The HIV Prevention Product Pipeline for Adolescents

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INTER-CFAR ARV FOR PREVENTION WORKING GROUP WEBINAR
JANUARY 8TH, 2018
Conflicts of Interest

I have no conflicts to report
Overview

1) Need for biomedical prevention options that are licensed for adolescents
2) Inclusion of children in research – funder perspective
3) Inclusion of children in research – regulatory perspective
4) Review of current pipeline for biomedical HIV prevention products and corresponding adolescent data (or lack thereof)
5) Conclusions
4,500 new HIV infections among adults (aged 15 years and older) every day

37% Among young people (aged 15-24 years)

- Among young women (15-24 years)
- Among young men (15-24 years)
Youth (aged 13-24) accounted for more than 1 in 5 new HIV diagnoses in 2014.
Effective HIV prevention programmes require a combination of behavioural, biomedical and structural interventions
Currently Available Products for Adults

✓ Condoms
✓ HIV Testing
  ✓ Home self-test kits
✓ Medical Male Circumcision
✓ HIV Treatment
✓ Pre-Exposure Prophylaxis (TDF/FTC PrEP)
When to Begin Adolescent Studies for New Biomedical Products?
The goal...

**CONCURRENT** licensure of adult and pediatric HIV prevention and treatment products

“The ability of adolescents to access safe and effective new products for HIV prevention and treatment is optimised by adolescent licensure at the same time these products are approved and marketed for adults. Many adolescent product development programmes for HIV prevention or treatment products may proceed simultaneously with adult Phase III development programmes.”

Hume, Lewis & Nelson, 2017
Policy for the Inclusion of Children in NIH Research (NIH NOT 98-024)

- The goal was to increase the participation of children in research so that adequate data would be developed to support treatment modalities for disorders and conditions that affect adults as well as children.

- Medical treatments applied to children were often based upon testing done only in adults; thus, evidence-based treatments less available to children due to their exclusion from studies.
  - These concerns were specifically articulated in Congressional directives to the NIH as reflected in language from the FY 1996 House and Senate Appropriations Committee reports

- Update: Applications submitted after January 25, 2016, for the purposes of inclusion policy, the age of a child will be defined as individuals under 18 years old
§46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that:

(a) The risk is justified by the anticipated benefit to the subjects;

(b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and

(c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in §46.408.
Regulatory Perspective

Pediatric Research Equity Act (2003): for new drugs, assessments of safety and effectiveness are required for all relevant pediatric sub-populations

- Safety CANNOT be extrapolated
- PK/dosing not usually extrapolated for children, but may be OK for adolescents
- Efficacy MAY be extrapolated depending on a number of criteria

When should pediatric trials begin?

- Proof of concept for prospect of direct benefit from human adult studies or animal disease models; varies by severity of disease and adequacy of available treatments
- For HIV prevention, evidence of antiviral activity must be available
- Once sufficient adult and/or animal data exist, pediatric development should begin

“The level of adult data necessary to support a prospect of direct benefit determination is less than the level of evidence required to establish efficacy.” (Hume, Lewis & Nelson, 2017)
To wait for adult efficacy or not?

If YES, then an efficacious product may be available which adolescents cannot access (e.g. PrEP).

If NO, then adolescents may be exposed to a SAFE but non-fficacious product (e.g. vaginal gel).
Product dependent

- Product use history
- Previously used for treatment?
- New formulation of old drug?
- Intended use of new product
Antibody-Mediated Prevention

<table>
<thead>
<tr>
<th>Cohort</th>
<th>IV Treatment</th>
<th>n=</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>North + South American MSM (2400)</td>
<td>VRC01 10 mg/kg</td>
<td>800</td>
<td>Every 8 wks x 10 doses</td>
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<tr>
<td></td>
<td>VRC01 30 mg/kg</td>
<td>800</td>
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<td></td>
<td>Placebo Control</td>
<td>800</td>
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<tr>
<td>HVTN 704 / HPTN 085</td>
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<tr>
<td>sub-Saharan African women (1500)</td>
<td>VRC01 10 mg/kg</td>
<td>500</td>
<td>Every 8 wks x 10 doses</td>
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<td></td>
<td>VRC01 30 mg/kg</td>
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<td></td>
<td>Placebo Control</td>
<td>500</td>
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<tr>
<td>HVTN 703 / HPTN 081</td>
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Adolescent IND Studies on PrEP
Oral Pre-Exposure Prophylaxis (PrEP)

- July 2012: TDF/FTC approved as PrEP based on efficacy data from iPrEx, Partners PrEP & TDF2 trials

FDA Approves First Medication to Reduce HIV Risk

- But US youth are under-represented in studies

- No PrEP data available on adolescent males or females under age 18

<table>
<thead>
<tr>
<th>Race</th>
<th>Frequency</th>
<th>Percent</th>
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</thead>
<tbody>
<tr>
<td>Black/African-American</td>
<td>5</td>
<td>17.86</td>
</tr>
<tr>
<td>White</td>
<td>13</td>
<td>46.43</td>
</tr>
<tr>
<td>Mixed/Other</td>
<td>5</td>
<td>17.86</td>
</tr>
<tr>
<td>Asian</td>
<td>5</td>
<td>17.86</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>28</strong></td>
<td><strong>100.0</strong></td>
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Adolescent PrEP Studies

- 5+ years post-approval for adults and no adolescent indication
- Additional safety and behavioral data in adolescents will be required to support a supplemental PrEP indication under age 18
  - ATN 110/113: PrEP demonstration projects and safety studies for young MSM ages 15-22 in the US
  - PlusPills: A demonstration open label study to assess the acceptability, safety and use of Truvada PrEP in healthy, HIV-uninfected South African adolescents, 15-19 years of age
ATN 113 Study Design

Pre-Screening Survey (venue-based or online) -> Ineligible or refuse survey

In-person screening visit (IC and screening labs) -> Ineligible based on labs

Baseline Visit (review labs & VL) -> Behavioral Intervention (PCC)

Behavioral Intervention (PCC) -> Week 0 – Dispense PrEP

Follow-up Visits (weeks 4, 8, 12, 24, 36, 48) -> HIV Seropositive Visits

Full prevention package iNSC

Week 48: Evaluate for EPH -> Extension Phase Visits

Hosek et al., JAMA Pediatrics, 2017
Baseline Demographics

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Black</td>
<td>33%</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>29%</td>
</tr>
<tr>
<td>White</td>
<td>14%</td>
</tr>
<tr>
<td>Other/Mixed</td>
<td>21%</td>
</tr>
<tr>
<td>Asian/PI</td>
<td>3%</td>
</tr>
</tbody>
</table>

**Mean age:** 16.5

**Sexual Identity:**
- Gay: 58%
- Bisexual: 28%
- Questioning: 6%

**Completed high school:** 18.4%

**Currently living with parents/family:** 88.5%

**Received public aid:** 76.9%

**Kicked out of house for being gay:** 15%

**Ever been paid for sex:** 17%

**Partners in past month:** 2

**CRAI w/last partner:** 60%

**Any positive STI test:** 15.4%
Safety

Well-tolerated overall

- No documented discontinuations due to side effects

Adverse Events

- Three Grade 3 adverse events (weight loss) in 2 participants deemed related to study drug
  - Grade 3 weight loss = 10-19%

No abnormal laboratory results
STI Diagnoses

Number of Diagnoses

Baseline | Week 24 | Week 48
---|---|---
Rectal Gonorrhea | Rectal Chlamydia | Syphilis | Any STI

"Any STI" count
HIV Incidence

3 seroconversions through week 48

HIV incidence = 6.41 per 100 person-years (95% CI: 4.9-25.8)
Adherence: TFV-DP in DBS

- WK 4 (n=72)
- WK 8 (n=71)
- WK 12 (n=67)
- WK 24 (n=61)
- WK 36 (n=58)
- WK 48 (n=51)
PlusPills Study Design

150 Healthy 15-19yo, Sexually active
40:60 M:F Masiphumelele and Soweto

Basic Package: HCT, MMC, PEP, condoms
Female condoms

Choice of daily, weekly or no SMSs

Adherence clubs

Screen, enroll. Package + PrEP

DBS + real time FB vs none

DBS + real time FB vs none

DBS + real time FB vs none

DBS + real time FB vs none

CHOICE: package +/-PrEP
Acceptability
Reasons for choice

DBS + real time FB vs none

DBS + real time FB vs none

DBS + real time FB vs none

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DBS + real time FB vs none

Final Visit

Gill et al., IAS 2017
### Baseline Demographics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age</td>
<td>18 years</td>
</tr>
<tr>
<td>Female / Male ratio</td>
<td>99/49</td>
</tr>
<tr>
<td>Completed Grade 12</td>
<td>23%</td>
</tr>
<tr>
<td>Living with parents/family</td>
<td>90%</td>
</tr>
<tr>
<td>Median age of Sexual Debut</td>
<td>14.5 years</td>
</tr>
<tr>
<td>Partner &gt; 5 years older</td>
<td>22%</td>
</tr>
<tr>
<td>Transactional Sex</td>
<td>3%</td>
</tr>
<tr>
<td>Had anal sex</td>
<td>6%</td>
</tr>
<tr>
<td>Condom at last sex act</td>
<td>74%</td>
</tr>
<tr>
<td>Always use a condom</td>
<td>34%</td>
</tr>
<tr>
<td>Alcohol in last 12 months</td>
<td>57%</td>
</tr>
<tr>
<td>Recreational drugs in last 12 months</td>
<td>15%</td>
</tr>
<tr>
<td>Any STI at screening</td>
<td>41%</td>
</tr>
</tbody>
</table>

**Age by Gender**

- **15 years**: Male: 10, Female: 12
- **16 years**: Male: 11, Female: 12
- **17 years**: Male: 12, Female: 13
- **18 years**: Male: 14, Female: 20
- **19 years**: Male: 13, Female: 14

Legend:
- **male**
- **female**
Safety

Well-tolerated overall
11% (n=16) participants experienced a grade 2 or 3 related side effect

Grade 2:
- 4 headaches
- 4 nausea and vomiting
- 2 abdominal pain
- 2 diarrhea
- 2 skin rash

Grade 3
- Two Grade 3 adverse events (weight loss) in 2 participants deemed related to study drug
  - Grade 3 weight loss = 10-19%

No abnormal Creatinine / LFT’s
STI Diagnoses

- Baseline: 45 cases (Chlamydia 4, Gonorrhea 23, Herpes 21)
- Week 12: 35 cases (Chlamydia 29, Gonorrhea 6, Herpes 0)
- Week 48: 36 cases (Chlamydia 33, Gonorrhea 3, Herpes 0)

"Any STI" count
Plasma TDF Levels
Conclusions (ATN 113/PlusPills)

- Adolescents males and females are still at high risk for HIV
  - In ATN 113, HIV incidence was high compared to other open label PrEP studies
- PrEP was well tolerated with minimal safety concerns
- Acceptability of PrEP, the overall study, and HIV testing and counseling was high
- Adherence to daily medications notoriously difficult for adolescents worldwide.
- PrEP usage and adherence diminished over time with less frequent visits
  - Adolescent implementation of PrEP needs developmentally-appropriate strategies, such as enhanced visit schedules and/or more frequent interactions (in-person or via mobile technology)
- In PlusPills, young women were not less adherent than young men
- STI diagnoses remained constant or dropped over the course of these studies
- sNDA based on ATN 113 data submitted to FDA on November 16th, 2017!!
Implementation of PrEP for Adolescents

Progress:
◦ Over 25 countries have PrEP approved for adults
◦ The EU just granted approval for PrEP for adolescents down to age 12

Significant barriers remain:
◦ Lack of prescriber knowledge, comfort
◦ Issues of parental/guardian consent
◦ Undesired disclosure of sexual activity, sexual orientation
◦ Insurance, cost, lack of access to medication assistance programs

Best practices for implementation and improving adherence being studied across populations in many countries
Adolescent-focused PrEP Studies in US

Studies currently underway or in development within the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN)…
Prevention Products
Under Regulatory Review
Dapivarine Vaginal Ring

Similar to vaginal rings commonly used for contraception except that it contains an antiretroviral (ARV) drug, dapivirine, instead.

Dapivirine belongs to a class of ARVs called non-nucleoside reverse transcriptase inhibitors that bind to and disable a key protein that HIV needs to make copies of itself.

The ring, which is made of a flexible material, sits high inside the vagina, where it slowly releases the drug over the course of the one month the ring is worn. Women can insert and remove it themselves.
ASPIRE/The Ring Study

HIV Prevention in ASPIRE and The Ring Study

27% reduction

31% reduction

However...

- In ASPIRE, HIV protection differed by age
- In fact, the ring was not effective among younger women ages 18-21 who used the ring least regularly.
- Higher levels of protection were seen in women who used the ring most regularly.
  - Among women who were 25 and older when they enrolled, 61% fewer acquired HIV in the dapivirine ring group compared to the placebo ring group
  - Further analysis of data found the age cutoff for HIV protection was age 21
    - Age 18-21 – no protection (and lowest adherence)
    - Age 22-45 – 56% fewer HIV infections among women in the dapivirine ring group vs. placebo group
Adolescent Studies on the Dapivirine Ring
MTN023/IPM 030
Project iMatter

- Phase 2a randomized, double-blind placebo controlled trial of a dapivirine vaginal ring in 15-17 year olds in the US
- Collaboration between Adolescent Trials Network and Microbicide Trials Network
- Dapivirine vaginal ring was developed and supplied by IPM
- 6 sites
  - ATN
  - Denver
  - Bronx
  - Boston
  - Memphis
  - MTN
  - Birmingham
  - Pittsburgh

Bunge et al., IAS 2017
Study Design

- Each visit: AE assessment, adherence, acceptability
- 2, 4, 12 and 24 weeks: blood and vaginal fluid for drug level
- Each month: returned ring for residual drug level
## Demographics

<table>
<thead>
<tr>
<th></th>
<th>Dapivirine (n=73)</th>
<th>Placebo (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean (SD)</strong></td>
<td>16.3 (0.8)</td>
<td>16.2 (0.7)</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>(15-17)</td>
<td>(15-17)</td>
</tr>
<tr>
<td><strong>Age at first menses</strong></td>
<td>11.7</td>
<td>11.7</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>(8-15)</td>
<td>(10-14)</td>
</tr>
<tr>
<td><strong>Latina or Hispanic</strong></td>
<td>22%</td>
<td>17%</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>47%</td>
<td>57%</td>
</tr>
<tr>
<td>White</td>
<td>27%</td>
<td>17%</td>
</tr>
<tr>
<td>Other</td>
<td>26%</td>
<td>26%</td>
</tr>
<tr>
<td><strong>Lifetime sexual partners, median</strong></td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>(1-23)</td>
<td>(1-12)</td>
</tr>
<tr>
<td><strong>No condom last sex</strong></td>
<td>49%</td>
<td>49%</td>
</tr>
<tr>
<td><strong>Anal sex no condom, ever</strong></td>
<td>21%</td>
<td>0%</td>
</tr>
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## Safety

<table>
<thead>
<tr>
<th></th>
<th>Dapivirine (n=73)</th>
<th>Placebo (n=23)</th>
<th>Odds Ratio</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants with one or more</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2 related AE</td>
<td>8 (11%)</td>
<td>2 (9%)</td>
<td>1.29 (0.25, 6.57)</td>
<td>1.00</td>
</tr>
<tr>
<td>Grade 3 or higher AE</td>
<td>3 (4%)</td>
<td>0 (0%)</td>
<td>--</td>
<td>1.00</td>
</tr>
<tr>
<td>Total</td>
<td>11 (15%)</td>
<td>2 (9%)</td>
<td>1.86 (0.36, 18.55)</td>
<td>0.73</td>
</tr>
</tbody>
</table>
Adherence

- Dapivirine plasma drug concentration > 95 pg/mL
  - 87% of plasma samples with levels suggestive of adherence to study product in the day prior to visit

- Dapivirine residual drug levels in used rings <23.5 mg
  - 95% of returned vaginal rings with levels suggestive of adherence over the past month

- Self report
  - 42% (95% CI, 32, 52) of participants reported that they never removed the ring except to replace it monthly.
  - Most removals were brief
Conclusions

▪ The dapivirine vaginal ring is safe and acceptable in 15-17 year old US girls
▪ Both plasma and residual vaginal ring drug levels indicated high adherence
▪ Consistency between dapivirine plasma levels and residual dapivirine levels in used rings supports appropriate study product use
Next Steps

▪ Dapivirine licensure package has been submitted to the European Medicines Agency; SA MCC and FDA to follow
  ▪ Safety data among adolescents are still needed

▪ MTN-034 (REACH) to begin in mid-2018
  ▪ A Phase 2a crossover trial evaluating the safety of and adherence to a vaginal matrix ring containing dapivirine and oral emtricitabine/tenofovir disoproxil fumarate in 16-21 year olds
  ▪ 4 sites: S Africa, Uganda, Kenya, Zimbabwe
Prevention Products Currently in Efficacy Trials
Cabotegravir (GSK1265744)

- Experimental, long-acting integrase inhibitor
- Well-suited for injectable formulation
- High genetic barrier to resistance
- PK profile – half life of 21-50 days -- allows once-daily oral or 1-3 month injectable dosing using nanosuspension formulation
- Being evaluated currently as injectable PrEP and HIV treatment
Adolescent Trials of Prevention Products Being Studied
HPTN 086: Adolescent CAB-LA Study

▪ **Purpose:** To establish the minimum safety, tolerability and acceptability data needed to allow expansion of the anticipated FDA indication for LA CAB to include youth down to age 15, potentially transforming the field of HIV prevention for youth and adolescents.

▪ A single arm, open label study using an enrollment design of sequential cohorts of decreased age

▪ ~100 youth (50 males, 50 females) ages 15-18

▪ US and South Africa

▪ Timeline Goal: To submit adolescent data with adult package for concurrent licensure
Other Products in the Prevention Pipeline
ARV-Based Prevention Pipeline

The pipeline of ARV-based prevention products includes oral pills, vaginal rings, vaginal and rectal gels, vaginal films, long-acting injectable ARVs. Not pictured are a range of multipurpose technologies in development that aim to reduce women’s risk of HIV and STIs, and provide effective contraception.

For up-to-date information on the ARV-based prevention pipeline, visit the HIV Prevention Research Database at www.avac.org/prrd.
Possible Study Designs

• Bridging studies

• Inclusion of adolescents in large Phase 3 trials
  ◦ Part of original protocol
  ◦ Sub-study

• Key Components:
  ◦ Pediatric/Adolescent expertise
  ◦ Adolescent-competent staff
  ◦ Adequate resources to give youth the time that they need
Conclusions

- Adolescents need access to powerful new biomedical prevention strategies
- The timeline for adolescent-approved products needs to be expedited -- concurrent licensure of adolescent and adult products is the goal!
- There is ethical and regulatory support for concurrent adolescent and adult trials
- When to launch an adolescent trial and what data are needed may be product dependent
Thank You!