Novel Study Designs to Assess Interventions to Improve Engagement of Adolescents in HIV

Kawango Agot, PhD, MPH, MPhil
Impact Research and Development organization, Kisumu, Kenya

Adherence 2019 • June 17-19 • Miami
Presentation Outline

• Background

• Rationale for Novel Study Designs

• Selected examples of Novel Study/Implementation Designs
  – SMART Design
  – Stepped Care Design
  – Differentiated Service Delivery
  – Human-Centered Design
    • Example of Human-Centered Design: Operation Triple Zero

• Conclusions
Background: HIV incidence in AYP in ESA is reducing but not fast enough

- Eastern and Southern Africa (ESA) is the epicenter of HIV globally, accounting for 53% of all infected persons and 44% of all new infections [UNAIDS, 2018].

- Despite a 30% reduction in HIV incidence in ESA between 2010-2017, AYP 15-24 years still account for 33% of new infections, of whom 75% are among AGYW [UNAIDS, 2018].

- In Kenya, 33% of new infections in 2017 were among adolescents 15-24 [Kenya HIV Estimates, 2018], down from 51% in 2014 [Kenya HIV Est., 2014]
  - Worrying: While 95% of 10-14 years are on treatment, ≈60% of 15-19 years are not

- Engaging adolescents in HIV prevention and treatment remain a challenge in ESA (and globally); hence the need to identify innovative strategies that work for them.
Background: Adherence waters still mucky for AYP

- **FEM-PrEP (18-34 yrs)** – only 28.5% had good adherence based on drug levels, while reported was 95% and pill count was 82% [Van Damme et al, 2012]

- **Fast Fwd**: In the RING and ASPIRE studies, efficacy of Dipivirine Vaginal Ring in young women 18-21 years was 15% and 27%, respectively, compared to 37% for RING and 56% for ASPIRE [Nel et al, 2016; Baeten et al, 2016].

- In Project PrEPare (OLE Demo; 15-17 yrs), 56% adherent (4 pills/wk) at week 4 visit, dropping to 17% at week 36, with highest drop at Week 24 [Hosek et al, 2017].
  - General trend: ring starts off relatively poorly and picks up with time; reverse for pills!

- Gaps remain in understanding how to deliver interventions to adolescents and young people (AYP) while maximizing adherence and continuation.
PrEP delivery among AGYW is porous (Oct 17-Mar-19)

Program Data, IRDO, Kisumu, Kenya
Examples of Novel Study/Implementation Designs to Improve Adolescent Engagement in HIV Care
No one size (of adherence interventions) fits all!

- Many PrEP projects provide similar adherence interventions to all participants without differentiated support strategies.
- A stepped approach to adherence support is needed for large-scale differentiated ART and PrEP adherence support.
- A stepped approach has been shown to be:
  - Feasible
  - Resource-saving
  - Analogous to models of differentiated HIV care

Source: Bekker 2018; Gill 2017
Ex. 1: SMART Design – Rationale

- **Sequential Multiple Assignment Randomized Trials (SMARTs)** are experimental designs for development of adaptive interventions.

- SMARTs allow us to:
  - Develop optimal adaptive intervention strategies to facilitate PrEP or ART adherence support among AGYW.
  - Identify important variables associated with response to a given intervention.
  - Evaluate decision rules for scaling up PrEP adherence support.

Source: Epstein 2011; Lei 2012; Murphy 2005
Novel Designs: SMART Design

• SMART is a design where the type or dosage of the intervention is individualized based on clients’ characteristics/clinical presentation.
  – Then are repeatedly adjusted in response to ongoing performance.

• The approach is premised on the fact that clients/patients differ in their responses to interventions.

• An adaptive intervention is a multistage process comprising of a sequence of decision rules on when and how the intervention should be modified in order to maximize long-term outcomes.
  – Decisions are based on clients’ characteristics plus intermediate outcomes collected during the intervention, such as their response and adherence.
  – Other considerations are expense, burden, tolerability/side effects, etc.
Novel Designs: SMART Design

• Why consider adaptive interventions?
  – Motivates the provision of subsequent intervention options for patients who do not respond adequately to the initial intervention (Options: Switch to an alternative intervention? Increase dose/intensity? Add another intervention?)
  – By randomizing participants multiple times, it’s possible to assess the effectiveness of each stage without having to conduct multiple studies.
  – SMARTs design also allows comparisons of different treatment options within the context of what happens in later stages
  – SMARTs generate data to inform development or improvement of adaptive interventions
Generic Ex. of SMART Design

Can start from here

Standard of Care

Intervention 1

Responders

Non-Responders

R

Continued Intervention 1

Increase dose or frequency of Intervention 1

Add Intervention 2 (Intervention 1+2)

Intervention 2

Responders

Non-Responders

R

Continued Intervention 2

Increase dose or frequency of Intervention 2

Add Intervention 1 (Intervention 1+2)
Actual Ex. of Smart Design: Linkage of AGYW to Care

All girls with HIV infection
Randomized (N = 108)
CD4, VL

R1

Standard Referral (N=54)

Enrolled in care after standard referral (N=?)

Not enrolled after standard referral (N=?)

Standard Referral plus SMS reminder to seek care (N=54)

R2

Enrolled in care after standard referral plus SMS (N=?)

Not enrolled after standard referral plus SMS (N=?)

SMS reminder to seek care

Economic incentive to facilitate linkage to care

Retention in care, VL at 12 months

Retention in care, VL at 12 months

Retention in care, VL at 12 months

Retention in care, VL at 12 months

Girls Pilot Study; NIH/NIAID 5R01AI122797, Kurth (PI)
Ex. 2: Novel Designs to improve adolescent engagement: Stepped Care Design

• Using a Stepped Care approach, providers implement the least intensive intervention needed to achieve the treatment goal
  – Intervention is progressively intensified until the goal is achieved, while observing clinical safety.
  – The interventions at the lowest levels may be sufficient for some.

Stepped Care Model, Hutchinson, 2006

DiSC Study; NIH UG3 HD096906; Kohler & John-Stewart (MPI)
Ex. of stepped adherence support

- PrEP adherence interventions for AGYW: we do not know which has the most impact and for whom

Adherence Counselling

Adherence is critical to provide protection against HIV.

- Suggest methods to remind the client to take the pill every day
  - For example:
    - Take the pill at the same time every day;
    - Incorporate it into your daily activities, like part of your morning routine or when a favourite TV show comes on;
    - Set an alarm;
    - Encourage partners, family members, or friends to remind you;
    - Use daily pillboxes
- Discuss what to do if a pill is missed – take it as soon as remember

Remember: Supporting pill-taking should be honest, direct, and non-confrontational

Steps to follow:
1. Assess how pill taking is going for PrEP client
2. Positively affirm client to support provider/client relationship
3. Identify a motivator to support effective pill taking
4. Provide PrEP education regarding effective use and effectiveness of PrEP
5. Identify barriers to effective use
6. Provide realistic strategies to address barriers
7. Discuss use of other HIV prevention measures that are relevant to situation
8. Client leaves with realistic and achievable plan to increase or sustain use

Source: Grimsrud 2015; Luque-Fernandez 2013; Solomon 2015; Lester 2010; Van der Straten 2014; Courtesy, Connie Celum
Ex. 3: Novel Designs: Adaptive experimental design – Differentiated Service Delivery (DSD)

- DSD is a client-centered approach, where services are adapted to better meet the needs of PLHIV and reduce unnecessary burdens on the health care system
- Takes the form of multi-month prescriptions, fast-track refills, community ART groups, flexible clinic opening hours, bypass clinician when collecting refills, etc.
  - Important to monitor service quality and outcomes

Source: Grimsrud et al, nd., IAS/UNICEF, WHO/PATA
Ex. 4: Novel Designs to improve adolescent engagement: Human-Centered Design

• Human Centered Design (HCD) => Putting people at the center of interventions.

• HCD prioritizes working with the people who are/will be the end-users of a new intervention, program, or product.

• Involves identifying barriers and facilitators and providing background support to enable end-users and their communities address them.
  - Recognizes that human barriers can be critical allies; treat as solutions, not problems

• Iterative implementation – the design team solicits continuous feedback from users, communities, and collaborators and adjusts appropriately
Ex. of Human-Centered Design: Operation Triple Zero

- **Goal**: Empower adolescents and young people living with HIV to take control of their health
- **Premise**: Infected and affected individuals are an integral part of the solution; not the problem
- Brings together 3 pillars in adolescent care (Adolescent, Caregiver, Healthcare Worker) to commit to 3 zeros
- **Interventions**: OTZ Clubs, adolescent champions, weekend & evening clinics, treatment buddies, DOT where needed.
- **Motto**: Heroes for Zeros & Zeros for Heroes; it takes a Hero to be a Zero and a Zero to be a Hero

Courtesy PEPFAR Website
Scale up of Operation Triple Zero in Kenya

OTZ Scale Up in Kenya

- **2016**
  - 1 County
  - 1 facility
  - 200 of 557 high volume sites (36%)
  - AYP’s in OTZ: 11,000 of 58,000 (19%)

- **2017**
  - 20 counties
  - AYP’s in OTZ: 47,401 of 58,000 (81%) Mar 2018

- **2018**
  - 27 counties
  - 465 of 557 high volume sites (83%)

- **2019**
  - 27 Counties
  - 527 of 557 high volume (95%) sites
  - 95% of AYP enrolled in OTZ
Scale up of Operation Triple Zero in Kenya

Results: Clinic Appointments & Adherence

- >93% kept clinic appointments

- Increase in self-reported adherence from 88% to 96%

Source: CTC Kenya Database, 2018
Scale up of Operation Triple Zero in Kenya

Results: Viral Suppression

VL Testing Results for Adolescents on ART in Western Kenya Counties (n = 66 site) May 2018

- Total 6053
  - Total in OTZ 4672 (77%)
  - Total non OTZ 1381 (23%)
  - Total with valid VL results 4613 (99%)
  - Total with valid VL results 1309 (95%)
  - VL <1000c/ml 4047 (88%)
  - VL <1000c/ml 949 (72%)

VL Testing Outcomes for Clients in OTZ: 10 - 24 yrs (n = 2742)

- Increase in viral suppression for all partners:
  - Baseline: 76%
  - Current (Mar 2018): 82%

Source: CDC Kenya Database, 2018

15 YEARS OF SAVING LIVES THROUGH AMERICAN GENEROSITY AND PARTNERSHIPS
When I joined secondary school, I experienced a lot of stigma. I stopped taking my medications and this led to deterioration in my health. Due to the busy school schedule I used to skip my clinic appointments. It happened that when I came to the clinic there was an OTZ club which I joined and was able to interact with my peers. My VL trends have been:

- Jun 5, 2018 – 491,000cp/ml
- Nov 16, 2017 – 27,200cp/ml
- Jan 15, 2018 – 107cp/ml

I have taken charge of my health. (18yr old Student).

UCSF Program, Kisumu (Courtesy PEPFAR website)
Conclusions

• New approaches “in the market” seek to segment users and identify what works for each category on the basis of their circumstances.

• Adaptive study designs help in identifying combinations and dosing of interventions for different segments of users.

• Then set parameters that inform when, where and how to give what (type and dosage of intervention) to whom.

• Adaptive interventions are optimized when service delivery is differentiated, when end-users are at the center, and when they are treated as partners in managing their health.
Acknowledgements

• Participants in the studies, who generated the data
• Funding institutions (NIH, USG-PEPFAR)
• Connie Celum, Nelly Mugo
• Kurth and Inwani, Girls Study, Homabay, Kenya
• Kohler and John-Stewart, DiSC Study, Kisumu and Homabay

Thank you!