Monitoring Adherence with PK

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Finding our way for how to do, and how to act on, real-time monitoring of adherence in clinical trials of HIV prevention

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Outline

- A discussion of the potential for real-time adherence monitoring in clinical trials
  - Why to monitor
  - What to measure
  - How to monitor, including who and when
  - What to do with the information

With examples of lessons learned/learning from ASPIRE and other studies

- Goal: understand the opportunities, recognize the challenges and limitations

Outline

- Why to monitor
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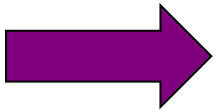
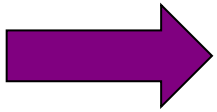
Clinical trials…ideal

- Here's what they teach you in school about how clinical trials are done:

An intervention is brought forward to a clinical trial



Intervention is delivered perfectly, all boxes are checked, everyone complies with the protocol



The study ends with a clear answer. The scientific process is affirmed.

Clinical trials…reality

- The reality is not as pristine

- Incomplete delivery of the intervention, by researchers or subjects, undermines the ideal randomized comparison

- Particular risk for studies that are of long duration, require ongoing intervention delivery, include a broader range of subjects, or are unblinded

The sausage-making of a clinical trial

Clinical trials…adherence

- For a once-off intervention, imperfect delivery can be minimal/zero
  - e.g., pre-operative antibiotics to avert surgical infection, male circumcision for HIV prevention
- In contrast, interventions that require repeated delivery ask for ongoing adherence
  - PrEP trials: monthly pick-up → daily pill-taking for 3 or more years (>1000 intervention points!)
  - Vaccine trials are not “immune”: in RV144, per-protocol delivery of the four-dose vaccine sequence was 75%

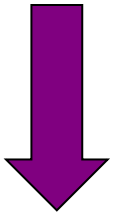
Learning from PrEP trials

	HIV protection: PrEP vs. placebo	% of blood samples with tenofovir detected
Partners PrEP	75%	81%
TDF2	62%	79%
BTS	49%	67%
iPrEx	44%	51%
FEM-PrEP	No HIV protection	<30%
VOICE	No HIV protection	<30%

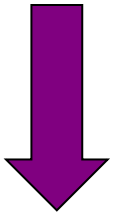
- Adherence → efficacy
  - Every trial had imperfect adherence
  - Adherence varied across studies and across study sites
- We really would have liked to have known about (and acted on) imperfect adherence before the end of trials ($, time, effort)

Evolving thinking

Clinical trials measure efficacy



Imperfect adherence in trials mean we are not always measuring efficacy, but a blinded study isn't measuring effectiveness either….



Can we maximize adherence to get closer to efficacy and figure out if a new prevention intervention works for stopping HIV?

Why to monitor adherence

- Adherence to prevention interventions cannot be assumed to be perfect
- There could be opportunity to act in real time.

Photo from the post-airport security area, Milwaukee, USA airport

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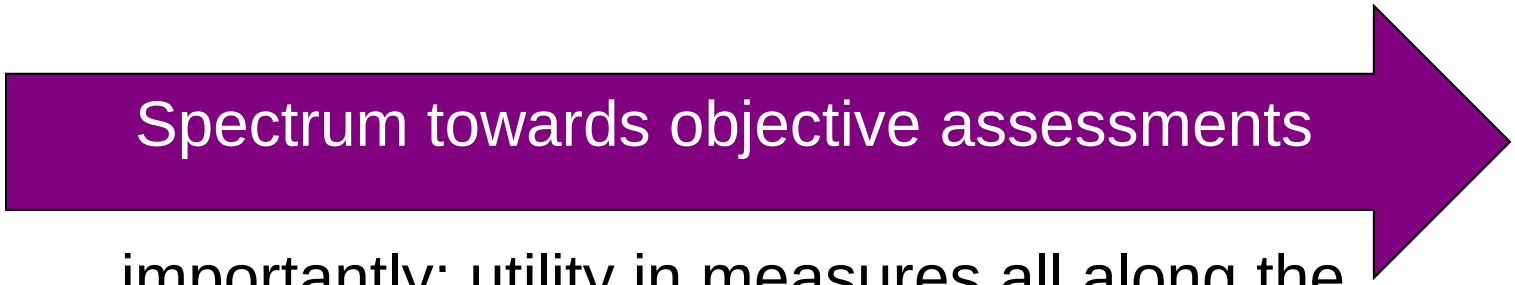
Measuring adherence

- What is the spectrum of real-time measures of adherence?

Indirect: retention, return for refills	Participant: self-report (survey, CASI)	Product: pill/applicator counts	Direct: real-time measure of active agent



importantly: utility in measures all along the spectrum

Towards direct measures

- Product administration
  - Microbicide applicator testing
  - Ring residual drug levels
- Product use
  - Detection / quantification of active agent in blood or genital fluids (often referred to as PK)
    - Remember: detection of tenofovir in blood strongly associated with HIV protection in TDF PrEP trials
- Product activity
  - Antiretroviral action (viral suppression in HIV treatment trials)

Potential additional measures

- Real-time notification of product use
  - Wisepill/Wisebag
- “Neutral” agents in active and placebo products solely for adherence monitoring
  - Thus could be monitored while preserving blinding

Keeping in mind…

- Logistics
  - Can testing be done sufficiently quickly to inform trial execution?
  - Is testing feasible, affordable?
- Blinding
  - In a placebo-controlled trial, how can testing be done but not unmask (to subject or investigator) randomization assignments?

Adherence measures in MTN-020

- ASPIRE obtains plasma (quarterly) and vaginal swabs (monthly), explicitly for testing for dapivirine. Returned rings are also saved.

- Early in the study, the protocol team proposed real-time monitoring of dapivirine in plasma:
  - Validated assay available, samples easy to collect/ship
  - While systemic absorption of dapivirine is low, it is not so low as to be unmeasurable, and phase I studies provided data on expected concentrations after ring insertion
  - Samples from all participants are tested, preserving blinding at study site

What to monitor for adherence

- Goal = objective measures of product administration/use/activity, paying attention to limitations of feasibility and preservation of blinding

- Measuring active drug (PK) is one direct, objective measure of adherence

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How to monitor

- Principles:
  - Use a systematic approach, documented for future reference
  - Sufficiently timely to be able to act on the results
  - Simple presentation for ready interpretability, both point-in-time and over time
  - If a blinded trial, done to preserve blinding of individual subject assignment – *thus, not at the individual participant level but at higher (site, study) level)*
  - In a nonblinded study, with a plan to roll back information to site/counselor/subject

Part of how is who and when

- Who
  - Who on the study team needs to know what is important but sensitive data?
- When
  - Can monitoring be done early enough in a study and frequently enough to initiate and monitor reaction?

How we are monitoring in MTN-020

- Monthly shipping, testing, and review of plasma dapivirine data, according to a pre-defined plan

- Information is reviewed by-site, rather than by-subject, preserving blinding. MOCK example:

SITE	% SAMPLES WITH DAPIVIRINE	*ADHERENCE ESTIMATE = middle column x 2 (since ½ expected placebo)*
1	50	100
2	48	96
3	40	80

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A Study to Prevent Infection with a Ring for Extended Use

How we are monitoring in MTN-020

- Adherence monitoring team, with members from the ASPIRE protocol team, Network, and NIH, reviews data
  - Data are conveyed securely to SDMC to ensure unblinding does not occur
  - Comparisons across sites and review of trends over time, both across and within sites
- Each site Investigator of Record also reviews the data, for her/his site and for all other sites (in a coded fashion)

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How to monitor

- Priorities
  - Timely assessment
  - With realistic goals (timing, # samples, costs)
  - Done with investment and involvement of the research team
  - Preserving trial integrity

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Responding to monitoring data

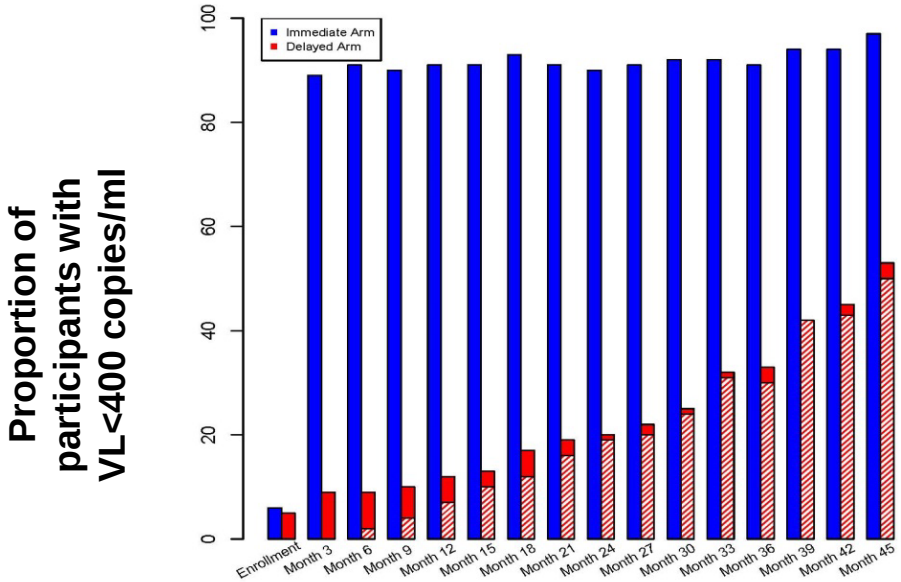
- This is the question. The reason to monitor adherence in real-time is to be able to react to address potential under-adherence.

Responding to monitoring data

- Possible points of intervention:
  - Individual subject
    - Enhanced counseling, new messaging, renewed attention, possible termination from the study
  - Study site
    - Revised approaches to recruitment, counseling, modify enrollment goals (up or down), site closure
  - Entire trial
    - Reconsideration of messages, acceptability, modifications to design or analysis, closure

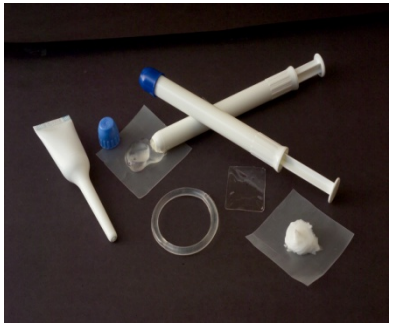
Example – HPTN 052

- Intervention: ART, *open-label*
- Monitoring: viral loads, done quarterly
- Action: intensive individual counseling
- Result: viral suppression was near-universal for those randomized to immediate ART (in blue)



Example – MTN 017

- Intervention: tenofovir gel & PrEP (open-label)
- Monitoring: tenofovir levels, in real-time
- Action: counseling, participant feedback
- Result: improve adherence, through notification of monitoring and feedback counseling



Example – MTN-020 (& IPM 027)

- Intervention: dapivirine vaginal ring (blinded!)
- Monitoring: plasma dapivirine, (residual ring levels)
- Action:
  - recalibrated adherence messages
  - re-approached participant engagement in HIV prevention and in research
  - adjusted site enrollment targets
- Result: *to be seen…*

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Maintaining analytic integrity

- Reactions to under-adherence must maintain trial analytic integrity:
  - Preserving power & blinding, clear design & outcomes
  - Must stand up to regulatory scrutiny
- Add-on analyses could be considered to complement primary ITT analyses, e.g.:
  - As-treated analyses
  - Censoring low adherence sites
  - Advanced statistical methods (causal inference) to address post-randomization effects
- What we don't want:

A bar in Seattle

Understanding adherence

- As important as actions taken in response to variations in adherence across participants and sites is understanding what that means for the HIV prevention intervention under investigation.
  - HIV risk perception
  - lack of interest in HIV prevention in general
  - lack of motivation in a placebo-controlled trial with an unproven product
  - the intervention (gel, pill, ring) itself?

Conclusions

- Real-time adherence/PK monitoring in clinical trials is an opportunity
- It is not without challenges and limits
- Considering key factors will be critical: why, what, and how to monitor and how to act on information

Increasing experience will show the benefits of this approach.

Thank you

MTN microbicide trials network

ASPIRE A Study to Prevent Infection with a Ring for Extended Use

National Institutes of Health

Statistical Center for HIV/AIDS Research & Prevention SCHARP

fhi360

Malawi College of Medicine – JHU Research Project

WRHI

MRC South Africa

CAPRISA Centre for the AIDS Programme of Research in South Africa

UNC Project - Malawi

International Partnership for Microbicides

University of Zimbabwe, School of Medicine

Desmond Tutu HIV Foundation