CONTROLLING THE HIV EPIDEMIC WITH ANTIRETROVIRALS

HIV

Treatment as Prevention and Pre-Exposure Prophylaxis

22-24 September 2013
Queen Elizabeth II Conference Centre, London
Adherence to PrEP
Elements of Success

K Rivet Amico, PhD
University of Connecticut
Connecticut, USA
Major findings from the evidence base gathered to date and future directions

**IN GENERAL (WITH CAVEATS) PREP IS EFFECTIVE**
- Studies completed to date generally support efficacy of PrEP, with exceptions
- Adherence relates to levels of protection
- Heterogeneity in product use is under study

**PREP ADHERENCE IS UNDER INVESTIGATION**
- Study product vs effective PrEP
  - Adherence may not resemble study product adherence
  - Success relies on taking it...but many questions remain

**IN PROGRESS AND CRITICAL QUESTIONS**
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**IN PROGRESS AND CRITICAL QUESTIONS**
### IN GENERAL (WITH CAVEATS) PREP IS EFFECTIVE

<table>
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<tr>
<th>Study</th>
<th>Efficacy</th>
</tr>
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<tbody>
<tr>
<td>PinP-TDF/FTC</td>
<td>75%*</td>
</tr>
<tr>
<td>PinP- TDF</td>
<td>67%*</td>
</tr>
<tr>
<td>TDF₂ – TDF/FTC</td>
<td>62%*</td>
</tr>
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</tr>
<tr>
<td>iPrEX – TDF/FTC</td>
<td>44%*</td>
</tr>
<tr>
<td>CAPRISA – Gel BAT₂⁴</td>
<td>39%*</td>
</tr>
<tr>
<td>VOICE- Gel Daily</td>
<td>14.7%</td>
</tr>
<tr>
<td>FemPrEP – TDF/FTC</td>
<td>6%</td>
</tr>
<tr>
<td>VOICE- TDF/FTC</td>
<td>-4%</td>
</tr>
<tr>
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<td>-49%</td>
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Other Countries are awaiting more evidence...

- Daily oral- PROUD
- Intermittent Oral- iPerGAY
- 1% BAT₂⁴ Gel- FACTS
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Adherence relates to levels of protection
## IN GENERAL (WITH CAVEATS) PREP IS EFFECTIVE

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<td>51%</td>
</tr>
<tr>
<td>CAPRISA – Gel BAT₂₄</td>
<td>39%*</td>
<td>38% - 98%</td>
</tr>
<tr>
<td>VOICE- Gel Daily</td>
<td>14.7%</td>
<td>22%</td>
</tr>
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<td>6%</td>
<td>37%</td>
</tr>
<tr>
<td>VOICE- TDF/FTC</td>
<td>-4%</td>
<td>29%</td>
</tr>
<tr>
<td>VOICE- TDF</td>
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<td>28%</td>
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IN GENERAL (WITH CAVEATS) PREP IS EFFECTIVE

Studies completed to date generally support efficacy of PrEP, with exceptions. The table below provides estimated adherence by drug concentration for various studies:

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<td>67-80%</td>
</tr>
<tr>
<td>TDF2-TDF/FTC</td>
<td>62%*</td>
<td>80%</td>
</tr>
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<td>49%*</td>
<td>67%</td>
</tr>
<tr>
<td>iPrEX-TDF/FTC</td>
<td>44%*</td>
<td>51%</td>
</tr>
<tr>
<td>CAPRISA-BAT24</td>
<td>39%*</td>
<td>38%-98%</td>
</tr>
<tr>
<td>VOICE-Gel Daily</td>
<td>14.7%*</td>
<td>22%</td>
</tr>
<tr>
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<td>6%*</td>
<td>37%</td>
</tr>
<tr>
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<td>4%*</td>
<td>29%</td>
</tr>
<tr>
<td>VOICE-TDF</td>
<td>49%*</td>
<td>28%</td>
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</tbody>
</table>

The graph below illustrates the relationship between adherence and efficacy:

**Efficacy by Adherence**

-60.00% to 100.00% adherence levels are shown on the x-axis, with corresponding efficacy percentages on the y-axis.
Drug Concentration Response
Adjusted for PK concentrations, differences in outcomes across trials largely driven by differences in adherence (once accounting for PK)

Slide from C. Hendrix 2013
‘If you take it, it works’: The importance of adherence

The single biggest Achilles heel in all the PrEP studies

EDITORIAL

Pre-exposure prophylaxis for HIV prevention: Ready for prime time in South Africa?

Eakle, Venter, & Rees S Afr Med J 2013
Sizable differences found in use of study product, between and within studies...challenges simple interpretation of outcomes.
Sizable differences found in use of study product...between and within studies
TFV-DP Detection

MTN-001 Crossover Study Minnis et al 2013

% WITH ADEQUATE DRUG LEVEL

USA

SAfr 44% 39% 84%
Ugand US

Time Points
Median TFV-DP Level
Drug Detection*
P <
(%) 94%

*Detection of TFV/FTC/TFV-DP or FTC-TP in plasma or PBMC [Anderson et al 2011]
• Non-adherence may signal poor acceptability, but could also signal community/cultural conflicts with the research paradigm itself.
• Study drug adherence may be driven by social/political climate, research, community and participant(s).

• 401 interviews 179 female microbicide trial participants, 28 interviews with partners, 42 focus groups community members [2005-2009]
Other factors influencing study drug NON-ADHERENCE:

- Age (younger)
- Gender (Male)
- Lower SES
- Heavy or binge alcohol use
- Lower perceived risk for HIV
- No sex [PinP] or polygamous marriage
PRODUCT NON-COMPLIANCE IN PREP TRAILS

- Young
- Unmarried
- Low perc risk
- Low perc benefit
- Low intentions
- Low motivation
- Distrust
- Intentional non-adherence
- Fearful
- Interferes with sex
- Lack partner support
- Stigma as participant
- HIV stigma
- Demanding difficult
- Poor match with culture
- Under study
- Placebo controlled
- No evidence
- Discomfort
- Complex messages
- Unclear procedures
- Long visits

Chesney 2000

Controlling the HIV Epidemic with Antiretrovirals
Treatment as Prevention and Pre-Exposure Prophylaxis
Hard to tell who will be non-adherent, but we may be able to tell who IS/IS NOT using product during a trial...

- Advances in dried blood spot analyses for oral dosing – 2 weeks in some cases [active drug]
- Advances in identifying what levels confer to in terms of oral dosing [active drug]
- Emerging work supporting EDM and unannounced pill counts [oral products]
- Wisebag, Taggants, SMS...

Monitoring/being monitored may not be an adherence promotion strategy (or successful in increasing accuracy of self-report) [Abbott et al., 2013; Minnis et al., 2013]

Still need to work through how to best intervene with monitoring data.

Adherence to Antiretroviral Prophylaxis for HIV Prevention: A Substudy Cohort within a Clinical Trial of Serodiscordant Couples in East Africa

Jessica E. Haberer¹, ², Jared M. Baeten³, ⁴, ⁵, James Campbell⁶, Jonathan Wangisi⁶, Elly Katabira⁷, Allan Ronald⁸, Elioda Tumwesigye⁹, Christina Psaros¹⁰, ¹¹, Steven A. Safren¹⁰, ¹¹, Norma C. Ware¹², Katherine K. Thomas³, Deborah Donnell³, ¹³, Meighan Krows³, Lara Kidoguchi³, Connie Celum³, ⁴, ⁵, David R. Bangsberg¹, ², ¹⁴

Controlling the HIV epidemic with antiretrovirals: Treatment as prevention and pre-exposure prophylaxis
Better Products May Promote Better Product Adherence in RCTs AND real-world open label

- Long acting agents - less frequent dosing
- Slow release (Dapivirine Vaginal Ring - ASPIRE)
- Dual purpose - Birth control + ARV; Lube + ARV
- On Demand or Intermittent PrEP

All other things being equal...
✓ Simpler is better.
✓ Products matched to common practices is better.
✓ Products that address multiple needs is better.

Does not eliminate adherence (acceptability, feasibility) from the picture but could minimize demands of it.
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**IN PROGRESS AND CRITICAL QUESTIONS**
### Some differences...

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<tr>
<th>User</th>
<th>Placebo Controlled Drug</th>
<th>Effective PrEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motivation for Enrollment/Uptake</td>
<td>Medical care Testing Resources</td>
<td>Comprehensive prevention plan Access to PrEP</td>
</tr>
<tr>
<td>Drug</td>
<td>May/may not be active drug Under investigation for efficacy and/or safety</td>
<td>Effective and safe</td>
</tr>
<tr>
<td>Why take it?</td>
<td>To contribute to research and community</td>
<td>To protect self from HIV infection/Sexual health</td>
</tr>
<tr>
<td>Consequence of non-use?</td>
<td>Jeopardize research and finding community solutions</td>
<td>No PrEP protection benefits (may or may not mean increased risk)</td>
</tr>
<tr>
<td>Duration of use?</td>
<td>Continuous while on-study</td>
<td>As needed? Times of risk?</td>
</tr>
</tbody>
</table>

- Interferes with sex
  - *PrEP*partner support
- Stigma as “PrEP” user participant

**NON-ADHERENCE Study drug vs Effective PrEP**

**Real world PrEP**

21 Some differences...
PREP ADHERENCE IS PRESENTLY UNKNOWN

- Study product vs effective PrEP
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- OLE enrolled from June 2011 to June 2012.
- OLE participation did not require PREP use.
- Of 1451 eligible for PrEP, 72% selected it (older, lower ed, recent nc-RAI)
- Of those on PrEP, 72% had detectable drug (older, higher ed)
PREP ADHERENCE IS PRESENTLY UNKNOWN

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Plasma Drug Detection by Region
iPrEx Randomized wk 8, OLE wks 4-12

<table>
<thead>
<tr>
<th>Region</th>
<th>Randomized</th>
<th>OLE</th>
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<tbody>
<tr>
<td>US</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>Brazil</td>
<td>70%</td>
<td>70%</td>
</tr>
<tr>
<td>Other</td>
<td>60%</td>
<td>60%</td>
</tr>
<tr>
<td>Andes</td>
<td>50%</td>
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- Study product vs effective PrEP
  - Adherence may not resemble study product adherence
  - Success relies on taking it; taking it may be higher among early adopters of an effective intervention (PrEP vs study product)...but many questions remain

- What will rates of adherence be among those choosing to use PrEP and will that differ dramatically by community or cohort or change over time?

INTERVENTION DEVELOPMENT

- What are the cycles of PrEP use and how does that influence adherence? How to support transitions?
- Should focus be on adherence interventions or prevention packages or menus? PREVENTION SYNERGY?
  - MP³ Projects; Integrated Demonstration Projects
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IN PROGRESS AND CRITICAL QUESTIONS
Demonstration Projects in Progress

- SMS text based reminders and motivators
- Text based outreach
- Targeted adherence support (increasing intensity with demonstrated non-adherence)
- Drug level feedback
- Integrated Protection Menus
- Delivery locations
IN PROGRESS

Other Projects in progress
- Detailed PK DOT study
- Intermittent adherence
- Safety of alternative ARVs
- Framing messages
- Media to inform
- ATN 110/113
CRITICAL QUESTIONS

How well will people adhere to PrEP in the real world?

• We have reason to be concerned - plenty of warnings from other prevention/treatment fields.

• Maybe we can expect higher rates of effective PrEP adherence then study product from the RCTs.

• Within many placebo controlled trials completed to date, participants with low/no intentions to use product OR disclose non-use have been identified.

• Will this also occur in open-label PrEP programs?
CRITICAL QUESTIONS

How well will people adhere to PrEP in the real world?

• As an open question - we can help reduce confusion by adopting appropriate terms

• Reserve use of term ‘PrEP adherence’ for open label effective PrEP adherence.
CRITICAL QUESTIONS
Will people want PrEP if it is available?

Drug utilization data from medical claims - starting TVD after Jan 1 2011

• Individuals on PrEP - 1,774 mixed prescribers (37% experienced with HIV treatment)

• Mdn Age: 37

• Women: 47%
CRITICAL QUESTIONS

Will stigma challenge PrEP uptake and adherence?

Interview Part 3: Toronto Health Promoter Chooses PrEP - "Maybe I should get a t-shirt made that says 'Truvada Whore' on it"

via Positive Lite (Canada)

Part 3 of an interview with Len Tooley, an HIV-negative gay guy who is taking pre-exposure prophylaxis. He works in Toronto as a gay men’s health promoter, HIV educator, tester and counsellor.

THE BLOG

Featuring fresh takes and real stories from HuffPost's signature lineup of writers

David Duran
Freelance journalist

Truvada Whores?

Posted: 11/12/2012 7:59 pm
Moving forward with both RCTs and roll out...

**Develop social science agenda to understand and promote product use in RCTs**
- Drivers of product use; strategies to promote product use (from recruitment to on-study); new designs (PrEP as an option); monitoring feedback strategies

**Targeted research on PrEP adherence**
- Potential success of PrEP will be characterized in demonstration studies – uptake, adherence, retention
- How common is poor adherence? Early? Late?
- How to best intervene to support? Integrated? Adherence?
- Monitoring and drug level feedback?

**Continue to work collaboratively**
Thank you

Special thanks for assistance, clarification or use of slides:
  Sybil Hosek
  Craig Hendrix
  Robert Grant
  Jessica Justman
  Pete Anderson
  Al Liu
  Michael Stirratt

*THIS PRESENTATION DOES NOT REPRESENT THE VIEWS OF ANY OF THE INDIVIDUALS LISTED HERE*