Long-acting Antivirals – Where Are We Headed? Are We Ready?

Carl W. Dieffenbach, Ph.D.
Director
Division of AIDS, NIAID
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Global HIV Statistics | 2017

People living with HIV in 2016 36.7 million [30.8 million – 42.9 million]
New HIV infections in 2016 1.8 million [1.6 million – 2.1 million]
Deaths due to AIDS-related illnesses in 2016 1 million [830,000 – 1.2 million]
Cumulative number who have contracted HIV 76.1 million
Cumulative deaths from HIV-related causes 35 million [28.9 million – 41.5 million]
# FDA-Approved Antiretroviral Drugs

<table>
<thead>
<tr>
<th>NRTIs</th>
<th>Pharmacokinetic Enhancers</th>
<th>Multi-Class Combinations</th>
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<tbody>
<tr>
<td>6 multi-drug combinations</td>
<td>Stavudine (TDF, TAF)</td>
<td>Atripla</td>
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<tr>
<td>Abacavir</td>
<td>Tenofovir</td>
<td>Complera</td>
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<td>Didanosine</td>
<td>Zidovudine</td>
<td>Descovy</td>
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<td>Emtricitabine</td>
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<td>Genvoya</td>
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<td>Lamivudine</td>
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<td>Juluca</td>
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<table>
<thead>
<tr>
<th>NNRTIs</th>
<th>PI</th>
<th>Fusion Inhibitor</th>
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<tbody>
<tr>
<td>Delavirdine</td>
<td>Atazanavir</td>
<td>Enfuvirtide</td>
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<td>Efavirenz</td>
<td>Darunavir</td>
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<td>Etravirine</td>
<td>Fosamprenavir</td>
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<td>Nevirapine</td>
<td>Indinavir</td>
<td></td>
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<tr>
<td>Rilpivirine</td>
<td>Lopinavir/ Ritonavir</td>
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<tr>
<th>Integrase Inhibitors</th>
<th>Entry Inhibitor</th>
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<tr>
<td>Bictegravir</td>
<td>Maraviroc</td>
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<tr>
<td>Elvitegravir</td>
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<tr>
<td>Dolutegravir</td>
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<td>Raltegravir</td>
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<td>Nelfinavir</td>
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<tr>
<td>Ritonavir</td>
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<td>Saquinavir</td>
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<td>Tipranavir</td>
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Source: FDA, March 2018
Life Expectancy of Recently Diagnosed Asymptomatic HIV-infected Patients Approaches that of Uninfected Individuals

A. van Sighem et al. on behalf of the ATHENA National Observational Cohort Study

- **Life expectancy** for HIV-infected patients (without AIDS) aged 25 yrs at six months postinfection

  **Men:** an additional 52.7 yrs (versus 53.1 yrs in general population)

  **Women:** an additional 57.8 yrs (versus 58.1 yrs in general population)
What Problems are Long-acting, Sustained Release Formulations Solving?

What New Problems are They Creating?
Adherence to drug regimens is of critical concern for chronic conditions.

Failure to adhere leads to low level viral replication and ultimately to the accumulation of HIV drug resistance (HIVDR) mutations.

Global prevalence of HIVDR is rising, mainly due to resistance to NNRTI.

Use of integrase strand transfer inhibitors (INSTIs) has been transformational.

Moving to long-acting is supposed to be the next revolution.
Long-acting, Less Frequent Dosing

- Does less frequent dosing lead to improved adherence?
  - From the contraception literature, the answer is yes
- What are the options for delivery?
  - Oral dosing weekly or biweekly will soon be feasible—will this be an improvement?
- Current injectables are bimonthly, TTP have this evolving to twice yearly
- For prevention, a single ARV will suffice but this may not be true for bNABs
- For therapeutics, three agents with matched pharmacology, no overlapping safety concerns are required—not there yet
Long-acting ARVs – Current Agents in Development

- Cabotegravir  INSTI (Phase 3)
- MK-8591  NRTTI (Phase 1, 2)
- Rilpiverine  NNRTI (Phase 3)
- Albuvirtide  Fusion Inhibitor (Phase 3)
- Ibalizumab  CD4 Blocker FDA Approved (TROGARZO)
- bNAb
Example: Elimination of Adherence Concerns

- Single dose delivery for post-exposure prophylaxis
Adherence – My Bottom Line

- Long-acting, sustained-release formulations do not eliminate the adherence challenges, they increase the urgency of getting patients back for redosing.
- Need to build in a window of time where patients can be safely redosed.
Managing the Safe and Effective Zone with Long Acting Formulations

What is the upper limit of drug tolerance?

With the long tail of a decay curve, resistance is a concern.
Pipeline for Prevention and Therapy
HPTN 083 Design

- **Phase 2b/3 trial CAB vs. daily oral TDF/FTC in men and transgender women who have sex with men**
  - Data on CAB activity support two-arm study design
  - Biases and challenges with daily oral tablets require double-blind double-dummy, non-inferiority design in men since a level of TDF/FTC efficacy in MSM can be estimated

- **Primary hypotheses**
  - CAB-based prevention will be non-inferior to a strategy of TDF/FTC-based prevention for HIV-uninfected MSM and TGW
HPTN 084 Design

- Phase 2b/3 trial CAB vs. daily oral TDF/FTC in men and transgender women who have sex with men
  - Data on CAB activity support two-arm study design
  - For women a double-blinded, double dummy superiority design has been implemented

- **Primary hypothesis**
  - CAB-based prevention will be superior to a strategy of TDF/FTC-based prevention for HIV-uninfected women
Limitations of Current Clinical Trial Designs

- The FDA is still requiring an oral lead in for all injectable and implantable formulations to evaluate the frequency of serious, early drug reactions.

- Long-term transition to initiation of treatment and prevention regimens with administration of the injectable or implantable is essential.
Long-Acting Injectable ARVs for Maintenance Therapy

Long-Acting Antiviral Agents for HIV Treatment
DA Margolis and M Boffito

Cabotegravir+Rilpivirine as Long-Acting Maintenance Therapy: LATTE-2 Week 32 Results
DA Margolis, W Spreen et al.
Protocol in Development: ACTG 5357

- Proof-of-concept study of long-acting cabotegravir (integrase inhibitor) + VRC01LS

- Goal: Maintain viral suppression in HIV-infected adults whose virus has been suppressed with conventional ART

- Collaborators: ViiV/GSK, NIAID VRC, DAIDS, ACTG

- Protocol chairs: Babafemi O. Taiwo, M.D., M.B.B.S. (Northwestern), Pablo Tebas, M.D. (Penn)
bNAbs
Potency and Breadth of HIV-1 Neutralizing mAbs

<table>
<thead>
<tr>
<th>Resistance (%)</th>
<th>CD4bs</th>
<th>V3-glycan</th>
<th>V12 apex</th>
<th>MPER</th>
</tr>
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<tr>
<td>13</td>
<td>20</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>46</td>
<td>38</td>
<td>27</td>
<td>54</td>
<td>2</td>
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Multi-clade virus panel (n=208)

IC80 Titer (μg/ml)

IC80 Titer (μg/ml)
Broader Coverage: Two Antibodies cover > 98% of Diverse Strains Globally

Passive Antibody Prevention as PrEP
HVTN703/704; HPTN 081/085

AMP = Antibody Mediated Prevention Studies
Phase 2b Efficacy (proof-of-concept)

Can a passively infused monoclonal antibody prevent HIV-1 infection in high risk adults

Chairs: Lawrence Corey, HVTN
        Myron S. Cohen, HPTN

Co-chairs: Srilatha Edupuganti
           Nyaradzo Mgodi

Mike Cohen (HPTN)  DAIDS NIAID  Larry Corey (HVTN)
VRC01 Concentrations Over Time

- Follow monthly
- Associate serum level with breakthrough infection

Associate antibody serum level with breakthrough infection

30 mg/kg
16 ug/ml
10 mg/kg
4 ug/ml

VRC01 Conc (mg/mL)

Weeks post infusion

Weeks since infusion
30 mg/kg group
10 mg/kg group
Sanofi/VRC Tri-specific Antibody

CODV-Fab (Sanofi)

• All 3 Fabs active
• Normal IgG PK in macaques
• GMP manufacturing in progress

Trispecific broadly neutralizing HIV antibodies mediate potent SHIV protection in macaques
Ling Xu1, Amarendra Pegu, Z-Y Yang et al (Science 2017),
Conclusions/Questions

- For long-acting prevention, maintaining and enhancing adherence is essential
- To help address adherence challenges, a range of methods of delivery and duration of coverage will be important
- For prevention, we will see a steady improvement and refinement in products
- For therapy, additional agents need to advance so that LA three drug combinations can be evaluated