HIV 2016: Recent Clinical Breakthroughs and What’s on the Horizon

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Disclosures: grant support from EBSCO, Gilead, Roche, Merck, Viiv

Thanks to Drs. Jared Baeten, Katie Bar, Alvaro Borges, Heather Bradley, Joe Eron, Jon Li, Shahin Lockman, James Whitney and Neha Patel for assistance with slides
Learning Objectives

Following completion of this session, learners will be better able to:

• identify recent breakthroughs in preventing HIV

• identify recent advances in the care of HIV-infected patients.

• evaluate ongoing efforts to improve future care of HIV-infected patients.
Case

- 40 yo F, originally from Haiti, admitted to the hospital with worsening odynophagia
- HIV antibody test is positive. CD4 count 75. HIV RNA 250,000 copies/mL

- She asks you 3 questions:
  - “How could this have been prevented?”
  - “How should I be treated?”
  - “Can my HIV be cured?”
HIV 2016:
Where are we now, where do we need to be?

• Breakthroughs in Prevention
• Breakthroughs in Treatment
• What’s on the Horizon – Can we cure HIV?
HIV: At Home and Around the World

New infections in 2014: 45,000

New infections in 2014: 2 million

US: 1.2 million living with HIV

Globally: 36.9 million living with HIV
HIV Prevention:
Bending the Epidemic Curve

- Who’s at Risk
- Getting to 90:90:90
- Pre-exposure prophylaxis (PrEP)
- Women-controlled prevention: Dapivirine Vaginal Ring

“How could this have been prevented?”
Estimated Lifetime Risk of HIV in US

- CDC analysis
- Lifetime risk: 1 in 99
- Marked discrepancies by race, risk group and geography

DC: 1 in 13; GA: 1 in 51; CT: 1 in 139; MA: 1 in 121; ND 1 in 670

Hess et al, CROI 2016, # 52
Ending the Epidemic with ART?

- Treatment and virologic suppression markedly reduce transmission\(^1,2\) ("Treatment as prevention")
- Modeling suggests that treating a high proportion of infected patients could end the epidemic by 2030\(^3\)
- UNAIDS Treatment Targets:

\[ \text{THE TREATMENT TARGET} \]

\[
\begin{array}{c}
\text{diagnosed} & 90\% \\
\text{on treatment} & 90\% \\
\text{virally suppressed} & 90\%
\end{array}
\]

\[=73\% \text{ suppressed}\]

Percentage of HIV+ People with HIV RNA Suppression

UNAIDS Target: 73% of all HIV+ people achieving viral suppression

Adapted from Levi J, et al. IAS 2015. MOAD0102.
Reducing HIV Transmissions in US: Expansion of Testing, Retention and Treatment

- >90% of transmissions are from undiagnosed HIV-infected patients or from those diagnosed but not retained in care
- CDC projects 265,000 HIV infections in next 5 years at current testing and treatment rates
- Achieving National HIV/AIDS Strategy goals (85% linked, 90% retained, 80% suppressed) → avert >185,000 infections
- Need to:
  - Expand testing (eg, inpatient and outpatient order sets)
  - Improve retention: innovative studies (eg Project HOPE)
  - Accelerate PrEP roll-out

Skarbinski et al, JAMA Int Med, 2015;
http://www.cdc.gov/nchhstp/newsroom/images/2016_croi_four_scenarios_graph.jpg
## PrEP 2016

### Randomized trials of TDF/FTC or TDF PrEP

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEX</td>
<td>MSM and transgender women in 6 countries (n=2499)</td>
<td>44% reduction in acquisition</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>Serodiscordant couples in Africa (n=4747)</td>
<td>67-75% reduction in acquisition</td>
</tr>
<tr>
<td>TDF2</td>
<td>Heterosexual adults in Africa (n=1219)</td>
<td>62% reduction in acquisition</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>Women in Africa (n=2120)</td>
<td>No HIV risk reduction</td>
</tr>
<tr>
<td>VOICE</td>
<td>Women in Africa (n=5029)</td>
<td>No HIV risk reduction</td>
</tr>
</tbody>
</table>

### Effectiveness even higher in real-world settings

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Effectiveness</th>
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<tbody>
<tr>
<td>PROUD</td>
<td>High-risk MSM in UK (n=545)</td>
<td>86% reduction in acquisition</td>
</tr>
<tr>
<td>TDF2-OLE</td>
<td>Men, women in Africa (n=229)</td>
<td>0 infections</td>
</tr>
<tr>
<td>Kaiser</td>
<td>People (mostly MSM) in San Francisco (n=657)</td>
<td>0 infections</td>
</tr>
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<50% ever took study drug
Limitations of TDF/FTC PrEP

- Importance of adherence with oral dosing
- Potential for renal and bone toxicity, especially with higher exposure (e.g. daily dosing)

Greater decline in eGFR with higher drug exposure

Decline in bone mineral density after starting TDF/FTC is reversible

Gandhi M et al, CROI 2016, #883; Grant R et al, CROI 2016, #48LB
New PrEP?

• Improve adherence:
  – Vaginal rings

• Decrease toxicity:
  – Maraviroc?
  – Tenofovir alafenamide (TAF)?
Women-controlled Prevention: Dapivirine Vaginal Ring

• High rate of HIV acquisition among women in Africa highlights need for women-controlled long-acting agents
• Vaginal rings containing hormones are licensed for contraception
• Dapivirine, an NNRTI, in vaginal ring studied in two phase 3 randomized trials (ASPIRE and RING) in Africa
• Women inserted ring containing dapivirine or placebo monthly

Dapivirine Vaginal Ring Reduces HIV Acquisition

- In ASPIRE, HIV incidence 27% lower in dapivirine gp than in placebo group
- >21 yo: 56% lower rate
- ≤ 21 yo, no protection (reduced adherence)
- Similar results in RING trial
- Demo projects needed to assess effectiveness in open-label settings

Alternative Agents for PrEP: Not Yet Ready for Prime Time

- **Maraviroc**: alone or with FTC or TDF compared to TDF/FTC: all 5 incident HIV infections occurred in MVC groups (drug level low or absent in several cases)

- **Tenofovir alafenamide (TAF)**:  
  - Lower plasma tenofovir (TFV) levels than with TDF → less renal, bone toxicity  
  - Protected macaques from infection  
  - In women who received a single dose, >50% had undetectable TFV-DP in vaginal or rectal tissue

HIV Prevention 2016

• Where are we now?
  – Multiple effective methods of preventing HIV: condoms, male circumcision, treatment as prevention, oral PrEP

• Where do we need to be?
  – Diagnose and treat many more people (95-95-95 by 2030)
  – Make PrEP easy to adhere to, accessible and controlled by those who most need it: long-acting formulations, alternative agents
“How should I be treated”?

Breakthroughs in Treatment

• State of the ART, 2016
  – When to start
  – What to start
  – Improving ART

*Where Do We Come From? What Are We? Where Are We Going?*
  – Paul Gauguin
When to START?

HIV-infected adults
CD4 count >500

- START enrolled 4685 pts from 35 countries
- Primary endpoint: serious AIDS-related event, serious non-AIDS-related event, or death
- May 2015: DSMB recommended offering ART to all participants
- Median age: 36 yrs; mean follow-up 3 yrs.
- Median baseline CD4 count 651. Deferred group: median CD4 count at ART initiation, 408

Immediate ART (n=2326)
Deferred ART (n=2359)
(CD4 Declined to <350 or AIDS-related event)

Insight START Study Group, NEJM, 2015
Immediate ART Prevents AIDS- and Non-AIDS Related Events

**Number of Serious Events**

- **Composite Endpoint**
  - Deferred ART (n=2359): 96
  - Immediate ART (n=2326): 42
  - 57% Reduction ($P<0.001$)

- **AIDS-Related Events**
  - Deferred ART (n=2359): 50
  - Immediate ART (n=2326): 14
  - 72% Reduction ($P<0.001$)

- **Non-AIDS Related Events**
  - Deferred ART (n=2359): 47
  - Immediate ART (n=2326): 29
  - 39% Reduction ($P=0.04$)

**Key Observations**

- **TB, KS, lymphoma** — most common AIDS-related events — all less frequent in immediate-ART group
- **Cancer rates** (combining AIDS/non-AIDS) lower in immediate-ART group
- **Decreased bacterial infections, improved quality of life** in immediate ART group

“When should I start treatment?”
→ You should start now!

**ART recommended for all HIV+ individuals, regardless of CD4 cell count**

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<tr>
<th>CD4 Cell Count</th>
<th>Recommendation</th>
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<tr>
<td>≤ 350</td>
<td>Al</td>
</tr>
<tr>
<td>350-500</td>
<td>Al</td>
</tr>
<tr>
<td>&gt;500</td>
<td>Al</td>
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</tbody>
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Al: strong recommendation, data from randomized clinical trials

**WHO on Sept 30, 2015: “Treat-all”**
“How should I be treated?”

First-line Treatment

**Two NRTIs**
- TDF/FTC
- or
- TAF/FTC
- or
- Abacavir/3TC

**Plus**

**Integrase inhibitor:**
- Raltegravir, Elvitegravir/cobi*,
  - Dolutegravir**
- or

**Boosted PI:**
- Ritonavir-boosted darunavir

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TDF: tenofovir disoproxil fumarate
TAF: tenofovir alafenamide

*Coformulated with TDF/FTC and TAF/FTC
**Coformulated with ABC/3TC
Tenofovir alafenamide (TAF)

- TAF: pro-drug of tenofovir that concentrates in cells, converted to tenofovir (TFV)
- TAF: 90% lower plasma TFV levels compared to TDF (tenofovir disoproxil fumarate)
- TAF compared to TDF for initial therapy:

![Diagram showing clinical trial data](image)

n=1733

TAF vs. TDF

- Virologic efficacy: E/C/F/TAF non-inferior to E/C/F/TDF
- TAF associated with:
  - Smaller decrease in bone mineral density (BMD)
  - Smaller decrease in eGFR
  - Less proteinuria
  - However, greater increases in cholesterol, LDL, HDL, TGs (identical changes in TC:HDL)

- Similar results in switch studies
- TAF approved down to eGFR > 30
- TAF active against HBV

Elvitegravir/c/FTC/TAF – Nov. 2015
FTC/TAF – April 2016
Darunavir/c/FTC/TAF – phase III

Individualizing Treatment

• Reducing pill burden: many regimens are 1-2 pills/day

• Addressing comorbidities:
  – Kidney disease: avoid TDF; favor ABC or TAF
  – Osteoporosis: avoid TDF; favor ABC or TAF
  – CV disease: prefer TDF or TAF

• Avoiding drug interactions:
  – Avoid PI- or cobi-containing regimen if patient on CYP3A4-metabolized medication, e.g. inhaled or injectable steroids
Long-acting Injectable Cabotegravir plus Rilpivirine Maintains Virologic Suppression

- Cabotegravir (CBG) and rilpivirine (RPV): nanosuspension formulations; half-lives of months
- VL <50 at wk 32
  - q 8 wk IM: 95%
  - q 4 wk IM: 94%
  - Oral: 91%
- 1 virologic failure in IM arm (no resistance; no detectable RPV)
- Injection site reactions mild (median 3 days)
- Patient satisfaction high

Latte-2 (n=309)

Induction Period

Week -20

Week -4

Day 1

CBG + ABC/3TC

IM CBG and LA-RPV q4 wk
n=115; 2 x 2 ml IG

IM CBG and LA-RPV q8 wk
n=115; 2 x 3 ml IG

Cont Oral Regimen
n=56

Wk 48 analyses will inform selection of dose for phase III studies.

HIV Treatment 2016

• **Where are we now?**
  – Multiple effective treatment options: Individualize therapy based on patient characteristics

• **Where do we need to be?**
  – Many infected people not receiving effective therapy
    • Stigma, substance use, mental illness, poor access to care
    • Need strategies to improve adherence – tear down barriers to care. Injectables? Implants? Vectored delivery?
  – Drugs that can be used safely and effectively for decades
    • Reduce renal, hepatic, bone, and neurologic toxicity
    • Minimal or no drug interactions (important as patients age)
  – New classes that overcome drug resistance as it emerges
“Can my HIV be cured?”

On the Horizon – Can We Cure HIV?
Why Should We Try to Cure HIV?

- Although life expectancy has improved, HIV+ people don’t live as long as HIV-negative people -- perhaps because of persistent inflammation, immune activation and associated end-organ diseases (CV disease, stroke, neurocognitive dysfunction, and other complications).
- Cost, side effects, impact on quality of life of indefinite ART.
- Need to maintain high level of adherence to ART to prevent drug-resistant virus.
- Stigma, discrimination, fear of transmission, isolation.

Adapted from slide from Joe Eron, MD.
What do we need to do to cure HIV?
Reducing the HIV Reservoir

Latently infected cells in patients on suppressive ART are “invisible” to the immune system.

Goals of current studies:

1. Develop agents to reverse latency and induce HIV expression to make cells vulnerable to clearance and

2. Develop interventions that enhance immune responses to clear infected cells
Strategy 1: Reverse Latency

- Latent HIV is transcriptionally silent. One mechanism may be histone deacetylation → “closed” chromatin
- Histone deacetylase (HDAC) inhibitors (vorinostat, romidepsin, panobinostat) induce viral expression but have little effect on HIV reservoir → inducing HIV expression alone may not kill infected cells

We need to understand how to more effectively reverse HIV latency.
May need to combine latency reactivating agents with immune enhancing interventions.

Single-dose vorinostat induces HIV expression

Mean 4.8-fold induction (range 1.5 - 10 fold)

• Toll-like receptor-7 (TLR-7)
  – Increases immune responses
  – Induces HIV expression

• TLR-7 agonist in SIV-infected macaques on suppressive ART:

  2 of 9 animals did not have viral rebound for > 3 m. after ART stopped

Whitney J et al, CROI 2016, #95LB.
Strategy 2: Improve Killing of Infected Cells:
Broadly neutralizing antibodies (bNAb)

- Potent and broad neutralization of a large variety of HIV isolates.
- Can be engineered to increase half-life or improve immune function
  - Bispecific antibodies, DARTs
- Entering clinical trials for prevention, treatment, reservoir reduction.

May need to combine antibodies that mediate killing of infected cells with latency reversing agents that induce HIV expression.

Bar K et al, CROI 2016, #32LB. Chun TW et al, CROI 2016, #311LB.
Can we cure HIV?

“It's tough to make predictions, especially about the future”
Can we cure HIV?

• Thus far, HIV has been cured only under extraordinary circumstances → HIV cure remains an aspirational goal.

• Studies are underway to test new ways of reversing latency and clearing infected cells. Combination approaches are likely to be needed.

• Increased knowledge of mechanisms of HIV persistence, how to accurately measure the HIV reservoir and how to reduce the reservoir are needed if we are to cure HIV.

• Given safety of antiretroviral therapy and uncertainties regarding risks of new interventions, cure studies must adhere to the highest scientific and ethical standards.
Bringing it All Back Home

- HIV transmission rates remain unacceptably high at home and around the world: expansion of testing, treatment, and PrEP needed to bend the epidemic curve
- Current PrEP is effective but has limitations (adherence challenges, toxicities). New prevention methods, including vaginal rings, long-acting injectables, and alternative agents under development
- ART continues to improve, with less toxic agents and (hopefully) long-acting options
- New approaches to prevent, treat and, perhaps, cure HIV continue to advance
World AIDS Day, 2013:

... the United States should be at the forefront of new discoveries into how to put HIV into long-term remission without requiring lifelong therapies -- or, better yet, to eliminate it completely.

Patient: One day I’d love to say, “I used to have HIV.”