Adherence in Oral PrEP & Microbicides

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Outline

1. Product adherence optimization and need for better measures.
2. Types of quantitative measures:
   - EMS: Electronic Event Monitoring Systems
   - IEM: Ingestion/Insertion Event Markers
   - Markers of other behaviors: sexual exposure
   - Other “smart”/ “objective” measures of use
3. Point of entry for targeted interventions
4. Understanding (Non-) adherence

Note: “objective” = respondent-independent
## Selected oral PrEP & microbicide trials (Africa)

<table>
<thead>
<tr>
<th>Name</th>
<th>Population</th>
<th>Estimated Adherence</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Self report</td>
<td>CPC</td>
</tr>
<tr>
<td><strong>TDF2</strong></td>
<td>557 ♀ &amp; 662 ♂</td>
<td>94%</td>
<td>84%</td>
</tr>
<tr>
<td><strong>Partners PrEP</strong></td>
<td>4758 sd ♀/♂ couples</td>
<td>98%</td>
<td>97%</td>
</tr>
<tr>
<td><strong>Fem-PrEP</strong></td>
<td>2120 ♀</td>
<td>95%</td>
<td>85%</td>
</tr>
<tr>
<td><strong>VOICE</strong></td>
<td>5029 ♀</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF</td>
<td></td>
<td>90%</td>
<td>87%</td>
</tr>
<tr>
<td>Truvada</td>
<td></td>
<td>91%</td>
<td>92%</td>
</tr>
<tr>
<td>TFV gel</td>
<td></td>
<td>91%</td>
<td>86%</td>
</tr>
</tbody>
</table>

*Ambia (review) 2013; Baeten (review) 2013; van der Straten 2012; Baeten CROI 2013; Marrazzo CROI 2013*
1. Adherence Optimization

**Definition:** Adherence (in trials) = participant’s use of study product as instructed

_The key to understanding adherence, like any scientific phenomena, is to accurately measure it._

Measurement is intrinsically embedded in the goal of adherence optimization
Adherence Optimization

- **Why measure adherence?**
  - Explain trial results/interpret findings
  - Entry point for adherence intervention
  - Outcome to evaluate interventions
  - Target appropriate populations for future trials

- **Why understand adherence behavior?**
  - Explain use/non-use in individuals
  - Identify modifiable behaviors
  - Tailor and optimize interventions
Because simple measures of adherence can mask substantially different underlying adherence problems, investigators should develop and use adherence measures that can capture different adherence patterns over time.

Source: IOM Methodological Challenges in Biomedical HIV Prevention Trials, 2008 Report
Dimensions of adherence

- **Initiation (1)**
  Time point for 1st dose

- **Execution (2)**
  Actual = Instructed dosing

- **Discontinuation (3)**
  Time point for last dose

- **Persistence (4)**
  Period between initiation and discontinuation

Adherence parameters in ~17K ppts; 95 studies

Sources: IOM report 2008; Blaschke et al., Ann.Rev.PT 2012; van der Straten et al., CHAR 2012
Adherence measures selection: focus on objectives

<table>
<thead>
<tr>
<th>Critical characteristic of measure</th>
<th>1. Explain trial results</th>
<th>2. Inform adherence intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>High accuracy</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Low participant burden/invasiveness</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Simple and low cost to implement</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Minimize opportunity for manipulation</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Minimize Hawthorne effect*</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Allows for real-time feedback</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

* This includes minimizing adding new procedures or behaviors associated with doing the measurement

See: Deschamps et al., 2006
# Dosing, delivery and measurement

<table>
<thead>
<tr>
<th>Dimensions of Adherence</th>
<th>Dosing &amp; Delivery Method</th>
<th>Continuous/Long acting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intermittent</td>
<td>Gel, Tablet, etc…</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time-driven</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Event-driven</td>
</tr>
<tr>
<td>Initiation</td>
<td>DOI</td>
<td>x</td>
</tr>
<tr>
<td>Execution</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Persistence</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>DOI</td>
<td>DOI</td>
</tr>
<tr>
<td></td>
<td>DOI</td>
<td>(na)</td>
</tr>
<tr>
<td></td>
<td>DOI</td>
<td>DOI</td>
</tr>
<tr>
<td></td>
<td>DOI</td>
<td>DOI</td>
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</tbody>
</table>

Other behaviors critical to adherence measurement

<table>
<thead>
<tr>
<th>Visit attendance</th>
<th>x</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual exposure</td>
<td></td>
</tr>
</tbody>
</table>

**Methods:**
- **User-dependent**
- **User-independent**

**DOI:** Directly observed/supervised insertion /ingestion /injection at the study clinic

**X:** accurate measurement is needed
2. Types of quantitative measures

<table>
<thead>
<tr>
<th>EMS: Electronic Event Monitoring Systems</th>
<th>IEM: Insertion* Event Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ AEB: Adherence execution behavior</td>
<td>□ AEB:</td>
</tr>
<tr>
<td>■ MEMS: bottle, jar</td>
<td>■ Applicator tests</td>
</tr>
<tr>
<td>■ Wisepill</td>
<td>□ DSA</td>
</tr>
<tr>
<td>■ Wisebag</td>
<td>□ UVA</td>
</tr>
<tr>
<td>■ Strip package monitor</td>
<td>□ VIRA</td>
</tr>
<tr>
<td>■ Electronic Trace Sheet Monitor</td>
<td>■ Combination:</td>
</tr>
<tr>
<td></td>
<td>■ Dual-marker applicator test</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Direct measures of use</td>
</tr>
<tr>
<td></td>
<td>■ Taggant/ Breath test</td>
</tr>
<tr>
<td></td>
<td>■ Ingested µchip</td>
</tr>
<tr>
<td></td>
<td>■ Adherence sensors</td>
</tr>
</tbody>
</table>

* Ingestion / Insertion / Injection
Trade-offs between measures

Opportunity for manipulation

Self-report
- SMS/cell phone
- CASI/FTFI

EMS:
- Wise-pill/bag
- MEMS

IEM:
- μchips; taggants
- Applicator tests

Target

REAL TIME  Near Time  Lag Time  Post-trial

Plasma; Hair

DBS

PBMC
EMS: Event Monitoring Systems

- **Strengths:**
  - Not product specific
  - Provides date & time stamp
  - Real-time monitoring (or near-time)
  - Blinding maintained

- **Accuracy?**
  - Pocket dosing (underestimation)
  - Curiosity events (overestimation)
  - Can be manipulated

- **Weaknesses:**
  - Adherence execution behavior (indirect)
  - Burden (opening, storage, disposal)
  - Cost
IEM: Applicator Tests

- **Strengths:**
  - Usable for any drug in gel applicator
  - Blinding maintained
  - Low tech

- **Accuracy**
  - May depend on applicator type
  - Assessors’ skills
  - Less likely to be manipulated

- **Weaknesses:**
  - Participant and staff burden
  - Adherence execution behavior
  - No date and time stamp
  - Cannot monitor real-time (near time?)

Dye Stain Assay

UV Light

Katzen et al., 2011  Moench et al., 2012
Applicator test studies, Bronx NY

**Study 1:** ♀ daily gel use (N=39)

**Study 2:** Couple BAT24 use (N=15)

Postsex RSID as biomarker of semen exposure

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van der Straten et al., STD in press 2013

Keller et al., STD in press 2013
Median adherence over 30 days per various measures (N=39)

- Frequency: 90%
- Rating scale: 80%
- Unused applicators: 87%
- Empty applicators: 83%
- UVA: 77%
- DSA: 77%
- Wisebag: 67%

Legend:
- Self-reports
- Clinic product counts
- Applicator tests
- EMS
Other “SMART” tools:

Cypak blister packs

http://www.medicationmonitors.net/
Ingestible event marker (Proteus):

- Ingestible microchip sensor device, activated upon ingestion
- Disposable body patch transmits to Bluetooth device
- >14,000 IEM ingestions recorded in adherence trials
- Positive detection accuracy of 99.3%, no adverse events

http://proteusdigitalhealth.com/
SMART® Adherence System

SMART® Medication

GRAS flavorant incorporated into a capsule as adherence-enabling markers (AEMs), generate exhaled drug ingestion markers (EDIMs).

Patient / Study Participant

Participant at home exhales into SMART® device.

SMART® Device

Breath analysis proves ingestion; wirelessly reports adherence in real-time.

Better Outcomes

Monitored call-back within minutes to participants who miss doses.

Slide: courtesy of D. Dennis; Xhale, inc. 2012
Adherence monitoring of rings

- **Ring adherence:**
  - Ring are new, raise some concerns
  - Removals: sex, menses, to clean…

- **ASPIRE MTN020:**
  - Visual inspection @ return visit
  - Plasma drug PK (blinded)
  - Vaginal swab PK
  - Biofilm on rings (lab stage)
  - Residual drug in rings
SMART Diaphragm

- Device can detect preterm birth earlier than current methods (in pilot phase)

- Measures collagen changes in the cervix
  - Electrodes to measure impedance
  - LED and photodiode to measure fluorescence

- Other adaptations possible: add sensors to a ring to monitor ring use. E.g. T° monitor; pH sensor

L. Rand, personal communication 2013; Etemadi et al., 2013
3. Point of entry for targeted PrEP interventions

- **REAL time**: reminder tools+ targeted counseling
  - Wisepill/Wisebag
  - Other EMS with real-time signaling
  - IEM like breath taggants linked to “smart” system

- **NEAR time**: targeted counseling
  - MEMS
  - Unannounced Product Count
  - Applicator tests (e.g. VIRA, UVA)

- **Lagged time**:
  - Drug Level
  - Applicator tests (e.g DSA, combination tests)
4. Understanding (non-) adherence: VOICE and Ancillary Activities

See OA#43 Monday IAPAC
Summary/Conclusion

1. Adherence measurement

- Objective measures can help interpret trial results
- With accurate measures, we can:
  - Evaluate interventions to optimize adherence
  - Identify correlates of adherence (or its components)
  - Test and compare useability/utility of measures

- Better measures should continue to be developed
  - Low cost and for use on site
  - Minimize burden to staff and participants
  - Able to distinguish the 4 components of adherence
  - Allow monitoring outside of trial setting
Summary/Conclusion (con’t)

2. Understand adherence behavior:
   - Explain use/non-use in different populations
   - Identify modifiable factors to optimize adherence
   - Identify which component of (non-) adherence is most problematic
   - Tailor and optimize interventions
   - Develop more user-friendly products and dosage
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