What’s New in HIV?
More Than You Think!

Nathan Cummins, MD
Consultant in Infectious Diseases
Assistant Professor of Medicine
Mayo Clinic Rochester

2016 Mayo Clinic 90th Annual Clinical Reviews
Disclosures

- Financial: None
- Off label usage: None
Epidemiologic Trends
Globally, 34.0 million people living with HIV in 2011

- Including **3.3 million children** less than 15 years

- **2.5 millions new infections** (including 330 000 children); 22% less than in 2001

- **1.7 million people died of AIDS** in 2011

- Each day almost 7,000 people newly infected

- Each day 3,950 more people on antiretroviral therapy

http://www.who.int/hiv/en/
Diagnoses of HIV Infection among Adults and Adolescents, by Sex and Transmission Category, 2014—United States and 6 Dependent Areas

**Males**

N = 36,138

- Male-to-male sexual contact: 82%
- Injection drug use (IDU): <1%
- Other: <1%
- Heterosexual contact: 5%

**Females**

N = 8,471

- Male-to-male sexual contact and IDU: <1%
- Heterosexual contact: 13%
- Other: 87%

**Note.** Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. All displayed data have been statistically adjusted to account for reporting delays and missing transmission category, but not for incomplete reporting.

- Heterosexual contact with a person known to have, or to be at high risk for, HIV infection.
- Includes hemophilia, blood transfusion, perinatal exposure, and risk factor not reported or not identified.
Diagnoses of HIV Infection among Adults and Adolescents, by Sex and Race/Ethnicity, 2014—United States and 6 Dependent Areas

Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. All displayed data have been statistically adjusted to account for reporting delays, but not for incomplete reporting.

a Hispanics/Latinos can be of any race.
Rates of Diagnoses of HIV Infection among Adults and Adolescents, by Age at Diagnosis, 2010–2014—United States

Note: Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. All displayed data have been statistically adjusted to account for reporting delays, but not for incomplete reporting.
Treatment trends

Treatment is prevention.
Prevention is treatment.
Expanding role of cART

• DHHS and IAS guidelines recommend cART for all HIV-infected persons regardless of CD4 T cell count.

• Recently published WHO guidelines recommend cART for all HIV-infected persons with
  • CD4 T cells of 500 cells/mm³ or less for adults, adolescents and older children
  • Or with active tuberculosis (TB) disease who are living with HIV; people with both HIV and hepatitis B virus (HBV) infection with severe chronic liver disease; HIV-positive partners in serodiscordant couples; pregnant and breastfeeding women and children younger than five years of age, all regardless of CD4 T cell count.
  • 26 million people eligible (9.7 million currently on therapy)
START Study: The initiation of antiretroviral therapy in HIV-positive adults with a CD4+ count of more than 500 cells per cubic millimeter provided net benefits over starting such therapy in patients after the CD4+ count had declined to 350 cells per cubic millimeter.

N Engl J Med
Volume 373(9):795-807
August 27, 2015
Antiretroviral Therapy for the Prevention of HIV-1 Transmission

- HPTN 052 - The early initiation of ART led to a sustained decrease in genetically linked HIV-1 infections in sexual partners.

N Engl J Med
Volume 375(9):830-839
September 1, 2016
• Partners-PrEP - In this study of 4758 HIV-1–serodiscordant heterosexual couples in Kenya and Uganda, daily antiretroviral prophylaxis (with tenofovir or emtricitabine–tenofovir) in the HIV-1–negative partner significantly decreased the risk of HIV infection.

N Engl J Med
Volume 367(5):399-410
August 2, 2012
Persons Living with Diagnosed or Undiagnosed HIV Infection
HIV Care Continuum Outcomes, 2012 — United States and Puerto Rico

N = 1,218,400

- 87.2% Diagnosed
- 39.1% Received medical care
- 36.2% Prescribed ART
- 30.2% Viral Suppression

National HIV Surveillance System: Estimated number of persons aged ≥13 years living with diagnosed or undiagnosed HIV infection (prevalence) in the United States at the end of 2012. The estimated number of persons with diagnosed HIV infection was calculated as part of the overall prevalence estimate.

Medical Monitoring Project: Estimated number of persons aged ≥18 years who received HIV medical care during January to April of 2012, were prescribed ART, or whose most recent VL in the previous year was undetectable or <200 copies/mL—United States and Puerto Rico.

www.cdc.gov
Trends in Survival and Complications
PLHIV on treatment can have a nearly, but not completely, normal life expectancy.

<table>
<thead>
<tr>
<th>Expected years of life remaining at age 20 among HIV-infected and HIV-uninfected individuals during 2007-2011, overall and by modifiable risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expected years of life remaining at age 20 (95% confidence interval)</td>
</tr>
<tr>
<td>HIV-infected</td>
</tr>
<tr>
<td>Overall</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HIV-infected and initiated ART with CD4 ≥500 cells/μL</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-uninfected</td>
</tr>
<tr>
<td>Overall</td>
</tr>
<tr>
<td>No hepatitis B or C</td>
</tr>
<tr>
<td>No drug/alcohol abuse</td>
</tr>
<tr>
<td>No smoking</td>
</tr>
</tbody>
</table>

P-values were obtained from z-tests.

Increasing recognition of metabolic complications in HIV

- Viral replication
- Adverse drug effects
- Chronic Inflammation
- Accelerated aging

"Metabolic" complications
-or-
HIV-associated, non-AIDS conditions
HIV and Accelerated Aging

- Immunosenescence
- Cardiovascular complications
- Age-related malignancies
- Cognitive decline
- Frailty
- Low BMD
- Fragility fractures


Molecular Cell 2016 62, 157-168 DOI: (10.1016/j.molcel.2016.03.019)
## Smoking and HIV

<table>
<thead>
<tr>
<th>Factor</th>
<th>Lost Life-Years</th>
<th>PAR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIV among never smokers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(never smoking HIV patients vs never smoking controls)</td>
<td>5.1 (4.4–5.8)</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Smoking among controls</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(smoking controls vs never smoking controls)</td>
<td>3.6 (3.1–4.0)</td>
<td>34.4</td>
</tr>
<tr>
<td><strong>Smoking among HIV patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(smoking HIV patients vs never smoking HIV patients)</td>
<td>12.3 (11.5–13.0)</td>
<td>61.5</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; PAR, population-attributable risk.
Tenofovir alafenamide (TAF) for initial treatment

Figure 4. Changes in spine and hip bone mineral density through week 48E/C/F/TAF=elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide. E/C/F/TDF=elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate.


*Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials*

*Lancet, Volume 385, Issue 9987, 2015, 2606–2615*

http://dx.doi.org/10.1016/S0140-6736(15)60616-X
TAF as switch therapy

Figure 2. Changes in osteopenia and osteoporosis (T-score defined) from baseline to week 48. Differences between regimens were significant (p<0.0001). TAF=tenofovir alafenamide. TDF=Tenofovir disoproxil fumarate.

Anthony Mills, Jose R Arribas, Jaime Andrade-Villanueva, Giovanni DiPerri, Jan Van Lunzen, Ellen Koenig, Richard Elion, Matthias Cavassini, Jose Valdez Madruga, Jason Brunetta, David Shamblaw, Edwin DeJesus, Chloe Orkin, David A Wohl, Indira Brar, Jeffrey L Stephens, Pierre-Marie Girard, Gregory Huhn, Andrew Plummer, Ya-Pei Liu, Andrew K Cheng, Scott McCallister

Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in antiretroviral regimens for virologically suppressed adults with HIV-1 infection: a randomised, active-controlled, multicentre, open-label, phase 3, non-inferiority study

Lancet ID, Volume 16, Issue 1, 2016, 43–52

http://dx.doi.org/10.1016/S1473-3099(15)00348-5
Treat “nearly all patients with Chronic Hepatitis C”

October 2015

Hepatitis C Guidance Underscores the Importance of Treating HCV Infection: Panel Recommends Direct-Acting Drugs for Nearly All Patients with Chronic Hepatitis C

Experts at the American Association for the Study for Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) have updated HCVguidelines.org, a website developed in collaboration with the International Antiviral Society-USA (IAS-USA) to provide up-to-date guidance on the treatment of hepatitis C virus (HCV). Based on expanded “real-world” experience with the tolerability and efficacy of newer HCV medications, the section on “When and in Whom to Initiate HCV Therapy” no longer includes tables that offer recommendations on how to prioritize patients for treatment.
<table>
<thead>
<tr>
<th></th>
<th>Simeprevir</th>
<th>Sofosbuvir</th>
<th>Ledipasvir</th>
<th>Daclatasvir</th>
<th>Paritaprevir, ritonavir, ombitasvir plus dasabuvir (PrOD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritonavir-boosted atazanavir</td>
<td>No data</td>
<td>No data</td>
<td>Ledipasvir ↑; atazanavir ↑&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Daclatasvir ↑&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Paritaprevir ↑; atazanavir ↑</td>
</tr>
<tr>
<td>Ritonavir-boosted darunavir</td>
<td>Simeprevir ↑; darunavir ↔</td>
<td>Sofosbuvir ↑; darunavir ↔</td>
<td>Ledipasvir ↑; darunavir ↔</td>
<td>Daclatasvir ↑; darunavir ↔</td>
<td>Paritaprevir ↓↑; darunavir ↓</td>
</tr>
<tr>
<td>Ritonavir-boosted lopinavir</td>
<td>No data</td>
<td>No data</td>
<td>No data&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Daclatasvir ↑; lopinavir ↑</td>
<td>Paritaprevir ↑; lopinavir ↔</td>
</tr>
<tr>
<td>Ritonavir-boosted tipranavir</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Simeprevir ↓; efavirenz ↔</td>
<td>Sofosbuvir ↔; efavirenz ↔</td>
<td>Ledipasvir ↓; efavirenz ↓&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Daclatasvir ↓&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No pharmacokinetic data:</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>Simeprevir ↔; rilpivirine ↔</td>
<td>Sofosbuvir ↔; rilpivirine ↔</td>
<td>Ledipasvir ↔; rilpivirine ↔</td>
<td>No data</td>
<td>Paritaprevir ↑; rilpivirine ↑</td>
</tr>
<tr>
<td>Etravirine</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>Daclatasvir ↓&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No data</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>Simeprevir ↔; raltegravir ↔</td>
<td>Sofosbuvir ↔; raltegravir ↔</td>
<td>Ledipasvir ↔; raltegravir ↔</td>
<td>No data</td>
<td>PrOD ↔↑ raltegravir</td>
</tr>
<tr>
<td>Cobicistat-boosted elvitegravir</td>
<td>No data</td>
<td>Cobicistat ↑&lt;sup&gt;a&lt;/sup&gt;; sofosbuvir ↑</td>
<td>Cobicistat ↑; ledipasvir ↑&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>No data</td>
<td>No data</td>
<td>Ledipasvir ↔; dolutegravir ↔</td>
<td>Daclatasvir ↔; dolutegravir ↑</td>
<td>Paritaprevir ↓; dolutegravir ↑</td>
</tr>
<tr>
<td>Maraviroc</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate</td>
<td>Simeprevir ↔; tenofovir disoproxil fumarate ↔</td>
<td>Sofosbuvir ↔; tenofovir disoproxil fumarate ↔</td>
<td>Ledipasvir ↔; tenofovir disoproxil fumarate ↑</td>
<td>Daclatasvir ↔; tenofovir disoproxil fumarate ↔</td>
<td>PrOD ↔; tenofovir disoproxil fumarate ↔</td>
</tr>
</tbody>
</table>

hcvguidelines.org
The search for an HIV cure
Current status of HIV cure

- Can occur (Berlin patient)
- Lots of ideas
- Many under early stage clinical development
- Significant hurdles
  - Latent viral reservoir
  - Incremental risk/benefit ratio
  - Regulatory
Curative strategies

Gene therapy
- Low accessibility
- Oncogenic potential?

Vaccination / immune based Rx
- Genotype specific?
- Toxicity concerns
- Curative vs preventative

Reactivation
- May not work alone
- May require multiple Rx
- Low cost, high accessibility

“To reach individuals living with HIV around the world, a curative regimen must be effective, simple, safe, and scalable,” Anthony Fauci.
Original Article

Gene Editing of CCR5 in Autologous CD4 T Cells of Persons Infected with HIV

Pablo Tebas, M.D., David Stein, M.D., Winson W. Tang, M.D., Ian Frank, M.D., Shelley Q. Wang, M.D., Gary Lee, Ph.D., S. Kaye Spratt, Ph.D., Richard T. Surosky, Ph.D., Martin A. Giedlin, Ph.D., Geoff Nichol, M.D., Michael C. Holmes, Ph.D., Philip D. Gregory, Ph.D., Dale G. Ando, M.D., Michael Kalos, Ph.D., Ronald G. Collman, M.D., Gwendolyn Binder-Scholl, Ph.D., Gabriela Plesa, M.D., Ph.D., Wei-Ting Hwang, Ph.D., Bruce L. Levine, Ph.D., and Carl H. June, M.D.

N Engl J Med
Volume 370(10):901-910
March 6, 2014
• Broadly neutralizing antibodies
  • Rare, naturally occurring anti-HIV antibodies that neutralize a broad range of viral isolates
• Potential applications
  • Passive immunization
  • Reverse engineering antigens to induce production of BNAb through vaccination
  • PEP
  • Adjunctive therapy to ART or cure regimens
Shock and Kill Hypothesis

The Depsipeptide Romidepsin Reverses HIV-1 Latency *In Vivo*

Ole S. Søgaard, Mette E. Graversen, Steffen Leth, Rikke Olesen, Christel R. Brinkmann, Sara K. Nissen, Anne Sofie Kjaer, Mariane H. Schleimann, Paul W. Denton, William J. Hey-Cunningham, Kersten K. Koelsch, Giuseppe Pantaleo, Kim Krogsgaard, Martin Tolstrup

Published: September 17, 2015 • http://dx.doi.org/10.1371/journal.ppat.1005142
What does the future hold?

- More vaccine trials
- Expanded role of PrEP
- Long acting injectable ARTs
- Universal statin therapy for PLHIV
- Early bisphosphonate therapy at ART initiation to prevent bone loss
- Democratization of HIV care
Questions & Discussion

cummins.nathan@mayo.edu