Electronic monitoring devices and SMS for adherence measurement and intervention in developing settings

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Outline

- Why adherence matters
- Adherence measures
  - Electronic adherence monitoring devices
  - SMS (texting)
- Pros/cons of working with devices in developing settings
- Data on
  - Measurement of adherence
  - Intervention delivery, including differentiated care
  - Contextualization of adherence
Why adherence matters for HIV clinical trials

- 100% adherence: measured efficacy ~ true biological efficacy
- 60% adherence: measured efficacy ~ 50% true efficacy

(Weiss, Emerg Theme Epidem, 2008)
Adherence and efficacy in PrEP trials

Adherence is critical for PrEP efficacy

(with permission from J. Baeten)
Adherence measurement

• Subjective measures:
  – Self-report (in person or via SMS or computer/tablet)

• Objective measures:
  – Pills counts (announced and unannounced)
  – Pharmacy refill
  – Electronic adherence monitors
  – Drug levels (plasma, PBMC, RBC, hair)

• Reliable adherence measurement increases confidence in clinical trial results

• May guide optimal adherence intervention, including differentiated care and contextualization
Electronic adherence monitors
## Electronic adherence monitors

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
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<tbody>
<tr>
<td>• Likely most objective measure of behavior and best means for</td>
<td>• Curiosity openings and pocket doses</td>
</tr>
<tr>
<td>differentiated intervention</td>
<td>• Requires adherence to the adherence measurement</td>
</tr>
<tr>
<td>• Provides patterns of adherence</td>
<td>• Potential Hawthorne effect</td>
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<tr>
<td></td>
<td>• Cost</td>
</tr>
<tr>
<td></td>
<td>• Not compatible with pill boxes</td>
</tr>
<tr>
<td></td>
<td>• Potential for stigma</td>
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</tbody>
</table>

(Sabin, JAIDS, 2015; Orrell, JAIDS, 2015)
Real-time data

**Pros:** Real-time intervention

**Cons:** Battery life, cellular reception
Partners PrEP Study

• Phase III, randomized clinical trial of tenofovir and tenofovir/emtricitabine
• N=1,147 (24% of 4,747 in the overall trial)
• Adherence measured with:
  – Self-report
  – MEMS (medication event monitoring system)
  – Unannounced pill counts
  – Drug levels
• Counseling intervention triggered by <80% adherence (i.e., differentiated intervention)
Comparisons with plasma tenofovir

(Musinguzi, AIDS, 2016)
Wisepill Intervention Study

63 individuals initiating ART
All receive real-time adherence monitoring

<table>
<thead>
<tr>
<th>Months</th>
<th>Arm A (scheduled SMS + real-time monitoring)</th>
<th>Arm B (triggered SMS + real-time monitoring)</th>
<th>Control (real-time monitoring only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Daily SMS</td>
<td>SMS for missed doses</td>
<td>No SMS</td>
</tr>
<tr>
<td>2</td>
<td>Weekly SMS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>SMS for missed doses</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>SMS for missed doses + social supporter notification (48 hr lapse)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>SMS for missed doses + social supporter notification (48 hr lapse)</td>
<td>SMS for missed doses + social supporter notification (48 hr lapse)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
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<tr>
<td>7</td>
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<td>8</td>
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<tr>
<td>9</td>
<td></td>
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</tbody>
</table>

(Haberer, AIDS, 2016)
Adherence improved with scheduled SMS

GEE regression analysis

<table>
<thead>
<tr>
<th></th>
<th>Study arm</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Scheduled SMS + real-time monitoring</td>
<td>Triggered SMS + real-time monitoring</td>
<td>Control (Real-time monitoring only)</td>
</tr>
<tr>
<td>Percent adherence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>92% (88-99)</td>
<td>84% (66-93)</td>
<td>90% (72-93)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>91% (9)</td>
<td>79% (18)</td>
<td>79% (22)</td>
</tr>
<tr>
<td>Intervention effect (p-value)</td>
<td><strong>11.1 (0.02)</strong></td>
<td>-0.7 (0.90)</td>
<td><strong>ref</strong></td>
</tr>
</tbody>
</table>

Lapses in adherence

<p>| | | | |</p>
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<tbody>
<tr>
<td></td>
<td>&gt;48 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>4 (1-9)</td>
<td>8 (2-10)</td>
<td>4 (2-16)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>7 (8)</td>
<td>11 (10)</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Intervention effect (p-value)</td>
<td><strong>0.6 (0.02)</strong></td>
<td>1.0 (0.80)</td>
<td><strong>ref</strong></td>
</tr>
<tr>
<td></td>
<td>&gt;96 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>1 (0-1)</td>
<td>2 (0-6)</td>
<td>2 (1-3)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1 (2)</td>
<td>3 (3)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Intervention effect (p-value)</td>
<td><strong>0.3 (&lt;0.001)</strong></td>
<td>0.7 (0.23)</td>
<td><strong>ref</strong></td>
</tr>
</tbody>
</table>

- Findings similar after removing probable unmonitored time and adjusting for gender
- No benefit from social supporter intervention, likely due to limited resources and complex dynamics
MPYA

- Monitoring PrEP in Young Adult women
- N=314 young women in 2 Kenyan sites
- Next generation Wisepill device
- Randomization to SMS reminders (choice of daily or triggered)
- Weekly SMS for longitudinal assessment of behavior and risk to match with adherence (i.e., contextualization of adherence)
- Goal of understanding prevention-effective adherence (*Haberer et al, AIDS, 2015*)
SMS

Worldwide Mobile Subscriptions

Source: Strategy Analytics, Wireless Operator Strategies
# SMS

## Pros

- Convenient
- Frequent data collection
- Relative anonymity

## Cons

- Still self-report
- “Can you hear me now?”
- Variable understanding of expected responses
- Literacy
- Shared phones
- Low battery, powered off
- Participant availability
- Cost

*(Lester, Lancet, 2010; Pop-Eleches, AIDS, 2011)*
Partners Demonstration Project

• Open-label study of integrated PrEP and ART among high-risk serodiscordant couples in East Africa
• Adherence measures via MEMS
• Sub-study: Partners Mobile Adherence to PrEP (PMAP)
• N= 393 (39% of 1,013 participants in project)
• Data used to define adherence in the context of HIV risk (i.e., prevention-effective adherence)
SMS surveys

<table>
<thead>
<tr>
<th>Enrollment</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>PrEP given (1 mo)</td>
<td>PrEP given (3 mo)</td>
</tr>
<tr>
<td>Survey training period</td>
<td>SMS survey</td>
</tr>
</tbody>
</table>

- **SMS #1**: What is your password?
- **SMS #2**: Since this time yesterday, did you have sex? Enter 1 for ‘yes’ or 0 for ‘no’.
  ...
- **SMS #7**: Did you take your study pill since this time yesterday? Enter 1 for ‘yes’ or 0 for ‘no’.
- Survey incentivized at ~$0.50 for completion
Partners Demonstration Project

• Total 16,512 SMS surveys completed
  – Mean of 47 surveys/participant
  – Mean of 4.8 survey periods/participant
  – 66% of all surveys sent

• Prevention-effective adherence

• HIV risk: condomless sex and <6 months of ART
  – Reported on 21% of survey-days
  – Concurrent mean PrEP adherence was 85% (SD 28)
Sex with HIV-infected partner (N=5,342 surveys from 342 participants)

<6 months partner ART use (N=4,717 surveys [88%] from 333 participants)

HIV risk (N=1,130 surveys [21%] from 194 participants)

PrEP adherence = 85% (SD 28)

<100% condom use (N=1,305 surveys [24%] from 201 participants)
Partners Demonstration Project

• While ART use was <6 months, mean PrEP adherence
  – Lower for survey-days not reporting versus reporting sex (78% v 85%, p<0.001)
  – Similar for survey-days reporting versus not reporting condom use (87% v 85%, p=0.85)

  – Indicates better adherence with higher risk
Summary

• Electronic monitoring
  – Provides only assessment of day-to-day adherence behavior
  – Allows for differentiated intervention/care

• Real-time adherence monitoring
  – Allows for real-time adherence intervention and contextualization via SMS
Summary

• SMS
  – May be associated with more accurate self-report through decreased recall and social desirability bias
  – Allows for real-time adherence monitoring and intervention
  – Can provide contextualization
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Partners Demonstration Project Team

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– Johns Hopkins: Craig Hendrix
– Fred Hutchinson Cancer Research Center: Dara Lehman
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Research participants

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Questions?

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