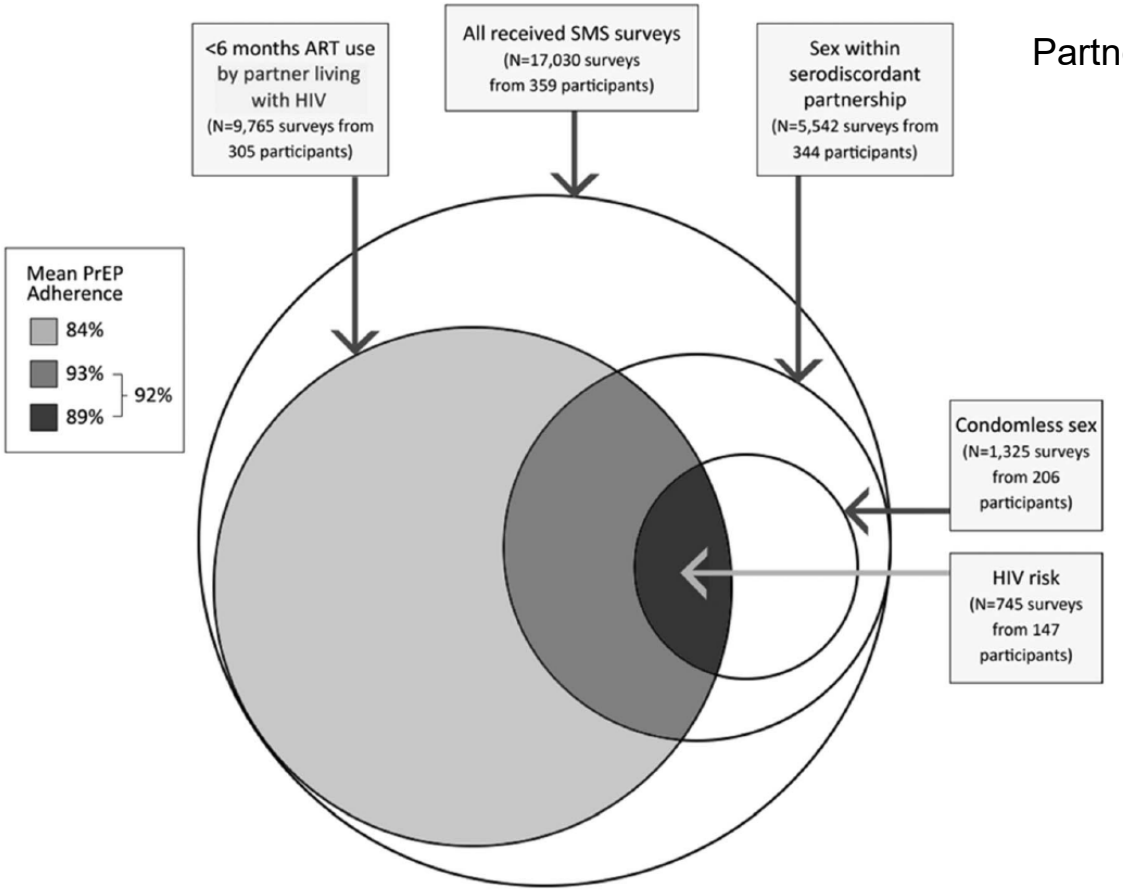

FIGURE 1. Mean PrEP adherence as associated with risk for HIV transmission. Circles indicate risk behaviors for HIV acquisition: <6 months of ART use by the partner living with HIV, sex reported within the serodiscordant partnership, and reported condomless sex. Mean reported PrEP adherence concurrent with each overlap of behaviors is shown in the legend.

(Haberer et al, JAIDS 2017)

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Comparison of measures

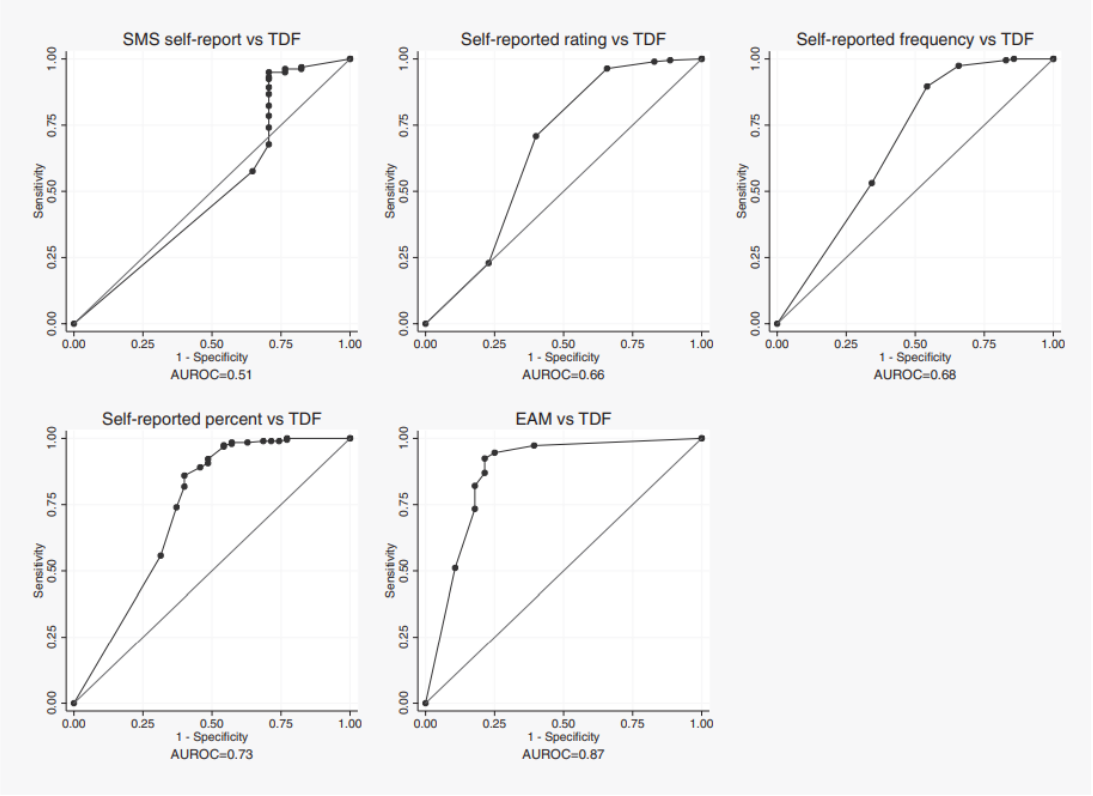

Fig. 1. Comparison of short messaging service, self-report and electronic adherence monitoring versus detectable plasma tenofovir. An area under the receiver-operating curve (AUROC) of 0.5 lies on the diagonal line and implies that discrimination was no better than random chance. AUROC over 0.8 is considered good [10].

(Musinguzi et al, AIDS 2018)

Take home points for measurement

There is no gold standard for adherence measurement

Every measure has its pros and cons

Multiple measures help increase the accuracy of adherence estimation

Key questions for deciding how to measure adherence

- What kinds of information do you need?
- How much effort can/should you put into adherence measurement?
- How do you want to link adherence support to specific participants and/or scenarios?

Acknowledgments

Many study participants and colleagues who have contributed to our understanding of medication adherence

NIMH, IMPAACT, ACTG, HANC Social Behavioral Working Groups

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Maria Pyra

Elizabeth Bukusi

Nelly Mugo

Kenneth Ngure

Jared Baeten

Claude Mellins

Rivet Amico

Ira Wilson

Jane Simoni

Many more…

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Adherence support

Kenneth Ngure, MPH, PhD

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Why Support Adherence?

Effective use of pre-exposure prophylaxis (PrEP) has been low among adolescent girls and young women (AGYW) in sub-Saharan Africa.

Study	Product	Population	Proportion with high adherence	Reference
HPTN 082 (Month 6)	Oral PrEP	AGYW	21%	Celum et al, PloS Med 2021
3P (Month 6)	Oral PrEP	AGYW	14%	Celum et al, JIAS 2020
DREAMS program	Oral PrEP	AGYW	6%	Cover et al, AIDS 2020
HOPE (Month 6)	Ring	Adult women	32%	Beaten et al, Lancet HIV 2021
MPYA (Month 6)	Oral PrEP	Young Women	5%	Haberer et al, Lancet HIV 2021

Slide adapted from Sarah Roberts

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Pharmacologic Measures- important

- PrEP and ART effectiveness reliant on adherence
- Pharmacologic adherence measures *critical* to interpretation of placebo-controlled PrEP trials
- Efficacy of TDF/FTC in iPrEx rose from 44% to an estimated 92% (CI 40, 99%) among those with detectable drug levels (plasma or PBMC)
- Two trials (FEM-PrEP & VOICE) showed no efficacy but was determined only due to measuring tenofovir in plasma

Adherence Measure	VOICE	FEM-PrEP
Self-report	91%	95%
Returned pill counts	92%	88%
Plasma TFV detection	29%	24%

Grant et al. NEJM 2010; Marrazzo et al. NEJM 2015; Van Damme et al. NEJM 2012; Baeten et al. NEJM 2012; Donnell et al. JAIDS 2014

Sharing Pharmacokinetic (PK) data with participants

DPV Cut-Offs for Ring	Adherence Category	TFV-DP Cut-Offs for Oral PrEP
Release rate ≥ 0.1071 mg/day	 HIGH LEVELS	4 or more doses per week: • TVF-DP >500 fmol/punch if participant did not have access* to oral PrEP in the previous month • Otherwise TFV-DP >700 fmol/punch
0.0321 mg/day <release rate< 0.1071 mg/day	 MEDIUM LEVELS	~1-3 doses per week: • 16.6 fmol/punch ≤ TFV-DP ≤ 499 fmol/punch if participant did not have access* to oral PrEP in the previous month • Otherwise 16.6 fmol/punch ≤ TFV-DP ≤ 699 fmol/punch
Release rate ≤0.0321 mg/day	 LOW LEVELS	No TFV-DP detected • TFV-DP <16.6 fmol/punch

DPV: Dapivirine; TFV-DP: Tenofovir diphosphate (active metabolite in oral PrEP).
**Having access to oral PrEP in the previous month means that the participant was in the oral PrEP product use period, or chose to use oral PrEP during period 3, in the previous month*

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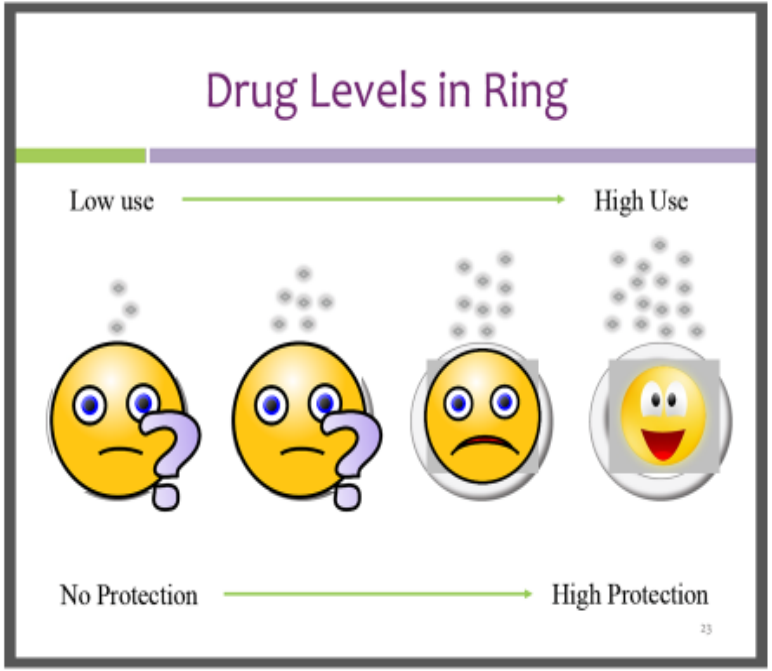
Results: Emotional Responses in MTN 025 [HOPE]



Katz AWK et al., *AIDS & Behav* 2022

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Lessons learnt in HOPE with Drug Feedback

- Participants valued the monitoring of protection level against HIV, but RDL was at times challenging and evoked strong reactions.
- Client-centered counseling helped to channel emotions and behavioral reactions positively.
- Emphasis on protection minimized confrontational interactions and facilitated alternative, but at times implausible, explanations.
- Several participants recommended improved test accuracy to more precisely reflect product use

Katz AWK et al., *AIDS & Behav* 2022

LC-MS/MS based pharmacologic metrics too hard to do routinely- need point of care test.

- Pharmacologic measures (PrEP drug levels in plasma, dried blood spots (DBS), hair)
- Current methods to measure PrEP drugs in biomatrices involve (mainly LC-MS/MS) → expensive, trained personnel, difficult to perform in real-time
- Urine emerging as an easy-to-collect measure

Matrix	PrEP analytes measured	Analysis platform
Plasma	TFV/FTC	LC-MS/MS[1-3]
PBMC	TFV-DP/ FTC-TP	LC-MS/MS[1,4]
DBS	TFV-DP/ FTC-TP	LC-MS/MS[5-7]
Hair	TFV/ FTC	LC-MS/MS[8], IR-MALDESI[9]
Urine	TFV	LC-MS/MS[3, 10-13]

[1]Hendrix ARHR 2016; [2]Hendrix PLOS One 2013; [3]Calcagno. Pharmacogenomics 2016; [4]Anderson Sci Trans Med 2012; [5]Castillo-Mancilla. ARHR 2013; [6]Castillo-Mancilla. ARHR 2015; [7]Zheng. J Pharm Biomed Anal 2014; [8]Liu PLOS One 2014; Rosen. Anal Chem 2016;[10]Koenig HIV Med 2017; [11]Simile. J Pharm Biomed Anal. 2015; [12]Haaland AIDS 2017; [13]Lalley-Chareczko. Antiviral Ther 2017

Slide courtesy of Monica Gandhi

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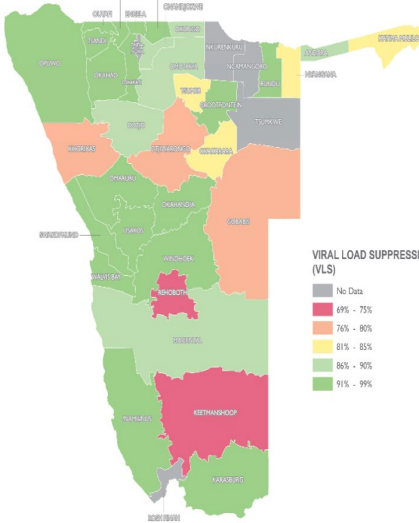
CDC Study: Adherence Intervention Using Urine Assay Improves Viral Suppression

- Urine Test put into 44 HIV clinics to allow monthly adherence checks for patients on TLD in N
- For patients who did not suppress despite enhanced adherence counseling (EAC)
- 200 PLWH enrolled with viral load >1000
- Data available to date:
  - **89% (113/127) now virologically suppressed by month 3; p<0.001**
  - **86% of participants and 91% of providers agreed/strongly agreed that the urine test should be in care**
  - **Remarkable as group did not originally suppress after counseling**

Viral Suppression b
Region in Namibia



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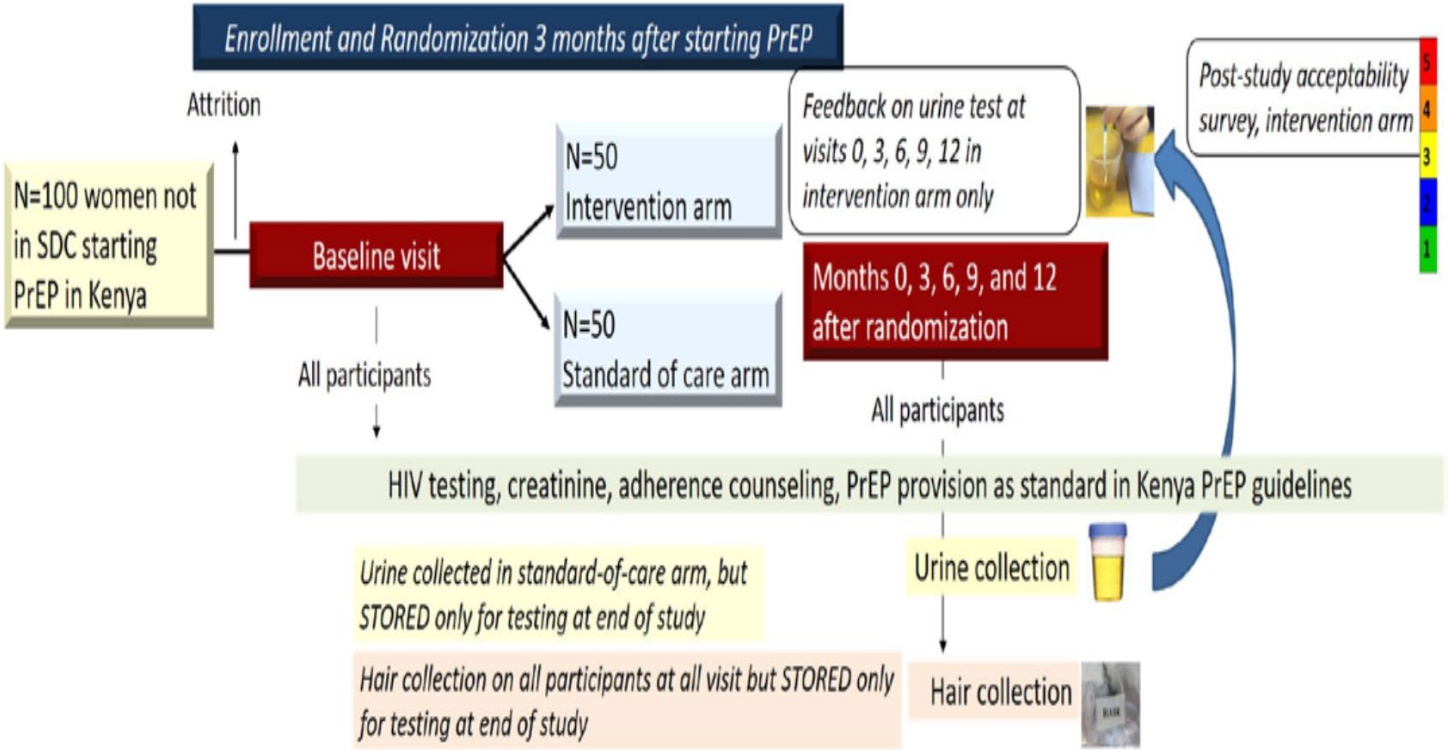
PUMA Study Design

Figure 7: Schedule of Evaluations for Participants in the SOC and Intervention Arm of the Pilot RCT



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Counseling MTN 025 (HOPE)

Adherence counseling based in Motivational-Interviewing (MI) and client-centered care	Existing counselors in clinical research sites were trained by a team of experts including clinical psychologists and community trainers. Counseling content was standardized and informed by evidence-based practices such as client-centered counseling and Motivational-Interviewing (MI). A tabletop flipchart and/or counseling manual was used to help guide counselors during sessions. Key aspects of MI incorporated into adherence counseling included a focus on working in collaboration with participants and expressing empathy.
Audio-recording counseling sessions for quality assurance	Audio-recording counseling sessions allows a team of experts and/or peers to carefully review counseling sessions, assess fidelity to the counseling guide, and provide constructive, detailed feedback to counselors. This practice has been found to be highly acceptable to study participants. Counselors receive reports rating each counseling session. In some studies, data from counseling sessions was used to triangulate other study data on participant adherence challenges.

Balán et al., *AIDS Care*, 2020 ; Balán et al., *AIDS and Behavior*, 2020; MTN BRWG Compendium

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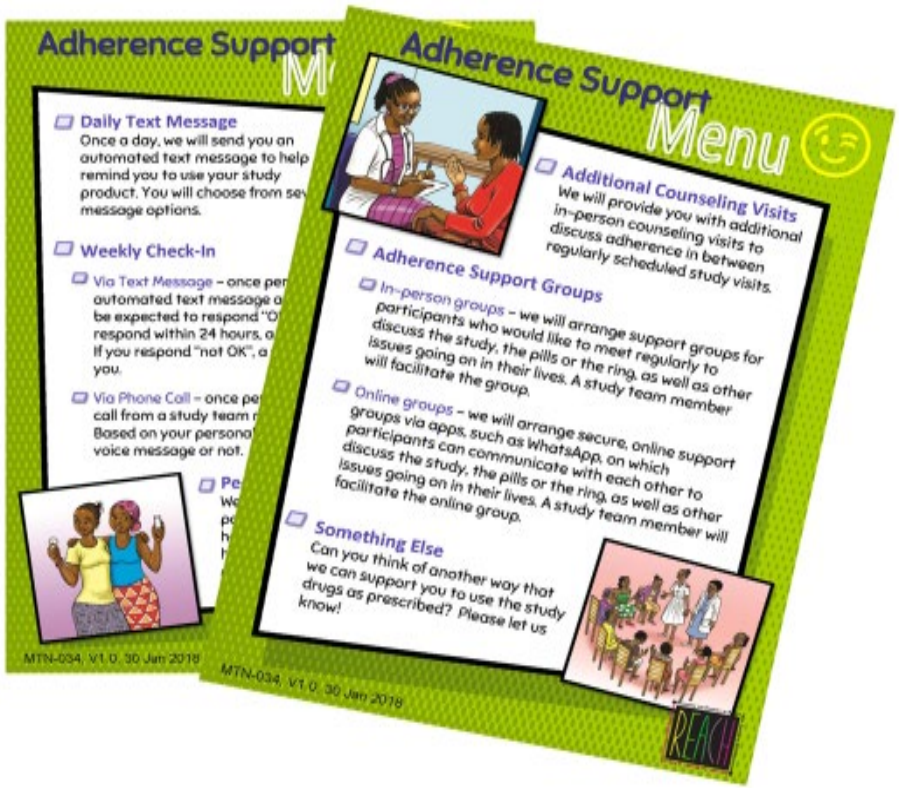
Adherence Support in MTN 034 (REACH) Study

Adherence support provided as a menu



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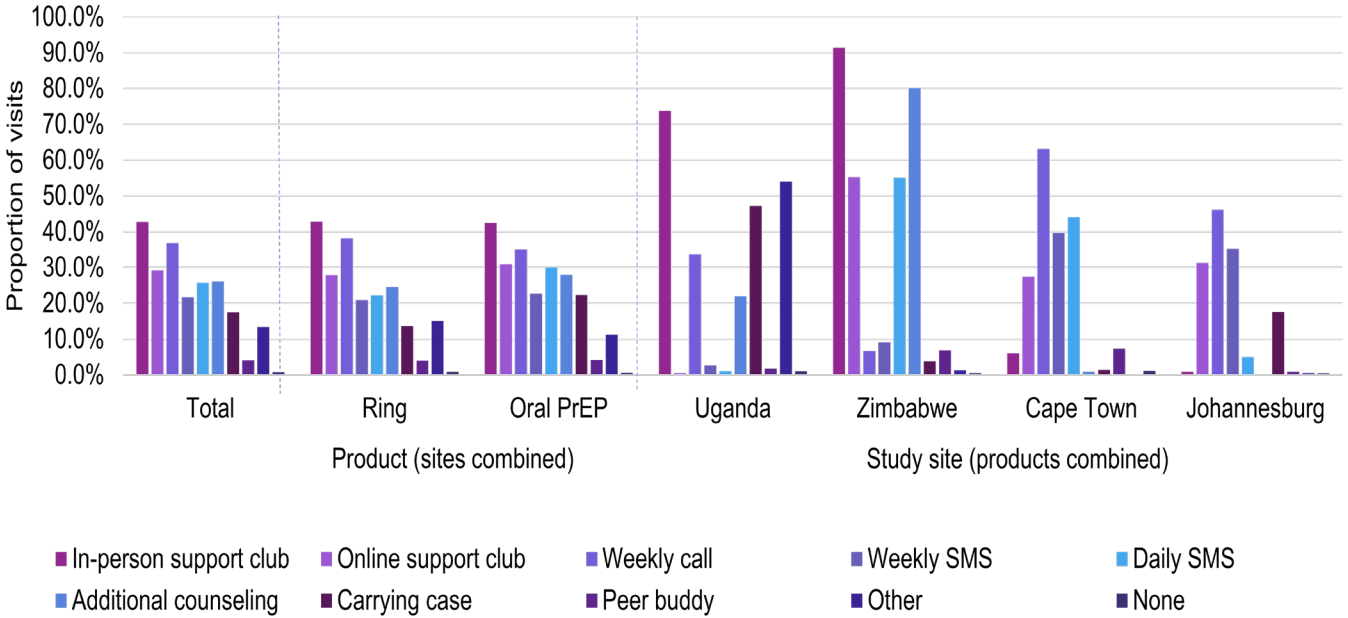
Preference of adherence support strategies



Roberts S., et al AIDS 2022

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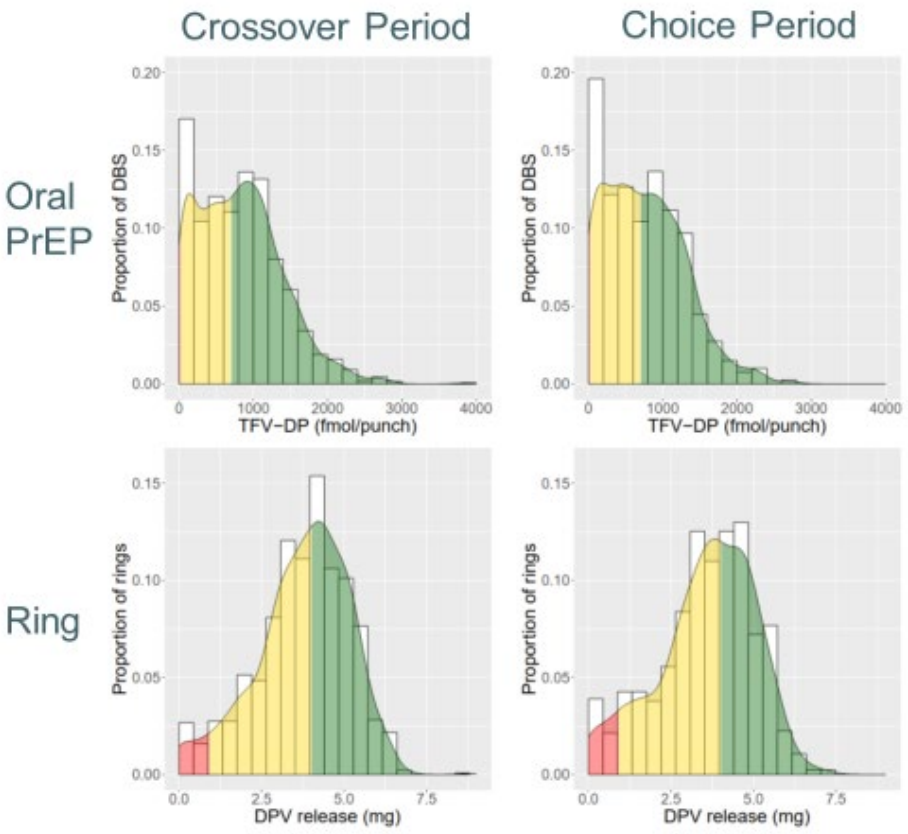
MTN 034 (REACH) Preliminary adherence Results

Comparing dapivirine ring use and oral PrEP adherence during the crossover and choice periods

Overall, participants used both the ring and oral PrEP consistently in the crossover and choice periods, with "some" to "high" adherence.

Fewer than 5% of visits were categorized as no or low adherence to study product



Ngure et al, CROI 2022

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Lessons learnt from REACH menu of adherence Support

- No single combination of menu options worked best. Across sites, participants selected a variety of strategies and sites had similarly high levels of adherence.
- The same strategies can be used to support both ring and oral PrEP use, although oral PrEP users may prefer daily reminders
- To support AGYW's effective PrEP use, programs should provide these components through mechanisms that are easily accessible, foster trust, promote peer-to-peer learning, and build confidence.
- Where drug level feedback is not affordable, other strategies are needed to reinforce success and facilitate honest discussion of adherence challenges.

Roberts S., et al AIDS 2022

Acknowledgments

Many study participants and colleagues (MTN 034. MTN 025, MPYA, PUMA) who have contributed to our understanding of medication adherence support

MTN, NIMH, IMPAACT, HANC Social Behavioral Working Groups

Sarah Roberts

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Nelly Mugo

Sharon Hillier

Ivan Balán

Rivet Amico

Stephen Gakuo

Jared Baeten

Ariane Van der Straten

Monica Gandhi

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Kenneth Mugwanya

Rivet Amico

Catherine Kiptinness

Many more…

..and the numerous funders and sponsors

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