The role of Integrase Inhibitors during HIV prevention

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AIDS Research Institute-IrsiCaixa
Fight AIDS Foundation
BCN Checkpoint

2nd Global HIV Clinical Forum: Integrase Inhibitors
Paris July 22th 2017
DISCLOSURES

• I have received a research grant from Gilead Sciences awarded to my institution
• I have participated in Advisory Boards of Merck, Gilead and ViiV Healthcare
• I am a Principal Investigator of the DISCOVER study
AGENDA

• Background
• What works for PrEP?
• Can we have better options for PrEP?
• Role of Integrase Inhibitors for PrEP
• Discussion
BACKGROUND

HIV diagnoses, by mode of transmission 2005-2014, EU/EEA

BACKGROUND

• Prevention based on ARV has become a cornerstone of HIV prevention
  • Treatment as Prevention
  • Post-Exposure Prophylaxis
• Pre-Exposure Prophylaxis (PrEP)
What works for PrEP?
<table>
<thead>
<tr>
<th>Population</th>
<th>Trials</th>
<th>Reduction in HIV incidence</th>
<th>Drug, delivery, regimen</th>
<th>Gaps in evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSM and transgender</td>
<td>• iPrEx</td>
<td>44%</td>
<td>TDF/FTC Oral Daily/on demand</td>
<td>TDF Topical</td>
</tr>
<tr>
<td></td>
<td>• PROUD</td>
<td>86%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• IPERGAY</td>
<td>86%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterosexual men and women</td>
<td>• Partners PrEP</td>
<td>63 - 84%</td>
<td>TDF +/- FTC Oral Daily</td>
<td>On demand</td>
</tr>
<tr>
<td></td>
<td>• TDF2</td>
<td>62%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>• CAPRISA</td>
<td>39%</td>
<td>TDF +/- FTC Gel/Oral Daily/on demand</td>
<td>Adherence, especially young &lt;25 women</td>
</tr>
<tr>
<td></td>
<td>• FEM-PREP</td>
<td>6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• VOICE</td>
<td>-49% - 15%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ASPIRE</td>
<td>27% - 61%</td>
<td>Dapivirine IVR, monthly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The Ring</td>
<td>31%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>People who inject drugs</td>
<td>• BTS</td>
<td>49%</td>
<td>TDF Oral Daily</td>
<td>Route of transmission</td>
</tr>
<tr>
<td>Trial</td>
<td>Efficacy</td>
<td>Adherence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------------------------------------------</td>
<td>-----------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAPRISA 004&lt;sup&gt;6&lt;/sup&gt;</td>
<td>1% tenofovir gel: 39%</td>
<td>51%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>iPrEx&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Oral daily Truvada: 42%</td>
<td>51%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partners PrEP&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Oral daily tenofovir: 67%</td>
<td>83%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral daily Truvada: 75%</td>
<td>81%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF2&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Oral daily Truvada: 62%</td>
<td>81%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEM-PrEP&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Oral daily Truvada: No Protection</td>
<td>24%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VOICE&lt;sup&gt;2&lt;/sup&gt;</td>
<td>TFV gel: No protection</td>
<td>23%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral daily tenofovir: No protection</td>
<td>28%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral daily Truvada: No protection</td>
<td>29%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The point estimate of efficacy for each study is listed and adherence estimates were determined by measuring drug levels from participant samples collected at varying time points.
<table>
<thead>
<tr>
<th>Study name</th>
<th>Target</th>
<th>Drug / Dosing</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrex (n=2499)</td>
<td>HSH</td>
<td>TDF/FTC QD vs placebo</td>
<td>Nausea, Weight decreased  BMD ~1%</td>
</tr>
<tr>
<td>US-MSM Safety (n=400)</td>
<td>HSH</td>
<td>TDF vs Placebo</td>
<td>Back pain  BMD ~1%</td>
</tr>
<tr>
<td>TDF2 (n=1219)</td>
<td>HTS men &amp; women</td>
<td>TDF/FTC QD vs placebo</td>
<td>Nausea, vomiting, dizziness (1st month)</td>
</tr>
<tr>
<td>Bangkok Tenofovir Study (n=2413)</td>
<td>IVDU</td>
<td>TDF</td>
<td>Nausea, vomiting (1st 2 months)</td>
</tr>
<tr>
<td>Ipergay ANRS (n=414)</td>
<td>HSH</td>
<td>On-demand TDF/FTC</td>
<td>Nausea, vomiting (1st 2 months)</td>
</tr>
</tbody>
</table>
What about in “real world”? Kaiser Permanente study

• 657 MSM
  • San Francisco
  • 32 months follow-up

• NO NEW HIV INFECTIONS

Always working?

- 2 cases of transmission by multi-resistant virus
- 1 unexplained case in the AMPrEP study
Can we have better options for PrEP?
DISCOVER study

A Phase 3, Randomized, Double-blind Study to Evaluate the Safety and Efficacy of Emtricitabine and Tenofovir Alafenamide (F/TAF) Fixed-Dose Combination Once Daily for Pre-Exposure Prophylaxis in Men and Transgender Women Who Have Sex With Men and Are At Risk of HIV-1 Infection

• N= 5,000

• Inclusion Criteria:
  • MSM and TGW (male at birth) who have at least one of the following:
  • condomless anal intercourse with at least two unique male partners in the past 12 weeks (partners must be either HIV-infected or of unknown HIV status)
  • documented history of syphilis in the past 24 weeks
  • documented history of rectal gonorrhea or chlamydia in the past 24 weeks
  • Adequate renal function
  • Adequate liver and hematologic function

Sponsored by: Gilead Sciences
Pros and Cons

- Less toxicity
  - Kidney
  - Bone

- But...
  - Start up syndrome
  - No efficacy of TAF shown for “on-demand” PrEP
  - Cost
Maraviroc

- HPTN 069/ACTG 5305: Phase II study of Maraviroc-based regimens for HIV PrEP in MSM
  - 5 seroconversions
  - 4 associated with undetectable or low drug levels
- HPTN 069/ACTG A5305: Phase II study of Maraviroc-containing regimens for HIV PrEP in United States women
  - No seroconversions

- Oral single-dose Maraviroc does not prevent ex vivo HIV infection of rectal mucosa in healthy HIV-1 negative human volunteers in tissue explants (Coll J et al. CROI 2016, Poster 964)
HPTN 076

Phase II Safety and Acceptability of an Investigational Injectable Product, TMC278 LA, for Pre Exposure Prophylaxis (PrEP)

- Long-Acting formulation of Rilpivirine vs. placebo
- N= 136 women at low risk for HIV infection
- Oral phase during 4 weeks, followed by 8 week intervals injections
- Ongoing follow-up

Sponsored by: Division of AIDS, US National Institute of Allergy and Infectious Diseases
Role of Integrase Inhibitors for PrEP

- Raltegravir
- Elvitegravir
- Dolutegravir
- Long-Acting injectable Cabotegravir
HPTN 077

A Phase IIa Safety, Tolerability and Acceptability Study of an Investigational Injectable HIV Integrase Inhibitor, GSK1265744, for PrEP in HIV Uninfected Men and Women

• Long-Acting formulation of Cabotegravir vs. placebo
• N= 194 men and women at low risk for HIV infection
• Oral phase during 4 weeks, followed by 8 or 12 week interval injections
• Results to be presented at IAS 2017

Sponsored by: Division of AIDS, US National Institute of Allergy and Infectious Diseases
ECLAIR: Phase 2A Safety and PK Study of Cabotegravir LA in HIV-Uninfected Men

Martin Markowitz,1 Ian Frank,2 Robert M. Grant,3 Kenneth H. Mayer,4 David A. Margolis,5 Krischan J. Hudson,5 Britt S. Stancil,6 Susan L. Ford,6 Alex R. Rinehart,5 William R. Spreen5

1The Aaron Diamond AIDS Research Center, an affiliate of the Rockefeller University, New York, NY; 2Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; 3Institute of Virology & Immunology, Gladstone Institutes, San Francisco, CA; Department of Medicine, University of California, San Francisco, CA; 4The Fenway Institute, Fenway Health, Boston, MA; Beth Israel Deaconess Medical Center, Boston, MA; Harvard Medical School, Boston, MA; 5ViiV Healthcare, Research Triangle Park, NC; 6FAREXEL International (formerly employed by GlaxoSmithKline), Research Triangle Park, NC

23rd Conference on Retroviruses and Opportunistic Infections: February 22-25, 2016; Boston, MA
ECLAIR study

• Primary objective:
  • To evaluate the safety and tolerability of CAB LA injection

• Study population:
  • Men at low risk for HIV infection (at least 1 casual sex partner in the past 24 months, no more than 3 within 3 months of screening)
ECLAIR Study Design

Phase IIa, randomized, multi-site, 2-arm, double-blinded study in men at low risk of acquiring HIV

<table>
<thead>
<tr>
<th>Oral phase</th>
<th>Injection phase</th>
<th>Follow-up phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>W5</td>
<td>W41</td>
</tr>
<tr>
<td>W2</td>
<td>W17</td>
<td>W53</td>
</tr>
<tr>
<td>W4</td>
<td>W29</td>
<td>W65</td>
</tr>
<tr>
<td></td>
<td></td>
<td>W77</td>
</tr>
<tr>
<td></td>
<td></td>
<td>W81</td>
</tr>
</tbody>
</table>

- CAB 30 mg PO QD
- Placebo PO QD
- CAB LA 800 mg IM Q12W
- Saline placebo IM Q12W
- Follow-up

Note: not all scheduled study visits are shown in this study schematic.

PO, orally; Q12W, every 12 weeks; QD, once daily.

Markowitz et al. CROI 2016; Boston, MA. Abstract 106.

23rd Conference on Retroviruses and Opportunistic Infections; February 22-25, 2016; Boston, MA
RESULTS

- CAB concentrations lower than expected

- 2 seroconversions:
  - one in the placebo arm
  - one 24 weeks after the final injection
## Table 1. ISR Symptoms in the Injection Phase

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>PBO (N=21)</th>
<th>CAB (N=94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with any ISR event, n (%)</td>
<td>12 (57)</td>
<td>87 (93)</td>
</tr>
<tr>
<td>Total number of injections, n</td>
<td>62</td>
<td>272</td>
</tr>
</tbody>
</table>

ISR events by maximum toxicity, n/N (%)^{b}

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>PBO</th>
<th>CAB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>17/62 (27)</td>
<td>250/272 (92)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>16 (26)</td>
<td>122 (45)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>1 (2)^c</td>
<td>101 (37)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>27 (10)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>4 (6)</td>
<td>26 (10)</td>
</tr>
<tr>
<td>Swelling</td>
<td>0</td>
<td>22 (8)</td>
</tr>
<tr>
<td>Nodule/Bump</td>
<td>0</td>
<td>21 (8)</td>
</tr>
<tr>
<td>Warm to touch</td>
<td>0</td>
<td>19 (7)</td>
</tr>
<tr>
<td>Bruising</td>
<td>1 (2)</td>
<td>16 (6)</td>
</tr>
<tr>
<td>Induration</td>
<td>0</td>
<td>15 (6)</td>
</tr>
</tbody>
</table>

^{a}Only ISRs with ≥10 events reported are presented. ^{b}Percentages are out of the total number of injections. With the exception of Grade 3 pain, all ISRs listed were Grade 1-2. ^{c}Subject was misdosed with CAB on the third injection.
Figure 2A. SMQ at Week 30: How Much P/D Have You Experienced With This Medication?

Figure 2B. SMSQ-s at Week 30: Satisfaction With Side Effects of Study Medication

Murray M et al. CROI 2016; Boston, MA. Poster 471
Tolerability and Acceptability of Cabotegravir LA Injection: Results From the ECLAIR Study

Figure 3. SMSQ-s: How Satisfied Would You Be to Continue With Your Present Form of Study Medication?

<table>
<thead>
<tr>
<th></th>
<th>Satisfied</th>
<th>Neutral</th>
<th>Dissatisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 6</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PBO (N=21)</td>
<td>86%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAB (N=97)</td>
<td>88%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Week 18</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PBO (N=21)</td>
<td>95%</td>
<td></td>
<td>8%</td>
</tr>
<tr>
<td>CAB (N=91)</td>
<td>81%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Week 30</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PBO (N=20)</td>
<td>100%</td>
<td></td>
<td>8%</td>
</tr>
<tr>
<td>CAB (N=86)</td>
<td>79%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Murray M et al. CROI 2016; Boston, MA. Poster 471
Experiences with long acting injectable (LAI) cabotegravir (CAB) as PrEP: a qualitative study among men participating in a Phase II study (ECLAIR) in New York and San Francisco

- 30 in-depth interviews including 26 trial participants and 4 clinical care providers (June-August 2015)
- Almost all participants experienced some level of side effects associated with LAI CAB, mostly temporary injection site soreness. Yet, all reported being satisfied and interested in continuing LAI CAB
- Participants described the convenience of LAI CAB and perceived advantage of not having to worry about adhering to a daily oral. Participants described the peace of mind associated with LAI CAB given the possibility for missed oral doses
- MSM participants, particularly in San Francisco, described a surrounding culture whereby MSM were expected to be on PrEP to be seen as safe sexual partners
- Providers expressed the need for guidelines to assist patients in choosing when to start, stop and/or transition between oral PrEP and LAI CAB

Kerrigan D et al. AIDS 2016, Durban
Experiences with long acting injectable (LAI) cabotegravir (CAB) as PrEP: a qualitative study among men participating in a Phase II study (ECLAIR) in New York and San Francisco

“Oh totally, especially if they’re already on PrEP, on Truvada, I would definitely recommend this as an alternative. And the fact that they don’t have to remember to take it every day, I think would make a big difference and people probably don’t need to be convinced very hard, or very much, to make the switch”. - MSM, SF

“I’m thinking why not do injectable PrEP because there could be that one night where you’re not even planning for that, you’re like oh wait I have to take pills for a week before I even consider doing this. Because for men who have sex with men, being spontaneous is there. The hookup culture is so prevalent, where I think it’s just smarter to take injectable PrEP.” - MSM, SF

Kerrigan D et al. AIDS 2016, Durban
HPTN 083

A Phase 2b/3 Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), for Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women who have Sex with Men

• N = 4,500
• Inclusion criteria:
  • Any condomless receptive anal intercourse in the 6 months prior to enrollment
  • More than five partners in the 6 months prior to enrollment (regardless of condom use and HIV serostatus)
  • Any stimulant drug use in the 6 months prior to enrollment
  • Rectal or urethral gonorrhea or chlamydia or incident syphilis in the 6 months
• Recruiting participants

Sponsored by: Division of AIDS, US National Institute of Allergy and Infectious Diseases

Source:
HPTN 083: Study Visit Schema

Blinded Injections & Safety Visits

Arm A
- CAB LA 600 mg IM at Weeks 5, 9, and Q8 Weeks thereafter Plus Daily Oral Placebo for TDF/FTC

Arm B
- Daily Oral TDF/FTC Plus Placebo for CAB LA IM at Weeks 5, 9, and Q8 Weeks thereafter

Step 1
- Oral Phase

Step 2
- Injection/Oral Phase

Step 3
- Open Label Follow Up

Key
- Cabotegravir oral
- Cabotegravir Oral placebo
- TDF/FTC oral
- TDF/FTC placebo
- Cabotegravir Injection
- Cabotegravir placebo injection

Source: HPTN HIV Prevention Trials Network
Pros and **Cons** of LA CAB

- Difficulty in withdrawing therapy for adverse effects once administered

- **Adverse events**
  - Injection site reactions: pain

- **Potential risk for development of resistance**
  - Long pharmacokinetic tail with low drug concentrations

- Barriers if only prescribed and delivered at hospitals
- Online survey
- 15,880 participants
- 12 European countries
- 15 June to 15 July 2016
- Recruited through dating apps/websites, Facebook and Twitter

85% felt PrEP should be delivered in a comprehensive prevention package (regular HIV testing, STI testing and treatment, peer support, etc.).

- Community-based health centers
- General Practitioner’s

were identified as the most appropriate places for future PrEP delivery.

Available at:
Pros and Cons

• Adherence
  • Better adherence expected

• Satisfaction
  • High in spite of SIR

• Preferences by potential users
  • “peace of mind”
Pros and Cons

• Reduced toxicity
  • less toxicity of Integrase Inhibitors
  • lower doses
  • avoidance of first-pass metabolism

• Indirectly contributing to decrease the transmission by improving adherence in HIV-infected individuals (TasP)
CONCLUSIONS

• Daily oral PrEP has proven effective in randomized clinical trials and implementation studies in MSM, discordant couples and PWID, but less so in other populations

• Efficacy strongly related to adherence

• LA injections may overcome barriers to adherence

• LA injections could be preferred by many potential users

• CAB is a potent Integrase Inhibitor that has been formulated into a LA nanosuspension

• LA CAB is a promising option for PrEP