Evaluating adaptive HIV pre-exposure prophylaxis adherence interventions for young South African women: Results from a sequential multiple assignment randomized trial

Jennifer Velloza, University of California San Francisco

Packaging HIV prevention for different populations
I have no relevant financial relationships with ineligible companies to disclose.
Acknowledgments


Sybil Hosek  Connie Celum  Sinead Delany-Moretlwe

R01 MH114544: Celum, Delany-Moretlwe
Background and Rationale

- **HIV pre-exposure prophylaxis (PrEP) scale up** for adolescent girls and young women (AGYW) in HIV endemic settings
- Challenges with **PrEP adherence and continuation** in this group
- Existing PrEP adherence interventions are **time- and cost-intensive**

- Widescale PrEP delivery requires **differentiated, person-centered support strategies** for AGYW with diverse HIV prevention needs

Celum et al., JIAS, 2022; Patel et al., AIDS, 2022; Stoner et al., AIDS & Beh, 2021; Gill et al., IAS Abstract #TUAC0207LB, 2017
Our overall goal was to test a stepped model of scalable PrEP adherence support strategies for South African young women.
Study Setting and Population

- Single-site, open-label sequential multiple assignment randomized trial (SMART)
- May 2019 – January 2022
Study Design

Determine who adheres well with minimal support:

Determine who needs more intensive interventions:

Monthly modules on:
- Depression and stress
- Healthy relationships
- Stigma and disclosure
- Alcohol, substance use
- Empowerment

Plus, South African standard-of-care counseling

Celum et al., PLoS Med, 2021
Study Design

Enroll HIV-negative adolescent girls and young women

Primary Randomization

2-way SMS + SOC counseling + Study visits at M1, M2, M3

WhatsApp support groups + SOC counseling + Study visits at M1, M2, M3

Secondary Randomization (for non-responders only)

Continue 2-way SMS with quarterly visits

Primary intervention + Drug-level feedback counseling at Months 3, 6

Continue WhatsApp with quarterly visits

Primary intervention + Problem-focused counseling at Months 4-9

Non-responders: Tenofovir diphosphate levels <500 fmol/punch or missed refills prior to M3

Primary Outcome Assessment: TFV-DP levels at Month 9
Statistical Analyses

1. Effect of primary randomized interventions (SMS versus WhatsApp) on PrEP adherence at Month 9
   • PrEP adherence defined as TFV-DP ≥ 700 fmol/punch
   • Intent-to-treat analysis
   • Estimated relative risks

2. Effect of secondary randomized interventions (drug-level feedback versus monthly counselling) on PrEP adherence at Month 9
   • Same as above
   • Restricted to non-responders
3. Optimal adherence support strategy for 4 dynamic treatment strategies
   • Generalized estimating equations (weighted and replicated SMART analysis)
   • Estimated probability of TFV-DP $\geq 700$ fmol/punch for the four strategies

First offer **2-way SMS**
   If responder, continue
   Else non-responder assigned to **SMS + Drug-level feedback counseling**

First offer **WhatsApp**
   If responder, continue
   Else non-responder assigned to **WhatsApp + Drug-level feedback counseling**

First offer **2-way SMS**
   If responder, continue
   Else non-responder assigned to **SMS + Monthly counseling**

First offer **WhatsApp**
   If responder, continue
   Else non-responder assigned to **WhatsApp + Monthly counseling**

Statistical Analyses
Screening, Enrollment, & Follow-up

401 screened
360 enrolled and randomized

180 assigned to 2-way SMS
- 85 (47.2%) re-randomized at M3:
  - 39 with TFV-DP <500 fmol/punch
  - 37 missed a visit prior to M3
  - 9 had TFV-DP <500 fmol/punch and missed a visit prior to M3

91 responders to 2-way SMS
- M9 retention: 80 (87.9%)

42 assigned to DLFB counseling
- M9 retention: 31 (73.8%)

43 assigned to monthly counseling
- M9 retention: 28 (65.1%)

174 included in ITT analysis
132 included in per-protocol analysis

180 assigned to WhatsApp
- 70 (38.9%) re-randomized at M3:
  - 32 with TFV-DP <500 fmol/punch
  - 35 missed a visit prior to M3
  - 3 had TFV-DP <500 fmol/punch and missed a visit prior to M3

35 assigned to DLFB counseling
- M9 retention: 23 (65.7%)

35 assigned to monthly counseling
- M9 retention: 25 (71.4%)

105 responders to WhatsApp
- M9 retention: 92 (87.6%)

174 included in ITT analysis
134 included in per-protocol analysis

41 excluded, including:
- 11 pregnant
- 10 living with HIV
- 6 planning to move
- 6 with no recent sex
- 1 with recent PrEP use
- 7 did not complete procedures or declined enrollment
### Participant Characteristics

#### Enrollment characteristics (N=360)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%) or Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>21 (20-23)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>144 (40.0%)</td>
</tr>
<tr>
<td>College education</td>
<td>32 (8.9%)</td>
</tr>
<tr>
<td>Number of sex partners</td>
<td>2 (1-2)</td>
</tr>
<tr>
<td>Never or rarely uses condoms</td>
<td>130 (36.1%)</td>
</tr>
<tr>
<td>Transactional sex</td>
<td>80 (23.9%)</td>
</tr>
<tr>
<td>Curable STI</td>
<td>113 (31.4%)</td>
</tr>
<tr>
<td>Intimate partner violence</td>
<td>195 (54.2%)</td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>185 (52.1%)</td>
</tr>
</tbody>
</table>

#### PrEP continuation and adherence

- Enrolled & on PrEP: 360
- Retained at M2: 281
- On PrEP at M2: 264
- Adherent at M2: 164
- Retained at M9: 279
- On PrEP at M9: 249
- Adherent at M9: 66

- PrEP continuation at M2: 94%
- Adherence at M2: 62%
- PrEP continuation at M9: 89%
- Adherence at M9: 27%
## Effect of Interventions

### Primary Interventions (N=348)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>% of Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-way SMS</td>
<td>19.5% (N=34)</td>
</tr>
<tr>
<td>WhatsApp</td>
<td>18.4% (N=32)</td>
</tr>
</tbody>
</table>

RR=1.06 (95% CI: 0.69-1.64)

### Secondary Interventions (N=155)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>% of Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLFB Counseling</td>
<td>5.3% (N=4)</td>
</tr>
<tr>
<td>Monthly Counseling</td>
<td>3.9% (N=3)</td>
</tr>
</tbody>
</table>

RR=1.33 (95% CI: 0.31-5.76)
## Dynamic Treatment Strategies

<table>
<thead>
<tr>
<th>Embedded dynamic treatment strategy</th>
<th>Estimated probability of high PrEP adherence</th>
<th>95% CI</th>
<th>Global p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMS, followed by monthly counseling for non-responders (N=134)</td>
<td>0.25</td>
<td>(0.18–0.34)</td>
<td></td>
</tr>
<tr>
<td>SMS, followed by drug-level feedback counseling for non-responders (N=133)</td>
<td>0.27</td>
<td>(0.19–0.36)</td>
<td>0.94</td>
</tr>
<tr>
<td>WhatsApp, followed by monthly counseling for non-responders (N=140)</td>
<td>0.24</td>
<td>(0.17–0.33)</td>
<td></td>
</tr>
<tr>
<td>WhatsApp, followed by drug-level feedback counseling for non-responders (N=140)</td>
<td>0.24</td>
<td>(0.17–0.33)</td>
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</table>
Conclusions

• **No significant differences** between intervention arms or dynamic treatment strategies
  • Strategies have a similar impact on adherence
  • Programs may adopt approaches based on preference and scalability
  • Did not compare these interventions to standard-of-care
  • Challenging to re-engage non-responders after 2 months
• SMART design was **feasible** to explore differentiated stepped adherence support
• PrEP adherence was **higher** than comparable cohorts
• Individual-level interventions likely **insufficient** to overcome structural barriers to PrEP for AGYW
  • Long-acting formulations

Celum et al., JIAS, 2020; Celum et al., PLoS Med, 2021; Celum et al., JIAS, 2022