Florence Mwangwa for the SEARCH Youth team

I have no relevant financial relationships with ineligible companies to disclose
Adolescents and young adults with HIV (AYAH)
• Suffer a disproportionate burden and have poorer treatment outcomes in sub-Saharan Africa
• *SEARCH study: 55% of youth 15-24 years vs 80% of adults >24 years achieved viral suppression after 2 years
• Have lower rates of retention in care
• Face many barriers to medication adherence and remaining in care during a time of many major life events

*Havlir DV,Balzer LB,Charlebois ED et al HIV testing and treatment with the use of a community health approach in rural Africa (supplement NEJM) pg15
Hypothesis: Dynamic HIV care model supporting patients and providers through these changes could improve clinical outcomes vs standard of care

<table>
<thead>
<tr>
<th>Interviews with AYAH</th>
<th>Barrier</th>
<th>Intervention [PRECEDE Concept]</th>
<th>Postulated Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>What makes taking medication HARDER? e.g. “Eventually I got married and had to stop medication for the sake of my husband as I had not disclosed my status.”</td>
<td>Life-stage changes (marriage, school) that affect adherence</td>
<td>Life-stage specific counseling [Predisposing]</td>
<td>Recurrent re-evaluation of life-stage events builds relationship between AYAH providers, and enables them to promptly act when social structures change</td>
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<tr>
<td>What makes attending appointments HARDER? e.g. “Sometimes I don’t want other people to see me when I come on my day of convenience”;</td>
<td>Structural</td>
<td>Choice of clinic access [Enabling]</td>
<td>Choice respects developing sense of autonomy among AYAH; multiple options allow clinic access be tailored to the case-specific pressures</td>
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<tr>
<td>Do you think that knowing your viral load helps you take your medications better? 88% replied yes; “It helps me because it gives me courage to take my medication”</td>
<td>Feedback/ motivation for adherence</td>
<td>Rapid viral load feedback &amp; counseling [Reinforcing]</td>
<td>Prompt identification of adherence issues. Concept of viremia adapts to abstract thinking development among AYAH.</td>
</tr>
</tbody>
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SEARCH-Youth Study Intervention

Barrier
Life-stage changes that affect adherence

Life-stage Assessment
- Start of each visit
- Guides discussion between providers and AYAH to reveal life events and issues.
- Prompts action to address new issues (e.g. referral to counseling for depression, assistance with disclosure)

Structural barriers to care

Feedback/motivation for adherence

Isolated providers struggle to address challenging cases

Rapid viral load feedback
- Results shared with patient in < 72 hours.
- Positive feedback or prompt discussion of adherence issues

Changes the AYAH clinical encounter on multiple levels:
- AYAH-provider interaction
- Clinic operations
- AYAH-cognition/communication
- Inter-provider collaboration

Choice of clinic Access
- Offered to address barriers to the next visit.
- After-hour visits, phone visits, offsite drug delivery

Provider E-collaboratives
- Providers often isolated in rural clinics
- WhatsApp platform for discussion of especially difficult cases
- Encrypted & de-identified info only
Methods

Design: Cluster randomized control trial
  • Randomization unit: clinics
Population: Females and males aged 15-24 years
  
    Inclusion criteria: HIV-infection, care in study clinic
Setting: Government sponsored health clinics in rural western Kenya and southwestern Uganda

Time period: Mar 2019- Mar 2022
Statistical Methods

Descriptive:
• Baseline demographics and
• Non-study secular influences

Primary endpoint: Percent with viral suppression (HIV RNA < 400c/mL) after 2 years of individual follow up
• Excludes participants who moved out of study region or transferred care
• Compared by arm with targeted minimum loss-based estimation (TMLE)*
• Pre-specified one-sided hypothesis testing at the 5% significance level

Power: With 28 clinics each with 50 AYAH, the study would have 83% power to detect a difference in virologic suppression 24% between control vs intervention clinics

Secondary endpoints:
• Intervention implementation and uptake

*Balzer, Biostatistics, 2021
Results

Consort
Baseline characteristics
Intervention implementation
Primary endpoint: viral suppression at 2 years
  • Subgroups and sensitivity analyses
28 clinics underwent randomization

Allocation

14 clinics were assigned to intervention
14 clinics were assigned to control

1031 persons were screened
987 persons were screened

19 persons were excluded
- Not in age range (n=18)
- Declined (n=1)

11 persons were excluded
- Not in age range (n=11)

1012 persons were enrolled
976 persons were enrolled

- Withdrawal (n=1)
- Enrolled at or after December 1, 2019 (n=96)

- Enrolled at or after December 1, 2019 (n=58)

915 persons included in analysis
918 persons included in analysis
Baseline characteristics

82% female
Median age: 21 years
40% single
58% had at least 1 child
75% on EFV/3TC/(TDF or ABC) at enrollment
74% suppressing viral replication <400 c/mL

Care status
• 34% recently engaged: started ART within the prior 6 months or at enrollment
• 62% engaged: started ART more than 6 months ago, with a clinic visit in prior 6 months
• 4% re-engaging: started ART more than 6 months ago, without a clinic visit in prior 6 months
84.5% of 785 participants, remaining in the region during the two-year study period, had 4+ life-stage assessments.

**Intervention Implementation: Life Stage Assessments**

- **Life-stage Assessment**
  - Guides discussion between providers and AYAH to reveal life events and issues.
  - At the start of routine visits, ~ every 3 months

**Diagram**

- Y-axis: Number of Participants
- X-axis: Number of Lifestage Assessments during Study Period

- Bars indicating distribution of assessments across the study period.
Intervention Implementation: Alternative Access Choice

- Off-site appointments, drug delivery were selected by many participants
- Varied by clinic
- Options useful during COVID disruptions

Alternative Access Choice
- To address barriers to the next visit.
- Offered if prompted and planned per participant choice
Intervention Implementation: Rapid Viral Load Feedback

- Median time to results delivery was 38.4 hours
- In 13/14 clinics, over 80% of VL results delivered within 72 hours
Intervention Implementation: Provider E-collaboratives

253 chats initiated for 128 unique participants

• Examples of Content:
  • Guidance about whether to order HIV resistance testing
  • Ideas on how to accommodate school schedule for visits
  • Assistance with navigating disclosure to school admin
  • Shared resources on regional COVID testing options

Provider E-collaboratives
  • WhatsApp platform for discussion of especially difficult cases
  • Encrypted & de-identified info only
Primary Endpoint: *Viral suppression at 2 years*

- **Endline:** 88% in intervention vs. 80% in control
- Relative effect: 1.10 (95%CI: 1.03-1.16); p=0.002

Graph showing:
- **Baseline:** 75% control, 73% intervention
- **Endline:** 80% control, 88% intervention

15% increase in intervention
5% increase in control
Primary Endpoint: Subgroups

Improvements across subgroups defined by baseline care status

Especially those re-engaging

85% in intervention vs. 53% in control

Relative effect: 1.60 (95%CI: 1.00-2.55) p=0.03

Engaged – started ART 6+ mo ago, with a clinic visit in past 6 mo
Recently Engaged – started ART ≤6 mo or at enrollment
Re-engaging – started ART 6+ mo ago, without a clinic visit in past 6 mo
Improvements across subgroups defined by sex and age group

Largest effect among the younger age group

- **85% in intervention** vs. **76% in control**
- **Relative effect: 1.13** (95%CI: 1.01-1.26); p=0.015

### Primary Endpoint: Subgroups 2

<table>
<thead>
<tr>
<th>Group</th>
<th>Relative Effect</th>
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<tbody>
<tr>
<td>Women</td>
<td>1.06 (1.00-1.13); p=0.026</td>
</tr>
<tr>
<td>Men</td>
<td>1.11 (0.98-1.25); p=0.044</td>
</tr>
<tr>
<td>15-19 years</td>
<td>1.13 (1.01-1.26); p=0.015</td>
</tr>
<tr>
<td>20-24 years</td>
<td>1.05 (0.99-1.11); p=0.040</td>
</tr>
</tbody>
</table>
Did the intervention still benefit participants who had switched to dolutegravir (DTG)?  YES

Majority of participants switched to DTG in both arms during study period
77% in intervention vs. 71% in control

The intervention was associated with higher probability of virologic suppression

In persons who had switched to DTG
  • 92% in intervention vs. 88% in control

In persons who had not switched to DTG
  • 70% in intervention vs. 64% in control
Summary of primary endpoint results

Multi-level SEARCH-Youth intervention increased virologic suppression compared to standard care
  • Overall and for key subgroups
  • During a period of transition to dolutegravir and the COVID-19 pandemic

Added to current efforts, life-stage-based assessment and support could help bring AYAH closer towards a goal of universal virologic suppression
Acknowledgments

Community and government partners in Uganda and Kenya

Uganda
Hellen Nakato Atuhaire
Moses Kamya
Jane Kabami
Brian Kamugisha
Dalsone Kwarisiima
Geoff Lavoy
Florence Mwangwa
Katherine Snyman
Bridget Nzarubara

USA
• Laura Balzer
• Doug Black
• Carol Camlin
• Edwin Charlebois
• Diane Havlir
• James Peng
• Sarah Puryear
• Theodore Ruel
• Starley Shade
• Josh Schwab
• John Schrom

Kenya
• George Agengo
• James Ayieko
• Elizabeth Bukusi
• Marilyn Nyabuti
• Winter Olilo
• Fred Opel
• Norton Sang
• Erick Wafula Mugoma

NICHD
• Bill Kapogiannis
• Sonia Lee

Huge thanks to clinical officers, laboratory staff, data teams, regulatory teams, and administrative staff!