Rethinking PrEP for adolescent girls and young women

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Disclosure

I am a co-investigator on two studies that received oral PrEP from Gilead (POWER study—formative; 3P’s for Prevention Study)
Young women are at risk

- We know adolescent girls and young women (AGYW) in sub-Saharan Africa are especially vulnerable to HIV
  - 3 out of 4 new infections in SSA are among young women < 24\(^1\)
  - 15-19 yr old girls are 4-5x more likely to acquire HIV than their male peers\(^2\)
  - High rates of unplanned pregnancy, non-consensual sex, inconsistent contraception use, inconsistent condom use
  - The youth bulge is coming...

\(^1\) UNAIDS (2017); UNICEF (2018) \(^2\)Dellar, Dlamini, Karim (2015)
High rates of STIs

- **HPTN 082** (n=412 females, 16-25)<sup>1</sup>
  - Median 4 vaginal sex acts during previous month; 1/3 reported never or rarely using condoms, 44% had partner > 5 yrs
  - 1/3 had a treatable STI at baseline; few risk or behavioural differences between those with / without STI

- **PlusPills** (n=99 females, 49 males 15-19 yrs)<sup>2</sup>
  - 40% had an STI at baseline. Wish and uChoose studies similarly high rates of STI at baseline and 3 months later (after treatment)

- **3Ps for Prevention** (n=200 females, 16-25)<sup>3</sup>
  - 32% had curable STI at baseline
  - 71% suspected partner had other partners
  - 19% reported experience of interpersonal violence in prev. year

- **Girl Power** (n=991 females, 15-24)<sup>3</sup>
  - 28% sexual debut ≤ 15 years; 37% STI symptom during last 6 months; 45% didn’t know partner’s HIV status
  - 72% no chance or a small chance would acquire HIV

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<sup>1</sup> Moretiwe et al, (CROI 2019)<sup>2</sup>Gill, Bekker (2017)<sup>3</sup>Celum et al (CROI 2019)<sup>4</sup>Bekker, Myers, Rosenberg (in draft)
Oral PrEP for young women

- Oral PrEP promises women a means of protection not dependent on partner agreement.
- Early trials found low levels of adherence among this high priority group (VOICE, FEM-PrEP).
- Oral PrEP is highly effective, when taken.

Reductions in HIV incidence vs adherence

Reduction in HIV incidence: % reduction in HIV incidence (%) vs Adherence estimated from drug concentrations.

Pearson correlation = 0.88, p<0.001
Demonstration project among South African adolescents 15-19 yrs old (n=99 females, 49 males) found higher adherence levels which decreased over time

- 1/3 persisted with PrEP (18% opted out at M3, 41% by M6, 43% by M9)

Gill, Bekker, et al. A Demonstration Open Label Study to Assess the Acceptability, Safety and Use of Truvada Pre-exposure Prophylaxis in Healthy... (IAS 2017)
POWER Study

- Considerable drop-off in first month of PrEP initiation

Kaplan-Meier Survival Analysis n=946

POWER Study persistence from month 1

- Persistence better in participants taking PrEP beyond month 1

Kaplan-Meier Survival Analysis of n=236

- 48% persistence at M3
- 40% persistence at M5
- 17% of participants that persisted beyond 1 month

Months (rounded 30 day intervals) since PrEP initiation

Kaplan-Meier Survival Analysis of n=236


Restart PrEP within 3 months
Median TFV-DP at month 3 was 485 fmol/punch (IQR 166,775): 25% 700, 23% 350-699, 36% detectable<349 and 16% undetectable.
3Ps for Prevention study

- High early adherence (n=200, 15-24 yrs).
  - By M3, half were taking the majority of doses (>700 fmol/punch) and least ‘medium protection’ (>350).

- TDF-DP levels were high; median TVF-DP:
  - 622 fmol/punch at 1 month
  - 707 fmol/punch at 2 months
  - 700 fmol/punch at 3 months

- High adherence (>700) was associated with:
  - Having an HIV+ or HIV-unknown partner
  - Curiously, not having sex in last 30 days
  - Disclosing PrEP use
  - Not reporting weekly alcohol use

Why aren’t AGYW taking PrEP?

- Demand creation challenges
  - Low concern about HIV / sense of personal risk, cultural norms unaccustomed to preventative pill-taking,
  - Concern about side effects, socio-economic stressors that limit personal agency and future-oriented thinking
- Lack elevated perception of risk
- Relationships change radically and often. They end. They deepen.
- Motivation difficult to sustain (boredom, novelty wears off)
  - General hassle, tediousness of pill-taking
  - Lack of intrinsic motivation (e.g. more motivated by research incentives)
- Habit formation difficult

Why aren’t AGYW taking PrEP?

- Adolescents glaze over at prospect of long-term PrEP use
  - Long-term benefits difficult to grasp over short-term hassle
- Negative focus on risk puts many adolescents off
- Lack of social support often a significant barrier
- Low community awareness puts AGYW in difficult position of having to educate and convince others
- Infrequent visits are demotivating
- Service delivery barriers will further discourage continuation as PrEP is rolled out beyond idyllic research environments
What constitutes success with PrEP?

- Success with ART ≠ success with PrEP
  - Study success vs real success (incidence reduction)
- Prevention-effective adherence paradigm (Haberer 2015)
  - Success is achieved because PrEP is used during all episodes of exposure.
  - Adherence may be periodic and mapped to periods of risk
  - ↑ protection, ↓ burden ↓ cost

Innovate: Time for new models

- Telling young people that when you start taking PrEP, you must take it every single day, for a prolonged period of time... isn’t working.

- Adolescents’ needs vary
- Adolescents’ needs vary over time
- Adolescents’ have preferences
  - HIV prevention should be tailored accordingly
Innovate: Limited period PrEP

- PrEP during periods of high-risk periods reduces need for treatment & prevention during other life stages
- Can we come up with a reasonable timeframe within a young person’s horizon that covers their greatest period of risk?

17-23 years

X – no need for PrEP here

22-28 years

PrEP while young & at high risk
Innovate: Seasonal PrEP

- What if we allowed *(encouraged?)* adolescents to cycle on and off PrEP?
  - Dependent on sexual behaviour / relationship dynamics

- PrEP for:
  - Casual sex
  - With new partners
  - Until couples testing
  - Literal seasons of risk (e.g. festive season)
  - Not for periods of inactivity...
Innovate: On-demand PrEP

- The level of adherence needed to achieve HIV protection is not clear; PrEP use may potentially permit behavioral imperfection
  - iPrEx: 2 PrEP doses/week might achieve a 76% reduction in HIV (rising to >95% for >4 doses/week)
  - Potentially related to intensity and route of viral exposure
- Need evidence to guide less-than-daily dosing of oral PrEP
  - 86% reduction with MSM (IPERGAY\(^1\))—*could this work for young women?*

\(^1\) Molina et al (2015)
Innovate: On-demand PrEP

- ↓ pills, ↓ side hassle, ↓ side effects, ↓ cost and ↓ monitoring
- ADAPT trial (Alternative Dosing to Augment PrEP Pill-Taking)\(^1\)
  - Formative research found that intermittent PrEP was favoured for lower time burden and side effects\(^2\)
  - Daily arm had better adherence & coverage of sex acts (2-1-1); higher TVF levels\(^1\)—result of habit formation?
  - Measured coverage, more than effectiveness. Post-sex dosing not great in the intermittent arms (Qual: mismatch between relaxation & action-orientation post-sex\(^3\))

- Will adolescents be able to plan sex as well as MSM?
  - 32% of women forecasted last sex, compared to 75% of men
  - Would results be quite different with ↑ awareness of PrEP?

\(^1\) Bekker et al, HPTN 067/ADAPT Cape Town... (CROI 2015); \(^2\) Mark, Amico et al (AIDS 2012) \(^3\) Amico et al, Experiences with HPTN 067... (2016)
A lexicon of intermittent PrEP (McConnell/AVAC)

1. Fixed or time-based dosing (*Status quo*)
   
   ![Fixed or time-based dosing diagram]

2. Event-based dosing (*On-demand*)
   
   ![Event-based dosing diagram]

3. Time-based plus event-based dosing
   
   ![Time-based plus event-based dosing diagram]

4. Periodic dosing (*Seasonal PrEP*)
   
   ![Periodic dosing diagram]
Innovate:

- What if we propose models with shorter timeframes or specific periods of risk?
- Where adolescents are supported in making informed choices about whether to stop/start PrEP?
- Through more frequent visits in which they can re-assess their current need for PrEP, not scolded for variable adherence?
  - Can we trust adolescents to figure out when they are most at risk?
  - What information would they need to figure out how best to cycle on and off PrEP?
CONRAD: A Phase II Evaluation of Daily (F/TDF) vs daily (F/TAF) vs Event-Driven (TFVp+FTC+INI) Oral PrEP in African Women
Integrate: Sexual health journey

- Position oral PrEP as a component of sexual risk reduction, not a standalone intervention
- PrEP persistence likely to depend on:
  - De-medicalising and de-stigmatising PrEP
  - Making PrEP convenient and as hassle-free as possible
- Adolescents want youth-friendly services, tailored to their needs
  - To feel welcomed, their needs prioritised
  - Confidentiality and privacy (ideally, their own space)
  - Flexibility, accessibility, convenience
  - Integrated services (one-stop shop)
Motivate: Time for a new approach

- Rethinking the language we use
  - How do you measure ‘*persistence*’ when someone only doses around sex?
  - ‘*Lost to follow-up*’: you have to be found?
  - ‘*Retention*’, ‘*Defaulters*’: what if you don’t see yourself as at risk?
  - Focus on ‘*tolerability*’, not ‘*side effects*’

- Focus on ‘*protection*’, not ‘*risk*’
  - PrEP helps healthy people be healthier (not for sick or ‘*risky*’ people)
  - Gain-framed messages can be more persuasive than loss-framed messages, particularly to adolescents\(^1\)

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\(^1\) Amico and Bekker (2019); Hull (2012). Photograph of Sr. Vece, 360HIV virtual reality film project: Sydelle Willow Smith
Evidence gaps: PrEP and adolescents

- What are the patterns of adolescent sex?
- What are the patterns with which adolescents are using PrEP?
- What do adolescents think is reasonable approach to adherence?
- What is the effectiveness of on-demand PrEP for young women?
- What strategies could help them succeed in taking PrEP on demand?
Conclusion

- PrEP is not ART. What we’ve learned from providing ART does not fit PrEP, especially for adolescents
  - Adolescents are not going to take a daily pill forever.
- Need better clinician guidelines for cycling on and off PrEP
- Need to figure out what to tell youth and how to keep them engaged in a broader journey of sexual health care
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