CO-CHAIRS

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Birmingham, Alabama

December 9-11, 2018 • National Harbor, MD
Gaylord National Hotel and Convention Center

This conference is funded by the Health Resources and Services Administration (HRSA) of the US Department of Health and Human Services (HHS) under grant number U1OHA28686 (AIDS Education and Training Centers National Coordinating Resource Center) awarded to the François-Xavier Bagnoud Center from the Rutgers University School of Nursing with a sub award to the International Antiviral Society–USA (IAS–USA) to sponsor this CME activity.
Sunday—December 9, 2018


- HIV 101. Fundamentals of HIV Infection
  David H. Spach, MD

- HIV 101. Applications of Antiretroviral Therapy
  Michael S. Saag, MD

- HIV 101. Clinical Manifestations of HIV: Prevention, Diagnosis, and Management
  Stephen P. Raffanti, MD, MPH

Plenary Lectures

- HRSA’s HIV/AIDS Bureau Updates
  Laura W. Cheever, MD, ScM

- Update on Cure Research for HIV Infection
  Robert F. Siliciano, MD, PhD
• Key Updates From Recent HIV Research Conferences  
  Melanie A. Thompson, MD

• Sexually Transmitted Infections: Gonorrhea, Chlamydia, Trichomoniasis, and Human Papillomavirus  
  Kimberly A. Workowski, MD

• The Great Imitator Revealed: Syphilis  
  Jeffrey D. Klausner, MD, MPH

• Issues in Liver Health and Disease: Overview for the Nonhepatologist  
  Kenneth E. Sherman, MD, PhD

**Monday—December 10, 2018**

**Plenary Lectures**

• Infectious and Other Complications of Immunobiologic Agents Used by Individuals With HIV Infection  
  Peter Chin-Hong, MD

• Investigational Approaches to Antiretroviral Therapy: New Strategies and Novel Agents  
  Joseph J. Eron, Jr, MD

• Elimination of Hepatitis C in Individuals With HIV Infection  
  David L. Thomas, MD, MPH

• Treating HIV in 2018—Interactive Cases From the Clinicians  
  Michael S. Saag, MD

• Cardiovascular Disease Management in HIV Infection  
  Turner Overton, MD

• Antiretrovirals for HIV Prevention: Optimizing the Use of PrEP and PEP in 2018  
  Raphael J. Landovitz, MD, MSc

• The Intersection of Intimate Partner Violence and HIV: Detection, Disclosure, and Implications for Treatment Adherence  
  Tami P. Sullivan, PhD

• Youth and HIV: Are We on Track to End This Epidemic?  
  Donna C. Futterman, MD

**Tuesday—December 11, 2018**

**Plenary Lectures**

• Top 10 Things to Know About the Older Patient With HIV Infection  
  Howard Libman, MD

• We Are Going to Need a Bigger Wrench: Improving Linkage and Retention in HIV Care  
  Carlos del Rio, MD

• New Developments in Opportunistic Infections: Interactive Case-Based Panel Discussion  
  Stephen P. Raffanti, MD, MPH

• Elimination of Pediatric HIV/AIDS: Where Have We Come From and Where Are We Going?  
  Karen P. Beckerman, MD, FACOG

• Opioid Withdrawal, Opioid Substitution Treatment, and HIV Infection  
  R. Douglas Bruce, MD, MA, MS
General Information

WELCOME AND GOALS
Welcome to the 2018 CLINICAL CONFERENCE at the Ryan White Conference on HIV Care & Treatment. The goals of the 2018 CLINICAL CONFERENCE are to:

- Provide key updates in HIV medicine for practitioners in Ryan White HIV/AIDS Program (RWHAP)-funded clinics and programs
- Facilitate networking and collaborations among attendees
- Equip attendees with information and tools for sharing this key information with clinic staff and colleagues

OVERVIEW
The 2018 CLINICAL CONFERENCE provides state-of-the-art updates on research, care, and treatment issues in the medical management of HIV infection for experienced HIV clinical decision makers.

Attendance is limited to 600 HIV physicians, nurse practitioners, and physician assistants in RWHAP-funded clinics and programs. A limited number of spots are reserved for RNs and PharmDs who are the primary clinical decision makers in their RWHAP-funded clinics or programs.

CONFERENCE FUNDING
This conference is funded by the Health Resources and Services Administration (HRSA) of the US Department of Health and Human Services (HHS) under grant number U10HA28686 (AIDS Education and Training Centers National Coordinating Resource Center) awarded to the François-Xavier Bagnoud Center from the Rutgers University School of Nursing with a sub award to the International Antiviral Society—USA (IAS—USA) to sponsor this CME activity

MEALS AND INCIDENTALS
Attendees are responsible for their transportation expenses to and from National Harbor, MD, hotel stay costs, meals, and all other expenses. Coffee and meals will NOT be provided. Please check with your project officer about expenses that are covered by your RWHAP award.

WEBSITE
For additional information about the 2018 CLINICAL CONFERENCE please visit the website at https://www.iasusa.org/event/rwcc2018

WEBCASTS AND PODCASTS
Webcasts and podcasts of the plenary lectures will be available within 10 business days following the conclusion of the conference. Please note: workshop presentations will not be recorded.

POSTCONFERENCE MATERIALS AND RESOURCES
As you know, an important goal of the 2018 CLINICAL CONFERENCE is to prepare attendees to be able to update their clinical colleagues who were not able to attend the conference. To that end, a Key Slide Training Guide with PowerPoint slides and webcasts of each plenary lecture will be available after the 2018 CLINICAL CONFERENCE. About 2 months after the conference, you will be asked to summarize the postconference updates and trainings that you have conducted for you clinic staff and colleagues.

DRUG AND PRODUCT DISCLAIMER
This activity may contain information about the investigational uses of drugs or products that are not approved by the US Food and Drug Administration. Please consult full prescribing information before using any medication or product mentioned in this activity.

The views and opinions expressed are those of the faculty and do not necessarily represent the opinions or recommendations of the IAS—USA.

WI-FI ACCESS AT THE CONFERENCE
Complimentary Wi-Fi access is provided at the Gaylord National Hotel and Convention Center. Network information is as follows:

1. Your Internet Network ID is: Ryan White 2018
2. Your password is: ryanwhite
   (case sensitive)
REGISTRATION AND INFORMATION DESK HOURS

The hours of the 2018 CLINICAL CONFERENCE registration and information desk, located on the Second Level outside the Maryland Ballroom are as follows:

- Saturday, December 8: 3:00 PM – 7:00 PM
- Sunday, December 9: 7:00 AM – 6:30 PM
- Monday, December 10: 7:30 AM – 6:00 PM
- Tuesday, December 11: 7:30 AM – 2:30 PM

BADGES

When you arrive at the 2018 CLINICAL CONFERENCE, please check in at the registration desk located on the Second Level outside the Maryland Ballroom to sign in and to pick up your name badge and CLINICAL CONFERENCE badge holder. You must have your name badge in order to access the conference and workshop rooms.

CONFERENCE ETIQUETTE

Please ensure all cell phones and pagers are off or are placed in SILENT mode. No flash photography is permitted in session rooms.

CLIMATE AND CLOTHING

The average temperature in National Harbor in December is a high of 48°F and a low of 33°F, and the average precipitation is 3 inches. Please check area forecasts before departing for the conference. Attire for the conference is business casual. Meeting rooms have the tendency to be quite cool; we advise you to dress accordingly.

CHILD CARE AND NEW MOTHERS

Children are not permitted in the meeting rooms, and child care will not be provided by the conference. If you are travelling with young children, please make arrangements in advance for child care during the conference sessions. There are nanny services available in the DC area. The Gaylord has recommended White House Nannies (301-654-1242), as they have worked on the property previously.

Private and semi-private areas are available for nursing mothers. Please go to the IAS-USA Office (Maryland 1-2) and speak with a staff member about the options.

NETWORKING AND SMALL MEETINGS

Space is available in Chesapeake 2 for networking and small meetings. Tables are on a first-come, first-serve basis. The space cannot be reserved.
The goals of the Health Resources and Services Administration (HRSA) of the US Department of Health and Human Services are to improve access to quality care and services, strengthen the health workforce, build healthy communities, and improve health equity. HRSA carries out 100+ programmatic initiatives designed to increase access to health care, improve quality and safeguard the health and well-being of the nation’s most vulnerable populations.

The HIV/AIDS Bureau (HAB) within HRSA is the largest single source of federal funding for outpatient HIV/AIDS care, serving low-income, uninsured and underinsured individuals. HAB administers the Ryan White HIV/AIDS Program. The Ryan White HIV/AIDS Program supports programs designed to increase access to care and treatment for underserved populations, reducing perinatal transmission, improving the health status of people with HIV disease, and improving the quality of life for those affected by the epidemic.

HAB has identified the following principles that guide its mission and programs: the HIV/AIDS epidemic is growing among traditionally underserved and hard-to-reach populations; the quality of emerging HIV/AIDS therapies can make a difference in the lives of people living with HIV disease; changes in the economics of health care are affecting the HIV/AIDS care network; and policy and funding are increasingly determined by outcomes. Around these principles, HAB has developed programs that focus on the most important issues in HIV/AIDS, including access to HIV/AIDS treatment, culturally-competent care for HIV as a chronic disease, treatment adherence, HIV risk reduction in the context of HIV primary care, data and evaluation, measuring outcomes, and reaching the most vulnerable populations affected by HIV.

The National HIV/AIDS Strategy (NHAS) for the United States: Updated to 2020 NHAS has 4 primary goals: 1) reducing new infections, 2) increase access to care and improve health outcomes for people living with HIV, 3) reduce HIV-related health disparities and health inequities, and 4) achieve a more coordinated national response to the HIV epidemic. HRSA/HAB works with its recipients to support and implement these goals.

This clinical conference further supports the principles of HAB and is funded under a cooperative agreement with HRSA.

The AIDS Education and Training Center National Coordinating Resource Center (AETC NCRC) provides education, capacity building, and other training resources for regional AETCs along with the coordination and organization of AETC network communities of practice to support the mission to offer timely, high-quality, state-of-the-science information to health care professionals working with existing and emerging populations affected by HIV. The AETC Program is a Ryan White HIV/AIDS program consisting of a network of AETC programs: 8 regional AETCs, 3 national AETCs, and 5 health profession training programs. This project is supported by the Health Resources and Services Administration (HRSA) of the US Department of Health and Human Services (HHS) under grant number U10HA28686 awarded to the François-Xavier Bagnoud Center from the Rutgers University School of Nursing.

The mission of the International Antiviral Society–USA (IAS–USA) is to improve the prevention, treatment, care, and quality of life for people with or at risk of HIV, hepatitis C virus (HCV), or other viral infections through high-quality, relevant, balanced, and needs-oriented education and information for practitioners and scientists who are actively involved in medical care and research.
International Antiviral Society–USA (continued)

Board of Directors

Nonstaff board members serve in a volunteer capacity and are not compensated for their roles in oversight and governance of the organization. As part of its duties, the board oversees the needs assessment, design, development, and evaluation of all educational programs. Visit www.iasusa.org/about/ias-usa-board-of-directors/ for a list of Board of Directors members.

Improving the Management of HIV Disease®: An Advanced CME Live Course in HIV Pathogenesis, Antiretrovirals, and Other Selected Issues in HIV Disease Management

- These full-day courses are designed for HIV specialists who are actively involved in HIV disease management or research. Nationally and internationally recognized faculty provide advanced-level presentations with balanced, timely, scientifically rigorous, and clinically relevant information about HIV disease management. These courses are held in several US cities each year. Visit www.iasusa.org/activities/live-courses/hiv-courses/ for upcoming courses.

A Small-Group Workshop on Evolving Strategies in Hepatitis C Management

- These half-day CME workshops are designed to improve the clinical care of people with hepatitis C. The small-group interactive workshops are limited to 50 clinical decision makers (physicians, nurse practitioners, PharmDs, and physician assistants). A limited number of spots are reserved for registered nurses who are the primary clinical decision makers in their clinics or practices. Visit www.iasusa.org/activities/live-courses/hepatitis-c-virus-courses/ for upcoming workshops.

Webinars

The IAS–USA offers state-of-the-art CME webinars led by nationally and internationally recognized faculty.

Each webinar lasts 75 to 90 minutes and addresses a current topic in HIV or HCV infection prevention and management and the treatment of concomitant conditions. Archived webinars now offer CME credit.

Conference on Retroviruses and Opportunistic Infections

The IAS–USA partners with the Conference on Retroviruses and Opportunistic Infections (CROI) Foundation to sponsor CROI, the most important HIV research conference worldwide. Webcasts, electronic posters, and abstracts from CROI 2014, CROI 2015, CROI 2016, CROI 2017, and CROI 2018 are available at www.CROIconference.org.

CROI 2019 will be held in Seattle, Washington, from March 4 to March 7, 2019.

Topics in Antiviral Medicine™

The IAS–USA publishes the peer-reviewed journal Topics in Antiviral Medicine™ 4 to 6 times a year as a resource for physicians and other health care practitioners who are actively involved in the care of patients with HIV or other viral infections. The journal offers CME credit and is indexed on Index Medicus/MEDLINE. To be added to our email list, please create an account on the IAS–USA website at www.iasusa.org. See the FAQ page for additional information on how to create an account. Subscriptions are complimentary and available in electronic format.

Treatment and Testing Guidelines

The IAS–USA sponsors the development of clinical practice guidelines. The guidelines are written by independent volunteer panels of researchers and clinicians from around the world and focus on management issues for which definitive evidence is lacking. Guidelines for viral load testing, antiretroviral therapy, behavioral and biomedical HIV prevention, HIV drug resistance testing, cytomegalovirus infection, and metabolic complications have been published. Recommendations on the use of antiretroviral drugs for treatment and prevention of HIV infection in adults, by the IAS–USA Antiretroviral Guidelines Panel, are published biannually in the Journal of the American Medical Association. Visit www.iasusa.org/resources/guidelines for updates.

recommendations of the International Antiviral Society–USA panel. JAMA. 2018;320[4]:379-396. JAMA offers free access to the paper at https://jamanetwork.com/journals/jama/article-abstract/2688574. The paper includes updated recommendations for the use of antiretroviral therapy in adults with established HIV infection, including when to start treatment, initial regimens, and changing regimens, along with recommendations for using antiretroviral drugs for preventing HIV among those at risk, including preexposure and postexposure prophylaxis.

Drug Resistance Mutations Projects
Through the HIV Drug Resistance Mutations Panel, the IAS–USA provides regular updates on the mutations associated with resistance to antiretroviral drugs. The information on relevant mutations is collected and reviewed by a panel of acknowledged leaders in the field. This information, last updated in January 2017, is available in Topics in Antiviral Medicine™, on pocket reference cards (available from the IAS–USA), and on the IAS–USA website at www.iasusa.org/resources/hiv-drug-resistance-mutations/.

Cases on the Web
Cases on the Web (COW) is a series of case-driven Internet-based CME activities sponsored by the IAS–USA to offer physicians convenient online access to enduring material and top-quality education. The COW program provides basic and advanced-level educational activities that are offered for CME credit for as long as each COW is active, after which time they remain available in the COW archive for reference use only. Visit www.iasusa.org/activities/cases-on-the-web/active-cows/ for a current list of COW activities.

Podcasts
Some past IAS–USA live CME courses are available as podcasts and may be downloaded from the IAS–USA website. Visit www.iasusa.org/resources/podcasts for details and a list of available presentations. Please note that these podcasts do not offer CME credit.

Key Slides
The IAS–USA offers a collection of downloadable key slides from presentations at conferences or past IAS–USA live courses. Presenters have selected the slides they consider the most informative and relevant. Key slides may be downloaded as PowerPoint files from the IAS–USA website at www.iasusa.org/resources/key-slides/.

For information about any of these programs, please contact the IAS–USA.
Phone: (415) 544-9400 • Fax: (415) 544-9401
E-mail: registration@iasusa.org • Website: www.iasusa.org
Conference Co-Chairs and Faculty

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The Johns Hopkins Medical Institutions
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Conference Faculty and Organizers Financial Relationships With Commercial Entities

FACULTY FINANCIAL DISCLOSURE

It is the policy of IAS–USA to ensure balance, independence, objectivity, and scientific rigor in all its educational activities. All parties with control over the content of IAS–USA activities (eg, members of the Board of Directors, Advisory Board Members, activity chairs, authors, faculty, and IAS–USA staff) are required to disclose to the organization and activity audience any financial interest or other relationship with the manufacturer(s) of any commercial product(s) or provider(s) of commercial services with interests discussed in the activity (eg, presentation or article) within the previous 12 months. Financial interests or other relationships can include receipt of grants or research support, status as employee or consultant, stock or options holder, paid lecturer, paid writer/author, or member of speakers’ bureau, of the party or of his or her spouse or partner. The ACCME defines a financial interest as an interest of any dollar amount.

The **ACCME defines** a **commercial interest** as “any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients. The ACCME does not consider providers of clinical service directly to patients to be commercial interests – unless the provider of clinical service is owned, or controlled by, an ACCME-defined commercial interest.”

It is IAS–USA policy to separate commercial promotion from its core educational and informational activities. Individuals who conduct marketing or promotional activities for commercial firms may not contribute to IAS–USA programs. A marketing or promotional activity includes any activity in which the commercial entity controls key elements, such as speaker or topic selection that could be used to serve the entity’s commercial interests (eg, speakers’ bureaus and advertorials). Individuals may not participate in most IAS–USA programs for 12 months after functioning in a promotional or marketing effort for a commercial firm. The Conference on Retroviruses and Opportunistic Infections (CROI), a research conference, does allow presenters to take part in such activities, but conflicts of interest are resolved before their CROI presentations.

IAS–USA policy requires that it resolve any real or apparent conflict of interest that may influence the development, content, or delivery of its educational activities prior to the activity being delivered to participants.

The IAS–USA has several mechanisms for resolving conflicts of interest in educational activities. If the conflict of interest cannot be resolved through these mechanisms, the party will be removed from the activity.

It is the policy of IAS–USA to publish the financial interests of all parties in control of the content of its activities on activity materials or, in cases where space is limited (eg, reprints of figures), on the IAS–USA website, through a web address printed on the activity material. This information will also be provided directly by the IAS–USA office upon request.

The IAS–USA documents the date of the disclosure along with financial relationship information. As previously stated, the information published will reflect financial conflicts incurred within the previous 12 months. Individuals who refuse to disclose financial interests will not participate in the CME activity. It should be understood that other organizations may have different policies with regard to financial conflicts and with regard to the time period covered in the disclosure of financial conflicts.

In collaborative projects (eg, publication of materials in medical literature), the IAS–USA may adhere to the additional disclosure and conflict-of-interest policies of the collaborating journal.
Below are the financial interests that faculty members of this conference have had within the past 12 months as of the date listed.

**Conference Co-Chairs**

Dr Cheever has no relevant financial affiliations to disclose. (Updated 11/28/18)

Dr Raffanti has no relevant financial affiliations to disclose. (Updated 11/28/18)

Dr Saag has received research grants and support awarded to his institution from Gilead Sciences, Inc, Merck, and Viiv Healthcare. He has also served as a consultant for Gilead Sciences, Inc, Merck, and Viiv Healthcare. (Updated 11/30/18)

**Speakers and Workshop Leaders**

Dr Beckerman has no relevant financial affiliations to disclose. (Update 11/26/18)

Dr Bruce has no relevant financial affiliations to disclose. (Updated 11/28/18)

Dr Chin-Hong has received research support from Karius. (Updated 11/15/18)

Dr del Rio has no relevant financial affiliations to disclose. (Updated 11/28/18)

Dr Eron has served as an ad hoc consultant to Janssen, Viiv Healthcare, Merck, and Gilead Sciences, Inc. His institution receives contracts for clinical research on which Dr Eron is the local principal investigator from Janssen Therapeutics, Viiv Healthcare, and Gilead Sciences, Inc. (Updated 11/19/18)

Dr Futterman has received service grants awarded to her institution from Gilead Sciences, Inc. (Updated 11/30/18)

Dr Klausner has received royalties from McGraw-Hill Education and Walters Kluwer (Updated 11/28/18)

Dr Landovitz has received research grants awarded to his institution from Gilead Sciences, Inc, and served as a consultant to Merck and Gilead Sciences, Inc. (Updated 11/29/18)

Dr Libman has no relevant financial relationships to disclose. (Updated 12/03/18)

Dr Overton has served as a consultant or advisor for Merck and Viiv Healthcare. (Updated 11/29/18)

Dr Sherman has received research grants or contracts awarded to his institution from AbbVie, Gilead Sciences, Inc, Intercept Pharmaceuticals, Inc, MedImmune, and Merck. He has served as an advisory board member or a consultant to Abbott Laboratories and Merck. He has also served on data safety monitoring boards for Watermark and Medpace. (Updated 11/17/18)

Dr Siliciano has no relevant financial affiliations to disclose. (Updated 12/03/18)

Dr Spach has no relevant financial affiliations to disclose. (Updated 11/13/18)

Dr Sullivan's spouse is employed by and holds stock and stock options in Achillion Pharmaceuticals. (Updated 11/12/18)

Dr Thomas has no relevant financial affiliations to disclose. (Updated 12/03/18)

Dr Thompson's institution has received grants for research from Bristol-Myers Squibb, CytoDyne, Frontier Biotechnologies, Gilead Sciences, Inc, GlaxoSmithKline, Merck, Roche Molecular Systems, Taimed, and Viiv Healthcare. (Updated 11/28/18)

Dr Workowski has received grants or research support from Gilead Sciences, Inc. (Updated 12/03/18)

**IAS–USA Staff**

Donna M. Jacobsen (Executive Director) has no relevant financial affiliations to disclose. (Updated 12/03/18)

**AETC NCRC Staff**

Andrea Norberg, MS, RN (Executive Director, Principal Investigator) has no relevant financial affiliations to disclose. (Updated 11/30/18)

John A. Nelson, PhD, CNS, CPNP (Program Director) has no relevant financial affiliations to disclose. (Updated 11/30/18)
SUNDAY, DECEMBER 9, 2018

**PRECONFERENCE SESSION: HIV 101. THE BASICS OF HIV PATHOGENESIS, INITIAL EVALUATION, ANTIRETROVIRAL THERAPY, AND CLINICAL MANIFESTATIONS**

8:00 – 8:15 AM  Welcome and Introduction  
Laura W. Cheever, MD, ScM

8:15 – 8:45 AM  HIV 101. Fundamentals of HIV Infection  
David H. Spach, MD

8:45 – 9:00 AM  Question-and-Answer Period

9:00 – 9:30 AM  HIV 101. Applications of Antiretroviral Therapy  
Michael S. Saag, MD

9:30 – 9:45 AM  Question-and-Answer Period

Stephen P. Raffanti, MD, MPH

10:15 – 10:30 AM  Question-and-Answer Period

10:30 – 10:45 AM  Closing Remarks

11:00 – 11:15 AM  Welcome to Day 1  
Michael S. Saag, MD

11:15 – 11:35 AM  HRSA’s HIV/AIDS Bureau Updates  
Laura W. Cheever, MD, ScM

11:35 – 11:45 AM  Question-and-Answer Period

11:45 AM – 12:15 PM  Update on Cure Research for HIV Infection  
Robert F. Siliciano, MD, PhD

12:15 – 12:25 PM  Question-and-Answer Period

12:25 – 1:55 PM  Lunch

1:55 – 2:25 PM  Key Updates From Recent HIV Research Conferences  
Melanie A. Thompson, MD

2:25 – 2:35 PM  Question-and-Answer Period

2:35 – 3:05 PM  Sexually Transmitted Infections: Gonorrhea, Chlamydia, Trichomoniasis, and Human Papillomavirus  
Kimberly A. Workowski, MD

3:05 – 3:15 PM  Question-and-Answer Period

3:15 – 3:45 PM  The Great Imitator Revealed: Syphilis  
Jeffrey D. Klausner, MD, MPH

3:45 – 3:55 PM  Question-and-Answer Period

3:55 – 4:25 PM  Issues in Liver Health and Disease: Overview for the Nonhepatologist  
Kenneth E. Sherman, MD, PhD

4:25 – 4:35 PM  Question-and-Answer Period

4:35 – 4:55 PM  Break

4:55 – 5:55 PM  Workshops
### CONCURRENT WORKSHOPS: SUNDAY, 4:55 – 5:55 PM

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<tr>
<th>S-1. Issues and Controversies in Antiretroviral Therapy (I)</th>
<th>S-5. Hepatitis C Virus Infection Management: Staging and Liver Health</th>
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<th>S-2. Issues and Controversies in Antiretroviral Therapy (II)</th>
<th>S-6. Unique Considerations for Adolescents With HIV Infection</th>
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<th>S-7. Primary Care for the HIV Practitioner</th>
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<td>Kimberly A. Workowski, MD</td>
<td>Howard Libman, MD</td>
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<td>Jeffrey D. Klausner, MD, MPH</td>
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MONDAY, DECEMBER 10, 2018

8:30 – 8:45 AM  Welcome to Day 2  
Laura W. Cheever, MD, ScM

8:45 – 9:15 AM  Infectious and Other Complications of Immunobiologic Agents Used by Individuals With HIV Infection  
Peter Ching-Hong, MD

9:15 – 9:25 AM  Question-and-Answer Period

Joseph J. Eron, Jr, MD

9:55 – 10:05 AM  Question-and-Answer Period

10:05 – 10:35 AM  Elimination of Hepatitis C in Individuals With HIV Infection  
David L. Thomas, MD, MPH

10:35 – 10:45 AM  Question-and-Answer Period

10:45 – 11:45 AM  Treating HIV in 2018—Interactive Cases From the Clinicians  
Michael S. Saag, MD

11:45 – 11:55 AM  Question-and-Answer Period

11:55 AM – 1:25 PM  Lunch

1:25 – 1:55 PM  Cardiovascular Disease Management in HIV Infection  
Turner Overton, MD

1:55 – 2:05 PM  Question-and-Answer Period

2:05 – 2:35 PM  Antiretrovirals for HIV Prevention: Optimizing the use of PrEP and PEP in 2018  
Raphael J. Landovitz, MD, MSc

2:35 – 2:45 PM  Question-and-Answer Period

2:45 – 3:15 PM  The Intersection of Intimate Partner Violence and HIV: Detection, Disclosure, and Implications for Treatment Adherence  
Tami P. Sullivan, PhD

3:15 – 3:25 PM  Question-and-Answer Period

3:25 – 3:55 PM  Youth and HIV: Are We on Track to End This Epidemic?  
Donna C. Futterman, MD

3:55 – 4:05 PM  Question-and-Answer Period

4:05 – 4:25 PM  Break

4:25 – 5:25 PM  Workshops
## CONCURRENT WORKSHOPS: MONDAY, 4:25 – 5:25 PM

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<td>Issues and Controversies in Antiretroviral Therapy (I)</td>
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<td>Controversies in PrEP Management: Making Good Decisions Without Good Data</td>
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<td>Learning Liver Lessons for Non-Liver Practitioners</td>
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<td>M-8.</td>
<td>Cardiovascular Disease Management in HIV Infection</td>
<td>Location: Maryland 5</td>
<td>Turner Overton, MD</td>
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TUESDAY, DECEMBER 11, 2018

8:30 – 8:45 AM  Welcome to Day 3  
Stephen P. Raffanti, MD, MPH

8:45 – 9:15 AM  Top 10 Things to Know About the Older Patient With HIV Infection  
Howard Libman, MD

9:15 – 9:25 AM  Question-and-Answer Period

9:25 – 9:55 AM  We Are Going to Need a Bigger Wrench: Improving Linkage and Retention in HIV Care  
Carlos del Rio, MD

9:55 – 10:05 AM  Question-and-Answer Period

10:05 – 11:05 AM  New Developments in Opportunistic Infections: Interactive Case-Based Panel Discussion  
Stephen P. Raffanti, MD, MPH

11:05 – 11:15 AM  Question-and-Answer Period

11:15 – 11:55 AM  Working Lunch (40 min to collect grab-and-go lunch)

11:55 AM – 12:25 PM  Elimination of Pediatric HIV/AIDS: Where Have We Come From and Where Are We Going?  
Karen P. Beckerman, MD, FACOG

12:25 – 12:35 PM  Question-and-Answer Period

12:35 – 1:05 PM  Opioid Withdrawal, Opioid Substitution Treatment, and HIV Infection  
R. Douglas Bruce, MD, MA, MS

1:05 – 1:15 PM  Question-and-Answer Period

1:15 – 2:15 PM  Workshops

CONCURRENT WORKSHOPS: TUESDAY, 1:15 – 2:15 PM

T-1. Issues and Controversies in Antiretroviral Therapy (I)  
Chesapeake F
Michael S. Saag, MD

T-2. Issues and Controversies in Antiretroviral Therapy (II)  
Chesapeake E
Joseph J. Eron, Jr, MD

T-3. Issues and Controversies in Antiretroviral Therapy (III)  
Maryland 3
David H. Spach, MD

T-4. Primary Care for the HIV Practitioner  
Maryland 4
Howard Libman, MD

T-5. Opioid Substitution Therapy and Addressing Chronic Pain  
Chesapeake D
R. Douglas Bruce, MD, MA, MS

T-6. Cardiovascular Disease Risk and Management  
Maryland 5
Stephen P. Raffanti, MD, MPH

T-7. Family Planning and Planning a Family: Pregnancy, Prenatal, and Postpartum Care  
Chesapeake 3
Karen P. Beckerman, MD, FACOG
The **2018 CLINICAL CONFERENCE** will provide state-of-the-art updates on research, care, and treatment issues in the medical management of HIV infection.

Upon completion of the **2018 CLINICAL CONFERENCE**, participants will be able to:

- Describe the new aspects of the Ryan White HIV/AIDS Program
- Describe new insights into HIV disease pathogenesis that impact clinical care, including opportunities for researching HIV cure
- Describe the most recent advances in antiretroviral therapy, including initial regimens, switching therapy, and investigational new drugs and approaches
- Describe the practical aspects of care for older HIV-infected patients
- Identify chronic opioid-dependent patients and develop treatment strategies for the management of these patients with opioid substitution therapy
- Apply new research data to the prevention of HIV infection, pre- and postexposure
- Describe the intersection between intimate partner violence and the increased risk of HIV infection
- Formulate state-of-the-art strategies for diagnosing and managing opportunistic infections, cardiovascular disease, and sexually transmitted infections in patients with HIV infection
- Identify the elements of the care continuum, including testing, engagement, treatment, and retention in care and their challenges
- Develop strategies for eradicating hepatitis C virus from your clinic
- Formulate treatment strategies for the management of liver-related complications

### EDUCATIONAL FORMAT

The **2018 CLINICAL CONFERENCE** will promote active participation by HIV practitioners throughout the 3 days of lectures, case-based panel discussions, workshops, and question-and-answer periods. Attendees are encouraged to bring cases and questions for discussion.

- **Lectures** provide state-of-the-art updates on timely and clinically relevant issues around HIV diagnosis and management, and management of related conditions.
- **Case presentations** outline patient histories, and attendees use an audience response system to register their diagnostic or treatment choices. Faculty members use clinical decision points in case presentations as springboards for discussing new data and current diagnostic and therapeutic topics in HIV management. Select case presentations are enhanced with a panel of experts.
- **Question-and-answer periods** give the audience, faculty, and panelists extended opportunities to review complex topics in HIV management.
- **Workshops** allow clinical decision makers to have time with experts. Each workshop is 60 minutes in length. Attendees should review their workshop assignment sheet for their individual schedule.

We encourage you to provide your comments and suggestions on the online conference evaluation and overall conference evaluation forms at [www.iasusa.org/events/rwcc2018/](http://www.iasusa.org/events/rwcc2018/)

Please note that photographing, videotaping, or audio recording presentations is not permitted. Webcasts of the lectures will be available at [www.iasusa.org/resources/webcasts/](http://www.iasusa.org/resources/webcasts/)

### ASSESSMENT OF NEEDS

The goal of the **2018 CLINICAL CONFERENCE** is to provide a comprehensive and timely overview of HIV treatment issues and current strategies in HIV medical care for practitioners in Ryan White HIV/AIDS Program, Parts A-, B-, C-, D-, and F-funded clinics/programs.

### INTENDED AUDIENCE

This is an advanced-level conference that is designed for physicians, nurse practitioners, physician assistants, and other key clinical decision makers in Ryan White HIV/AIDS Program-funded clinics and programs who are experienced in HIV medicine.
Continuing Education Credits

ACCREDITATION STATEMENT AND CME CREDITS

Physicians (MD, DO, and international equivalents) are eligible to receive CME credit for participation in the 2018 CLINICAL CONFERENCE.

The International Antiviral Society–USA (IAS–USA) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The IAS–USA designates this live activity for a maximum of 20.00 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

ABIM MOC POINTS FOR INTERNAL MEDICINE SPECIALISTS AND SUBSPECIALISTS

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 20.00 MOC points in the American Board of Internal Medicine’s (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider’s responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

NURSING CONTINUING EDUCATION CONTACT HOURS

Educational Review Systems is an approved approver of continuing nursing education by the Alabama State Nursing Association, an accredited approver by the American Nurses Credentialing Center’s Commission on Accreditation. Provider # 5-115. This program is approved for 20.00 hours of continuing nursing education.

Educational Review Systems is also approved for nursing continuing education by the state of California, the state of Florida, and the District of Columbia.

PHARMACY CONTINUING EDUCATION CONTACT HOURS

Educational Review Systems is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education. This program is approved for 20.00 hours (2.0 CEUs) of continuing pharmacy education credit. Proof of participation will be posted to your NABP CPE profile within 4 to 6 weeks to participants who have successfully completed the post-test. Participants must participate in the entire presentation and complete the course evaluation to receive continuing pharmacy education credit.

Day 1 ACPE # 0761-9999-18-331-L02-P, Day 2 ACPE # 0761-9999-18-332-L02-P, Day 3 ACPE # 0761-9999-18-333-L02-P

AMERICAN ACADEMY OF FAMILY PHYSICIANS (AAFP) CREDITS

This Live activity, 2018 CLINICAL CONFERENCE at the National Ryan White Conference on HIV Care and Treatment, with a beginning date of 12/09/2018, has been reviewed and is acceptable for up to 19.75 Prescribed credit(s) by the American Academy of Family Physicians. Physicians should claim only the credit commensurate with the extent of their participation in the activity.
CLAIMING CME CREDITS OR A CERTIFICATE OF PARTICIPATION

Obtaining CME credit, ABIM MOC points, Nursing or Pharmacy credits, or a certificate of participation will require that you complete an evaluation of the activity. After the activity has ended, a link to the evaluation form and a posttest will be activated in your IAS–USA account under My Activities.

How to Claim CME Credits and/or ABIM MOC Points

1. Go to http://www.iasusa.org/ and log in to your IAS-USA account.
2. Hover over your name and click My Activities.
3. Find the relevant activity in the table and, in the far-right column, click on the gray sunburst icon ().
4. Complete the evaluation,
5. When you get to the end of the evaluation, click Submit Form. Click Take the CME/ABIM MOC posttest to start the test. Note: Be sure to indicate whether you will be claiming ABIM MOC points, which will require a passing grade of 70%
6. After completing the posttest, you will be directed to the online claim form, where, once logged in, you will enter the requested information and then click Submit.
7. FINAL STEP: Answer "Yes" to the question Are you a licensed physician." A certificate will then be available for you to print. You can also view your certificate from your IAS–USA account under My Activities. Find the relevant activity in the table and, in the far-right column, click on the green sunburst icon (●) to print your certificate. Submit the claim form no later than 30 days after the date of the activity.

ABIM MOC points are intended for internal medicine physicians in the United States who are maintaining their ABIM certification. The points will only be awarded after the successful completion of the posttest. The ABIM will upload the points to your member account after 30 days and notify you by email when it has done so.

How to Claim Pharmacy Credits

Be sure to provide your 6 digit NABP CPE number and your date of birth on your IAS–USA profile. Your claim will not be approved without them.

1. Go to www.iasusa.org and log in to your IAS–USA account.
2. Hover over your name and click My Activities.
3. Find the relevant activity in the table and, in the far-right column, click on the gray sunburst icon (●).
4. Complete the evaluation,
5. When you get to the end of the evaluation, click Submit Form.
6. You will be directed to the online claim form, where, once logged in, you will click Submit.
7. FINAL STEP: Once you click Submit, answer “No” to the question Are you a licensed physician. A certificate will then be available for you to print. You can also view your certificate from your IAS–USA account under My Activities. Find the relevant activity in the table and, in the far-right column, click on the green sunburst icon (●) to print your certificate. Submit the claim form no later than 30 days after the date of the activity.

We work with Educational Review Systems to deliver credit to pharmacy professionals, and your credits will be posted to your NABP CPE profile directly from that organization.

How to Claim Nursing Credits

1. Go to www.iasusa.org and log in to your IAS–USA account.
2. Hover over your name and click My Activities.
3. Find the relevant activity in the table and, in the far-right column, click on the gray sunburst icon (●).
4. Complete the evaluation.
5. When you get to the end of the evaluation, click **Submit Form**.
6. You will be directed to the online claim form, where, once logged in, you will click **Submit**.
7. **FINAL STEP:** Once you click **Submit**, answer “No” to the question *Are you a licensed physician.* A certificate will then be available for you to print. You can also view your certificate from your IAS–USA account under **My Activities.** Find the relevant activity in the table and, in the far-right column, click on the **green sunburst icon** (☀️) to print your certificate.

Submit the claim form **no later than 30 days** after the date of the activity.

We work with Educational Review Systems to deliver credit to nursing professionals, and your credit notification will be emailed directly from that organization.
How to Use Poll Everywhere

SMS text messaging instructions

- Text KEYWORD “IASUSA334” to “22333” once to join the session.
- Text your answer using: 1, 2, 3, 4, or etc.
- The initial KEYWORD you text is remembered. For the next poll question, you only have to submit 1, 2, 3, etc, in your SMS text message.

Responding via the web

- During the presentation, an instructor will display a Poll Everywhere activity on-screen. The visualization will display a web address that looks like PollEv.com/iasusa334.
- From your phone, laptop, or tablet you’ll enter the web address and be taken to a screen that allows you to respond to the activity.
Learning Objectives

After attending this presentation, learners will be able to:

- Summarize events of early HIV infection
- List the sequence of laboratory markers following HIV acquisition
- Describe basic mechanisms of antiretroviral therapy

Fundamentals of HIV: Outline

- Pathogenesis of HIV Transmission and Early Infection
- Diagnosis and Management of Acute HIV
- Natural History of Untreated HIV Infection
- HIV Life Cycle and Mechanisms of ARV Medications
Pathogenesis of HIV Transmission and Early Infection

Transmission of HIV

Chronic HIV infection
HIV-Negative

HIV Quasispecies

Infection with Founder Virus
Sexual Transmission and Founder HIV: Prime Infection


**Host Cellular Receptors Involved in HIV Infection**

**HIV Sexual Transmission Usually Caused by R5-Tropic HIV**
Clinical Manifestations of Acute HIV Infection

- Fever
- Lethargy
- Myalgias
- Rash
- Headache
- Pharyngitis
- Adenopathy

Patients %

N = 160


Acute HIV: Seroconversion Window Period

Antibody Titer

Days Following HIV Acquisition

Acute (Primary) HIV: Symptomatic Disease

HIV RNA (copies/mL)

Antibody Titer

Days Following HIV Acquisition
Laboratory Diagnosis of Acute HIV

![Graph showing the timeline of HIV antibody, HIV RNA, and HIV p24 antigen levels following HIV acquisition.]

Acute HIV: Diagnosis

- **HIV-1/2 Antigen/Antibody Immunoassay**
  - Positive

- **HIV-1/HIV-2 Ab Differentiation Immunoassay**
  - HIV-1 (-)
  - HIV-2 (+)

- **HIV-1 NAT**
  - Positive

Early HIV Infection and Test Reactivity

![Graph showing the timeline of HIV RNA, 4th generation antigen-antibody, 3rd generation antibody, and Western Blot test results following HIV acquisition.]

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National Harbor, Maryland, December 9-11, 2018
Acute HIV Diagnosis (Very Early Infection)

HIV-1/2 Antigen/Antibody Immunoassay

HIV-1/HIV-2 Ab Differentiation Immunoassay

HIV-1 NAT

Source: Centers for Disease Control and Prevention, January 2018.

Acute (Primary) HIV: High Transmission Risk

- Unaware of HIV status
- High "viral load"
- Low titers of neutralizing antibodies

Homogeneity of transmission-capable HIV
Acute HIV: Partner Notification Extremely Important

Acute HIV Treatment: Urgency to Treat

- Minimize immune damage
- Limit infection of latent reservoir pool
- Prevent high risk forward transmission of HIV

Treatment of Acute HIV—ARS Question

- A 23-year old man is diagnosed with acute HIV, with an HIV RNA level of 324,000 copies/mL. An HIV genotypic drug resistance test is ordered. The decision is made to start treatment now. What ARV regimen would you recommend?
  1. Doravirine-tenofovir DF-lamivudine
  2. Dolutegravir-abacavir-lamivudine
  3. Darunavir-cobicistat-tenofovir alafenamide-emtricitabine
  4. Dolutegravir-ritpivirine
Acute HIV Treatment: Adult and Adolescent ARV Guidelines

• Treatment recommended for all with acute HIV
• Order HIV genotypic drug resistance test prior to treatment
• Can initiate ART before results of resistance test available
• Recommended Regimens (Rating AIII)
  - Boosted-Darunavir + (TDF-FTC or TAF-FTC)
  - Dolutegravir + (TDF-FTC or TAF-FTC)
• Modify regimen if need with drug resistance test results

Natural History of Untreated HIV

Early HIV Infection and Set Point
Immune Response, HIV RNA Levels, and Progression


CD4 Cell Progression Without Antiretroviral Therapy

Viremic HIV Controller
### HIV Elite Controllers

- **Graph:**
  - **Y-axis:** HIV RNA (copies/mL)
  - **X-axis:** Years
  - **Legend:**
    - Not Receiving Antiretroviral Therapy
    - Elite Controller

### Elite and Viremic Controllers

- **Graph:**
  - **Y-axis:** CD4 Cell Count
  - **X-axis:** Years
  - **Legend:**
    - Not Receiving Antiretroviral Therapy
    - Elite Controller
    - Viremic Controller

### CD4 Cell Progression Without Antiretroviral Therapy

- **Graph:**
  - **Y-axis:** CD4 Cell Count
  - **X-axis:** Years
  - **Legend:**
    - Not Receiving Antiretroviral Therapy
HIV Life Cycle and Mechanism of ARV Medications

HIV Life Cycle

Illustration: David Spach, MD

Major Antiretroviral Therapy Drug Classes

Illustration: David Spach, MD
HIV Reverse Transcription

HIV RNA → Reverse Transcriptase → HIV DNA

HIV Reverse Transcription: Conversion of HIV RNA to DNA

Nucleotides (human)

HIV DNA → Reverse Transcriptase → HIV RNA

HIV Reverse Transcription: Conversion of HIV RNA to DNA

Nucleotides (human)

Primer → Template → Reverse Transcriptase → HIV DNA
Inhibition of HIV Reverse Transcription: NRTI

Illustration: David Spach, MD

Slide 50 of 73

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Inhibition of HIV Reverse Transcription: NNRTI

Reverse Transcriptase

NNRTI Binding Pocket

Polymerase Active Site

NNRTI Inhibitor

Illustration: David Ehlert, CMI and David Spach, MD

Inhibition of HIV Reverse Transcription: NNRTI

Reverse Transcriptase

NNRTI Binding Pocket

Polymerase Active Site

NNRTI Inhibitor

Illustration: David Ehlert, CMI and David Spach, MD

Altered Polymerase Active Site

Inhibition of HIV Reverse Transcription: NNRTI

Reverse Transcriptase

NNRTI Inhibitor

Illustration: David Ehlert, CMI and David Spach, MD
HIV Integration and Integrase Strand Transfer Inhibitors (INSTIs)

Illustration: David Ehlert, CMI and David Spach, MD

HIV Integrase

HIV Integrase Dimer

C-terminal domain
N-terminal domain
Catalytic core domain
Catalytic triad

Illustration: David Ehlert, CMI and David Spach, MD

HIV Integration into Host DNA

HIV DNA
Integrase
Integrase
Host DNA

Illustration: David Spach, MD
HIV Integration into Host DNA

HIV DNA

Host DNA

HIV Integration into Host DNA: Strand Transfer

HIV DNA

Host DNA

HIV Integration into Host DNA: Proviral DNA

Proviral HIV DNA

Host DNA

Host DNA
Integrase Strand Transfer Inhibitor ("Integrase Inhibitor")

Integrase Strand Transfer Inhibitor

Integrase Enzyme Active Site

HIV Integrase

Illustration: David Ehlert, CMI and David Spach, MD

Integrase Strand Transfer Inhibitor

HIV DNA

Integrase Strand Transfer Inhibitor

Host DNA

Host DNA

Illustration: David Spach, MD

HIV Proteolytic Processing and Protease Inhibitor (PI)
HIV Protease Inhibitor

Protease Inhibitor  Block Proteolytic Cleavage  Result: Immature Virion

Fundamentals of HIV: Summary

- Pathogenesis of HIV Transmission and Early Infection
- Diagnosis and Management of Acute HIV
- Natural History of Untreated HIV Infection
- HIV Life Cycle and Mechanisms of ARV Medications

Question-and-Answer
Learning Objectives

After attending this presentation, learners will be able to select antiretroviral therapy in patients who:

- Are starting initial therapy
- Have persistently low-level viremia
- Are pregnant or considering pregnancy
- Are experiencing virologic failure / resistance
Initiate ART As Soon As Possible After HIV Diagnosis

- Rapid start (including same day as diagnosis) ART, unless that patient is not ready to commit to starting therapy
- Structural barriers should be removed
- Samples for HIV-1 RNA level; CD4 cell count; HIV genotype for NRTI, NNRTI, and PI; HLA-B*5701 testing; laboratory tests to exclude active viral hepatitis; and chemistries should be drawn before beginning ART, but treatment may be started before results are available.
- NNRTIs (possible transmitted resistance) and abacavir (without HLA-B*5701 results) should not be used for rapid ART start
- ART should be started as soon as possible (but within 2 weeks) after diagnosis of most opportunistic diseases

Question

What regimen should I use as initial therapy?
Case 1

- 48yo man presents with newly diagnosed HIV infection
- Asymptomatic
- **Initial:** HIV RNA 28,000 c/ml
  CD4 count 650 cells/ul
- Other labs are normal; HLA-B57 positive
- Genotype is Wild-type virus
- No prior medical history. Normal renal function
- Ok to start therapy if you think he should

---

HIV: Antiretroviral Therapy

- Integrase Inhibitors
- Entry Inhibitors
- Protease Inhibitors
- Nucleoside RTI
- Non-Nucleoside RTI

---

**Recommended Initial Regimens: InSTI Plus 2 nRTIs**

- Bictegravir/TAF/emtricitabine
- Dolutegravir/abacavir/lamivudine
- Dolutegravir plus TAF/emtricitabine
- (Raltegravir plus tenofovir / emtricitabine)*

*NIHS Guidelines, AIDSVu
Tenofovir DF (TDF) Versus Tenofovir Alafenamide (TAF)

- TDF = tenofovir disoproxil fumarate; TFV = tenofovir; MP = monophosphate; DP = diphosphate

Case 2

- 48 yo man presents with newly diagnosed HIV infection
- Asymptomatic except for weight loss / fatigue
- Initial: HIV RNA 760,000 c/ml
- CD4 count 21 cells/ul
- Other labs are normal; HLA-B57 negative
- Genotype is Wild-type virus
- No prior past medical history. Normal renal function
- Ok to start therapy if you think he should
The 7-8 initial regimens we'll probably be using most

| INSTI-based | • BIC/FTC/TAF  
|             | • DTG + FTC/TAF  
|             | • DTG/3TC/ABC  
|             | • DTG/3TC  
|             | • RAL + FTC/TAF (once daily) |
| PI-based    | • DRV/c + FTC/TAF |
| NNRTI-based | • ETV/FTC/TAF  
|             | • DOR/3TC/TDF |

Tenofovir and COBI Interact with Distinct Renal Transport Pathways

- The active tubular secretion of tenofovir and the effect of COBI on creatinine are modulated by distinct transport pathways in renal proximal tubules.

Tenofovir and COBI Interact with Distinct Renal Transport Pathways

- Anion Transport Pathway
  - OAT3
  - MRP4
  - Blood (Basolateral) → Urine (Apical) → Active Tubular Secretion

- Cation Transport Pathway
  - OCT2
  - H+MATE1
  - Blood (Basolateral) → Urine (Apical) → Active Tubular Secretion

Lepist E, et al. ICAAC 2011; Chicago. #A1-1724
Recommended Initial Regimens: If an InSTI Is Not Available

- Darunavir/cobicistat/TAF (or TDF)/emtricitabine*
- Darunavir boosted with ritonavir plus TAF (or TDF)/emtricitabine
- Efavirenz/TDF/emtricitabine
- Elvitegravir/cobicistat/TAF (or TDF)/emtricitabine
- Raltegravir plus TAF (or TDF)/emtricitabine
- Rilpivirine/TAF (or TDF)/emtricitabine (if pretreatment HIV RNA level is <100,000 c/mL and CD4 cell count is >200/µL)
- Fixed-dose D/c/TAF/FTC tablet approved July 2018

* Small increase in median due to blockade of Ccr secretion
  - DTI does not affect actual glomerular filtration rate (GFR)
  - Median increase in Ccr is 0.25 mL/min

Case 3

- 30 yo woman presents with newly diagnosed HIV infection
- Asymptomatic
- Initial: HIV RNA 128,000 c/ml
  - CD4 count 350 cells/ul
- Other labs are normal; HLA-B57 neg
- Genotype shows M184V and K103N mutation
- No prior medical history. No children. Does not plan to become pregnant.
- Ok to start therapy if you think she should

Recommendations for Switching for Virologic Failure

- Virologic failure should be confirmed and, if resistance is identified, a prompt switch to another active regimen
- Dolutegravir, plus 2 NRTIs (with at least 1 active by genotype) after initial treatment failure with an NNRTI
- A boosted PI plus 2 NRTIs (with at least 1 active NRTI) for initial treatment failure of an InSTI-containing regimen
- Dolutegravir plus at least 1 fully active other agent may be effective in the setting of raltegravir or elvitegravir resistance. Dolutegravir should be dosed twice daily in this setting

Laboratory Monitoring

IAS–USA Recommendations 2018
Recommended Laboratory Monitoring

▪ Pre-ART: CD4 cell count, plasma HIV-1 RNA, HAV, HBV, and HCV serologies, serum chemistries, estimated CrCl rate, complete blood cell count, urine glucose and protein, STI screening, fasting lipids
▪ Genotypic testing for RT and Pro mutations for all patients
▪ HLA-B*5701 and CCR5 tropism testing results must be confirmed prior to initiating therapy with abacavir or maraviroc, respectively.

Recommended Laboratory Assessments and Monitoring Across the HIV Care Continuum

Recommended Laboratory Monitoring (Cont.)

▪ Once HIV RNA level is <50 c/mL, monitor every 3 months until virus is suppressed for at least a year. Then, monitoring can be reduced to every 6 months if the patient maintains adherence
▪ CD4 cell counts every 6 months until counts >250/µL for at least 1 year with concomitant viral suppression. Then no longer monitor CD4 counts unless virologic suppression is lost
▪ Age- and risk-appropriate screening for STIs at various anatomical sites, anal or cervical dysplasia, TB, general health, and medication toxicity is recommended
▪ Once a viral load is >50 c/mL, repeat test within 4 weeks and reassess for adherence and tolerability
▪ Measurement of viral load at 4 to 6 weeks after starting a new ART regimen is recommended
Recommended Laboratory Monitoring (Cont.)

- Repeating assay within 4 weeks if HIV RNA level remains above the limit of quantification by 24 weeks after starting new treatment or if rebound above 50 c/mL occurs
- Tropism testing at the time of virologic failure of a CCR5 inhibitor


Question

What regimen should I use as initial therapy in a pregnant patient*?

*(or a patient considering pregnancy)

Case 4

- 30 yo woman presents with newly diagnosed HIV infection
- Asymptomatic, 2.5 months pregnant
- Initial: HIV RNA 28,000 c/ml
- CD4 count 650 cells/ul
- Other labs are normal; HLA-B57 neg
- Genotype is Wild-type virus
- No prior medical history. First pregnancy
- Ok to start therapy if you think she should
Dolutegravir in pregnancy: Background

- No fetal toxicity or teratogenicity in animal studies described in manufacturer’s submission for regulatory approval\(^1\)
- High placental transfer of DTG relative to other ARVs in an ex vivo study\(^2\)
- "Unexpected placental transfer of DTG with fetal accumulation and then slow neonatal clearance"\(^3\)
- 18 May 2018: Report of Neural tube defects in 4/426 (0.9%) babies born to women taking DTG in Botswana… compared to 14/11,173 (0.1%) non-DTG\(^4\)

DOI: 10.1056/NEJMc1807653 ; 24 July 2018

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NTD Prevalence Difference by Exposure

- NTD Prevalence Difference 2016 vs. 2012

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Question

Should I change a regimen when low level detectable virus is present?
Case 5

- 55 yo man referred to you for evaluation
- Diagnosed 18 years ago with HIV infection
- Initial: HIV RNA 936,000 c/ml
  CD4 count 70 cells/ul
- Current: HIV RNA 85 c/ml (prior value 62 c/ml)
  CD4 count 525 cells/ul
- Started on NEL/D4T/3TC; subsequently treated with
  - LOP/r / TDF/FTC,
  - EFV/FTC/ TDF (tdc).
  - Now DTG / DRV/c / 3TC
- No historical resistance tests are available

Virologic Responses on Antiretroviral Therapy

Virologic Suppression


Virologic Blip

**Case 9**

- 48 yo man presents with newly diagnosed HIV infection
- Asymptomatic except for weight loss / fatigue
- Initial: HIV RNA 160,000 c/ml
  - CD4 count 221 cells/ul
- Other labs are normal; Started on ARV Rx
- Returns for a 3 month follow up visit
- HIV RNA < 20 c/ml; CD4 390 cells/ul

**Question**

How should I counsel a patient with undetectable HIV RNA about sexual transmission risk?
**Recommendations for HIV Prevention**

- HIV-seropositive and -negative individuals should be reminded that **condoms are required to prevent acquisition of non-HIV STIs**
- Quarterly screening for asymptomatic STIs for all populations with high rates of bacterial STIs and incomplete condom use
- PrEP for populations whose annual **HIV incidence is at least 2%**
- Daily TDF/emtricitabine for men and women and transgender individuals at risk of sexual exposure and people who inject drugs
- 1-week lead-in time with daily dosing for rectal, penile, and vaginal exposures, with daily TDF/emtricitabine to ensure adequate tissue levels are achieved

---

**Question-and-Answer**
Learning Objectives

After attending this presentation, learners will be able to describe:

- The natural course of HIV-related disease
- Principles of diagnosis of most common clinical presentations
- Principles of prevention of disease
- Best resources for prevention and management of HIV related disease.

Three Decades of Treatment Issues

- **1980s**: AIDS described, PCP kills 90% of pts., clinicians develop skills in diagnosing, treating and preventing complications.
- **1990s**: First effective treatments, patients respond, death rates drop.
- **2000s**: New toxicities arise, resistance is critical, adherence issues emerge, limitations of therapy become apparent.
- **2007**: Second round of effective antiretroviral agents-integrase and CCR5 inhibitors.
- **2013**: Serious talk of “cure”.
- **2015**: PREP
Three Decades of Treatment Issues

- **1980s**: AIDS described, PCP kills 90% of pts., clinicians develop skills in diagnosing, treating, and preventing complications.
- **1990s**: First effective treatments emerge, death rates drop.
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- **2007**: Second round of effective antiretroviral agents - integrase and CCR5 inhibitors.
- **2013**: Serious talk of “cure”.
- **2015**: PREP

The most effective way to prevent HIV related disease is to control the virus.
Rachel

- A 22-year-old woman presents to clinic to establish care. She feels well.
- She tested HIV positive at a health fair 3 months ago. Had never been tested before.
- PE is unremarkable. Labs were drawn 2 months ago and are unremarkable. STI screens are negative.
- Pertinent labs: 623 cells/mm³, 34%; HIV-1 RNA is 46,232 copies/ml.

She asks if she is more likely to get sick now.
Rachel

- Rachel is in the asymptomatic stage of HIV infection.
- Her "virologic setpoint" will be set and remain relatively stable over time.
- Her CD4 count will decline about 50-100 cells/mm³/year.
- Her risk for some infections may be slightly increased compared to HIV – age matched controls:
  - MTB: increased risk of infection and active disease
  - VZV: increased risk and may have higher incidence in younger patients

Jason

- 41 year old man diagnosed with HIV infection 4 years ago. He was initially started on HAART, did well for a while then fell out of care.
- Returned to re-establish care 4 months ago and missed follow up appointment.
- Labs at that time revealed a CD4 count of 304 cells/mm³ and 17% and an HIV-1 RNA PCR of 234,211 copies/ml.
- He calls the service complaining of increased fatigue, some weight loss and chills. He reports "feeling terrible".

CD4 count >200 cells/mm³; %>14

- Goals: reassure patient that he is not currently at great risk for ADEs.
- Evaluate for non-HIV related illnesses.
- Initiate HAART if ready and all lab data is available.

CD4 count <200 cells/mm³; %<14

- Focused clinical visit looking for localized signs or symptoms.
- Aggressive Of work up based on symptoms and signs.
- May need emergent hospital based evaluation.
Preventing Disease

In addition to maintaining immune competence with effective antiretroviral therapy, prophylaxis and vaccination are essential components of HIV management.

Anthony

- 44-year-old male construction worker living in Memphis, TN who is now enrolling in care. He was diagnosed 6 years ago, had been on meds in the past but none for about 2 years. He feels well with no specific complaints.
- Labs reveal a CD4 count of 134 cells/mm$^3$ (8%). HIV 1 RNA PCR 311,232 copies/ml. HAV serology +, anti-HBc +, Toxoplasma IgG+

Preventing disease

- Recommendations for prevention of first episode of OIs are specific to HIV disease stage, prior vaccination status and geographic location.
- Recommendations for treatment of AIDS-related OIs include recs for secondary prophylaxis and maintenance therapy.
- Recommendations for discontinuing prophylaxis and restarting prophylaxis and maintenance therapy are listed separately.
- Tables 1, 2 and 4 Guidelines for the prevention and treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents.
### Opportunistic Infection

<table>
<thead>
<tr>
<th>Infection</th>
<th>Indication</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCP</td>
<td>CD4 &lt; 200 or 14%</td>
<td>Multiple options</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>CD4 &lt; 100</td>
<td>Multiple options</td>
</tr>
<tr>
<td>MTB</td>
<td>≥25% LTBI screen or contact</td>
<td>Per Protocol</td>
</tr>
<tr>
<td>MAC</td>
<td>&gt;50 CD4 cells, no active dz</td>
<td>Multiple options</td>
</tr>
<tr>
<td>S. Pneumoniae</td>
<td>All patients</td>
<td>Timing different for CD4 count</td>
</tr>
<tr>
<td>Influenza A and B</td>
<td>All patients</td>
<td>Inactivated</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Sexual exposure</td>
<td>Within 10 days</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td>CD4 &lt; 150, high risk</td>
<td>Itraconazole has high C/I</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td>CD4 &lt; 250 cells</td>
<td>Reccomended</td>
</tr>
<tr>
<td>VZV</td>
<td>CD4 &gt; 200, high risk</td>
<td>Bacitracin</td>
</tr>
<tr>
<td>HPV</td>
<td>Up to 45 years of age</td>
<td>New recommendations</td>
</tr>
<tr>
<td>HIV</td>
<td>serology</td>
<td>Epidemic considerations</td>
</tr>
<tr>
<td>Malaria</td>
<td>Travel specific</td>
<td>Same as HIV - travelers</td>
</tr>
<tr>
<td>Pneumococcus</td>
<td>CD4 &lt; 100 cells, endemic</td>
<td>Rural SE Asia</td>
</tr>
</tbody>
</table>

### Setting up the patient for successful care.

- **Effective Linkage:**
  - HIV 101, materials and time to talk;
  - Initial labs with rapid provider follow up;
    - Labs: UA, HAV, HBV, HCV, Toxoplasma, Treponemal Ab-serologies; MTB screen, urine GC/Chlamydia screen, HLA B5701, HIV-1 Genotype, CD4 count/HIV-1 RNA PCR.

- **Retention in care:**
  - Rapid initiation of HAART;
  - Patient intake navigation;
  - Follow-up on missed appointments;
  - Multiple access points for clinical care.

### Resources

- Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents
  https://aidsinfo.nih.gov/guidelines

- Regional AETCs: SEAETC.com

- HIV Essentials Paul Sax (2017)
Question-and-Answer
HRSA’s HIV/AIDS Bureau Updates
Laura W. Cheever, MD, ScM
Associate Administrator
Chief Medical Officer
HIV/AIDS Bureau
Health Resources and Services Administration
Rockville, Maryland

HRSA HAB Vision and Mission

Vision
Optimal HIV/AIDS care and treatment for all.

Mission
Provide leadership and resources to assure access to and retention in high quality, integrated care, and treatment services for vulnerable people living with HIV/AIDS and their families.

HRSA HAB Priorities

• Achieve the goals of NHAS 2020/PEPFAR 3.0
• Build leadership
• Enhance partnerships
• Support integration
• Increase data utilization
Viral Suppression among RWHAP Clients, by State, 2010 and 2016—United States and 2 Territories

Viral suppression: ≥1 OAHS visit during the calendar year and ≥1 viral load reported, with the last viral load result <200 copies/mL.

Puerto Rico and the U.S. Virgin Islands.


Listening Session
Tuesday, December 11
5:00-6:30 pm
Chesapeake 10/11/12

Update Overview

• 2019 Budget
• RWHAP policy
• Clinical activities
HRSA RWHP FY 2019 Full-Year Appropriation - $2,318,781

Part A 28% $655,876
Part B 57% $1,315,005
ADAP $900,313
Part C 9% $201,079
Part D 3% $75,088
Part F - AETC 1% $33,611
Part F - Dental 1% $13,122
SPNS 1% $25,000

HRSA RWHP Appropriations History FY 1991-FY 2019

Update Overview

• 2019 Budget
• RWHP policy
  • Policy Clarification Notices
  • Viral suppression messaging
  • RWHP Part D Reimagine
• Clinical activities
Policy Clarification Notices Updates

- Updates reflect recipient and stakeholder feedback
- Updates reduce administrative burden
- Revised two PCNs
  - PCN #15-02: Clinical Quality Management Policy Clarification Notice
  - PCN #16-02: Ryan White HIV/AIDS Program Services: Eligible Individuals and Allowable uses of Funds
- Released two new PCNs
  - PCN #18-01: Services for Clarifications Regarding the Use of Ryan White HIV/AIDS Program Funds for Health Care Coverage Premium and Cost Sharing Assistance
  - PCN #18-02: The Use of Ryan White HIV/AIDS Program Funds for Core Medical Services and Support People Who are Incarcerated

Revised Policy Clarification Notices

- PCN #15-02: Clinical Quality Management Policy Clarification Notice
  - Emphasizes useful and meaningful measures
  - Number of measures based on clients receiving service
  - Revision reduces administrative burden
- PCN #16-02: Ryan White HIV/AIDS Program Services: Eligible Individuals and Allowable uses of Funds
  - Eight service categories were revised to further clarify current policy
  - Revisions address many frequent questions about categories
  - Outreach Services category revisions replace 12-01
  - Explicit regarding telehealth as an allowable modality

2018 Policy Clarification Notices

- PCN #18-01: Clarifications Regarding the Use of Ryan White HIV/AIDS Program Funds for Health Care Coverage Premium and Cost Sharing Assistance
  - Provides clarifications related to Medicare premiums and cost sharing
  - Aligns and clarifies current policy from three PCNs
- PCN #18-02: The Use of Ryan White HIV/AIDS Program Funds for Core Medical Services and Support Services for People Who are Incarcerated
  - Clarifies conditions in which recipients may provide RWHP services
  - Services may be provided on a transitional basis in prisons
  - Services may be provided on a short-term basis in jails
HRSA HAB Approved Viral Suppression Messages

- Several large studies have demonstrated that people living with HIV (PLWH) who have consistent viral suppression do not sexually transmit HIV.
- People living with HIV who take HIV medications daily as prescribed and who achieve and maintain an undetectable viral load have effectively no risk of sexually transmitting the virus to an HIV-negative partner.
- Sharing messages about viral suppression with people living with HIV may have a profound impact on how they feel about themselves, their life choices, and reduce stigma and discrimination.

Role of Recipients and Subrecipient Sites

- HRSA encourages ongoing discussions about the impact of viral suppression for PLWH.
- Discussions with PLWH should:
  - Be supported by all staff (e.g., case manager, social worker, medical provider, etc.)
  - Use consistent language.
  - Include tailored messages regarding a person’s viral suppression and sexual health practices.
  - Reinforcing prevention of other sexually transmitted infections.

Clinical Outcomes: Viral Suppression among Women, Infants, Children, and Youth Served by RWHAP, 2016—United States and 3 Territories:

- 86.6% of Women
- 73.3% of Youth (2-11)
- 84.7% of Children & Adults Under 20
Leveraging RWHAP Part D: Some Questions to Address

• What are overarching considerations or directions for the RWHAP Part D program specifically to better target its resources to maximize national impact at improving linkage, engagement in care, and health outcomes for the WICY populations?
  • Given existing resources, what are the current gaps that the RWHAP Part D program is not meeting for the WICY population?
  • Are there specific subpopulation challenges that should be approached differently with the RWHAP Part D funds?
  • How should the RWHAP and the other Parts of the RWHAP be leveraged effectively to get improved results for the WICY population?

RWHAP Part D Program Listening Session

• **Purpose:** Gather feedback on how to strategically target Part D program to maximize its national impact
• **Date:** Tuesday, December 11, 2018
• **Time:** 5:00 pm – 6:15 pm
• **Location:** Gaylord National Harbor Hotel and Convention Center, Woodrow Wilson A
Update Overview

- 2019 Budget
- RWHAP policy
- Clinical activities
  - Retention Measure
  - HCV Elimination within the RWHAP
  - STI activities
  - AETC National Curriculum
  - Focus on special populations and dissemination of evidence informed interventions

RWHAP Retention Measure

- Two visits at least 3 months apart with a prescribing provider
- HHS Treatment Guidelines do not specify frequency of clinician visits
- Current measure is not consistent with current practice
- Consider changes to allow at least one visit with a prescribing provider and at least one viral load test or another visit within 12 month period.
- Listening session Monday, December 10, 2018, at 5:45 pm. Location: Gaylord National Harbor Hotel and Convention Center, Annapolis 1

Clinical Activities Update

- Hepatitis C Elimination
  - Two initiatives focused on jurisdictional models
  - Importance of data and improved surveillance
  - Medicaid/CMS/HRSA Affinity Group
  - Technical assistance resources including curriculum
- STI Interventions
  - SPNS funded Improving Sexually Transmitted Infection
  - Testing and Treatment among People Living with or at Risk for HIV
  - Increase/improve screening and treatment of STIs
- Clinic level and systems level interventions
Focus on Special Populations and Dissemination

- SPNS: Integrating HIV Innovative Practices
- SPNS: Using Evidence Informed Interventions to Improve Health Outcomes among PLWH (E2i)

Building Futures: Supporting Youth Living with HIV
- Improve health outcomes among youth
- Toolkit of strategies to better engage and serve youth

Contact Information

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Connect with HRSA

To learn more about our agency, visit
www.HRSA.gov

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Question-and-Answer
Learning Objectives

After attending this presentation, learners will be able to:

• Describe the basic mechanisms that allow HIV to persist despite ART
• Describe the cause and time course of viral rebound following interruption of ART
• Describe current approaches for achieving a cure
**HIV replication dynamics**

- **Set point**
- **Limit of detection**
- **Residual viremia**
- **R₀ = 10**
- **t₁/₂ = 1d**
- **t₁/₂ = 14d**

References:
- Wei et al. Nature 1995
- Ho et al, Nature 1995
- Perelson et al, Nature 1997
- Dornadula et al, JAMA 1999
- Dinoso et al, PNAS, 2009
- Robb and Ananworanich, COHA, 2016

**Physiology of resting and activated CD4+ T cells**

**Response of resting T cells to antigen**
Recall response of memory T cells to antigen

Infection of activated and resting CD4+ T cells

Establishment and maintenance of a latent reservoir
Slow decay of latently infected CD4+ T cells

Time to eradication > 73.4 years

Finzi et al., Nature Med., 1999

HIV replication dynamics

Limit of detection
Set point
Stop ART
ART


Slow decay of the reservoir

$t_\text{1/2} = 44$ months

Crook et al., JID 2015
Chronic Hepatitis C infection

- Continuous, high level viremia
- Rapid viral evolution
- Drug resistance with suboptimal treatment

Feld et al., NEJM, 2015

Dose Response Curve

Shen et al., Nat Med 2008
Jilek et al., Nat Med 2012

Inhibition of HCV replication by direct acting antiviral drugs

- HCV antivirals also have steep dose response curves that produce very high levels of inhibition
- HCV infection is readily curable
- HCV has no latent form

Koizumi et al., PNAS 2017
ART is completely suppressive but not curative due to latent reservoir

- Host immune system, including latently infected cells, largely eliminated by condition regimen (chemo + irradiation and by graft vs host disease.
- Donor cells protected from HIV infection due to absence of CCR5

“Boston Patient B”

The Mississippi baby

These delayed rebound cases prove that HIV can persist in a latent form for years and then begin to replicate.
HIV replication dynamics

- **Set point**
- **Limit of detection**
- **$R_0 = 8 - 10$**
- **$t_{1/2} = 1d$**
- **$t_{1/2} = 14d$**

Plasma HIV-1 RNA (copies/ml) vs. Time (months)

---

**HIV replication dynamics**

- **Set point**
- **Limit of detection**
- **$R_0 = 8 - 10$**
- **$t_{1/2} = 1d$**
- **$t_{1/2} = 14d$**

Plasma HIV-1 RNA (copies/ml) vs. Time (months)

---

**Viral rebound**

- Rebound in ~14 d
- Exponential
- Multiple latently infected cells reactivate per day
- Long delays only when <1 cell reacts per day

Plasma HIV-1 RNA (copies/ml) vs. Time after interruption of ART (months)
Approaches to cure

- Reservoir reduction results in a delay of rebound
- Sterilizing cure if reservoir is eliminated

Approaches to cure

- Immunologic interventions may allow control of viral replication
- Permanent control of viremia = Functional cure

The HIV envelope spike

Bonsignori et al, Imm Rev 2017
Broadly neutralizing antibodies

- Neutralize diverse HIV isolates
- Arise slowly, generally after virus has already escaped
- Can be administered passively as infusion or with AAV vectors
- Block infection and target infected cells for killing

Effects of antibodies

Slight delay with bNAb infusion

Bar et al, NEJM 2016
Scheid et al, Nature 2016
Salantes et al, JCI 2018
Rebound dynamics

Drug washout
Appearance of productively infected cells
Exponential growth

Time after interruption of ART (months)

Plasma HIV-1 RNA (copies/ml)

Reservoir reduction and time to rebound

Stop ART

Time after interruption of ART (months)

Reservoir reduction vs immune control

Stop ART

Patients on ART

Boston patients

Mississippi baby

Time after interruption of ART (months)
The shock and kill approach for eliminating latent HIV

LRA in clinical trials

- Histone deacetylase inhibitors – promote gene expression
- Toll-like receptor agonists – activate the innate immune response

Current status of LRA trials

- Numerous LRAs identified in model systems
- Few shown to work ex vivo with cells from patients
- Some evidence for slight transient increases in plasma HIV RNA after LRA treatment indicating some reactivation of latent HIV
- In clinical trials, no reduction in the reservoir yet demonstrated

Targeting the reservoir using antibodies

Study Design

- Barouch et al, CROI 2018
Targeting the reservoir using antibodies

Barouch et al, CROI 2018

Problems with the “kill” phase

- Infected cells may not die quickly after reversal of latency
- Cytolytic T lymphocyte (CTL) response is “exhausted”
- Unless treatment is started during acute infection, most of the viruses in the latent reservoir have CTL escape mutations
- Vaccines to enhance the cytolytic T cell response may be needed

T cell activation
Latency reversing agents (LRAs)†
Shock Kill

T cell exhaustion

PGT121 + GS-9620 Delays Time to Viral Rebound Following ART Discontinuation

Barouch et al, CROI 2018
Conclusions

- ART stops viral replication but does not eliminate latent HIV
- Reactivation of latently infected cells leads to viral rebound after ART interruption
- Current cure efforts are focused on eliminating the latent reservoir
- Broadly neutralizing antibodies have been isolated and developed as agents to block viral entry and target productively infected cells
- Reservoir reduction will likely the identification of effective latency reversing agents and effective kill strategies
- Long delays in viral rebound will require a 1000 fold reduction in the reservoir
Question-and-Answer
Key Updates From Recent HIV Research Conferences

Melanie A. Thompson, MD
Principal Investigator
AIDS Research Consortium of Atlanta
Atlanta, Georgia

Learning Objectives

After attending this presentation, learners will be able to:
▪ Discuss obstacles to Ending the Epidemic
▪ Discuss evidence for treatment as prevention
▪ Describe newly approved antiretrovirals
The Global Epidemic
IAC 2018

People with HIV can live a near-normal lifespan, free of AIDS, with early and continuous ART.

We know how to prevent new HIV infections.

We Are NOT on Track to End AIDS.

Experts Warn of a Return of the AIDS Epidemic
A campaign to end AIDS by 2030 is faltering worldwide
By Jon Cohen | Jul. 31, 2018, 4:05 PM

Hope for ‘end of Aids’ is disappearing, experts warn

HIV/AIDS complacency risks reversing progress on ending epidemic, conference hears
HIV Pandemic in 2018

- 1.8 Million NOT on ARV
- 19.4 million NOT suppressed

...a widening deficit of political will and financial capacity...

---

Photo credit: Avert.org, Global Burden of Disease Health Financing Collaborator Network, Lancet 391: May 5, 2018
The HIV pandemic is not on track to end, and the prevailing discourse on ending AIDS has bred a dangerous complacency and may have hastened the weakening of global resolve to combat HIV.

The Lancet Commission, 2018

Without further reductions in HIV incidence, a resurgence of the epidemic is inevitable

The Lancet Commission, 2018

...intensified efforts are required to address HIV among populations and settings that are being left behind
HIV Treatment Cascade among MSM Across Sub-Saharan Africa

- N=16
  - 40.0% (95% CI: 26.8, 54.7)
- N=6
  - 30.8% (95% CI: 11.3, 60.7)
- N=44
  - 25.6% (95% CI: 20.5, 31.5)

10.2% 25.6% 7.9%

90:90:90 Cascade – Europe 2016

PLWHIV diagnosed
Diagnosed on ARV
On ARV with undetectable VL
PLWHIV with undetectable VL

New HIV Cases in Eastern Europe and Former Soviet Union

- Armenia
- Belarus
- Kazakhstan
- Moldova
- Tajikistan
- Uzbekistan

Presented by Stefan Baral, IAC 2018 Plenary; Source: Сант Петербург, 5 октября 2017 г.
Fulton County, GA (Atlanta)
New HIV Dx 2010-16 Black Gay/Bi Men By Age

African Americans, Latinos Have Highest Rates of New HIV Diagnosis in SF - 2017

Black Men Living With HIV Have Highest Mortality Rate

What’s HOT in HIV Prevention?

Treatment Is Prevention!
ZERO HIV Transmissions When Virus is Durably Suppressed
Undetectable = Untransmittable

PrEP Works – But Is Underutilized

Photo credit: Opposites Attract Study
PARTNER 2: Serodifferent Partners

- HIV+ partner had HIV RNA < 200 c/mL
- Gay male couples from Partner 1 & 2
  - 783 couples
  - 76,991 condomless sex acts (6,301 with STI)
- 15 HIV transmissions **ZERO** from main partner
  - Receptive anal intercourse with ejaculation from HIV+ partner: upper limit 95% CI = 0.57%
Time spent above viral threshold during 12 mo after HIV dx by year of dx, San Francisco, 2008-2016

Cochran-Armitage test for trend p<0.0001 for each threshold

Hughes A, et al. IAC 2018, xxxx

221 New HIV Diagnoses in San Francisco, 224 Deaths = Decreased Prevalence 2017

U=U Only if You Are U

And half of PLWH are not U!
PrEP Works!

Daily vs. On-Demand PrEP in Paris: Year One Experience

Observational, not randomized
- 98.8% MSM
- 0.5% Trans
- 0.8% Hetero

Prévenir HIV Incidence (mITT Analysis)

n=1594 Included; 124 through Month 12

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Follow-Up Pts-years</th>
<th>HIV Incidence per 100 Pts-years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF/FTC (Daily)</td>
<td>443</td>
<td>0 (0.0-0.5)</td>
</tr>
<tr>
<td>TDF/FTC (On Demand)</td>
<td>506</td>
<td>0 (0.0-0.7)</td>
</tr>
</tbody>
</table>

Mean Follow-up in this Open-Label Cohort: 7 months (SD: 4)

Incidence of study discontinuation:
3.3/100 PY including 1.3/100 PY who discontinued PrEP

85 HIV-infections averted

PrEP Works! But...

Among persons with indications for PrEP use in 2015,
- 8% were prescribed PrEP during 9/15-8/16
- 14% of White
- 1% of Black
- 3% of Hispanic/Latino

Siegler et al, CROI 2018. Abstract #1022LB
Breakthrough Infection Rare But Possible

- Total to date of 6 breakthroughs with well documented high PrEP adherence
- 5/6 had M184V mutation; 3/6 had TFV mutations (K70R or K65R)
- Newest case from San Francisco City Clinic
  - High adherence by 3 measures
  - M184V + non-NRTI mutations; no TFV mutations
  - Index partner had M184V + same non-NRTI mutations

Cohen S, et al. IDWeek, Abstract 1298; Cohen S, Lancet HIV, online corrected proof 29NOV2018

What’s HOT in ART Research?

- New Drugs, New Formulations
- New Paradigms, (New Problems)

Bictegravir
Single Tablet Regimen (BIC/FTC/TAF)

Wohl D, et al. IDWeek 2018 LB4

Resistance
BIC = 0
DTG = 5

D/C due to AE
BIC = 0
DTG = 5

Wohl D, et al. IDWeek 2018 LB4
Doravirine: Initial Therapy and Maintenance of Viral Suppression

DOR/3TC/TDF is non-inferior to EFV/FTC/TDF at Week 48/96

DRIVE AHEAD

DOR + 2NRTI is non-inferior to DRV/r + 2NRTI at Week 48/96

Protocol-Defined Virologic Failure = 1.3% DOR v 0.4% Control Arm

DRIVE FORWARD

Molina J et al. IAC 2018 LBPEB017; Orkin C, et al. IDWeek 2018, LB1; Kumar P, et al. IDWeek 2018

DRIVE SHIFT

Baseline

Week 96

Randomization 2:1

N=1141

Week 48

Primary endpoint

Stable bPI ≤ 6

mos

VL < 50 c/mL ≤ 6

mos

Week 24

Interim analysis

D/C/F/TAF

D/C/F/TAF

Continue bPI + F/TDF

D/C/F/TAF late switch

2.

Eron J, IDWeek 2018, Abstract 1768

Darunavir/cobi/FTC/TAF (D/c/F/TAF):

First PI-based Single Tablet Regimen

AMBER: D/c/F/TAF vs D/c + FTC/TDF in ART naive persons¹

D/c/F/TAF Arm: HIV RNA < 50 c/mL

91% vs 88% Week 48

85% vs 84% Week 96

EMERALD: Switch from Boosted PI to maintain viral suppression²

D/c/F/TAF Switch Arm: HIV RNA < 50 c/mL

95% Week 48

91% Week 96

DIAMOND Week 24: Rapid Start Efficacy Results

D/C/F/TAF (800/50/200/70 mg)

Day 1 (screening/baseline)

Day 3 (11 week)

Safety assessment of baseline laboratory data**

Week 4 (7 days)

Review baseline resistance data**

Week 24 analysis

Week 48 (primary endpoint)

Eligible patients:

- Adults ≥18 years of age

- ≥12 weeks from newly diagnosed HIV-1 infection

First dose of D/C/F/TAF was received:

- As soon as within 24 hours of screening/baseline visit

- Before results of the baseline safety and resistance laboratory tests were available

DIAMOND Week 24:

FDA Snapshot (N=109)

Observed (n=98)

- No discontinuations due to lack of efficacy; no PDVF

- Mean CD4 count increase 176 cells/mm³ at Week 24

Huhn G et al. IAC 2018 Abs WEPEC200
Ibalizumab for Multidrug Resistant HIV
(Failing regimen with evidence of 3-4 class resistance)

TMB 301 25 Week Results

<table>
<thead>
<tr>
<th></th>
<th>ITM ADC (N=19)</th>
<th>Comparator (N=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (± SD) VL reduction</td>
<td>1.7 ± 1.3 log_{10}</td>
<td>2.2 ± 1.4 log_{10}</td>
</tr>
<tr>
<td>Median VL reduction</td>
<td>1.8 log_{10}</td>
<td>2.5 log_{10}</td>
</tr>
<tr>
<td>Percent with VL≤100 copies</td>
<td>59%</td>
<td>55%</td>
</tr>
<tr>
<td>Percent with VL&gt;100 copies</td>
<td>59%</td>
<td>60%</td>
</tr>
<tr>
<td>Percent with ≤1.5 log_{10} reduction</td>
<td>58%</td>
<td>74%</td>
</tr>
<tr>
<td>Percent with &gt;1.5 log_{10} reduction</td>
<td>46%</td>
<td>81%</td>
</tr>
</tbody>
</table>

* All 15 patients with VL ≤50 copies/mL at Week 25 maintained viral suppression for Week 48

TMB 311 48 Week Results

Wholesale Acquisition Cost = WAC

$108,960 Annually

Drug Wholesale Acquisition Cost per month (per year)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Wholesale Acquisition Cost per month (per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doravirine</td>
<td>$1,380 ($16,560)</td>
</tr>
<tr>
<td>DOR/3TC/TDF</td>
<td>$2,100 ($25,200)</td>
</tr>
<tr>
<td>D/c/F/TAF</td>
<td>$3,482 ($41,784)</td>
</tr>
<tr>
<td>BIC/FTC/TAF</td>
<td>$2,946 ($35,352)</td>
</tr>
<tr>
<td>DTG + 3TC</td>
<td>$2,001 ($24,012)</td>
</tr>
</tbody>
</table>

Matt Sharp

Photo credit: Avert.org
US Drug Pricing: The Simple Version

Generics

Average Wholesale Price (AWP)
Wholesale Acquisition Cost (WAC)
Average Manufacturer Price (AMP)
Nonfederal Average Manufacturer Price (Non-FAMP)
Federal Supply Schedule (FSS) Price
Federal Ceiling Price
Federal Ceiling; "Big 4" Price
Best Price
Medicaid Price
340B Price
Private sector prices
Rebates to PBMs
Copay assistance
Other price concessions
Unit rebate: 23.1% / 13% of AMP or AMP – Best Price
plus CPI penalties
76% of non-FAMP minus additional discounts
Supplemental rebates and discounts negotiated (including ADAPs)
Supplemental discounts negotiated (VA and DoD)
Negotiation on most-favored commercial customer price

Successful and Unsuccessful Strategies for Initial Therapy

GEMINI 1-2: 48 Weeks
DTG + 3TC for Initial Therapy (HIV RNA < 500k c/mL)
• Non-inferior to DTG + TDF/FTC
• No treatment-emergent resistance
MONCAY: DTG vs DTG/ABC/3TC for Maintenance of Viral Suppression

- 158 patients: HIV RNA < 50 c/mL ≥ 12 mo on DTG/ABC/3TC
- Week 24: DTG non-inferior to DTG/ABC/3TC (94% vs 96%)
- Week 48: 7 virologic failures on DTG
  - INSTI resistance emergent in 2/7 on DTG vs 0 on DTG/ABC/3TC
  - DSMB recommended to stop immediately the study

IMHO: Abandon 24 wk primary endpoints for phase III/IV trials!
Abandon DTG monotherapy!

Antiretrovirals Alone Will NOT End AIDS!

Don’t Forget: “Non-AIDS” Diseases Kill!
Care Cascades Must Be Improved

![Graph showing percentages of people with different conditions.]

Opioid Substitution Therapy for PLWH

- Facilitates ART initiation
- Increases adherence to ART
- Reduces treatment discontinuation
- Increases viral load suppression
- Improves HIV prevention benefit of ART

Integrated Opioid Substitution Tx & ART Service Delivery Kazakhstan & Tajikistan

<table>
<thead>
<tr>
<th>Proportion of PLHIV enrolled in OST on ART</th>
<th>% of PLHIV enrolled in OST on ART w VL suppression (&lt;1000 c/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>42%</td>
<td>91%</td>
</tr>
<tr>
<td>41%</td>
<td>80%</td>
</tr>
<tr>
<td>59%</td>
<td>75%</td>
</tr>
<tr>
<td>67%</td>
<td>87%</td>
</tr>
<tr>
<td>63%</td>
<td></td>
</tr>
</tbody>
</table>

Deryabina A, IAC 2018 Plenary
How Do We Improve Care Engagement?

If customers stop coming to the restaurant, the chef doesn’t ask “What’s wrong with the customers?”
It’s time to improve the restaurant!
- David Malebranche, MD MPH

Focus on Structural Barriers Rather Than Individual Behaviors

• Reduce barriers to care engagement
  – Rapid test and treat options
  – Mobile medical teams
  – Peer navigation, case manager, home grown community interventions
  – Patient reminders
• Social interventions: housing, food, employment, education
• General health initiatives – health is NOT just HIV
• Get rid of anti-LGBT and HIV criminalization policies

Key Elements of Syndemics

1. Disease Concentration
   – 2 or more diseases concentrate in a particular social context (population, geography, etc.)
2. Disease Interaction
   – Interactions between epidemics at individual and population level amplify disease burden
3. Large scale social forces
   – Harmful social conditions drive the disease concentration and synergistic interaction
Syndemic Approach to Structural Barriers to Care

- HIV
- TB
- DM
- Economic instability
- Food insecurity

Each syndemic condition increased the odds of transmission risk behavior by 1.84 (OR=1.84; 95%CI=1.67, 2.01). Satyanarayana S, et al. AIDS 2018.

Advocacy is Needed!

- Tell Your Legislators...
  - Maintain – and increase – program funding for HIV, STI, viral hepatitis, TB, substance use and mental health
    - There is not enough money or staff to take care of all the patients (50% nationally) who are out of care!
    - Flat funding for Ryan White, inadequate funding for STIs will NOT end the epidemic...
  - Oppose policies that decrease care access and create stigma (including HIV criminalization laws)
  - Address syndemic factors: housing, jobs, transportation, food insecurity, education
  - Support the rights of PLWH
Acknowledgements

Thanks for advice/slides/inspiration
• Authors whose work I presented
• Photographers whose photos I stole from the internet
• Participants in clinical trials
• People living with HIV

Question-and-Answer
Learning Objectives

After attending this presentation, learners will be able to:

▪ Describe the current epidemiology of the most common STIs
▪ Identify current treatment recommendations for gonorrhea, chlamydia, trichomoniasis
▪ Describe the current trends in gonococcal antimicrobial resistance

STIs are on the rise in the US

1.7 million cases of chlamydia 22% increase since 2013
555,608 cases of gonorrhea 67% increase since 2013
30,644 cases of syphilis 70% increase since 2013

Limitations of case report data:

▪ Not all STIs are nationally notifiable (HPV)
▪ Most STIs are asymptomatic, only those diagnosed can be reported
▪ Trends are influenced by screening coverage and reporting practices
Proportion* of MSM Attending STD Clinics with Primary and Secondary Syphilis†, Urogenital‡ Gonorrhea, or Urogenital‡ Chlamydia by HIV Status§, STD Surveillance Network (SSuN), 2017

<table>
<thead>
<tr>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>15</td>
</tr>
<tr>
<td>20</td>
</tr>
</tbody>
</table>

- P&S syphilis
- GC urogenital‡
- CT urogenital‡

- 10-12 State Health Departments (SSuN)
- Visit level data
- Enhanced case data
- Common protocols

* Proportions represent the overall average of the mean proportions by jurisdiction.
† Includes SSuN jurisdictions that reported data on at least 20 patients with a diagnosis of primary and secondary syphilis in 2017.
‡ Includes results from both urethral and urine specimens.
§ Excludes all persons for whom there was no laboratory documentation or self-report of HIV status.

---

**STI Testing during HIV care**

- Initial care visit
  - Syphilis serology
  - NAAT (gonorrhea, chlamydia)
  - MSM (rectum, pharynx, urethra)
  - Hepatitis A,B,C
  - Women–Cervical pap test (HIV OI guidelines); Trichomonas (NAAT)
  - Screening dependent on risk (3-6 mo)
    - New sex partner, partner with concurrent partners or more than one partner, or partner with an STI
    - High risk behavior
    - Partner services, prevention counseling

---

**What about Rectal GC/CT Screening for women?**

- 5499 women rectal CT/GC tests + other sites rectal positivity 10.8%
- * 75% of GC/CT had a rectal infection only

Women with rectal GC/CT rectum were more likely to have genital or pharyngeal GC/CT
Gonorrhea

Gonorrhea — Rates of Reported Cases by Sex, United States, 2008–2017

During 2012-2017, the rates of reported GC increased:
- 112% among males
- 40% among females

Estimated Proportion* of MSM, MSW, and Women Among Gonorrhea Cases by Jurisdiction, STD Surveillance Network (SSuN), 2017

* Estimate based on weighted analysis of interviews from respondents in a random sample of reported gonorrhea cases during January to December 2017. Data are weighted for non-response and other sources of selection bias (see supporting materials).

† California data exclude San Francisco (shown separately).
Gonorrhea Clinical Manifestations

<table>
<thead>
<tr>
<th>Anatomic Site</th>
<th>Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td></td>
</tr>
<tr>
<td>Urethra</td>
<td>Urethritis</td>
</tr>
<tr>
<td>Epididymis</td>
<td>Epididymitis</td>
</tr>
<tr>
<td>Pharynx</td>
<td>Asymptomatic, Nasopharyngitis</td>
</tr>
<tr>
<td>Rectum</td>
<td>Asymptomatic, Proctitis</td>
</tr>
<tr>
<td>Eye</td>
<td>Conjunctivitis</td>
</tr>
<tr>
<td>Systemic</td>
<td>Disseminated Gonococcal Infection (DGI)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Females</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix</td>
<td>Cervicitis</td>
</tr>
<tr>
<td>Fallopian tube</td>
<td>Salpingitis/Pelvic Inflammatory Disease</td>
</tr>
<tr>
<td>Urethra</td>
<td>Urethritis</td>
</tr>
<tr>
<td>Epididymis</td>
<td>Epididymitis</td>
</tr>
<tr>
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</tr>
</tbody>
</table>

Clinical Case—ARS Question 1

- 23 yo female G4P1
- Ankle swelling, pain, migratory polyarthritis, skin lesion left finger

What is the best method to make a diagnosis of DGI?

1. Joint aspiration
2. Blood culture
3. Lesion aspiration
4. Vaginal swab

Disseminated Gonococcal Infection (DGI)

- Estimated to account for 0.5-3% of gonococcal infections
- Risk factors: female, menses, pregnancy, terminal complement deficiency
- Clinical presentation
  - Monoarticular arthritis
  - skin lesions (petechial or pustular) + tenosynovitis + polyarthralgia
  - Perihepatitis, endocarditis, meningitis
- Blood + tenosynovitis/arthralgia > monoarticular arthritis
- Mucosal site infection often asymptomatic (NAAT)
- Antimicrobial susceptibility (AST) testing (culture)
Changing Patterns of DGI

DGI Cases by Site in ABCs, 2015–2017
- Demographics: 41% female, MSM 15.4%, Male 38%
- 30% > 45 yrs

<table>
<thead>
<tr>
<th>Site</th>
<th>Proportion of DGI Cases to Reported GC Cases (in Surveillance Area)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA</td>
<td>2/29,637 (0.007%)</td>
</tr>
<tr>
<td>GA-DPH</td>
<td>3/9,770 (0.031%)</td>
</tr>
<tr>
<td>GA-MSA</td>
<td>21/29,323 (0.072%)</td>
</tr>
<tr>
<td>Total</td>
<td>26/68,730 (0.0385)</td>
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Site Proportion of DGI Cases to Reported GC Cases (in Surveillance Area)

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</tr>
<tr>
<td>Total</td>
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</tr>
</tbody>
</table>

Neisseria gonorrhoeae — Percentage of Isolates with Elevated Azithromycin Minimum Inhibitory Concentrations (MICs) (≥2.0 µg/ml), Elevated Ceftriaxone MICs (≥0.125 µg/ml), and Elevated Cefixime MICs (≥0.25 µg/ml), Gonococcal Isolate Surveillance Project (GISP), 2008–2017

Percentage of Isolates with (A) Elevated Azithromycin MICs and (B) Elevated Ceftriaxone MICs with Other Resistance Phenotypes, GISP, 2017

- Azithromycin RS (n=11)
- Ceftriaxone RS (n=5)

No overlap in 2017

- Azithromycin-RS: reduced azithromycin susceptibility (MIC ≥ 2 µg/ml); ceftriaxone-RS: reduced ceftriaxone susceptibility (MIC ≥ 0.125 µg/ml)
**Gonorrhea**

- **United States**
  - Ceftriaxone 250 mg IM in a single dose PLUS Azithromycin 1 g orally in a single dose
- **United Kingdom**
  - Ceftriaxone 1 gram IM in a single dose
- **Europe (European CDC)**
  - Ceftriaxone 500 mg IM in single dose PLUS Azithromycin 2 gm orally in a single dose
- **Japan**
  - Ceftriaxone 1 gm IV/IM in a single dose

- Optimize therapeutic regimen
- PK/PD (site of penetration)
- Concentration dependent vs independent regimen
- Bacterial burden
- Mutational frequency to resistance
- Resistance suppressive targets do not guarantee eradication
- Novel agents (Zoliflodacin, Gepotidacin)

**Treatment Failures**
- Most apparent treatment failure likely due to reinfection
- If treatment failure suspect, obtain culture/susceptibility test + ensure partner treatment
- Dual therapy in UK (Filer 2016)
- Ceftriaxone MIC of 0.5mg/L, azithromycin MIC of >256mg/L in UK, Australia (March 2018)

**Global Antibiotic Research and Development Partnership**

- Launched by WHO and Drugs for Neglected Disease Initiative in 2016
- Draft of acceptable GC target product profiles and timeline
- Research and Development plan
  - Accelerate the development of a new clinical entity
  - Evaluate the potential of existing antimicrobials and combinations
  - Explore co-packaging and fixed dose combinations
  - Development of simplified treatment guidelines

**Chlamydia**
Chlamydia — Rates of Reported Cases by Sex, United States, 2000–2017


LGV inguinal syndrome
- C. trachomatis L1, L2, L3
- Herpetiform genital ulcers and/or papules
- Tender, fluctuant, inguinal lymphadenopathy (buboes)
LGV Proctitis

- MSM and women - rectal chlamydia NAAT
- PCR based genotyping
- Protocoitisis +/- perianal ulcers
- Presumptive tx (doxy 100 mg bid x 21 d)
- Painful perianal ulcers or mucosal ulcers presumptive therapy for HSV
- Short course therapy 7-14 d GUM clinic in UK (Simon, STD 2018)

Notes from the Field Cluster of Lymphogranuloma Venereum Cases Among Men Who Have Sex with Men – Michigan, August 2015–April 2016

- 38 reports of LGV among MSM with HIV infection
- Median age 26 (19-60), median CD4 483 (270-1271)
- 21/38 confirmed by CDC (19 symptomatic proctitis, 2 penile ulcer)
- Concomitant infections
  - 6/38 (16%) incident HIV
  - 4/38 (11%) hepatitis C
  - 6/38 (16%) syphilis
  - 8/38 gonorrhea (8% oral, 13% rectal)

LGV in MSM, NYC Sexual Health Clinics

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases</th>
<th>HIV positive</th>
<th>HIV negative</th>
<th>None</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>12</td>
<td>0</td>
<td>12</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>2013</td>
<td>10</td>
<td>1</td>
<td>9</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>2014</td>
<td>8</td>
<td>1</td>
<td>7</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>2015</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

*Figures for 2012-2015 are estimates.*
Chlamydia Treatment

- Azithromycin vs Doxycycline
  - Meta-analysis (Kong 2014)
  - Doxy > Azi 3% (urogenital)
  - Doxy > Azi 7% (sx urethral)
- Rectal Infection
  - Several retrospective studies
- Doxy > Azi rectal
  - STI CTG RCT Azi vs Doxy (axx)
- LGV
  - Axx vs sx (duration of therapy)
- Reinfection is common
  - Retest in 3 mo

Human Papillomavirus

HPV Natural History

- HPV is the most common STI
  - The majority of sexually active people will become infected
- Initially most persons have no symptoms
  - Anogenital warts, low-risk (LR) HPV rarely cause cancer
- High-risk (16, 18) HPV infection may cause anogenital and oropharyngeal cancer
  - Most high risk HPV infection clears within 2 years
  - Minority develop high-grade squamous intra-epithelial lesions
  - HSIL can progress to cervical cancer 1/80 per year
Type specific Anal HPV Prevalence, Among Men

Sexual Preference and HIV Infection Strong
Independent Predictors of Male Anal HPV16


Oropharyngeal Cancer is the most common HPV associated cancer

Anal Cancer
Increased 2.7%/yr male and 0.8%/yr female
Primary prevention

- HPV vaccination
  - Adolescents
  - Catch-up in adults (less effective)

Secondary prevention

- Screening and treatment for HSIL
  - Ablative or destructive therapies
  - Immunological therapies
  - Cancer indications
  - Antiviral or immune-modulatory treatments

HPV Vaccine

**Nanovalent HPV Vaccine**

- Types 6, 11, 16, 18, 31, 33, 45, 52, 58
- FDA approved to prevent warts, cervical, vulvar, vaginal and anal cancer

- 2 doses for males/females aged 9-14
- 3 doses for males/females aged 15-26
- Immunocompromised patients need 3 doses, regardless of age of initiation

Cervical Intraepithelial Neoplasia Grades 2 and 3 — Prevalence per 1000 Person-Years Among Female Enrollees in Private Health Plans Aged 15–39 Years, by Age Group and Year, 2007–2014

Vaccinating females leads to substantial herd protection from HPV in heterosexual men.

Proportion of Australian-born heterosexual men attending sexual health clinics with genital warts by age group, 2004-2011

HPV Vaccination in Gay, Bisexual Men

Proportion of Australian-born GBM attending sexual health clinics with anogenital warts, 2004-11

HPV Vaccination, Gay and Bisexual Men, 18-26yo

Table 1: Vaccine efficacy against HPV-6, 11, 16, or 18-related head and neck squamous cell carcinoma and oral cancer in the per-protocol efficacy population.

<table>
<thead>
<tr>
<th>End Point</th>
<th>qHPV Vaccine (N=299)</th>
<th>Mucosa (N=299)</th>
<th>Overall Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anal cancer</td>
<td>194 4 183.1 1.6 208 16 413.8 3.9 79.0 (62.3 to 90.8)</td>
<td>194 0 181.8 0.0 208 6 413.8 2.4 100.0 (76.0 to 99.9)</td>
<td>194 4 183.1 1.6 208 16 413.8 3.9 79.0 (62.3 to 90.8)</td>
</tr>
<tr>
<td>Oral cancer</td>
<td>194 4 183.1 1.6 208 11 413.7 2.6 62.4 (32.5 to 77.3)</td>
<td>194 3 183.9 0.6 208 13 417.2 3.1 62.4 (32.5 to 77.3)</td>
<td></td>
</tr>
</tbody>
</table>

* The per-protocol efficacy population consisted of participants who were seronegative and had HPV DNA-negative mouth and laryngeal samples on day 0. Those vaccine type, were negative for vaccine-type DNA through month 7, and did not have any protocol violations. To analyze...
HPV Vaccination in HIV+ Adults >27 yrs

Table 2: Vaccine Efficacy for Persistent Anal Infection, Persistent End Infection, Anal High-Grade Squamous Intraepithelial Lesions on Anal Biopsy, and Advanced Anal Dysplasia

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Vaccine Group</th>
<th>Control Group</th>
<th>Efficacy (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent anal infection</td>
<td>n</td>
<td>n</td>
<td></td>
</tr>
<tr>
<td>Ascending single infection at end visit</td>
<td>258</td>
<td>27</td>
<td>22% (9% to 35%)</td>
</tr>
<tr>
<td>Persistent infection only</td>
<td>296</td>
<td>15</td>
<td>31% (16% to 46%)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>277</td>
<td>237</td>
<td>31% (16% to 46%)</td>
</tr>
<tr>
<td>Persistent anal infection</td>
<td>n</td>
<td>n</td>
<td></td>
</tr>
<tr>
<td>Ascending single infection at end visit</td>
<td>296</td>
<td>318</td>
<td>31% (16% to 46%)</td>
</tr>
<tr>
<td>Persistent infection only</td>
<td>234</td>
<td>205</td>
<td>31% (16% to 46%)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>216</td>
<td>237</td>
<td>31% (16% to 46%)</td>
</tr>
<tr>
<td>Estimation of anal high-grade squamous intraepithelial lesions on anal biopsy outcome*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cure (%)</td>
<td>236</td>
<td>264</td>
<td>31% (16% to 46%)</td>
</tr>
<tr>
<td>Abnormal and curable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 52</td>
<td>236</td>
<td>264</td>
<td>31% (16% to 46%)</td>
</tr>
<tr>
<td>Week 100</td>
<td>131</td>
<td>123</td>
<td>31% (16% to 46%)</td>
</tr>
<tr>
<td>Week 180</td>
<td>131</td>
<td>123</td>
<td>31% (16% to 46%)</td>
</tr>
</tbody>
</table>

Tertiary prevention

Screening for cancer: early diagnosis and curative chemoradiation

Does Treating HSIL Prevent Anal Cancer?

- Anchor Study
  - Assessment of anal HSIL treatment in reducing anal cancer in HIV+ men/women vs active monitoring: digital anorectal exam
  - Ablative therapies: infrared coagulation, electrosurgery, and TCA
  - Estimated recruitment > 5000, 5 year follow up
  - Patients randomly assigned to treatment or active monitoring arms
  - Estimated completion mid 2022

ClinicalTrials.gov: NCT02135419

Trichomonas
**Trichomonas vaginalis**

- Single-celled protozoan parasite
- Adheres to epithelial cells
  - Male or female urethra
  - Female vagina, vulva
- Causes local inflammation
- Variable spectrum of disease
  - 70–85% of women and 77% of men are asymptomatic
  - Vaginitis, urethritis, prostatitis
  - Associated with increased susceptibility to other STIs (HIV), adverse pregnancy outcomes, low birth weight

**T. vaginalis Epidemiology**

<table>
<thead>
<tr>
<th>Source</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Add Health</td>
<td>2.8%</td>
</tr>
<tr>
<td>NHANES 2013-2014</td>
<td>2.8%</td>
</tr>
<tr>
<td>Primary Care</td>
<td>3.1%</td>
</tr>
<tr>
<td>STD Clinics</td>
<td>6.0%</td>
</tr>
<tr>
<td>Incarcerated Drug Use</td>
<td>13.0%</td>
</tr>
<tr>
<td>Arizona HPV infection</td>
<td>26.0%</td>
</tr>
<tr>
<td>Patel, CID 2018</td>
<td>38.0%</td>
</tr>
</tbody>
</table>

- Female sex
- Black race
- Older age
- High risk
- Lower poverty

**Table 3. Comparative Prevalence of Sexually Transmitted Infections in the General, Race/Ethnicity-Clinical US Population 15–50 Years**

<table>
<thead>
<tr>
<th>Infection</th>
<th>Prevalence</th>
<th>Men</th>
<th>Women</th>
<th>Other Races/Ethnicities</th>
<th>Crude Adjusted</th>
<th>Adjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>TV ATIN</td>
<td>12.6 (1.3)</td>
<td>15.6 (1.3)</td>
<td>1.2 (0.3)</td>
<td>16.0 (4.2)</td>
<td>16.0 (4.2)</td>
<td>16.0 (4.2)</td>
<td>16.0 (4.2)</td>
</tr>
<tr>
<td>CV ATIN</td>
<td>6.6 (0.5)</td>
<td>16.0 (1.7)</td>
<td>6.6 (0.5)</td>
<td>16.0 (1.7)</td>
<td>16.0 (1.7)</td>
<td>16.0 (1.7)</td>
<td>16.0 (1.7)</td>
</tr>
<tr>
<td>HSV2 genital</td>
<td>16.0 (1.7)</td>
<td>16.0 (1.7)</td>
<td>16.0 (1.7)</td>
<td>16.0 (1.7)</td>
<td>16.0 (1.7)</td>
<td>16.0 (1.7)</td>
<td>16.0 (1.7)</td>
</tr>
<tr>
<td>Other Infections</td>
<td>16.0 (1.7)</td>
<td>16.0 (1.7)</td>
<td>16.0 (1.7)</td>
<td>16.0 (1.7)</td>
<td>16.0 (1.7)</td>
<td>16.0 (1.7)</td>
<td>16.0 (1.7)</td>
</tr>
</tbody>
</table>
Trichomonas vaginalis and HIV acquisition

- TV increased risk of HIV 1.5X

Trichomonas

- Screen at initial visit HIV+ (NAAT)
- Rx: Metronidazole HIV+ 500 mg bid x 7 days (Kissinger, 1999)
- Options to Nitroimidazoles
  - Single agent vs Combination therapy
  - Intravaginal- paromomycin, boric acid
  - Secnidazole
- Clinical treatment failure
  - Re-infection, Nonadherence
  - Antimicrobial resistance
- Retesting 3 months after treatment
- Management of persistent infection
  - Up to 17% at 3 months
  - Reinfection from untreated partner is common
  - Infection with MTZ-resistant strains: ~4-10%
    - Tinidazole-resistant ~1%
  - No clear relationship to clinical treatment failure
  - Susceptibility testing if resistance suspected (CDC)

STI Screening and Management

www.cdc.gov/std/tg2015
National Network of STD Clinical Prevention Training Centers (NNPTC)

- Clinical Training and Consultation Network
  - Visit: www.STDCCN.org
- Resources and tools for STD treatment
- STD Clinical Toolbox App
- Visit: www.nnptc.org

National STD Curriculum

- www.std.uw.edu
- Self-Study Modules
- Modular learning
- Free continuing education credits (CME and CNE)

Question-and-Answer
The Great Imitator Revealed: Syphilis

Jeffrey D. Klausner, MD, MPH
Professor of Medicine and Public Health
University of California Los Angeles
David Geffen School of Medicine
Los Angeles, California

Learning Objectives

After attending this presentation, learners will be able to:

▪ List the differential diagnosis of an anogenital ulcer
▪ Describe the preferred treatment for syphilis by stage
▪ Cite at least 3 means of syphilis prevention

Case

44 year old man with new painless lesion near his anus

Had a new sex partner 2 weeks ago
**Anogenital Ulcer**

**Differential Diagnosis**

**Sexually transmitted diseases**
- Primary syphilis
- Genital herpes
- Chancroid

**Other**
- Fixed drug reactions
- Staph/ strep infections
- Autoimmune conditions
- Trauma
- Malignancy

---

1000x darkfield microscopy

*Treponema pallidum pallidum*, bacterial spirochete

---

**Primary syphilis – penile chancre**
Injectable Penicillin G Benzathine
Treatment of Choice for Primary Syphilis

- Single intramuscular injection penicillin G benzathine 2.4 MU
- Prophylactic treatment:
  - Syphilis case contacts < 90 days
  - Notify partners up to 3 months

Penicillin G benzathine cures syphilis

N=328, 52% HIV+, Tanzania  
Riedner, G. et al. NEJM, 2005

Case

- 24 yo male with new onset of rash on chest and back, recently started on ART (ABC/3TC/DTG), has one regular partner
Secondary syphilis: trunk rash

Secondary syphilis: palmar and plantar lesions

Differential Diagnosis: Generalized Rash

- Trunk rash
- Secondary syphilis
- Viral exanthem, including acute HIV infection
- Phymysis rosea
- Drug eruption
- Lichen planus
- Psoriasis
- Sarcoidosis
- Palmoplantar rash
- Secondary syphilis
- Erythema multiforme
- Rocky Mountain spotted fever
Secondary syphilis: split papules, “moth-eaten” alopecia, mucous patches, and condyloma lata

Case

- RPR 1:16
- TPPA positive

Injectable Penicillin G Benzathine
Treatment of Choice for Secondary Syphilis

- Single intramuscular penicillin G benzathine
- Prophylactic treatment:
  - Syphilis case contacts < 90 days
  - Notify partners up to 6 months

CDC, 2015
Epidemiology

CDC: STD rates skyrocketing in United States

Syphilis rates are on the rise, and dating apps may be playing a role, experts say

Syphilis Rates Sharp Among Newborns

Along with an increase in adult infections, the rate of infants born with the disease has reached a 20-year high.

New Cases of Syphilis at Highest Rate Since 1994

Rate (per 100,000 population)

Primary and Secondary Syphilis — Reported Cases by Sex and Sexual Behavior, 37 States*, 2013–2017

* 37 states were able to classify ≥70% of reported cases of primary and secondary syphilis as either MSM, MSW, or another category for each year during 2013–2017.
Congenital Syphilis — Reported Cases by Year of Birth and Rates of Reported Cases of Primary and Secondary Syphilis Among Women Aged 15–44 Years, United States, 2008–2017

ACRONYMS: CS = Congenital syphilis; P&S = Primary and secondary syphilis.

---

Case

- 32 HIV-infected male, on HAART for 2 years, virologically suppressed
- New to your office with RPR reactive at 1:32, TPPA reactive
- Asymptomatic

---

Latent syphilis
All Those Syphilis Tests

- Non-treponemal tests (RPR, VDRL)
  - Detects antibody to cardiolipin-lecithin-phospholipids
  - Rise and fall with infection and treatment over time
  - 4-fold change in titer (1:2 to 1:8 or 1:64 to 1:16) is significant
  - Specificity = 98% (false-positives in IDU, auto-immune, etc)

- Treponemal tests (TPPA, FTA-Abs, TP EIA, rapid TP)
  - Detects antibody to Treponemal antigen
  - More sensitive and develop earlier
  - Stay positive for “life” (85%)
  - Indicate past or current infection

Klausner, Current STD Diagnosis and Management 2007

Injectable Penicillin G Benzathine
Treatment of Choice for Latent Syphilis, Unknown Duration

- Intramuscular injection 2.4 MU benzathine penicillin weekly x 3
- Prophylactic treatment:
  - Syphilis case contacts < 90 days
  - Notify partners up to 12 months

CDC, 2015

Case

- 44 year old HIV-infected female, occasionally exchanges sex for money or drugs
- C/o 1 week headache, ringing in right ear with some hearing loss
- RPR 1:16, TPPA reactive
Indications for CSF Analysis

- Neurological findings
- Ocular abnormalities
- Tertiary disease (dementia, aortic, gumma)
- Treatment failure (lack of 4-fold decline at 6, 12 or 24 m)

CDC STD Treatment Guidelines, 2015

Syphilis and HIV infection

- Multiple chancres
- May present with overlapping primary and secondary manifestations
- Rarely abnormal serology but slower decline
- Increased risk early neurosyphilis

Zetola and Klausner, Clin Inf Dis 2007

Syphilis increases HIV viral load and decreases CD4 cell counts in HIV-infected patients with new syphilis infections

Katie Berkebus*†‡, Pragya Patel*§, McKenzy Taylor†, Peter R. Korobelnik, Robert H. Bush*, Scott D. Haberlong, Jeffrey E. Klausner*†‡

AIDS, 2004
Prevention

• Individual level
  – Reduce exposure
  – Reduce risk of infection after exposure
  – Reduce sequelae of infection

• Population level
  – ↓ R₀ (reproductive number)
  – Reduce duration infection

Screening, Treatment and Partner Services

CDC Screening Recommendations for Syphilis

• Pregnancy
  – First visit
  – Repeat at 28-32 weeks in high-prevalence areas

• Men who have sex with men
  – Every year
  – More frequently (every 3 months) if
    • > 1 partner past 12 months
    • Meet partners online or sex venues
    • Have sex in conjunction with illicit drug use (especially methamphetamine)
    • Have sex partners who participate in those activities

CDC STD Treatment Guidelines, 2015
Increased Testing Associated with Decreased Secondary Syphilis, Australia, 2007-2014

Chow et al. Clin Inf Dis 2017

Syphilis Chemoprophylaxis

Table 1. Results of GBST for 50000 Men

<table>
<thead>
<tr>
<th>GBST</th>
<th>No. Positive</th>
<th>Follow-Up positive</th>
<th>HIV-infected</th>
<th>HIV-uninfected</th>
</tr>
</thead>
<tbody>
<tr>
<td>D. 5</td>
<td>5</td>
<td>2</td>
<td>0.04</td>
<td>0.005</td>
</tr>
<tr>
<td>D. 6</td>
<td>6</td>
<td>3</td>
<td>0.08</td>
<td>0.015</td>
</tr>
<tr>
<td>D. 9</td>
<td>9</td>
<td>4</td>
<td>0.12</td>
<td>0.025</td>
</tr>
<tr>
<td>D. 11</td>
<td>11</td>
<td>5</td>
<td>0.16</td>
<td>0.045</td>
</tr>
<tr>
<td>D. 14</td>
<td>14</td>
<td>7</td>
<td>0.20</td>
<td>0.060</td>
</tr>
</tbody>
</table>

Bates R et al. JTD 2015
Doxy 200 mg after sex
73% decline in syphilis

Summary

• Think syphilis
• Screen, Treat, Treat partners, Screen
• Prevention works…if funded
• Doxycycline prophylaxis is highly promising
Learning Objectives

After attending this presentation, learners will be able to:
- Describe changing epidemiology of viral hepatitis
- Describe new hepatitis B vaccine strengths and limitations
- Know when and how to screen for NAFLD/NASH

EVOLUTION OF LIVER INJURY IN HIV

Sherman KE et al, HEPATOLOGY COMM, 2017

NOT ON THE RADAR
HAV
HDV
TOPICS

- VIRAL HEPATITIS
  - Changing Epi and New Concerns
  - HBV New Vaccine
- NAFLD/NASH
  - Increased Recognition
  - New Therapies?

HEPATITIS A

- Increase frequency of reporting
  - <2000 Cases reported by CDC in 2016
  - >7000 Cases reported by CDC in October, 2018
  - Significant increase seen in European cities among MSM

---

Arkansas Officials Warn Of Another Possible Hepatitis A Outbreak

The AP (10/10/18) reports the Arkansas Department of Health is warning about another potential outbreak of Hepatitis A after a patient with a positive test was traced to a dental office. The Arkansas Department of Health is warning about another potential hepatitis A exposure in "an employee of Murdock's Catfish in Jonesboro." The Arkansas Department of Health said the employee may have infected multiple others.

The U.S. Centers for Disease Control and Prevention (CDC) updated this outbreak on Friday afternoon to a total of 119 cases of Hepatitis A from eight states. Forty-seven of these individuals have been hospitalized, but no related deaths are being reported.

What do hepatitis A cases among food workers mean for you? Eight questions answered

Terry DeMio and Anne Sakey, Cincinnati EnquirerPublished 10:50 p.m. ET Updated 5:22 a.m. ET Sept. 5, 2018

The Centers for Disease Control and Prevention on Friday said it had identified 119 cases in eight states of Hepatitis A linked to a outbreak among food workers in Hawaii. The outbreak started in August and the CDC said it was linked to a smoothie bar.

Arkansas is also seeing a hepatitis A outbreak. The Arkansas Department of Health said an employee of Murdock's Catfish in Jonesboro tested positive for the disease.

The outbreak on Friday afternoon brought the total number of cases to 119 in eight states. Forty-seven of the cases have been hospitalized, but no deaths have been reported.

The CDC said that 119 people have been ill with Hepatitis A since August. That's more than the 109 cases linked to the outbreak in 2016 and the highest number since 2002.

The disease is spread through the fecal-oral route, typically through eating or drinking food or water that is contaminated with feces, or through sexual contact.

The CDC said that people who have hepatitis A may not have symptoms, but can still spread the disease to others. The disease is usually not spread through casual contact, like shaking hands, hugging, or kissing.

People who have Hepatitis A can spread the disease to others for several days before they show symptoms. The window for transmission is about two weeks before symptoms begin to two weeks after symptoms begin.

The symptoms of Hepatitis A typically begin within two weeks of exposure and can include:

- Fever
- Fatigue
- Abdominal pain in the upper right side of the body
- Nausea
- Vomiting
- Jaundice (yellowing of the skin and eyes)
- Dark urine
- Light-colored stools

The disease can range from mild to severe. In some cases, it can lead to liver damage or even death.

People with Hepatitis A should avoid drinking alcohol while they are sick and should avoid close contact with other people until they are well and their doctor recommends it.

People who have been exposed to Hepatitis A should get vaccinated to prevent the disease. The vaccine is effective if given within two weeks of exposure.

The Hepatitis A vaccine is given in two doses, usually six months apart. People who have been exposed to Hepatitis A should get their first dose as soon as possible after exposure.

People who have Hepatitis A should avoid caring for others or going to work or school if they are sick. They should also avoid doing activities that involve contact with other people's blood, such as blood donations or body piercing.

The Hepatitis A vaccine is recommended for all people aged 6 months and older, including those who travel to countries with high rates of Hepatitis A, those who have had previous contact with Hepatitis A, and those who work in healthcare settings.

The vaccine is not recommended for pregnant women, people with a history of hepatitis B, or people with a history of liver disease.

The CDC recommends that everyone get vaccinated against Hepatitis A at least once in their lifetime. The vaccine is available without a prescription at many pharmacies.

The Hepatitis A vaccine is a safe and effective way to prevent this serious disease. People who are at risk for Hepatitis A should get vaccinated to protect themselves and their loved ones.

The vaccine is available without a prescription at many pharmacies. People who are at risk for Hepatitis A should get vaccinated to protect themselves and their loved ones.

The Hepatitis A vaccine is a safe and effective way to prevent this serious disease. People who are at risk for Hepatitis A should get vaccinated to protect themselves and their loved ones.
CLINICAL PRESENTATIONS

- Asymptomatic disease without jaundice
- Symptomatic, self-limiting disease with jaundice for less than 8 weeks
- Cholestatic jaundice lasting more than 10 weeks
- Relapsing acute hepatitis, with two or more instances over a 10-week period
- Acute hepatic failure

HEPATITIS B

- First new vaccine in more than 20 years approved by FDA
- Hepisav-B (Dynavax)
  - Contains CPG 1019 Adjuvant + 20 mcg Hepatitis Surface Antigen (recombinant)
  - Two doses effective in Immunocompetent Patients
  - Three dose regimen studied in those with CKD
- No data in HIV-infected Persons
VACCINE ADHERENCE

- National Survey of Adults Receiving First HBV Vaccination
  - N = 535,759
- Completion of Vaccine Series Determined

RESULTS
- No significant difference by age group

Efficacy endpoints-HEPLISAV-B

FDA approval

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>SPR (95% CI)</th>
<th>Difference in SPR (95% CI)</th>
<th>Difference in % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENGERIX-B</td>
<td>90.1% (89.3, 91.0)</td>
<td>90.1% (89.3, 91.0)</td>
<td>90.1% (89.3, 91.0)</td>
</tr>
<tr>
<td>HEPLISAV-B</td>
<td>98.1% (96.9, 99.2)</td>
<td>98.1% (96.9, 99.2)</td>
<td>98.1% (96.9, 99.2)</td>
</tr>
<tr>
<td>VRBPAC</td>
<td>97.9% (96.7, 99.0)</td>
<td>97.9% (96.7, 99.0)</td>
<td>97.9% (96.7, 99.0)</td>
</tr>
</tbody>
</table>

SPR = Seroprotection rate

HEPLISAV-B
Diabetes Patients

Seroprotection Rate (%)

- HEPLISAV-B
- ENGERIX-B

Efficacy
HEPLISAV-B Dialysis Patients

- Multicenter, randomized trial
  - N= 507 vaccine and HBV exposure naive
  - HEPLISAV B 3 dose regimen vs. 4 doses Engerix B 40 mcg (2 20 mcg shots)
  - Powered for non-inferiority, 10% margin

- RESULTS
  - Both non-inferiority and several secondary superiority measures met

---

HBV/HIV Coinfection

- Lamivudine Breakthrough

HDV Significance

- HDV infection is associated with
  - Increased liver disease severity in setting of both superinfection and coinfection with HBV
  - More rapid rates of disease progression and early cirrhosis.
  - Increased risk of HCC (up to 3x fold in HBV-cirrhosis)
HDV TESTING RECOMMENDATIONS among HBsAg+ Individuals

- **AASLD Guidelines:** "Laboratory tests should include assessment of liver disease, markers of HBV replication, and tests for coinfection with HCV, HDV, or HIV.

- **EASL Guidelines:** Other causes of chronic liver disease should be systematically looked for including co-infections with HDV, HCV, and/or HIV (A1)."

- **APASL Guidelines:** "Other causes of chronic liver disease should be systematically looked for, including co-infections with HDV.”

Screening Study Results

- 1007 HBsAg (+)
  - 852 HIV Negative (84.6%)
  - 115 HDV Ab Tested (13.2%)  
    - 155 HIV Positive (15.4%)
    - 8 HDV Ab Tested (5.1%)
  - All HDV Ab negative
  - 4 HDV Ab Positive (3.3%)

P= 0.003
n.s

Safaie et al, VIRUS RES, 2018
Summary of Screening

- HDV testing is rarely performed in HBsAg+ subjects in our system.
- Patients with HIV are less likely to have been tested than those without HIV.
- Gastroenterologist/Hepatologists are more likely to order HDV testing than other health care providers.
- The rate of HDV positivity in a mid western city was 3.3% (95% C.I. range 0.9% - 8.2%).

WHAT IS NAFLD?

- FATTY LIVER (>5% Steatosis)
- Non-Alcoholic (<21 drinks/week or less)
- NAFLD (ALT Elevated)
- NASH
FATTY LIVER
A Continuum of Disease

NATURAL HISTORY of NASH

NASH 5-20% CIRRHOSIS 22-33% LIVER RELATED DEATH or TRANSPLANT
8-10% in 7 Years
HCC

LIVER TRANSPLANTATION TRENDS
NASH CIRRHOSIS
NAFLD/NASH IN HIV

Prevalence


Risk Factors for NALFD in those with HIV

Metabolic syndrome
- Obesity
- Visceral and ectopic obesity
- Hypertension
- Hyperglycemia

HIV Medications (NRTI/PI)
- Pancreatico-biliary diversion
- Total parenteral nutrition

Hormonal disturbances
- Hyperthyroidism
- Hypopituitarism
- Hypogonadism
- PCOS

Steatosis
NASH
Cirrhosis

OBESITY in U.S.

OBESITY in U.S.
**Diagnostic/Management Algorithm**

**NAFLD in HIV**

<table>
<thead>
<tr>
<th>Clinical Suspicion of NAFLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal Liver Enzymes</td>
</tr>
<tr>
<td>Imaging Suggesting Fat in Liver</td>
</tr>
<tr>
<td>Laboratory Tests to rule out other causes of liver disease</td>
</tr>
</tbody>
</table>

**FIB-4**

- **FIB-4** < 1.5 and APRI < 0.5
- **FIB-4** > 3.25 or APRI > 1.5
- **FIB-4** > 1.5 < 3.25 or APRI > 0.5 < 1.5

- **High probability of significant fibrosis**
- **Non-invasive assessment and early referral to hepatologist**
- **Consider liver biopsy (especially if DM or elevated CAP > 240)**
- **Low probability for significant fibrosis**
- **Periodic monitoring**
- **Non-invasive assessment**

---

**NAFLD/NASH TREATMENT**

**TARGETS OF OPPORTUNITY**

- Metabolic Controllers
- Oxidative Stress
- Hepatic Fibrosis
- Apoptosis
- Necrosis
- Inflammation

---

**CONCLUSION**

- Liver Disease remains an important consideration in those with or without HIV infection
- Viral infections that were rare have become common again
- Changes in cART management require awareness of coinfections
- NAFLD/NASH is a growing problem
Learning Objectives

After attending this presentation, learners will be able to:

▪ List the types of conditions for which biologic agents may be prescribed for people with HIV infection

▪ Explain the mechanism of action in general of these agents to a patient in your practice so that he or she may understand why certain opportunistic infections and other complications may arise

▪ Describe the array of infectious and other complications that may arise with these agents

▪ Design strategies that you can use in clinic to prevent infectious and other complications in your patients
HIV-infected patients living longer


Life expectancy in US declines for 2 years in row

OECD, CDC, The Economist Jan 4, 2018

Autoimmune disease and cancer increase with age

National Harbor, Maryland, December 9-11, 2018
Immunobiologics treat autoimmune disease and cancer

- Rheumatoid arthritis
- Vasculitis
- Crohn disease
- Ulcerative colitis
- Psoriasis

Anti-CD20
- Rituximab

Checkpoints block
- Ipilimumab

CAR-T cells

What is a “biologic”?  
- Any biologically derived product
- Binds or interferes with a specific molecular target
  - Monoclonal antibodies
  - Receptor analogues
  - Chimeric small molecules
- Abbreviations placed at the ends of the names of therapeutic agents convey specific information relating to their structure:
  - “-cept” refers to fusion of a receptor to the Fc part of human IgG1
  - “-mab” indicates a monodonal antibody (mAb)
  - “-ximab” indicates a chimeric mAb
  - “-zumab” indicates a humanized mAb

Who is the most immune suppressed?

- Heme malignancy/stem cell transplant
- Organ transplant
- Autoimmune disease treatment
- Solid tumor treatment
- Congenital/acquired immune deficiency
- Hyposplenism
Who is the most immune suppressed?

- Heme malignancy/stem cell transplant
- Organ transplant
- Autoimmune disease treatment
- Solid tumor treatment
- Congenital/acquired immune deficiency
- Hyposplenism

Type of immune defect related to drugs used

- **Humoral immunity**
  - Rituximab (anti-CD20)
  - Hyposplenism
  - CVID (low IgG)

- **Cell-mediated immunity**
  - Solid organ transplant
  - Stem cell transplant
  - TNF-α inhibitors
  - Steroids
  - Other biologics

- **Innate (PMNs) immunity**
  - Cancer chemorx
  - Chronic gran dz (CGD)

How is this different from HIV immunosuppressed patients?

<table>
<thead>
<tr>
<th>Immune defect</th>
<th>HIV</th>
<th>Non-HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death of CD4+ T-cells</td>
<td>Death of CD4+ T-cells</td>
<td>Heterogeneous</td>
</tr>
<tr>
<td>CD4+ count</td>
<td>CD4+ count</td>
<td>No reliable tests available</td>
</tr>
</tbody>
</table>
Case

- 56 year-old woman with HIV (CD4 360, VL <50) with Crohn disease managed with infliximab and 6-MP
- Presents to ED complaining of shortness of breath x 3 weeks
- What else do you want to know?

Case

- 56 year-old woman with HIV (CD4 360, VL <50) with Crohn disease managed with infliximab and 6-MP
- Presents to ED complaining of shortness of breath x 3 weeks
- PPD negative prior. Lives in New York. Came back 4 weeks ago from a trip to Puerto Rico where she visited family and helped with property clean up

Case

- 56 year-old woman with HIV (CD4 360, VL <50) with Crohn disease managed with infliximab and 6-MP
- Presents to ED complaining of shortness of breath x 3 weeks
- What do you check next?
**Case**
- 56 year-old woman with HIV (CD4 360, VL <50) with Crohn disease managed with infliximab and 6-MP
- Presents to ED complaining of shortness of breath x 3 weeks
- Urinary histoplasma antigen positive. Chest CT: symmetric nodules

Diagnosis: Acute histoplasmosis
Case courtesy Dr. Camille Kotton, MGH/Harvard

**TNF-α inhibitors: tuberculosis**
- Post-marketing survey of TB cases following release of infliximab (1998-2001)
- 70 cases of TB
- Median time to diagnosis: **12 weeks** (range 1-52)
- TB characteristics
  - Extrapulmonary disease: 57%
  - Disseminated disease: 24%

Keane J. NEJM. 2001

**TNF-α inhibitors: mycobacteria and fungi**
- Survey of serious infection on TNF-α inhibitors in the US
  - Non-tuberculous mycobacteria: 32
  - TB: 17
  - Histoplasmosis: 56
- FDA alert 2008: 256 cases of histoplasmosis in patients on TNF-α inhibitors

Winthrop KL. CID. 2008
**Case**
- 42 year-old male with Crohn disease x 3 years, started on infliximab after persistent diarrhea 5 months prior
- Admitted with 3 weeks shortness of breath, low grade temps, dry cough. No help with amoxicillin x 1 week
- What is your differential diagnosis?

**Case** courtesy Dr. Ivan Hung, University of Hong Kong

---

**Case**
- Sputum AFB negative x 3
- Sputum AFB Cx negative
- Respiratory virus PCR negative
- Chest CT: ground glass opacities
- BAL DFA+ P. jiroveci
- HIV Ab positive
- Diagnosis: Pneumocystis pneumonia
- Treated with clindamycin and primaquine (TMP/SMX allergic)
- Started ART

**Case** courtesy Dr. Ivan Hung, University of Hong Kong
Case

- 74 year-old HIV-negative man with interstitial lung disease and chronic lymphocytic leukemia on idelalisib
- Admitted with progressive shortness of breath on exertion and dry cough for 1 month
- Diagnosis: Pneumocystis pneumonia

Case courtesy Dr. Jen Mulliken, UCSF

Biologics and PCP

- Retrospective analysis of 2198 patients (across 8 studies) with relapsed CLL or NHL
- Patients on idelalisib +/- co-therapy (ritux or ritux/benda)
- PCP RR: 12.5
- Median time to PCP: 141 days
- No standard PCP prophylaxis guidance

Sahn LH, Blood, 2016 Furman, NEJM, 2014

Case

- 69 year-old HIV-negative woman with low grade lymphoma, treated only with rituximab (anti-CD20)
- Months after treatment, develops slowly progressive mental status changes
- CSF PCR positive for JC virus and MRI consistent with PML
- Diagnosis: Progressive Multifocal Leukoencephalopathy (PML)

Case courtesy Dr. Camille Kotton, MGH/Harvard
Biologics and viral infections

- **Hepatitis B** reactivation
  Reactivation with TNF-α inhibitors reported
  Rituximab – common

- **JC virus** (progressive multifocal leukoencephalopathy)
  Natalizumab – must check JCV IgG
  Rituximab – reports, less common

- **Varicella zoster virus**

Cancer immunotherapy in the beginning

How Jimmy Carter beat cancer

New immunotherapy drug behind Jimmy Carter’s cancer cure
Checkpoint blockade: a billion dollar industry

- Block the inhibitory receptor with monoclonal antibodies (CTLA-4, PD1)
- Target the immune system – not the cancer
- May lead to autoimmune disease & immune-related adverse events
- Infection risk may increase as immune suppression used to treat complications of therapy

Skin and hair depigmentation after treating melanoma with anti-CTLA-4

Case

- 52 year-old male with HIV (CD4 450, VL <50 on abacavir/dolutegravir/lamivudine) with skin squamous cell cancer. Enrolled in AMC-095 trial. On nivolumab x 1 year. Presents with focal incontinence and diarrhea
- Diagnosis: Checkpoint inhibitor associated colitis
- Treated with prednisone high dose and infliximab. Nivolumab stopped
- Skin cancer in partial remission

Case courtesy Dr. Jackie Wang, UCSF
Gene therapy was a boy’s last chance to stop leukemia. And it worked.
PBS
March 4, 2018

“CAR” Adoptive T cell therapy: CAR T cells
- Chimeric Antigen Receptor (CAR) T cells are genetically modified T cells
- T cells respond when tumor cell surface antigen recognized
- Substantial immune-related adverse events (cytokine release syndrome)
- Infection risk may increase as immune suppression used to treat complications of therapy

Evaluation prior to TNF-α inhibitor use
- HIV
  Is patient adequately immune reconstituted? CD4>200. Any drug interactions?
- TB risk
  Check PPD or IGRA, CXR, take TB history
- Endemic mycoses/fungi
  Take travel history, symptom check
- Hepatitis B
- Vaccines
  Check hepatitis B surface antigen and core antibody
Evaluation during biologic use

- HIV
  Is patient maintaining good immune function? CD4?

- Infection vs "Infection"
  Is patient experiencing any known adverse effect associated with the biologic?

- Vaccines
  Live vaccines usually contraindicated

- Be vigilant
  Your patient may have a new complication not previously reported

Anti-TNF inhibitors in patients with CD4<500

HIV-infected patients started on biologics

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients</th>
<th>Age (mean±SD)</th>
<th>ART at time of biologic agent</th>
<th>Viral suppression at time of biologic agent</th>
<th>Baseline CD4 cell count prior to biologic?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatology</td>
<td>35</td>
<td>44</td>
<td>3/2</td>
<td>3/0</td>
<td>603</td>
</tr>
<tr>
<td>Papulosquamous (3)</td>
<td>4</td>
<td>34</td>
<td>2/2</td>
<td>2/2</td>
<td>603</td>
</tr>
<tr>
<td>Psoriasis (4)</td>
<td>4</td>
<td>34</td>
<td>2/2</td>
<td>2/2</td>
<td>603</td>
</tr>
<tr>
<td>Lichen planus (1)</td>
<td>4</td>
<td>34</td>
<td>2/2</td>
<td>2/2</td>
<td>603</td>
</tr>
<tr>
<td>Rheumatology</td>
<td>36</td>
<td>34</td>
<td>2/2</td>
<td>2/2</td>
<td>752</td>
</tr>
<tr>
<td>Arthritis rheumatic (1)</td>
<td>45</td>
<td>34</td>
<td>2/2</td>
<td>2/2</td>
<td>603</td>
</tr>
<tr>
<td>Rheumatoid arthritis (4)</td>
<td>45</td>
<td>34</td>
<td>2/2</td>
<td>2/2</td>
<td>603</td>
</tr>
</tbody>
</table>

Fink DL et al, Int J STD&AIDS, 2017
Learning Objectives

After attending this presentation, learners will be able to:

▪ List the types of conditions for which biologic agents may be prescribed for people with HIV infection
▪ Explain the mechanism of action in general of these agents to a patient in your practice so that he or she may understand why certain opportunistic infections and other complications may arise
▪ Describe the array of infectious and other complications that may arise with these agents
▪ Design strategies that you can use in clinic to prevent infectious and other complications in your patients

Thanks Michelle Hermiston, Ivan Hung, Camille Kotton, Jen Muliken, Brian Schwartz, Paul Volberding, Jackie Wang

Question-and-Answer
Investigational Approaches to Antiretroviral Therapy: 
New Strategies and Novel Agents

Joseph J. Eron MD
Professor of Medicine
University of North Carolina
Chapel Hill, North Carolina

Learning Objectives

After attending this presentation, learners will be able to:

▪ Describe characteristics of a new NNRTI (doravirine) in last stage development for treatment-naive patients
▪ List several two-drug combinations that are being evaluated for initial or maintenance therapy
▪ Describe the mechanisms of action and potential uses of 2 entry inhibitors in development for patients with resistant virus

Outline of the Talk

▪ New Agents for Initial Antiretroviral Therapy
▪ New Strategies for Initial ART and treatment switch (including long-acting therapy)
▪ Novel Agents for Resistant Virus
▪ New Agents in Early Development
What is needed for initial therapy?

- We have convenient, safe, effective unboosted integrase inhibitor therapy – do we need something else?
- Alternatives to INSTI – based therapy?
  - NNRTI – based therapy
    - with better tolerability.
    - less resistance and fewer dosing restrictions.
  - PI – based therapy
    - more convenient
    - Fewer drug-drug interactions
- Exposure to fewer agents?
  - Two drug combinations
  - Alternative dosing strategies

---

**AMBER: Single Tablet DRV/cobi/TAF/FTC vs. DRV/cobi plus TDF/FTC**

- Virologic response at Wk 96 consistent across subgroups
  - BL VL >75 100,000 copies/mL, BL CD4+ 3/4, 200 cells/mm³:
    - age ≥50 yrs, sex, race
  - Resistance analysis in 9/15 patients with protocol defined virologic failure with DRV/cobi/FTC/TAF vs 8/19 in control arm through Wk 96
    - 1 patient with M184V/I in each arm
    - No evidence of emergent DRV, primary PI, or TFV RAMs
- Better bone density changes and renal makers

---

**Very Low Resistance Emergence with Boosted PI Regimens**

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>PI</th>
<th>Wk</th>
<th>Genotypes</th>
<th>Major PI Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASTLE[^1]</td>
<td>440</td>
<td>ATV/RTV</td>
<td>96</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>442</td>
<td>LPV/RTV</td>
<td>96</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>ACTG 5202[^2]</td>
<td>450</td>
<td>ATV/RTV</td>
<td>96</td>
<td>56</td>
<td>0</td>
</tr>
<tr>
<td>Study 10[^3]</td>
<td>105</td>
<td>ATV/RTV</td>
<td>144</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>ARTEMIS[^4]</td>
<td>340</td>
<td>DRV/RTV</td>
<td>96</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>340</td>
<td>LPV/RTV</td>
<td>96</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>FLAMINGO[^5]</td>
<td>242</td>
<td>DRV/RTV</td>
<td>48</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>ACTG 5257[^6]</td>
<td>605</td>
<td>ATP/RTV</td>
<td>96</td>
<td>75</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>605</td>
<td>DRV/RTV</td>
<td>96</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td>Single Tablet Regimen[^7][^8][^9][^10]</td>
<td>362</td>
<td>DRV/cobi</td>
<td>48</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>363</td>
<td>DRV/cobi</td>
<td>48</td>
<td>NR</td>
<td>0</td>
</tr>
</tbody>
</table>

Two Drug Regimens for Initial Therapy

- **Rationale**
  - "nuc-saving" – a need that seems less common
  - advanced renal disease or TFV or ABC intolerance
  - Minimize ARV exposure for therapy that will last for decades
  - Cost

- **Strategies**
  - Boosted PI plus INSTI (NEAT 001)
  - Boosted PI plus 3TC (GARDEL and ANDES studies)
  - Dolutegravir plus 3TC (PADDLE, A5353, GEMINI)

---

**Snapshot Analysis by Visit: Pooled ITT-E Population**

![Graph showing virologic outcomes by visit](image)

*Based on Cochran-Mantel-Haenszel stratified analysis adjusting for the following baseline stratification factors: plasma HIV-1 RNA (≤100,000 or >100,000 copies per mL) and CD4+ cell count (≤200 or >200 cells per micrometer). Calculated from a repeated measures model adjusting for study, treatment, visit (repeated factor), baseline plasma HIV-1 RNA, baseline CD4+ cell count, treatment and visit interaction, and baseline CD4+ cell count and visit interaction.*


---

**Proportion of Participants With Plasma HIV-1 RNA <50 c/mL at Week 48 (Snapshot Analysis) by Baseline Plasma HIV-1 RNA**

![Graph showing proportion by viral load](image)

*Calculated from a repeated measures model adjusting for study, treatment, visit (repeated factor), baseline plasma HIV-1 RNA, baseline CD4+ cell count, treatment and visit interaction, and baseline CD4+ cell count and visit interaction.*

CAB 30 mg + ABC/3TC PO QD for 20 weeks (N=309)

**Induction period**

LATTE-2: Study of Long Acting Cabotegravir and Rilpivirine – 96 week data

**Maintenance period**

Add RPV PO QD 4 weeks

Maintenance of HIV-1 RNA <50 c/mL

** Comparable Response Across Arms**

Week 96 HIV-1 RNA <50 c/mL by Snapshot (ITT-ME)

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>HIV-1 RNA &lt;50 c/mL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAB + RPV LA Q8W (n=115)</td>
<td>100</td>
</tr>
<tr>
<td>CAB + RPV LA Q4W (n=115)</td>
<td>98</td>
</tr>
<tr>
<td>CAB + NRTIs PO (n=56)</td>
<td>92</td>
</tr>
<tr>
<td>Q4W IM</td>
<td>94</td>
</tr>
<tr>
<td>Q8W IM</td>
<td>92</td>
</tr>
</tbody>
</table>

**Results**

- 309 patients were enrolled (ITT-exposed): 91% male, 20% non-white, and 19% ≥100,000 c/mL. HIV-1 RNA 236 patients were randomized into the MP; 253 completed MP with 252 entering EP. 3.0%

**Table 1. Snapshot Outcomes at Week 160**

<table>
<thead>
<tr>
<th>Outcome at W160</th>
<th>Q8W IM n (%)</th>
<th>Q8W IM n (%)</th>
<th>Optimized Q8W IM n (%)</th>
<th>Optimized Q8W IM n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WID due to AE</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>WID due to other reasons</td>
<td>3 (3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Notes:**
- HIV-1 RNA <50 c/mL, %
- Data presented for the optimized Q8W IM arm as a number (%) of patients in that arm, with standard errors (SE), 95% confidence intervals (CI), and p-values
- **ITT-ME** includes all patients who were randomized to the MP and had ≥1 IM injection or ≥1 week of RPV treatment

**Slide 14 of 37**

**Slide 15 of 37**

**Slide 16 of 37**
NEW THERAPY FOR RESISTANT VIRUS

HIV Entry Inhibitors

* = FDA approved
Ibalizumab

• Humanized monoclonal Ab: binds CD4 on host cells; blocks HIV entry (post attachment inhibitor)¹
• Active against CCR5 and CXCR4 tropic HIV
• No cross resistance with other ARVs²
• IV infusion: 2,000 mg loading dose then 800 mg every 2 wks
• Duration of infusion: 15-30 min

¹Emu B et al, Abstract 1686, IDWeek 2017; ²Weinheimer S et al, CROI 2018

Ibalizumab in Persons with Multi-Drug Resistant HIV

• Phase 3 trial: 40 heavily treatment experienced pts with 3-class ARV resistance, ≥3 active drug
• Primary endpt: VL drop >0.5 log₁₀ C/mL
  • 3% during control period
  • 83% after loading dose
• Regimen optimized at day 14
  • Wk 24: VL <200 in 50%
• Expanded access: viral suppression to wk 48

Fostemsavir (FTR): Oral HIV Attachment Inhibitor

• Prodrug of tamsavir: binds to gp120, inhibits HIV attachment to CD4
• Phase 3 trial in heavily treatment experienced patients with VF (BRIGHTE)
Fostemsavir (FTR): Phase 3 Trial (BRIGHTE)

At wk 24, 54% of randomized and 36% of non-randomized pts who received FTR + OBR achieved VL <40

"Regulatory submissions are currently anticipated to take place in the 2019/2020 timeframe"

BRIGHTE: Efficacy at Wk 48 (FDA Snapshot)

<table>
<thead>
<tr>
<th>Outcome at Wk 48, n (%)</th>
<th>Randomized Cohort (n = 272)</th>
<th>Nonrandomized Cohort (n = 99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 RNA &lt; 40 c/mL (virologic success)</td>
<td>146 (54)</td>
<td>38 (38)</td>
</tr>
<tr>
<td>HIV-1 RNA = 200–400 c/mL</td>
<td>187 (68/101) (70)</td>
<td>43 (40/44) (46)</td>
</tr>
<tr>
<td>HIV-1 RNA ≥ 400 c/mL (virologic failure)</td>
<td>104 (38)</td>
<td>52 (53)</td>
</tr>
<tr>
<td>Data-in window not below threshold</td>
<td>72 (30)</td>
<td>33 (33)</td>
</tr>
<tr>
<td>D/c for lack of efficacy</td>
<td>6 (2)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>D/c for other reason while not below threshold</td>
<td>9 (3)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Change in OBT</td>
<td>17 (6)</td>
<td>14 (14)</td>
</tr>
<tr>
<td>No virologic data</td>
<td>22 (8)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>D/c due to death or diagnosis of death</td>
<td>13 (5)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>D/c due to other reasons</td>
<td>52 (2)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Missing data during window but on study</td>
<td>2 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Median CD4 cell count change vs BL, cells/mm³ (IQR)</td>
<td>127 (54 to 304)</td>
<td>25 (5 to 121)</td>
</tr>
</tbody>
</table>

NOVEL AGENTS IN EARLY DEVELOPMENT
Long-acting NRTTI: MK-8591 (EFdA)

- Nucleoside RT translocation inhibitor (NRTTI)
- Half life of active anabolite: ≈ 80-130 hr
- Humans: single oral dose as low as 0.5 mg suppressed HIV RNA for >7 days

MK-8591 is More Potent Against WT and M184V/I Viruses Than Approved NRTIs

<table>
<thead>
<tr>
<th>Compound</th>
<th>Virus</th>
<th>IC₅₀ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MK-8591</td>
<td>WT</td>
<td>0.2 ± 0.1</td>
</tr>
<tr>
<td>TAF</td>
<td>WT</td>
<td>2.4 ± 0.3</td>
</tr>
<tr>
<td>AZT</td>
<td>WT</td>
<td>2.0 ± 0.3</td>
</tr>
<tr>
<td>TDF</td>
<td>WT</td>
<td>7.3 ± 2.1</td>
</tr>
<tr>
<td>FTC</td>
<td>WT</td>
<td>103.3 ± 18.6</td>
</tr>
</tbody>
</table>

Study in healthy volunteers: daily doses as low as 0.25 mg expected to lead to HIV suppression

Phase 2b trial in people with HIV, in combination with doravirine (NNRTI) and 3TC, has started (DRIVE2Simplify)
- Daily dosing
- Potential for once weekly or even once monthly dosing
- "Partners wanted"

MK-8591 achieve target levels with only 0.25 mg dose
Gilead’s capsid inhibitors inhibit HIV capsid function, resulting in aberrant core assembly/disassembly via multiple steps in HIV replication cycle.

GS-6207 is a potent inhibitor of all major HIV-1 subtypes and is more potent than currently marketed ARVs.

GS-6207 is more potent than currently marketed ARVs.
Plasma PK in Rats and Dogs Following a Single SC Dose

- Single subcutaneous injection maintains plasma concentrations well above paEC\textsubscript{95} for >24 weeks in dogs
- PK supports long acting administration, potentially Q3M or longer, in humans

paEC\textsubscript{95}: plasma averaging adjusted effective concentration required to inhibit replication by 95%

[Graph showing plasma concentrations over time for rats and dogs with different doses]
HIV-1 discovered
ZDV monotherapy
ZDV/3TC
Triple Drug Therapy
Single Tablet Regimens
Integrase Era
LONG Acting Injectable
2 drug regimen
Implantable ART
bNAbs for therapy
1983
1987
1995
1996
2006
2012
2019
2025
Antiretroviral Therapy: The Future

Acknowledgements
- Judy Currier
- Dan Kuritzkes
- Raphael Landovitz
- Carey Hwang
- Michael Aboud
- Chloe Orkin
- Kathleen Squires
- Trip Gulick
- Raj Gandhi
- Jay Glober

Question-and-Answer
Elimination of Hepatitis C in Individuals With HIV Infection
David L. Thomas, MD, MPH
Professor of Medicine
The Johns Hopkins Medical Institutions
Baltimore, Maryland

Learning Objectives
After attending this presentation, learners will be able to:
▪ List the 2030 elimination goals for HCV infection
▪ Compare treatment of HCV infection in a person with HIV infection and someone without

Global health importance of hepatitis – mortality 1990-2013

ARS Question 1: Which is most true about the elimination of HCV?

1. Applies to both new infections and mortality
2. Based on 90:90:90
3. Impossible without HCV vaccine
4. Will be impossible in HIV/HCV with current HCV treatments
5. Is on target in the USA

WHO Hepatitis Elimination Goals

90% reduction in incidence

<table>
<thead>
<tr>
<th></th>
<th>2015</th>
<th>2020 (30%)</th>
<th>2030</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV</td>
<td>~1.75 million</td>
<td>~1.23 million</td>
<td>175,000</td>
</tr>
</tbody>
</table>

WHO Hepatitis Elimination Goals

65% reduction in mortality

<table>
<thead>
<tr>
<th></th>
<th>2015</th>
<th>2020 (10%)</th>
<th>2030</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV</td>
<td>~400,000</td>
<td>~360,000</td>
<td>140,000</td>
</tr>
</tbody>
</table>
Targets to eliminate hepatitis C

<table>
<thead>
<tr>
<th>Intervention</th>
<th>2015</th>
<th>2020</th>
<th>2030</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV diagnosed</td>
<td>20%</td>
<td>30%</td>
<td>90%</td>
</tr>
<tr>
<td>HCV treatment</td>
<td>1%</td>
<td>3 million</td>
<td>80%</td>
</tr>
<tr>
<td>Donations screened</td>
<td>97%</td>
<td>97.5%</td>
<td>100%</td>
</tr>
<tr>
<td>Harm reduction (syr/person/yr)</td>
<td>27</td>
<td>200</td>
<td>300</td>
</tr>
<tr>
<td>Safe injection</td>
<td>95%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Global cascade of HCV care and 2030 WHO elimination goals: 90/80 target

- Infected
- Diagnosed
- Treated
- Cured

Elimination prefix cascade

- Eradication
- Elimination
  - Micro-elimination
    - HIV positive
  - National
    - Nano-elimination
  - Post-elimination
    - Clinic
    - Patient
Efficacy of SOF/LDV in HIV Co-infected patients

- 335 patients
  - 82% male, 34% AA, 98% geno 1
  - 55% experienced
  - 20% cirrhosis
  - All 10 relapses were in AA
  - 8/10 on EFV

Efficacy of SOF/VEL in HIV/HCV Coinfection

- Patients
  - 86% male
  - 45% AA
  - 18% cirrhosis
  - 62% GT1a, 11% GT3
- Eligible ARV regimens
  - RPV
  - RAL or EVG/c
  - Pi/r (47%)
  - TDF (86%)
  - 55% boosted TDF regimen

- Patients with SVR12 in key subgroups:
  - Patients with cirrhosis: 19/19 (100%)
  - Treatment-experienced patients: 29/31 (94%)

Efficacy of G/P in HIV/HCV Coinfection

- GT3 TE excluded
- Most ART allowed: boosted regimens (DRV/LPV, or EVG)
  - Only 1 on EVG/cob; no boosted PIs enrolled
- Demographics: 8-wk treatment course
  - 18% Black
  - 19% TE
  - 16% GT3
  - 88% F0-F1

BT= GT3 cirrhosis @ wk 8
93% SVR in cirrhotics (14/15)
Efficacy of elbasvir/grazoprevir in HIV Co-infection

- C-EDGE, 218 patients

Treatment of HCV in HIV/HCV Coinfection

Cure of HCV in HIV-infected reduces ESLD and HCC

Limbaluk: JAMA 2012; Berenguer: Hepatol 2009; Merchante: J Antimicrob. Ther 2018
Reinfection threatens HCV elimination

GECCO Cohort: 2239 P-Y follow-up
- 12% MSM, 37% IDU
- 87% of reinfections: MSM
- 83% of reinfection: HIV+
- 2239 P-Y follow-up

Persons Free From Reinfection, %
Persons at Risk
Time, Year
27/64 With 2nd Reinfection (18.8/100 P-Y)
95% CI
Survivor Function

NEAT Network

Persons With Reinfection, %
Transmission mode
Overall IDU MSM
Elimination of HCV in JHU HIV-Clinic

- >8000 HIV infected, predominantly African American, PWID
- 1998 - hepatitis clinic imbedded
- 2004 - clinical trials and expanded treatment
- Low treatment uptake with IFN-era

Very low uptake 1998-2004

Mehta AIDS 2006; Wansom OFID 2017; Falade-Nwulia Hepatology 2017

---

Elimination of HCV in JHU HIV-Clinic

- >8000 HIV infected, predominantly African American, PWID
- 1998 - hepatitis clinic imbedded
- 2004 - clinical trials and expanded treatment
- Low treatment uptake with IFN-era
- Feb 2014-March 2016, 246 (96.5%) of 255 starting ART SVR12

Very low uptake 1998-2004

Mehta AIDS 2006; Wansom OFID 2017; Falade-Nwulia Hepatology 2017

---

HCV Care Continuum among 594 HIV/HCV infected patients in an urban HIV clinic

Chronic HCV

- Referred
- Evaluated
- Prescribed
- Initiated
- Cured
- Reinfeeted

---
**Elimination of HCV in JHU HIV-Clinic**

- Notable changes to enrollment:
  - Excluded: individuals with diabetes or severe kidney disease.

**HCV Treatment Initiation Across Intervention Groups**

![Graph showing HCV treatment initiation across intervention groups.](image)

- **Usual Care**: 47
- **Peer Mentors**: 83
- **Cash Incentives**: 17

**Elimination of HCV in HIV infected in Netherlands**

- Athena cohort >98% of HIV pos in recognized in Netherlands
- 69% MSM, 15% PWID
- DAAs made available in 2015
- 15 months of data through Feb 2017
Elimination of HCV in HIV infected in Switzerland

- Swiss HIV cohort study with yearly anti-HCV testing (MSM)
- Oct 2015-June 2016: one time RNA screening detected 8 infections
- SVR in 121 of 122 Rx elbasvir grazoprevir and 39 others of 177

Slide 31 of 52

Braun CID 2018; Braun CID 2018
Elimination of HCV in HIV infected in Switzerland

- 3722 retested HCV PCR from March to November 2017, 28 men (0.8%) positive
  - 16 (57%) as incident
  - 12 (43%) as chronic
- Reinfection sequences clustered from other EU countries

Elimination of HCV in HIV infected persons in France

Population description per year

Elimination of HCV in HIV infected persons in France

HCV incidence (all infections)
2.27 million persons are HIV/HCV coinfected

Public health response to eliminate HCV

- Elimination of HCV worldwide requires shifting to public health response
- HIV example is most fitting
  - ART given to >20 million persons (>240 million person months)
  - Cost of HIV ~20 billion USD/year
- Can build on HIV infrastructure for HIV/HCV elimination
- Need to address reinfection
WHO goals for elimination of hepatitis C

- "A world where viral hepatitis transmission is stopped and everyone has access to safe, affordable and effective treatment and care" WHO

- Elimination: Reduction to zero of the incidence of infection caused by a specific agent in a defined geographical area as a result of deliberate efforts; continued measures to prevent re-establishment of transmission are required. Example: measles, poliomyelitis.
Why elimination and not eradication?

HCV could be eradicated

- Every HCV-infected person can be detected
- Eradicate infection by treatment
- Humans are only source
- Transmission can be prevented
- Public health importance

HCV could be eradicated

- Every HCV-infected person can be detected
- Eradicate infection by treatment
- Humans are only source
- Transmission can be prevented
- Public health importance
- International commitment
Learning Objectives

After attending this presentation, learners will be able to select antiretroviral therapy in patients who:

- Are starting initial therapy
- Have persistently low-level viremia
- Have a baseline M184V mutation
- Are pregnant
- Are eligible for PrEP

Question

What regimen should I use as initial therapy?
Case 1

- 48 yo Male presents with newly diagnosed HIV infection
- Asymptomatic
- **Initial:** HIV RNA 28,000 c/ml
  - CD4 count 650 cells/ul
- Other labs are normal; HLA-B57 positive
- Genotype is Wild-type virus
- No prior medical history. Normal renal function
- Ok to start therapy if you think he should
Recommended Initial Regimens: InSTI Plus 2 nRTIs

- Bictegravir/TAF/emtricitabine
- Dolutegravir/abacavir/lamivudine
- Dolutegravir plus TAF/emtricitabine
- (Raltegravir plus tenofovir / emtricitabine)*

*HHS Guidelines; AIDSinfo

Virologic Response by Visit (FAS)
HIV-1 RNA <50 copies/mL, Missing=Excluded Analysis

Case 2
- 48 yo Male presents with newly diagnosed HIV infection
- Asymptomatic except for weight loss / fatigue
- Initial: HIV RNA 760,000 c/ml
- CD4 count 21 cells/ul
- Other labs are normal; HLA-B57 negative
- Genotype is Wild-type virus
- No prior past medical history. Normal renal function
- Ok to start therapy if you think he should
Recommended Initial Regimens: If an InSTI Is Not Available

- Darunavir/cobicistat/TAF (or TDF)/emtricitabine*
- Darunavir boosted with ritonavir plus TAF (or TDF)/emtricitabine
- Efavirenz/TDF/emtricitabine
- Elvitegravir/cobicistat/TAF (or TDF)/emtricitabine
- Raltegravir plus TAF (or TDF)/emtricitabine
- Rilpivirine/TAF (or TDF)/emtricitabine (if pretreatment HIV RNA level is <100,000 c/mL and CD4 cell count is >200/µL)
- Fixed-dose Dor/TDF/3TC tablet approved July 2018

Snapshot Outcomes at Week 48 for GEMINI-1 and -2

Virologic Efficacy: HIV-1 RNA <50 copies/mL, Missing=Excluded Analysis
Baseline HIV-1 RNA >100,000 copies/mL

*Based on Cochran-Mantel-Haenszel stratified analysis adjusting for the following baseline stratification factors: plasma HIV-1 RNA (≤100,000 c/mL vs >100,000 c/mL) and CD4+ cell count (≤200 cells/mm³ vs >200 cells/mm³).

Virologic outcome

Adjusted treatment difference (95% CI)

GEMINI-1
GEMINI-2

DTG + TDF/FTC
-6.7
-0.7
4.9
2.6

DTG + 3TC
-1.5
-2.6
4.9
2.6

Virologic success
Virologic nonresponse
No virologic data

GEMINI-1 DTG + 3TC (N=356)
GEMINI-1 DTG + TDF/FTC (N=358)
GEMINI-2 DTG + 3TC (N=360)
GEMINI-2 DTG + TDF/FTC (N=359)
Snapshot Analysis by Visit: Pooled ITT-E Population

Figure 3. Proportion of Participants With HIV-1 RNA <50 c/mL

Table 1. Proportion of Participants With HIV-1 RNA <50 c/mL by Subgroup

Study visit

-40 0 50 100

HIV-1 RNA, c/mL, %

80 90 100

60 70 80

0 20 40 60 80 100

Original measles model adjusting for study, visit (repeated factor), baseline plasma HIV-1 RNA, baseline CD4+ cell count, treatment, and visit interaction, and baseline CD4+ cell count and visit interaction.
Tenofovir and COBI Interact with Distinct Renal Transport Pathways

- The active tubular secretion of tenofovir and the effect of COBI on creatinine are mediated by distinct transport pathways in renal proximal tubules.

**Anion Transport Pathway**

- OAT3
- MRP4

**Cation Transport Pathway**

- OAT1
- OCT2
- H⁺
- MATE1
- COBI
- Creatinine
- Tenofovir

Lepist E, et al. ICAAC 2011; Chicago. #A1-1724

Question

What is likely the best approach to Long-Acting ARV formulations?
Case 3 (Long-acting “LA” Agents Available)

- 48 yo Male presents with newly diagnosed HIV infection
- Asymptomatic except for weight loss / fatigue
- Initial: HIV RNA 160,000 c/ml
  CD4 count 221 cells/ul
- Other labs are normal; HLA-B57 negative
- Genotype is Wild-type virus
- No prior past medical history. Normal renal function
- Ok to start therapy if you think he should

LATTE-2: Virologic Outcomes With LA Cabotegravir + Rilpivirine as Maintenance Therapy

- Injection site reactions: mild/moderate; transient
- High participant satisfaction
- Ongoing phase 3 trials (FLAIR, ATLAS): every 4-wk dosing; results in 2018
  ATLAS-2M: every 8-wk dosing; results in 2019

Long-acting NRTI: MK-8591 (EFdA)

- Nucleoside RT translocation inhibitor (NRTTI)
- Half life of active anabolite: ≈ 80-130 hr
- Humans: single oral dose as low as 0.5 mg suppressed HIV RNA for >7 day
- Study in healthy volunteers: multiple daily doses as low as 0.25 mg expected to lead to HIV suppression
- Phase 2b trial in people with HIV, in combination with DOR and 3TC, has started (DRIVE2Simplify)
  - Daily dosing
Question

What regimen should be used as initial therapy when an M184V mutation is present?

Case 3

- 30 yo Female presents with newly diagnosed HIV infection
- Asymptomatic
- **Initial:** HIV RNA 128,000 c/ml
  CD4 count 350 cells/ul
- Other labs are normal; HLA-B57 neg
- Genotype shows **M184V and K103N mutation**
- No prior medical history. No children. Does not plan to become pregnant.
- Ok to start therapy if you think she should
Question

Seems like we are now starting ARV therapy for about everyone, what about starting therapy immediately at time of diagnosis?

Case 4

- 30 yo Male was diagnosed with HIV infection 4 hours ago in the ER
- Asymptomatic
- Initial: HIV RNA 17,000 c/ml (HIV DNA positive)
  - CD4 count 470 cells/ul
- Other labs are normal; HLA-B57 neg
- Genotype determined from DNA is wild-type
- No prior medical history.
- Ok to start therapy if you think he should

Same Day ART – A Randomized Trial

- Home based testing in rural Lesotho
- Newly HIV +, no other chronic conditions requiring care, randomized to usual care vs. same day ART
  - Usual Care: labs, 2 clinic visits → ART
  - Same Day: no labs, 30 days TDF/3TC/EFV
- End Points – 3 month care linkage and % HIV RNA <200 c/mL at 12 months

<table>
<thead>
<tr>
<th>274 patients</th>
<th>Usual Care</th>
<th>Same Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>% 3 months linked</td>
<td>43</td>
<td>69</td>
</tr>
<tr>
<td>% 12 months suppressed</td>
<td>34</td>
<td>50</td>
</tr>
</tbody>
</table>
Expeditied ART – Experience in Atlanta

- Grady reduced barriers, with goal to begin ART within 72hrs
- Pre-intervention days to ART = 22, Post-intervention days to ART = 4.

<table>
<thead>
<tr>
<th>Pre-REACH (n=117)</th>
<th>Post-REACH (n=90)</th>
<th>ORR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attended scheduled appointment</td>
<td>85 (73)</td>
<td>75 (61)</td>
</tr>
<tr>
<td>Achieved viral suppression</td>
<td>97 (84)</td>
<td>83 (68)</td>
</tr>
</tbody>
</table>

Do INSTIs Cause IRIS?

- ART naive adults/children in Africa, CD4 <100
- Randomized to ART vs. ART + 12 weeks RAL
- IRIS judged by blinded committee based on clinical description and timing with regard to ART

<table>
<thead>
<tr>
<th></th>
<th>ART</th>
<th>ART + RAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number Subjects</td>
<td>902</td>
<td>933</td>
</tr>
<tr>
<td>Mean Baseline CD4</td>
<td>38</td>
<td>36</td>
</tr>
<tr>
<td>% Baseline VL &gt; 100k</td>
<td>77</td>
<td>74</td>
</tr>
<tr>
<td>Δ VL @ wk 4</td>
<td>-3.4 L</td>
<td>-2.7 L</td>
</tr>
<tr>
<td>% Mortality @ wk 24</td>
<td>10.9</td>
<td>10.2</td>
</tr>
<tr>
<td># Fatal IRIS</td>
<td>36</td>
<td>31</td>
</tr>
<tr>
<td># All IRIS</td>
<td>89</td>
<td>86</td>
</tr>
</tbody>
</table>

Should I change a regimen when low level detectable virus is present?
Case 5

- 55 yo male referred to you for evaluation
- Diagnosed 18 years ago with HIV infection
  - **Initial**: HIV RNA 936,000 c/ml
    - CD4 count 70 cells/ul
  - **Current**: HIV RNA 85 c/ml (prior value 62 c/ml)
    - CD4 count 525 cells/ul
- Started on NEL/D4T/3TC; subsequently treated with
  - LOP r/ TDF/FTC
  - EFV/ FTC/ TDF (dc).
  - Now DTG / DRV/c / 3TC
- No historical resistance tests are available

Question

What regimen should I use as initial therapy in a pregnant patient?

Case 6

- 30 yo woman presents with newly diagnosed HIV infection
- Asymptomatic; 2.5 months pregnant
  - **Initial**: HIV RNA 28,000 c/ml
    - CD4 count 650 cells/ul
- Other labs are normal; HLA-B57 neg
- Genotype is Wild-type virus
- No prior medical history. First pregnancy
- Ok to start therapy if you think she should
Intracellular concentration of Tenofovir-DP is 4-5 times higher for TAF compared to TDF

Does this expose the fetus to a higher risk of birth abnormalities?

Does this lower the risk of vertical transmission?

Andrew Hill, 2016 WHO meeting

Dolutegravir in pregnancy: Background

- No fetal toxicity or teratogenicity in animal studies described in manufacturer's submission for regulatory approval
- High placental transfer of DTG relative to other ARVs in an ex vivo study
- "Unexpected placental transfer of DTG with fetal accumulation and then slow neonatal clearance"
- 18 May 2018: Report of Neural tube defects in 4/426 (0.9%) babies born to women taking DTG in Botswana...compared to 14/11,173 (0.1%) non-DTG

DOI: 10.1056/NEJMc1807653; 24 July 2018

NTD Prevalence Difference by Exposure

<table>
<thead>
<tr>
<th>Exposure to DTG</th>
<th>Prevalence Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>During Conception</td>
<td>-0.05% (-0.2%, 0.1%)</td>
</tr>
<tr>
<td>After Conception</td>
<td>-0.05% (-0.2%, 0.1%)</td>
</tr>
</tbody>
</table>

National Harbor, Maryland, December 9-11, 2018
### Interface of ART and OIs: OI Prophylaxis

- **Mycobacterium avium complex (MAC)**
  - Primary MAC prophylaxis not recommended if effective ART is initiated immediately
- **Pneumocystis jiroveci pneumonia**
  - Primary prophylaxis is still recommended for those who meet CD4+ cell count criteria

### Question

Should I stop abacavir in older patients?
**Case 7**

- 62 yo male started on ARV Rx years ago (resistance history: wild type virus) **returns to you for care after 4 years** (Rx'd elsewhere)
- Has been through several regimens; now on ABC/3TC/DTG (fdc)
- **Now:** HIV RNA < 20 c/ml (persistently)
  - CD4 560 cells/ul
  - Cholesterol 180 mg/dl (HDL 52 / LDL 100)
  - Creat 1.3 / eCrCl = 80 cc/min
- Smoker
- PMHx negative (No cardiac history)
- On atorvastatin and daily low-dose ASA

---

**ABC → TAF – Effect on Platelets**

- 61 pts on ABC/3TC containing regimen randomized to continue or to switch to TAF/FTC. Platelet aggregation measured by platelet reactivity

![Platelet Reactivity Graph](image)

- Switch to TAF/FTC resulted in less reactivity of platelets by collagen assay
- Does this explain possible CV risk associated with ABC? In the Framingham study ADP response was much more predictive for CVD than collagen response

---

**Question**

Should I switch from EFV / FTC / TDF (fdc) in a patient who has been on it for the last 10 years?
Case 8
- 55 yo Female referred to you for evaluation
- Diagnosed 14 years ago with HIV infection
- Initial: HIV RNA 36,000c/ml
  CD4 count 150 cells/ul
- Current: HIV RNA <20 c/ml
  CD4 count 525 cells/ul
- Started on EFV + FTC/ TDF (fdc) in Jan 2004
- Changed to STR in 2006. Only regimen.
- Reports no symptoms currently. Creatinine 0.8 (eGFR > 60 cc/min)
- Generally feels well

Question
Should I give PrEP to a sero-negative partner of a successfully treated HIV patient?

Case 9
- 45 yo Male makes an appointment to request PrEP
- His partner is HIV positive and has been on successful ARV Rx for 17 years (consistently <50 c/ml)
- Generally feels well
- No significant PMHx
- No medications
- Denies any partners outside of his relationship with his partner
Study Design

Open-Label Prospective Cohort Study in the Paris Region

- Eligibility criteria:
  - 1,200 participants
  - HIV-negative high-risk adults
  - Recombinant Condom
  - C接受ors: CDMR
  - BMI ≥ 20
  - BMR Ag-negative
  - On Demand

- Study design:
  - 15% reduction in new HIV diagnoses among MSM in the Paris Region

- Participants opted for either Daily or On-Demand PrEP and could switch regimens.
- Follow-up every 3 months with 4th Gen ELISA HIV test and plasma creatinine.
- STI screening at physicians’ discretion (guidelines recommend every 3 months in MSM).
- Condoms, safe sex, risk reduction and adherence counseling.
- On sexual behavior.

Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics (Median, IQR) or (n, %)</th>
<th>Daily (n=726, 60%)</th>
<th>On-Demand (n=484, 40%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30 (20-40)</td>
<td>30 (20-40)</td>
<td>0.10</td>
</tr>
<tr>
<td>MSM</td>
<td>750 (95)</td>
<td>905 (95)</td>
<td>0.44</td>
</tr>
<tr>
<td>Heterosexual men or women</td>
<td>7 (1.0)</td>
<td>5 (1.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Transgender</td>
<td>6 (1.1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>No regular sex partner</td>
<td>380 (23)</td>
<td>437 (23)</td>
<td>0.41</td>
</tr>
<tr>
<td>History of PrEP use</td>
<td>493 (64)</td>
<td>515 (62)</td>
<td>0.29</td>
</tr>
<tr>
<td>Use of Condoms</td>
<td>128 (17)</td>
<td>124 (14)</td>
<td>0.65</td>
</tr>
<tr>
<td>No. condomless sex acts in prior 4 weeks</td>
<td>8 (1.6)</td>
<td>2 (0.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>No. sexual partners in prior 3 months</td>
<td>16 (2.3)</td>
<td>19 (1.5)</td>
<td></td>
</tr>
</tbody>
</table>

* All test sexual intercourse: incidence: GHS, MSM, neighborhood.

HIV Incidence (mITT Analysis)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Follow-Up Pts-years</th>
<th>HIV Incidence per 100 Pts-years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF/FTC (Daily)</td>
<td>443</td>
<td>0 (0-0.8)</td>
</tr>
<tr>
<td>TDF/FTC (On-Demand)</td>
<td>506</td>
<td>0 (0-0.7)</td>
</tr>
</tbody>
</table>

Mean Follow-up in this Open-Label Cohort: 7 months (SD: 4)

Incidence of study discontinuation:
3.3/100 PY including 1.5/100 PY who discontinued PrEP

85 HIV-infections averted*
Question

How should I counsel a patient with undetectable HIV RNA re sexual transmission risk?

Case 10

- 48 yo Male presents with newly diagnosed HIV infection
- Asymptomatic except for weight loss / fatigue
- Initial: HIV RNA 160,000 c/ml
  CD4 count 221 cells/ul
- Other labs are normal; Started on ARV Rx
- Returns for a 3 month follow up visit
- HIV RNA < 20 c/ml; CD4 390 cells/ul
Conclusion

• Undetectable = Untransmissible (U = U)
• Debate about how soon to initiate ARV Rx after diagnosis of HIV
• Presence of M184V does not effect initial Rx much (except for use of ABC at higher viral load)
• DTG may be OK in pregnant women; TAF pending more data. Stay tuned!
• Do not need to change ARV therapy if persistent low level viremia
• 2:1:1 PrEP is an emerging approach for prevention in select populations
Question-and-Answer
Learning Objectives

After attending this presentation, learners will be able to:

- Describe changing epidemiology of CVD in HIV
- Identify risk factors for CVD in HIV
- Develop patient-centered strategies to prevent CVD
**Case**

- A 45 yo white male presents for care.
  - He smokes and had a BMI of 24.5 kg/m².
  - BP is 145/86. He does not exercise.
  - CD4 count is 325 c/mm³ (16%)
  - Plasma HIV RNA of 42,000 cp/mL.
  - Total cholesterol is 196 mg/dL, LDL 125 mg/dL, HDL 25 mg/dL, TG 175mg/dL.
- What is the most important intervention to reduce cardiovascular disease risk?

**CVD Mortality Higher in HIV-positive, even with Suppressed HIV Virus.**

- 145,009 HIV+ subjects 2001-2012
  - 71% male, median age 49 yrs
  - CVD mortality 54% ↑increase (7→13%) - Decreasing in gen population
  - aHR 1.54 (95% CI: 1.47-1.62)
    - Adjusted for age, sex, race/ethnicity, location, and year
  - Rate if VL > 400cp/mL: 7.7/1000pt yr
  - Rate if VL suppressed: 3.9/1000pt yr
  - General population: 3.2/1000pt yr

**Trends In Presenting CD4 Counts**

- Median CD4 Counts for New Patients by Year
  - CD4 counts at clinic entry are increasing!
Lifespan increased but increased burden of CVD

- 1.5-2 fold increased risk

**Impact of HIV on risk comparable to traditional risk factors including HTN, DM and hyperlipidemia.**

- Increased risk for
  - Myocardial infarction
  - Ischemic stroke
  - Heart failure
  - Pulmonary Hypertension
  - Venous thrombosis

<table>
<thead>
<tr>
<th>Risk Factor Contribution to CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk Factor</strong></td>
</tr>
<tr>
<td>Pressure</td>
</tr>
<tr>
<td>Weight</td>
</tr>
<tr>
<td>Height</td>
</tr>
<tr>
<td>Age</td>
</tr>
</tbody>
</table>


Impact of HIV on risk comparable to traditional risk factors including HTN, DM and hyperlipidemia.

Increasing Burden of CVD among Adult PWH

Males Aged >25 years

Females Aged >25 years

Risk Factor Contribution to CVD

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th><strong>Impact</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure</td>
<td>210/105</td>
</tr>
<tr>
<td>Weight</td>
<td>280/290</td>
</tr>
<tr>
<td>Height</td>
<td>180/190</td>
</tr>
<tr>
<td>Age</td>
<td>180/190</td>
</tr>
</tbody>
</table>


Increased CVD Risk is Multifactorial

**Interplay between**

- Traditional Risk Factors
- HIV-specific Risk Factors
  - (Immune activation/Inflammation)
- ART-related toxicities
- Certain behaviors (i.e. smoking)
- Disparities in access/receipt of care

The Inflammation Hypothesis

- Many pathogenic stimuli induce a similar inflammatory response.
  - Interleukins
  - Tumor Necrosis Factor
  - TGF-beta
- With removal of the stimulus, inflammation decreases
  - Healing occurs
- When the stimulus persists
  - Pathogenic responses occur
    - Fibrosis
    - Tissue destruction
    - Altered function
    - Progressive Disease


---

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    - Progressive Disease

HIV INFECTION

END ORGAN DISEASE


---

Residual CV Disease Risk With Suppressed Viremia

- Vascular inflammation is greater with HIV infection
  - Increased metabolically active macrophages
  - Greater non-calcified, metabolically active, rupture-prone plaque


---
Potential Interventions Beyond Suppressive ART

- Smoking cessation
- Key lifestyle factors
  - Diet
  - Exercise
- ART Switch
- Lipid lowering therapy, aka statins
- Address other traditional factors
  - HTN
  - DM/Insulin resistance

Statins Reverse Atherosclerosis!

- **Atorvastatin**: Reduction in Coronary Artery Plaque Volume by coronary CT angiography (CCTA).
  - Coronary plaque in:
    - 52% of the HIV group (also rupture-prone noncalcified plaque)
    - 36% of the HIV-negative group
  - Regression with Atorvastatin beyond expected with LDL lowering alone

KEY RECOMMENDATIONS

- Clinicians should be aware that HIV-infected patients are at increased risk for ASCVD.
- Risk is independent of major established risk factors.
- A fasting lipid panel should be obtained in all newly identified HIV-infected patients.
- For primary prevention, HIV infection may be counted as an additional risk factor for risk stratification.
- Statin therapy is first-line therapy for elevated LDL-C and non-HDL-C.
- Drug-drug interactions must be considered.
  - Atorvastatin, rosuvastatin, and pitavastatin are preferred agents.
Don’t Forget: 
The “ABCDEs” of Cardiovascular Disease Management

A: Aspirin  
B: Blood pressure  
C: Cholesterol  
D: Diabetes  
E: Exercise  
S: Smoking

ASPIRIN Use For Primary Prevention

US Preventive Services Task Force

Population | Recommendation
---|---
Age <50 yrs | Insufficient: Evidence to Recommend
Age 50-59 with 10% CVD risk | Low Dose ASA for primary CVD prevention
Age 60-69 with 10% CVD risk | Low Dose ASA for primary CVD prevention (Unless bleeding risk prohibits)
Age >70 yrs | Insufficient: Evidence to Recommend

Cross-sectional study from UAB 1917 HIV Clinic
- Only 17% who qualified were prescribed ASA

Underutilization of ASA for primary CVD prevention.
How to Beat Inflammation and Prevent CVD

- Adherence to HIV medications. Stay undetectable.
- Smoking cessation.
- Maintain normal weight.
- If overweight, lose at least 5-10% of body weight.
- Exercise.
- Have a healthy diet.
- Cut down on alcohol, avoid drugs.

We Mind Very Much If You Smoke

- Tobacco use decreased in the US population.
  43% in 1964 → 19% in 2010.
  Remains leading cause of preventable death → Contributing to >440,000 deaths annually.
- 40-60% of PLWH continue to smoke tobacco.
  Independent risk factor for all cause mortality.

Lifestyle Modification: Diet

- Cutting 500 calories per day will decrease your weight by 1-2 lbs week.
- Watch portion sizes.
- Watch liquid calories (soda, juice, fruit drinks).
- Go natural.
  - Avoid foods in boxes and cans (less salt and preservatives).
  - Maximize fresh fruits and vegetables.

Effect of Cutting 500 cal/day for 8 wks in Obese HIV neg Persons

- Significant declines in inflammation:
  - CRP
  - IL-6
  - TNFα
  - Homocysteine.
Lifestyle Modification: Exercise

- 150 minutes/week of exercise (minimum)
  - Do something you like (combination of cardio/strength)
- Set a fitness goal (e.g., 5K race)
- Find a fitness buddy
- Unplug
- Be active during day: If job is sedentary, take breaks to walk
- Take stairs rather than elevator; park further away to walk to work

Exercise Training Reduced Oxidative Stress and Improves Functional Status in HIV

- 8 week intervention of 24 sessions (aerobic, resistance, or combined)
  - Significant improvements in muscular strength and cardiopulmonary function.

HIV and CVD Summary

- HIV and its therapy contribute to cardiac risk along with the traditional host factors
- Controlling viral replication partially reduces CVD risk.
- Early ART may significantly mitigate HIV-associated CVD risk.
- No reliable inflammatory markers to predict risk.
- Currently available risk scores fail to accurately estimate CVD risk in the setting of HIV infection.
- Smoking cessation, dietary and exercise interventions are effective.
- Statins may provide benefit in addition to lipid lowering effects.
- HOWEVER, more data are needed to inform use in traditional low risk populations.
Question-and-Answer
Learning Objectives

After attending this presentation, learners will be able to:

▪ Describe the current evidence for the efficacy of TDF/FTC PrEP
▪ List the range of PrEP agents currently in development
▪ Describe the pros and cons of seamless PEP to PrEP transition
Effectiveness of Daily TDF/FTC in Clinical Trials

- PROUD (TDF/FTC)
- IPRSAY (TDF/FTC)
- Patience PrEP (TDF/FTC)
- Prudence PrEP (TDF)
- TDF2
- IP/EX
- CAPRI/SA 004
- VOICE (TDF/FTC)
- FemPrEP
- VOICE (TDF/FTC)

Percentage of Participants’ Samples with detectable drug levels

SS Abdool Karim, personal communication

PrEP Utilization

- These data represent 41% of unique individuals who have started TDF for PrEP from 2012-3Q2016.
- https://www.census.gov/quickfacts/table/PST045215/00

*Other indicates American Indian or Alaska Native, Native Hawaiian or Pacific Islander


PEP to PrEP Transition

- PEP is a response to an acute exposure
- Some pts who present for PEP may be at recurrent risk for HIV
- When monitoring PEP, ascertain if the pt would benefit from PrEP
- It is important to confirm if the pt is HIV infected prior to transitioning from PEP to PrEP
- PEP entails taking up to 3 medications daily for 28 days; PrEP entails 1 pill/day while risk persists
  - Counseling about the importance of adherence is indicated

NY nPEP Guideline. 2014.
PEP to PrEP Transition – But HOW?

- No data (“Data Free Zone”)
- The concern: Could PEP “fail” – that is – patient is actually HIV infected, suppressed and antibody response attenuated due to 3-drug PEP – and now transition to PrEP (2 drugs) will lead to viral resistance
- Any hiatus in PrEP/PEP in a high-risk individual is a window for HIV acquisition.
- No perfect way to rule out HIV acquisition between test acquisition and resulting IN ANY CIRCUMSTANCE
- Best Practice: Perform Ag/Ab test at Week 4 of PEP (while still on PEP) and then seamlessly de-escalate to 2-drug PrEP.

---

**Maraviroc**

Objective: To evaluate the safety and tolerability of four ARV regimens for PrEP in MSM and Women

- Maraviroc: HPTN 069/ACTG 5305
- MVC
- FTC
- TDF

---

**Maraviroc**

- Coreceptor Binding
- Virus-Cell Fusion
- CD4 Binding

- CCR5 inhibitors
  - PRO 140
  - Vicriviroc
- CCR5 antagonists
  - PRO 542
  - TAK 652
- CCR2 antagonists
  - BMS-267668
  - TNX-355
- Chemokine (RANTES) receptor antagonist
- AMD-070
- KRH-2215

---

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Maraviroc: HPTN 069/ACTG 5305 Results

<table>
<thead>
<tr>
<th>Arm</th>
<th>Demographics</th>
<th>First reactive HIV+ test</th>
<th>HIV RNA (cps/mL)</th>
<th>CD4 cells (/mm$^3$)</th>
<th>Plasma drug conc. at seroconversion visit (ng/mL)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVC+TDF</td>
<td>black MSM</td>
<td>4W</td>
<td>122,150</td>
<td>357</td>
<td>MVC=0, TFV=0</td>
</tr>
<tr>
<td>MVC</td>
<td>Asian MSM</td>
<td>16W</td>
<td>981</td>
<td>294</td>
<td>MVC=145</td>
</tr>
<tr>
<td>MVC</td>
<td>mixed MSM</td>
<td>24W</td>
<td>106,240</td>
<td>325</td>
<td>MVC=0</td>
</tr>
<tr>
<td>MVC</td>
<td>white MSM</td>
<td>30W</td>
<td>13,626</td>
<td>828</td>
<td>MVC=6.7</td>
</tr>
<tr>
<td>MVC</td>
<td>black MSM</td>
<td>48W</td>
<td>52,191</td>
<td>804</td>
<td>MVC=0.7</td>
</tr>
</tbody>
</table>

* expected pre-dose steady state MVC = 32 ng/ml
† undetectable plasma drug concentrations at study visit

Estimated HIV incidence per 100 Person-Years (with 95% CIs)

TAF/FTC: Works for Treatment - - How about PrEP?

TAF 25 mg results in >90% lower TFV plasma levels

OAT, organic anion transporter; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV, tenofovir.

Rates of Detectable TFV/TFV-metabolite detection in Female mucosal tissues – single dose

Efficacy of TAF/FTC Against Vaginal and Rectal SHIV Infection

Adapted from Massud, CROI 2018, Abstract 85
Adapted from Massud, JID, 2016

Rectal Exposures

Vaginal Exposures

TAF/FTC for PrEP: DISCOVER

Objective: To assess HIV incidence in MSM and TGW who have sex with men and who are administered daily TAF/FTC or TDF/FTC

Primary Endpoint: Seroconversion rate/100 p-y

n=2500

FTC/TAF (200/25 mg) QD

FTC/TDF (200/300 mg) QD

Switch option

Long-Acting Agents: Good, Bad, or Ugly?

When administering agents with long t1/2 in non-removable method
- May require oral lead-in to assess toxicity before administering LA formulation
- May have prolonged
- Sub-therapeutic tail; concern for poorly adherent

Theoretical Infection-Exposure-Resistance Relationships

Markowitz et al, Lancet HIV 2017;4:e331-40
**Long-Acting Injectables: Rilpivirine**

- Rilpivirine LA is a long-acting nanosuspension for delivery via IM injection (regulatory approvals for HIV treatment in combination with other ART agents – in development with CAB LA)
- **Agent class:** Non-nucleoside reverse transcriptase inhibitor
- **Half-life:**
  - Oral: 45 hours
  - Injectable: 90 days

---

**HPTN 076: RPV LA In low-risk HIV-uninfected women**

**Objective:** To evaluate the safety and acceptability of rilpivirine LA in healthy, HIV-uninfected females.

<table>
<thead>
<tr>
<th>WEEKS</th>
<th>4</th>
<th>52</th>
<th>76</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM 1</td>
<td>Daily oral RPV 1200 mg every 8 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 91</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARM 2</td>
<td>Daily oral placebo every 8 weeks</td>
<td></td>
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<tr>
<td>N = 45</td>
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</tr>
</tbody>
</table>

Follow-up phase (tail phase)

---

**HPTN 076: Phase 2 Safety Results**

- Two 2mL IM injections every 8 weeks were safe, well-tolerated, and acceptable to women
- Lower quartile RPV concentrations were consistently above the PA-IC₉₀ 8 weeks post injection at all time points
- Cold chain required
**Seroconversion during pharmacokinetic tail after 300 mg IM dose**

![Graph showing seroconversion](image)

**Long-acting Injectables: Cabotegravir**

- Cabotegravir LA is a long-acting suspension for delivery via IM injection (Currently in advanced development for Maintenance of virologic suppression [with RPV LA] and PrEP-monotherapy)
- Agent class: Strand-transfer integrase inhibitor
- Half-life:
  - Oral: 40 hours
  - Injectable: 40-65 days

**CABOTEGRAVIR**

**DOLUTEGRAVIR**

**CAB LA: Phase 2 #1 – ECLAIR Study**

**Objective:** To evaluate the safety and tolerability of the injectable agent in HIV-uninfected US men.

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Hydrocortisone</th>
<th>Follow-up</th>
<th>Two x 2-ml injections IM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st clinic visit</td>
<td>Strong placebo</td>
<td>Strong placebo</td>
<td></td>
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<tr>
<td>2nd clinic visit</td>
<td>Strong placebo</td>
<td>Strong placebo</td>
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<tr>
<td>3rd clinic visit</td>
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<td>43rd clinic visit</td>
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<tr>
<td>47th clinic visit</td>
<td>Strong placebo</td>
<td>Strong placebo</td>
<td></td>
</tr>
</tbody>
</table>
**ECLAIR: Predicted vs Observed CAB LA PKs**

[Graph showing predicted vs observed CAB LA PKs with time on the x-axis and plasma concentration on the y-axis.]

Markowitz et al, Lancet HIV 2017

**ECLAIR: CAB C, Following Each Injection and PK tail**

[Bar charts showing the percentage of participants for each injection and week after the final injection.]

Modified from Markowitz et al, Lancet HIV 2017

**CAB LA in Development: HPTN 077**

**Objective:** To evaluate the safety, tolerability, and pharmacokinetics of CAB LA in healthy, HIV-uninfected males and females.

[Diagram showing the study design and timelines for Cohort 1 and Cohort 2.]
HPTN077: CAB C, Following Each Injection

Adapted from Landovitz, R. IAS. 2017

---

CAB LA pharmacokinetic tail by sex at birth


Ka, terminal half life, and estimated Time to LLOQ

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>( k_a ), ( \mu g/mL\cdot day ) (95% CI)</td>
<td>0.02 (0.01, 0.05)</td>
<td>0.01 (0, 0.04)</td>
</tr>
<tr>
<td>( t_{1/2\text{app}} ), days (95% CI)</td>
<td>42.5 (13.5, 133.9)</td>
<td>64.6 (19.2, 217.1)</td>
</tr>
<tr>
<td>Median time to LLOQ, weeks (range)</td>
<td>42.7 (20.4, 134)</td>
<td>66.3 (17.7, 182)</td>
</tr>
</tbody>
</table>

*17% of the \( t_{1/2\text{app}} \) variability was explained by sex and BMI
HPTN 083 and 084: Phase 3 for CAB LA PrEP

Objective: To evaluate the safety and efficacy of CAB LA compared to TDF/FTC for PrEP in HIV uninfected MSM/TGW (083) and cisgender women (084)

Antibodies Used in Vaccination Efforts

<table>
<thead>
<tr>
<th>VIRUS</th>
<th>PRODUCT DESCRIPTION</th>
<th>INDICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td>Concentrated human gamma globulin</td>
<td>Prevention</td>
</tr>
<tr>
<td>Polio</td>
<td>Concentrated human gamma globulin</td>
<td>Prevention</td>
</tr>
<tr>
<td>CMV</td>
<td>Cytomegalovirus Immune Globulin</td>
<td>Prevention</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Immune serum globulin (ISG)</td>
<td>Prevention (travel)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Hepatitis B Immune Globulin</td>
<td>Post Exposure</td>
</tr>
<tr>
<td>Rabies</td>
<td>Rabies Immune Globulin</td>
<td>Post Exposure</td>
</tr>
<tr>
<td>RSV</td>
<td>mAb (palivizumab) for prophylaxis of high risk infants</td>
<td>Prevention in High Risk Infants</td>
</tr>
<tr>
<td>VZV</td>
<td>Varicella Zoster Immune Globulin</td>
<td>Post Exposure</td>
</tr>
</tbody>
</table>

Schematic of an HIV-1 gp120/gp41 trimer interacting with bNAbs

Comparison of Breadth and Potency of bNabs vs 208 Diverse Isolates

- CD4 binding site
- MPER
- High mannose V3 loop
- V1/V2 loop
- gp41/gp120 interface

Study Schema for The AMP Studies

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>MSM &amp; TG in the Americas</th>
<th>Women in SSA</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRC01 10 mg/kg</td>
<td>900</td>
<td>500</td>
<td>1300</td>
</tr>
<tr>
<td>VRC01 30 mg/kg</td>
<td>900</td>
<td>500</td>
<td>1300</td>
</tr>
<tr>
<td>Control</td>
<td>900</td>
<td>500</td>
<td>1300</td>
</tr>
<tr>
<td>Total</td>
<td>2700</td>
<td>1500</td>
<td>4200</td>
</tr>
</tbody>
</table>

10 infusions total & Infusions every 8 weeks
Study duration: ~22 months

Implantable Devices

- Reversible with removal
- Long-acting (months to years)
- Potential for Multi-purpose
- Current development
  - TAF, CAB, EFdA
  - Others

Gunawardana, et al., AAC 2015
**Monthly Dapivirine Ring**

- Flexible silicone vaginal ring developed by IPM
- Woman-initiated
  - Self-inserted monthly
- Discreet
- Slowly releases ARV dapivirine
- Reduced women’s HIV-1 risk by ~30% in two Phase III trials
- Interim data from open-label studies show greater use and suggest ~50% risk reduction
- New interim data presented at R4P
- Under regulatory review

---

**Microneedles**

Donnelly R, Queen’s Univ, Belfast.
DeMuth, Retrovirology, 2012.
Microneedles

- Plasmids expressing SIV-Gag + poly(I:C) in mice
- Adenoviral vectors expressing SIV-gag Adjuvanted recombinant HIV-1 CN54gp140
- Queens University (Belfast)/PATH/IVIVPog Council/LTS/USAID - CAB

Conclusions

- TDF/FTC PrEP has set a high bar for preventive effectiveness
- Long-acting preparations will solve some challenges, not all – but will be available imminently
- Future is ripe with possibility in implants, antibody mediated protection, and microneedles
- On-demand options are needed
- More options are better
Thank you

- Ryan Kolton
- Quarraisha Abdul-Karim
- Trip Gulick
- Ian McGowan
- Marybeth McCauley
- Zeda Rosenberg
- Mike Cohen
- Wafaa El-Sadr
- Susan Buchbinder
- John Mascola
- Ryan Donnelly
- Charlie Flexner/LEAP

- Sybil Hosek
- Sheryl Zwerski
- Nirupama Sista
- Leslie Cottle
- Lucio Gama
- Trevor Hawkins

Thank you
Youth and HIV: Are We on Track to End This Epidemic?
Donna C. Futterman, MD
Professor of Pediatrics
The Albert Einstein College of Medicine
Bronx, New York

Learning Objectives
After attending this presentation, learners will be able to:
▪ Describe which youth are most vulnerable to HIV infection
▪ List 3 reasons why youth are vulnerable to HIV infection
▪ List 3 challenges in HIV prevention among youth

Adolescents Living with HIV is a Global Issue
- AIDS - #1 killer of adolescents (10-19) in Africa and #2 worldwide
- 2.1 million adolescents living with HIV worldwide
- Youth 15-24 are 37% incident infections: 380,000 new HIV infections yearly in youth (60% girls)
- Every hour, 26 new infections among youth 10-19

UNAIDS, 2017
HIV in the US

- 40K new US cases; 16K among youth (13-29)
  - 40% of new diagnoses, 23% of population
  - Average 2.7 years from infection to diagnosis
  - Females are 16% of adolescent cases
  - South had 52% of cases
- In 2014, 90% diagnoses among males were gay/bisexuals
  (22-23 yo highest at 34/100,000)
  - 52% were black (390/100,000)
  - 22% Hispanic/Latino, and 16% white
  - 1.2 million people in US living with HIV
  - 1 in 8 (12.8%) are unaware of their infection
  - 52% of youth with HIV are unaware

Incidence of HIV Diagnoses among MSM Youth of Color

Men Who Have Sex With Men (MSM) accounted for 81% of youth newly diagnosed with HIV in 2016

Of those, 79% were Young Men of Color, primarily in the South

CDC HIV Care Continuum 2017

- 22% diagnosed
- 21% receiving care
- 20% retained in care
- 19% virally suppressed
Optimizing the Care Cascade: HIV Testing

- Most HIV+ youth don’t know
  - Majority not symptomatic
  - Need routine and targeted testing
    - Routine testing needed in clinical sites
    - Outreach-based (schools, communities, venues)
- Address consent and confidentiality with minors
- Test all youth
  - Undisclosed sexual activity/abuse and perinatally infected

Recommendations for Routine HIV Testing

- Achieve routine testing in medical settings
- Expand targeted testing
  - Frequent testing for MSM, Trans men and women, new immigrants, persons in neighborhood with high seroprevalence, injection drug users, migrant workers, homeless persons, history of incarceration, substance use or mental health issues
- Address acute infection
  - Acutely infected persons are highest transmitters of HIV
- Improve Referral and Engagement
  - Significant numbers of HIV+ individuals are out of care
  - All testing sites should be centers for referral and engagement
  - Engage HIV negative and at-risk individuals into care

Youth Susceptibility to HIV/STD

**Behavioral vulnerability**
- Age of experimentation: 55% sex by 12th gr
- Homophobia and gender power imbalance
- Mental illness, substance use, sexual abuse

**Biological vulnerability of females > males**
- Immature cervix
- STDs often asymptomatic
- More efficient: male to female
- Uncircumcised males at increased risk

**Socioeconomic vulnerability**
- Lack: health care coverage, confidentiality
- Inadequate sex education
- Poverty, race/ethnicity, immigration, housing

Source: IOM/YRBS
Record High of Youth STIs

STI incidence among youth aged 15-24 has hit a record high in 2016, rising for the 3rd year in a row.

1.0 million CASES OF CHLAMYDIA among youth 15-19
218,000 CASES OF Gonorrhea among youth 15-19
6,470 CASES OF Syphilis among youth 15-19

Optimizing Care: Youth-friendly HIV Care

- Providers who are knowledgeable, nonjudgmental
- Confidentiality and Consent
- See adolescents separately from parents
- Cohort youth to single day
- Socioeconomic issues: poverty, schools, housing & transportation challenges
- Empowering youth to live with HIV
- Coping/Mental Health
- HIV care
- Prevention

Treatment Issues

- Adherence/Viral Load Suppression
- Disclosure
- Ongoing risk of transmission
- Reproductive health
- Behavioral and psychological concerns
- Transition to Adult Care
Optimizing the Care Cascade: Viral Suppression

- Immediate treatment is game changer
- Check pubertal development for dosing
- Developmental issues key
  - Concrete and present-oriented thinking
  - Adverse events may seem intolerable
  - Meds rebellion as a form of independence
- Mistrust providers yet trust misinformation from peers - learn barriers and motivators
- Perinatally infected have unique needs
- Sustained viral load suppression 44% among youth

Undetectable = Untransmittable

- U=U works for long term “undetectables” able to adhere to ART and remain in care
- How big is this population?
  - US: 30% of HIV+ are Virally Suppressed (CDC 2014)
  - NYC: 74% of HIV+ VS (NYC DoHMH 2016)
  - Youth less likely to sustain VLS
  - How do these estimates reflect U=U potential?
- Many vulnerable to being detectable
  - Personal and structural instability
  - Newly infected
  - Youth

Medical Problems of Perinatally Infected Youth

Treatment
- Lack of pediatric formulations and PK data
- HIV drug resistance from serial mono therapy
- Poor adherence to antiretroviral therapy
  - Adolescent independence vs lifelong treatment

Complications Related to HIV or its Treatment
- Central nervous system abnormalities
- Metabolic and cardiovascular disease
- Bone loss
- Renal disease
Transitioning
Youth aging into/out of adolescent care

- Facilitate transition from supportive to independent and responsibilities from parent/provider to patient
- Promote growth, self-expression and personal decision making
- Choose adult clinic with multidisciplinary services
- Traumatic for youth to leave trusted providers
- Uncomfortable in the presence of adult patients
- Consider phased transition (case manager, GYN)

AMeyerson 2006

LGBTQ-Friendly Care

Welcoming environment
- Cohort youth to same day
- Signal you are happy to discuss gender & sexual identity
- Challenges of EMR: Gender and orientation
- Include LGBTQ imagery in materials
- Gender neutral bathrooms

Confidentiality
- Assure patients of confidentiality (EOB)

LGBT Youth

- Same developmental tasks as all youth and most grow to be healthy adults
- Must develop healthy, integrated identity amidst negative stereotypes/prejudice, often without family support
- More susceptible to emotional distress, psychiatric morbidity, multiple disparities, stigma, abuse, violence, isolation
- Particular challenges of TG youth: childhood to adolescents
“You can't be gay, you'll shame the family”

Prevention

US prevention leaves youth vulnerable
- Mass media promotes sex but not safer sex
- Strong and sustained promotion of condoms and other prevention strategies
- Abstinence “only” sex education shown ineffective
- Comprehensive sex education offers better foundation and is wanted by most parents

Behavior change is very difficult
- Prolonged interventions more successful
- Successful programs combine skill and knowledge

PrEP Efficacy, Safety, and Adherence for Youth

ATN 110 (N=200)
Young MSM 18-22
4 seroconversions through week 48
No drug resistance found
Adherence was good overall but varied by race/ethnicity (e.g., AA)
Adherence dropped across both studies after week 12 indicating a need to address long-term prevention adherence among youth.
Approved by FDA for use by minors >35k in 2018

ATN 113 (N=79)
Young MSM 15-17
3 seroconversions through week 48
PrEP was well tolerated with minimal safety concern
Substantial drop-outs need for ongoing retention/engagement strategies

Young MSM 18-22

4 seroconversions through week 48
PrEP Use by Age & Race/Ethnicity

There were over 145,000 PrEP users in the U.S. in 2017
Over 20% of new HIV diagnoses in 2016 were among Youth, yet only 11% of all PrEP users were younger than 25 years. 700,000 US youth could benefit from PrEP.

PrEP Use by Age & Race/Ethnicity

Total PrEP Use by Race/Ethnicity September 2016
- African American: 24%
- Hispanic: 26%
- White: 10%
- Asian: 10%
- Multiracial/Other: 7%

Estimated New HIV Infections by Race/Ethnicity 2015
- African American: 44%
- Hispanic: 26%
- White: 13%
- Asian: 10%
- Multiracial/Other: 7%

We’ve mapped good routes to ETE.
Let’s make sure no one gets lost along the way.

Testing is more routine
- But still exceptional/cumbersome in medical settings

Treatment saves lives & prevents infections
- But not all have access or can be ideally adherent: Challenges of U=U

PreP prevents infections
- But not all have access or can be ideally adherent

Condoms perceived as old school prevention
- But are critical to preventing other STIs
Addressing Youth Challenges: 6 take home points

- New generation every 5 years
- Sustain & refresh sex education & social marketing efforts
- HIV is MIA in most young peoples’ consciousness
- HIV no longer feared: treatable & invisible
- Duality re HIV Infection: inevitability vs. invulnerability
- Fear of disclosure: HIV, sex and sexual orientation
- Confidentiality & Consent hard to implement
- Vulnerable youth are vulnerable in multiple ways
  - Economic, racial, gender, and sexual orientation disparities
Learning Objectives

After attending this presentation, learners will be able to:

• Identify epidemiologic characteristics of the older HIV-infected patient
• Define the impact of HIV infection on the normal aging process and the development of comorbidities
• Describe specific HIV comorbidities with focus on coronary artery disease, its predisposing conditions, and premature bone loss
• Explain changing mortality patterns in the modern era of antiretroviral therapy

HIV Epidemiology in Older Adult

• Since the 1980s, the percentage of HIV-infected patients over the age of 50 has gradually increased
• In 2015, 17% of newly diagnosed cases of HIV infection were in adults ≥ 50 years old with many having AIDS
• African Americans accounted for 43% of cases, whites for 36% of cases, and Hispanics/Latinos for 17% of cases
• In 2014, approximately 45% of HIV-infected persons in the US were ≥ 50 years old, 27% were ≥ 55 years old, and 6% were ≥ 65 years old
• MSM is the most common mode of transmission in older men, and heterosexual contact is the most common mode in older women
New HIV Diagnoses by Age
United States, 2015

People Living with HIV by Age
United States, 2014

Issue 1
HIV infection, even when controlled, is associated with chronic immune activation that is superimposed upon immunologic senescence in the older adult
The Effect of Normal Aging on Health

Issue 2
Older persons may be diagnosed later and have more advanced HIV infection at presentation

Issue 3
There is a less robust immunologic response to antiretroviral therapy in this population
Immunologic Response to ART

- Among 12,196 treatment-naive patients in NA-ACCORD who initiated ART (observational cohort), immunologic response after 24 months of therapy decreased with increasing age starting at 40, but there was no effect on viral suppression.
- A prospective study that evaluated treatment outcomes in 3,015 patients (401 of whom were over age 50) found that, despite better virologic control, clinical progression to an AIDS-defining diagnosis was higher (HR 1.52; 95% CI 1.2-2.0).

---

Issue 4

In general, older HIV-infected patients have better medication adherence but an increased risk of drug toxicity.

---

Medication Adherence

- Literature has reported up to 95% adherence in older HIV-infected patients.
- In a recent meta-analysis, older age reduced the risk for non-adherence by 27% (RR 0.72; CI 0.64-0.82).
- Those studies assessing short-term and long-term non-adherence showed a significant reduction in both groups (RR 0.75; CI 0.64-0.87 and RR 0.65; CI 0.50-0.85, respectively).

---
Drug Toxicity

- A higher rate of adverse events (64% vs. 35%) on protease inhibitors was reported in patients older than 60 compared to those under 40.
- Another study of 508 treatment-naïve patients found that regimen changes due to toxicity were associated with increasing age.
- May be from age-related decrease in renal and hepatic function, decrease in serum albumin level, and changes in cytochrome p450 enzyme system.


Issue 5

HIV-infected patients accumulate “age-related” diseases at a younger chronological age.

Hypothesis is that increased immune activation and long-term chronic inflammation contribute to premature aging in this population.

Chronic Complications by Age and HIV Status

17%  12%  9%  6%  3%  0%
90%  80%  65%  42%  21%  16%
9%  8%  31%  6%  15%  28%
Chronic Complications by Age and HIV Status

- Retrospective analysis of HIV-infected outpatients compared to seronegative persons (case-control study) from 2002 through 2009
- Examined cardiovascular disease, hypertension, diabetes mellitus, bone fractures, and renal failure
- Independent predictors of polyopathy (p < 0.001) included older age (OR 1.11), male gender (OR 1.77), CD4 nadir below 200 (OR 4.46), and duration of antiretroviral therapy (OR 1.01)

Incidence of CAD is higher than that in HIV-negative patients matched for age and gender.

CAD risk calculator results need to be interpreted in context of increased risk in the HIV-infected population.

HIV Infection and Coronary Artery Disease (1)

- Incidence of CAD is higher than that in HIV-negative patients matched for age and gender.
- Studies have demonstrated an increase in subclinical atherosclerosis (e.g., CMI thickness) and clinical endpoints (e.g., acute MI).
- HIV infection is associated with increased soluble and cellular markers of inflammation, endothelial dysfunction, and altered coagulation, all of which have been shown to contribute to cardiovascular disease.

HIV Infection and Coronary Artery Disease (2)

- Degree to which HIV infection itself, antiretroviral therapy, and other risks contribute to increased risk in this population is unknown.
- High prevalence of traditional risk factors in this population.
- Protease inhibitor class appears to be associated with higher risk of CAD; some data suggesting abacavir and efavirenz may also increase risk.
- Discontinuation of ART is associated with higher risk of CAD.
The Risk of Coronary Artery Disease in HIV-Infected Patients


Pooled Risk Ratio for Cardiovascular Disease in HIV-infected Persons

ACC/AHA CV Risk Calculator

Uses data primarily from non-Hispanic whites and African Americans in the United States. Concerns about accuracy of results have been made (statin recommendations, DM yes vs. no categorization, FMH of premature CAD not included).
Traditional Risk Factors for Atherosclerosis (1)

- **Hypertension**: Use of ambulatory BP monitoring for diagnosis; new definition of hypertension and treatment target (ACC/AHA Hypertension Guideline (J Am Coll Cardiol 2017); no important drug interactions
- **Diabetes Mellitus**: Increased risk of DM in HIV-infected patients, HgbA1c may underestimate glycoemia, and DM-HIV detrimental effect on renal function (BMJ Open Diabetes Res Care 2016, Diabetes Care 2009, and Acquir Immune Defic Syndr 2012); no important drug interactions

Traditional Risk Factors for Atherosclerosis (2)

- **Hyperlipidemia**: Simvastatin and lovastatin are contraindicated with protease inhibitors and cobicistat; atorvastatin, rosuvastatin, and pitavastatin can be used as alternatives; in this setting, it is prudent to start with low dose of drug and monitor for toxicity
- **Cigarette Smoking**: HIV-infected patients are more likely to smoke and less likely to quit compared to the general population (Ann Intern Med 2015); HIV-infected smokers lose more life-years to smoking than to HIV-related conditions (Clin Infect Dis 2013); no important drug interactions

Issue 7

HIV infection and its treatment and comorbidities have been associated with premature bone loss
Premature Bone Loss (1)
- Osteopenia, osteoporosis, and pathological fractures have been described
- Osteopenia is asymptomatic condition
- Osteoporosis may present with fractures of vertebrae, forearms, or hips
- HIV infection itself, TDF, protease inhibitors, alterations in vitamin D metabolism, and lactic acidemia related to older NRTI drugs may be contributing factors to premature bone loss

Premature Bone Loss (2)
- Immobility, cigarette smoking, excessive alcohol use, chronic renal disease, hypogonadism, hyperparathyroidism, hyperthyroidism, and steroid use accentuate bone loss
- Optimal use of bone densitometry as screening test in this population is uncertain; HIVMA advises baseline in postmenopausal women and men ≥ 50 years of age
- Calcium and vitamin D should be given in high-risk patients; regular exercise and smoking cessation should be advised

Antiretroviral Exposure and Risk of Osteoporotic Fractures

Effect of TDF Exposure on Risk of Any Fracture and Osteoporotic Fractures


Issue 8

Increasing age may be a risk factor for HIV-associated neurocognitive dysfunction, although studies examining this issue are limited

HIV Infection in the Older Patient (1)

- Longitudinal study comparing 106 HIV-infected patients over 50 years of age to 96 patients between 20-39 years of age showed a three-fold higher risk of dementia on multivariate analysis
- Study adjusted for race, education, depression, substance abuse, ART, CD4 count, and viral load
- Depression appears to be more common in older HIV-infected persons compared to seronegative age-matched controls

Neurocognitive Dysfunction

Issue 9

Lung, hepatic, and anal cancers occur at a younger age in HIV-infected adults compared to seronegative persons.

Malignancies

- Observational studies suggest that lung, hepatic, and anal cancers occur at younger age in HIV-infected adults compared to seronegative persons.
- Using 15 HIV and cancer registry databases in the US, including 212,055 persons with AIDS, the age of diagnosis of non-AIDS-defining cancers was examined.
- Only lung and anal cancers were seen in AIDS patients at younger age (median 50 years old vs. 54; p < 0.001) than expected.


Issue 10

Mortality in HIV-infected persons has fallen substantially over past two decades with non-AIDS-related conditions now accounting for the majority of deaths.
Mortality Trends

- In the D:A:D study, 3,909 deaths occurred among 49,731 subjects followed from 1999 through 2011
- Crude mortality rate of 12.7 per 1000 person-years
- AIDS-related causes were responsible for 29% of deaths, non-AIDS-related cancers for 15%, liver disease for 13%, and cardiovascular disease for 11%
- Deaths attributable to AIDS-related events decreased from 34% to 22%
- Proportion attributable to non-AIDS-defining malignancies increased from 9% to 23%

Mid-point Life Expectancy Estimates at Age 20 Years in Three Calendar Periods, Overall and by Sociodemographic Characteristics, 2000–2007

Samji H, Cescon A, Hogg RS et al. 2013; PLOS ONE. https://doi.org/10.1371/journal.pone.0081355

Question-and-Answer
We Are Going to Need a Bigger Wrench: Improving Linkage and Retention in HIV Care

Carlos del Rio, MD
Hubert Professor of Global Health
Rollins School of Public Health
Professor of Medicine
Emory University School of Medicine
Atlanta, Georgia

Learning Objectives

After attending this presentation, learners will be able to:

▪ Describe the interventions that will impact linkage and retention in HIV care
▪ List barriers to linkage and retention in HIV care
▪ Implement ways to monitor linkage and retention in HIV care in their practice

In order for a person to benefit from HIV treatment success it is necessary to:

- Diagnose their HIV infection
- Link infected individuals to outpatient care
- Start antiretroviral therapy
- Have patients adhere to therapy
- Retain patients in care

Engagement in care
### The spectrum of engagement in care

<table>
<thead>
<tr>
<th>Not in HIV Care</th>
<th>Engaged in HIV Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unaware of HIV infection</td>
<td>Aware of HIV infection (not in care)</td>
</tr>
<tr>
<td>Receiving some medical care but not HIV care</td>
<td>Entered HIV care but lost to follow-up</td>
</tr>
<tr>
<td>Cyclical or intermittent user of HIV care</td>
<td>Fully engaged in HIV care</td>
</tr>
</tbody>
</table>

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### Definitions

- **Linkage to care** is the process of engaging newly diagnosed HIV-infected persons into HIV primary care.
- **Entry into care** after HIV diagnosis, defined as a visit with an HIV care provider authorized to prescribe ART.
- **Retention in care** is attending required provider visits for primary HIV care.
- **Engagement in care** embodies the distinct but interrelated process of linkage and retention in care.
~31% not linked  
~50% not retained  
~20% UDVL  
~21% undiagnosed

The U.S. HIV Care Continuum


50% not engaged

U.S. HIV Care Continuum, 2014

Diagnosed*  Linked (1 mos)  Received Care  Retained in Care  Virally Suppressed  National goals

90%  80%
National HIV/AIDS Strategy – by 2020

TESTING – Increase HIV serostatus knowledge to at least 90%

Increase LINKAGE to care within 1 month of Dx to 85%

RETENTION: Increase retention in continuous care to 90%

Increase proportion of HIV Dx’d persons with VIRAL SUPPRESSION by 80%

Linkage to Care

Proportion linked to care within 1 month of Dx

Poor linkage is associated with:

- Delayed receipt of antiretrovirals
  - Immune damage
- Higher rate of virologic failure
  - HIV transmission
- Increased morbidity and mortality
  - More hospitalizations
  - More ED visits
**Intervention to Improve Linkage: ARTAS**

- 273 participants, 4 cities
- 78% diagnosed <6 m
- more likely to enter care
- 90 d of strength-based case management (CM)
- Older clients, those with much outside help and non-crack users more likely overall to enter care.

Replicated in ARTAS II

---

**Linkage to Care - challenges**

- Providing newly diagnosed patients with timely appointments with HIV care providers upon diagnosis
- Resources for short-term case manager/system navigators to support follow up for patients who need it
- Capacity of care system to meet demand for HIV care
- Complexity of patients lives, including many with serious co-morbid conditions

---

**Retention in Care**

- Proportion in continuous care (3 or more visits in preceding 12 months at least 3 month apart)
Retention in care over time is suboptimal

<50% retained in care by 5 years*

*IeDEA-WHO Collaboration 2015  * Losses include transfers and deaths

Most new HIV infections are now coming from people out of care

Retention in Care

- Consistent retention in care has been associated with:
  - Faster time to virologic suppression
  - Lower cumulative viral load burden
  - Improved immune function
  - Decreased mortality
  - Decreased engagement in HIV transmission behaviors
Measuring Retention in Care

- There is no “gold standard”
- Five commonly used measures are:
  - Missed visits
  - Appointment adherence
  - Visit constancy
  - Gaps in care
  - HRSA performance measure for retention in care

Mugavero ML, et al. AIDS Patient Care and STDs, 2010

Measuring Engagement in HIV Medical Care

<table>
<thead>
<tr>
<th>Measure</th>
<th>Missed visit data needed?</th>
<th>Ease of calculating</th>
<th>Observation time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missed visit</td>
<td>Yes</td>
<td>Easy</td>
<td>~1 day</td>
</tr>
<tr>
<td>Visit adherence</td>
<td>Yes</td>
<td>Moderate</td>
<td>~1 year</td>
</tr>
<tr>
<td>No-show rate</td>
<td>Yes</td>
<td>Moderate</td>
<td>~1 year</td>
</tr>
<tr>
<td>Constancy:</td>
<td>No</td>
<td>Moderate</td>
<td>~1 year</td>
</tr>
<tr>
<td>Gap in care</td>
<td>No</td>
<td>Easy</td>
<td>~1 year</td>
</tr>
<tr>
<td>HRSA/HAB</td>
<td>No</td>
<td>Moderate-to-difficult</td>
<td>1 year</td>
</tr>
<tr>
<td>DHHS</td>
<td>No</td>
<td>Moderate-to-difficult</td>
<td>2 years</td>
</tr>
</tbody>
</table>


Monitoring missed visits

- 676 patients initiating first HIV care at 2 sites, 2007-2010
- 63% achieved VL<50 copies/mL in a median 308 days
- Patients with more “no show” visits experienced delayed VL suppression (HR=0.83 per “no show” visit, 95% CI= 0.76-0.91)
- Visit non-adherence was independently associated with greater cumulative VL burden (log_{10}VCY) during the first two years in care (Beta coefficient=0.11 per 10% visit non-adherence, 95% CI=0.04-0.17)

Mugavero et al. JAIDS. 2012; 59 (1): 86-93
Early retention in care

- The first year in outpatient HIV medical care is a dynamic, formative & vulnerable time
- Poor early retention in care associated with:
  - Delayed / failed antiretroviral therapy (ART) receipt
  - Delayed time to VL suppression and greater cumulative HIV burden
  - Increased sexual risk transmission behaviors
  - Increased risk of long-term adverse clinical events
  - Worse ART adherence, CD4 & VL response and increased long-term mortality following ART start

Ulett et al., AIDS Pt Care STDS 2009;23, Giordano et al., JAIDS 2003;32, Metsch et al., Clin Infect Dis 2008;47, Mugavero et al., Clin Infect Dis 2009;48, Giordano et al., Clin Infect Dis 2007;44

Slide 26 of 48

- Six HIV-specialty clinics
- Pre-intervention (2008-09) vs intervention (2009-10) periods
- Clinic attendance improved 7% during the intervention period for keeping 2 consecutive visits and 3% for all visits kept

Slide 27 of 48

A Low-Effort, Clinic-Wide Intervention Improves Attendance for HIV Primary Care

The Ponce Care Continuum: Long Term Retention and VS

<table>
<thead>
<tr>
<th>Duration</th>
<th>Retention</th>
<th>Viral Suppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 Months</td>
<td>16%</td>
<td>52%</td>
</tr>
<tr>
<td>24 Months</td>
<td>44%</td>
<td>64%</td>
</tr>
<tr>
<td>36 Months</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>Anytime</td>
<td>3%</td>
<td>2%</td>
</tr>
</tbody>
</table>

N = 633
N = 595
N = 582

Benefits of engagement in care

- **For individuals:**
  - improvements in initiation and adherence to ART
  - better immunologic and virologic outcomes
  - lower mortality

- **For society:**
  - reduced HIV transmission (U = U)

Engagement in Care is a dynamic process

- “Consistently High” (25%)
- “Steadily Declining” (16%)
- “Early Increasing” (17%)
- “Late Increasing” (15%)
- “Consistently Low” (26%)
Predicting who is at risk of poor engagement

Risk Prediction Tool for Medical Appointment Attendance Among HIV-Infected Persons with Unsuppressed Viremia

Epidemiological term introduced in 2009 by Gill and Krentz

What is Churn?

Epidemiological term introduced in 2009 by Gill and Krentz

Patients cycling in and out of a local HIV program
Patient navigators

- Coordinate treatment care
  by assisting patients with completing necessary medical paperwork, scheduling, confirming, rescheduling and also accompanying patients to medical and treatment appointments, and facilitating communication between patients and care providers.

- Provide health education
  by providing written information, discussing diagnostic tests and treatment options, and answering questions.

- Assist patients to overcome personal barriers
  by addressing lack of transportation, lack of childcare, lack of insurance, and lack of health knowledge.

- Provide psychosocial or emotional support
  - either directly or by making appropriate referrals to social workers or support groups.

Contingency Management

- The systematic reinforcement of desired behaviors and the withholding of reinforcement or punishment of undesired behaviors.
- Effective strategy in the treatment of alcohol and other substance use disorders.
- Has also been found to be useful in cocaine addiction.
- Used in other chronic conditions.
Viral Suppression Rate

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6-months</th>
<th>12-months</th>
<th>Baseline</th>
<th>6-months</th>
<th>12-months</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAU</td>
<td>11.0%</td>
<td>10.0%</td>
<td>11.3%</td>
<td>9.6%</td>
<td>16.0%</td>
<td>13.3%</td>
</tr>
<tr>
<td>PN</td>
<td>33.6%</td>
<td>33.6%</td>
<td>39.1%</td>
<td>33.6%</td>
<td>42.0%</td>
<td>33.6%</td>
</tr>
<tr>
<td>PN+CM</td>
<td>34.1%</td>
<td>30.0%</td>
<td>35.7%</td>
<td>33.6%</td>
<td>42.0%</td>
<td>33.6%</td>
</tr>
</tbody>
</table>

TAU (n=6), PN (n=6), PN+CM (n=6)

χ² (2) = 6.54, p = .04

Primary Outcome

χ² (2) = 0.78, p = .68

Same-day HIV testing with initiation of antiretroviral therapy versus standard care for persons living with HIV: A randomized unblinded trial

Koenig et al, July 25, 2017

Haiti (GREENRED), standard gave ART 3 weeks post testing, same day had to pass readiness questionnaire (only 7 failed), all given initial TDF/3TC/EFV, changed if CrCl < 50

Grady Infectious Disease Program (Atlanta): Pre-REACH Steps from Clinic Door to Provider Visit

Remove Institutional Barriers

Standard ART

n=336

Same Day ART

n=347

Unadjusted RR

(vs standard ART)

Retained at 12 mo with VL<50

43.8%  53.0%

1.21

Retained at 12 mo with VL<1000

51.7%  61.1%

1.18

Retained at 12 mo, any VL

71.6%  79.8%

1.12

Death

5.6%  2.9%

0.51
Grady IDP: Post-REACH Process

Increased Upfront Time
Time to VS decreased by 27d

Implementation of a Rapid Entry Program Decreases Time to Viral Suppression Among Vulnerable Persons Living With HIV in the Southern United States

- 10 weeks – 90 patients who were new to clinic and not suppressed (excludes those re-engaging)
- Improved time to VS
- No change in retention
- Program closed due to volume – reopened with some funding

ART immediately after Dx

<table>
<thead>
<tr>
<th>BENEFITS</th>
<th>CONCERNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased viral suppression at 12 months</td>
<td>No significant trend towards reduced mortality</td>
</tr>
<tr>
<td></td>
<td>No reduced lost to follow up</td>
</tr>
<tr>
<td></td>
<td>Trend towards increased risk of being lost to</td>
</tr>
<tr>
<td></td>
<td>Vs</td>
</tr>
</tbody>
</table>

Interventions to improve linkage, retention, VS

- Linkage to care:
  ARTAS, 2005

- Retention in care:
  - Retention through enhanced personal contacts, 2014
  - Warm, reliable point of contact; someone cares
  - Rapid entry/same day ART, 2016
  - Patient navigator / CWH (mixed evidence)

- Viral Suppression
  - Rapid entry/same day ART, 2016


Engagement in Care and ART Adherence

- Systematic monitoring of time to care linkage after initial HIV diagnosis, retention in care, reengagement in care, ART adherence, and rates of viral suppression

- Brief, strengths-based case management after HIV diagnosis to facilitate linkage to care

- Systematic monitoring of missed clinic visits and rapid intervention after a missed visit

- Personal telephone and interactive text reminders in advance of scheduled appointments and shortly after missed appointments (e.g., 24-48 hours)

- Adherence monitoring using patients’ self-report obtained by validated adherence instruments and pharmacy refill data

Engagement in Care and ART Adherence

- Rapid HIV test algorithms may be used to confirm a preliminary positive rapid test result, allowing for same-day referral to treatment from nonclinical settings.
- Use of public health surveillance in conjunction with clinic-level data to guide individual-level linkage and reengagement in care activities.
- Cash financial incentives for clinic appointment attendance and achievement of viral suppression are generally not recommended as a retention-in-care strategy.
- Data-driven risk stratification to identify high-acuity, high-need patients for combination intervention strategies to improve care engagement and viral suppression.
- Screening for and addressing housing instability, food insecurity, ongoing substance use, psychiatric disorders, medication adverse effects, and pill burden.

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Question-and-Answer
New Developments in Opportunistic Infections: Interactive Case-Based Panel Discussion

Stephen P. Raffanti, MD, MPH
Professor of Medicine
Vanderbilt University
Nashville, Tennessee

Learning Objectives

After attending this presentation, learners will be able to:

- Describe the current trends in opportunistic infections (OIs) in the U.S.
- List the more common OIs in the U.S.
- Describe the concept of immune reconstitution inflammatory syndrome (IRIS)
- Identify appropriate resources for diagnosing and managing OIs

Overview

- Opportunistic Infections
  - A brief history and where we are now.
  - What’s new:
    - Providers
    - Patients
    - Pathogens
    - Diagnostic tools
    - Contemporary cases
Limitations of the presentation

- It is just a talk.
- There are over 40 OIs listed in the guidelines.
- It is an attempt to give a general overview with direction to find the details.
  - The clinician should feel comfortable developing a coherent work up based on patient centered evaluation, then look up the treatment.
- It is experience based.

Pablo A.

- Over about 11 months he developed weight loss, fatigue, night sweats, dysphagia, and decreased memory.
- In September of 1982 he was diagnosed with HTLV III infection.
- His initial CD4 count was 9 cells/mm³.
- He died in December 1985 in Perth Amboy New Jersey.

AIDS 1985- One Patient’s Experience

- 322 IV insertions
- 14 hospital admissions
- 11 months of hospital stay
- 60 phlebotomies
- 32 chest x-rays
- 5 CT scans of head
- 3 abdominal ct scans
- 6 bronchoscopies
- 8 intubations
- 4 lumbar punctures
- 3 bone marrows
- 5 cycles of chemo
- 2 lymph node bx
AIDS 1985- One Patient’s Experience

- 322 IV insertions
- 14 hospital admissions
- 11 months of hospital stays
- 60 phlebotomies
- 32 chest x-rays
- 5 CT scans of head
- 3 abdominal CT scans
- 6 bronchoscopies
- 8 intubations
- 4 lumbar punctures
- 3 bone marrows
- 5 cycles of chemo
- 2 lymph node bx

Pablo’s illnesses included:
PCP (3), MAC, esophageal candidiasis, disseminated VZV, cryptococcal meningitis, wasting, dementia, cardiomyopathy, NHL.

Pablo never received a medication to treat his HIV or prevent any of his OI's.

So where are we now?
Not all HIV infections are diagnosed, and once diagnosed many persons have already experienced substantial immunosuppression.

CDC estimates that in 2015, 15% of the people with HIV in the United States were unaware of their infections. Among those with diagnosed HIV, more than 50% had had HIV for more than 3 years and approximately 20% had a CD4 T lymphocyte (CD4) cell count <200 cells/mm³ (or <14%) at the time of diagnosis.

So who gets OIs?

- Newly diagnosed with HIV and AIDS diagnoses coinciding.
- Patients with advanced disease lost to care.
- Global patients.
- Poorly managed patients in care.

What about providers?
Physician Shortage

- "US Healthcare system is in a period of marked uncertainty."
- >1/3 of all physicians will be >65 in the next 10 years
- Shortage between 40,800 and 104,900 physicians by 2030
- Caps placed 20 years ago on federal Medicare funding for residency training makes it difficult to expand GME.
- Congress needs to raise the caps to train more physicians.

Kirsch et al, JAMA May 2017

Bottom line…


Over the next few years the cohort of US HIV clinicians who trained and practiced in the era of high OI incidence will leave the workforce.
OIs in 2018

- Jesse, a thirty-six-year-old male, arrives at the clinic as a new patient. He has never been in care before.
- HPI: Has had increasing fatigue, weight loss, chills, some night sweats, some headache when he climbs stairs. He has a chronic cough that he has had “for years”. No blurred vision, no GI symptoms, does admit to missing some appointments.
- SH: Grew up in New York, MSM, sexual debut at age 14. First tested positive in June 2018. Thinks he had a negative test a few years ago. Now lives in Memphis, unemployed. He occasionally drinks whiskey (6 shots a week), daily marijuana and occasionally injects opioids that he buys on the street. Last injected about 6 weeks ago.

Jesse

- PE: T99.2, RR 14, BP 112/74 WT 142 LB BMI 20.6 Pulse O2 93%; thin alert, slightly slow response time, lungs are clear. Abnormal findings include 1/3 short term recall, absent achilles reflexes, increased patellar reflexes. Fine motor and gait are impaired. Skin is dry and some scaling along scalp line. Fundoscopic exam is limited but wnl.
- Labs:
  - H/H 12.4/35%; WBC 2.3, Creatinine .67, Electrolytes wnl. LFTs with very minimally elevated AST and ALT.
  - HIV-1 RNA 643,221 copies/ml, CD4 cell count 86/4%. Trep Ab and T-spot negative. Toxoplasma, HBV, and HAV serologies show past infections. HCV Ab negative. HIV 1 genotype shows wild type virus.

- A panel of tests are ordered to evaluate for an active OI;
- Serum Cryptococcal Ag, Urine Histoplasma AG, Toxoplasma serology, T-Spot, Blood culture for AFB, plasma CMV PCR and a CXR which is read as no acute changes.
- A room air ABG is obtained which shows a pO2 of 67mm and a large A-a gradient.
Patient is admitted and undergoes bronchoscopy with BAL.
GMS stain is positive for pneumocystis.

PJP

Organism: P. jiroveci; ubiquitous, 2/3 children seropositive by age 4;
Transmission: probable airborne, reactivation=new acquisition;
Incidence: 70-80% of AIDS pts. prior to prophylaxis, now most common new
ADE or in untreated patients.
Prognosis: lethal if untreated; advanced HIV and severe PCP carry 20-40%
mortality.
Risk factors: CD4<200 cells/mm$^3$ (90%), CD4 <14%, thrush, wasting,
recurrent pneumonia, elevated HIV-1 RNA

PJP

- Clinical presentation depends on duration of illness, concurrent morbidities and
  patient's activity level.
- Early disease: fever, dry cough, some dyspnea on exertion, normal CXR and pO2;
  O2 % sat is not ideal marker; (RA-ABG is critical!)
- Moderate to severe disease: fever, non-productive cough, progressive dyspnea,
  chest discomfort, headache; associated advanced HIV disease symptoms;
- Pneumothorax in a patient at risk should be considered PCP until proven otherwise.
- Imaging: early disease may have normal CXR; “classic” findings are butterfly
  interstitial pattern, all radiologic patterns have been reported. High resolution CT
  can help determine appropriate course.
- Newer diagnostic options like PCR for PJP and serum 1,3B-D-glucan assay do add
  much to the work up and treating presumptive PJP is rarely appropriate.
**PJP**
- Clinical presentation depends on duration of illness, concurrent morbidities and patient’s activity level.
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- Newer diagnostic options like PCR for PJP and serum 1,3B-D-glucan assay do add much to the work up and treating presumptive PJP is rarely appropriate.

**Cryptococcal disease**
- Patient has a non-contrasted CT scan of the head which only shows some cerebral atrophy.
- LP yields: OP of 24 cm, 4 WBCs, Glucose is normal and protein is slightly elevated. Indian ink and cryptococcal Ag are positive.
- He is admitted for induction therapy for cryptococcal meningitis.

**Cryptococcal Meningitis**
- C. neoformans is an encapsulated yeast, inhaled into the small airways where it usually causes sub-clinical disease; dissemination to the CNS is not related to pulmonary response.
- C. neoformans produces no toxins and evokes little inflammatory response. The main virulence factor is the capsule.
Cryptococcal Meningitis

- Clinical manifestations:
  - Headache (70-90%), fever (60-80%), malaise (76%), stiff neck (20-30%), photophobia (6-18%), seizures (5-10%), nausea (true meningismus is rare)
  - Average duration of symptoms is 30 days.
  - Predictors of poor outcomes are altered mental status, increased opening pressure, WBC<20 cells/mm^3.
  - Diagnosis made by CSF examination with India ink (74-88%), Crypto Ag serum/CSF (99%), CSF culture.
  - Level of Crypto Ag is not indicative of severity of disease nor a marker of response to therapy. Serum Crypto Ag can rule out clinical disease in HIV positive but not negative patients.

Jesse

- Jesse is started on induction therapy with liposomal amphotericin therapy in addition to oral flucytosine. Repeat LP reveals a normal OP and similar indices. He does well and is discharged home on oral fluconazole.
- Two days prior to discharge he is started on HAART.
- Ten days after discharge he presents to his clinic follow up appointment, feeling better, minimal headache, increased appetite, gaining weight.
- Ten days later he calls the service complaining of increased headache, feeling poorly.

Cryptococcal disease and HAART

- Initiation of HAART in a patient with active cryptococcal disease can cause immune reconstitution inflammatory syndrome in up to 30% of patients.
- Recommendations are to delay from 2-10 weeks prior to initiating HAART.
- Signs of IRIS should be monitored and evaluated immediately.
CMV
- Jesse is evaluated by the ophthalmologist and no signs of CMV retinitis are seen.
- A contrasted MRI of the brain shows some mild white matter disease.

CMV Disease
- Disseminated viral infection which causes disease in advanced (CD4 < 50 cells/mm$^3$) AIDS.
- CMV seropositivity highest in MSM and IVDU.
- Usually reactivation disease.
- Several reports of IRIS related disease.
- Clinical manifestations are related to end-organ damage:
  - Retinitis (30% of AIDS patients)
  - Cystitis (5-10% of AIDS patients)
  - Esophagitis (<10% of AIDS patients)
  - Neurologic disease (<5% of AIDS patients)

CMV Retinitis
- Most common presentation of CMV infection.
- >60% with unilateral disease; will progress to second eye if untreated.
- Symptoms include floaters, scotomata, field cuts, decreased acuity.
- Progresses rapidly, in “stops and starts”, can be sight threatening in 24 hours.
- Painless, rarely associated with new systemic symptoms.
- Several reports of IRIS and IRU related to CMV.
CMV Disease

Diagnosis:
- Retinal disease: recognition of classic findings in at-risk patient, serology not useful; viremia negative in 30% of patients.
- GI disease: biopsy with histology demonstrating intranuclear inclusion bodies with inflammatory reaction at edge of ulcer;
- Culture results are not adequate to demonstrate active disease;
- Neurologic disease may depend on CSF findings or brain biopsy.

Malcolm

- 61-year-old male with longstanding HIV infection, intermittent treatment due to competing issues of poverty, IDU and schizo-affective disorder is admitted through the ED with severe malaise, hypotension, fever, diarrhea, pancytopenia.
- PE reveals cachectic male, somewhat obtunded, significant periorbital swelling with discoloration left upper eyelid. He has 2+ left lower extremity edema, scattered crackles on lung exam.
- CT of the chest and abdomen shows diffuse adenopathy in axillary, perihilar and inguinal distribution. Scattered nodular infiltrates in both lung fields with effusion in left base.

Malcolm

- Labs reveal:
  - Hgb/Hct 8.1/23; WBC 1.1, Plt 64,000
  - Creatinine 2.0, LFTs mildly elevated
  - CRP 34, LA 1.0
  - CMV PCR 640 copies/ml; EBV PCR 2320 copies/ml; HHV 6 undetectable, HHV8 2320 copies/ml;
  - UA shows TNTC WBC, bacteria; urine and blood cultures pending.
  - Serum cryptococcal antigen is positive, titer pending.
- Patient is transferred to the MICU, intubated and fluid support, broad spectrum antimicrobials are initiated.
One new (old) pathogen

- Human Herpesvirus-8
  - Etiologically associated with all forms of Kaposi sarcoma (KS)
  - Still the most common cancer PLWHA in the U.S.
- Also associated with:
  - Primary Effusion Lymphoma (PEL)
  - Multicentric Castleman's Disease (MCD)
  - KSHV inflammatory cytokine syndrome (KICS)
- KS is still the most common clinical manifestation of HHV-8 infection.
  - PEL, MCD and KICS are much less common and are seen usually in the setting of extreme immune suppression.
- The risk of developing KS is inversely proportional to the CD4 cell count but recent reports suggest an increase in immune competent patients.
- Tissue diagnosis is still critical, peripheral blood HHV-8 PCR is not helpful.

Carlos

- 38 year old Guatemalan HIV + male admitted for fever, chills, weight loss, abdominal pain, pancytopenia with splenomegaly.
- He reports increasing fatigue and progressive dyspnea.
- CD4 count is 32 cells/mm$^3$; HIV 1 RNA is 680,343 copies/ml.
- Imaging is consistent with multifocal pneumonia.
- He is admitted to the ICU.

Carlos

- Patient initially requires volume support and pressors.
- ID, pulmonology, hematology and general surgery are consulted.
- Imaging also reveals massive splenomegaly with prominent mass effect on adjacent organs.
- Differential includes: infectious (AFB, fungal, EBV, malaria), lymphoma, myeloproliferative disorders, and rheumatologic disease.
- He is treated with broad spectrum antibiotics, antivirals and IV IgG is also started.
- Workup including BM biopsy, cultures, HHV-8 are negative.
- Hematologic workup reveals elevated ferritin, IL2R and other findings consistent with HLH; massive splenomegaly thought to be related to underlying lymphoma.
- Plan is to start HLH protocol, splenic embolization before diagnostic/therapeutic splenectomy.
Carlos

- Patient is readmitted emergently to the ICU from a hematology clinic visit for sepsis, pneumonia.
- Comprehensive infectious work up is again negative.
- Patient responds to antibiotics, fluids, and is discharged home for elective splenectomy when appropriate.
- Working diagnoses are AIDS, HLH, splenomegaly secondary to underlying malignancy and resolving HCAP.

Carlos

- During his work up the following diagnoses were considered:
  - Bacterial sepsis, PCP, disseminated AFB (MTB, MAU), fungal (Cryptococcosis, Histoplasmosis, Coccidioidomycosis, Aspergillosis), and viral infections (EBV, CMV, HHV 8) strongyloidiasis, malaria.
  - He received PCP prophylaxis, empiric therapy directed at fungal and bacterial pathogens.
  - A diagnosis was made of HLH based on lab (ferritin, cytopenia) and clinical picture.
  - He received IVIgG for his splenomegaly.

A routine peripheral blood smear revealed underlying disease.
Leishmania on Peripheral Blood Smear

Geographic OIs

Guidelines
- Malaria
  - Sub-Saharan Africa, SE Asia
- Penicilliosis marneffei
  - SE Asia, South China
- Leishmaniasis
  - Tropics, sub-tropics and Southern Europe
- Chagas Disease
  - Latin America
- Isosporiasis (Cystoisosporiasis)
  - Tropical and Sub-tropical

Additional
- MTB
  - Everywhere
- Histoplasmosis
  - Ohio and Mississippi River Valleys, Central and South America
- Coccidiomyosisis
  - Southwestern US, Mexico and South America

So what is new?
- There are less patients presenting with OIs but about 20% of newly diagnosed are at risk for developing an OI.
- Fewer practicing clinicians have extensive experience diagnosing and treating OIs.
- There have been few new technologies that change evaluation of OIs significantly.
- Initiation of HAART in the setting of an active OI must be timed appropriately.
- IRIS must be anticipated and evaluated when appropriate.
- Primary and secondary prophylaxis guidelines are updated, as well as when to discontinue prophylaxis.
So what is old?

- The main pathogens: PJP, MAC, Cryptococcus, MCV, Toxoplasma and bacterial pneumonias still account for most of the serious OIs.
- More harm will likely be done by missing common OIs rather than the rare exotic:
  - PJP: think of it, check oxygenation, don't treat empirically.
  - Cryptococcal disease: no meningismus, no inflammatory component in the CSF.
- Prioritize the work up in a immune suppressed patient with multiple complaints and abnormal lab results.

Resources

- Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents
  https://aidsinfo.nih.gov/guidelines
- Regional AETCs: SEAETC.com
- HIV Essentials Paul Sax (2017)
Elimination of Pediatric HIV/AIDS: Where Have We Come From and Where Are We Going?

Karen P. Beckerman, MD, FACOG
Associate Professor of Clinical Obstetrics & Gynecology
Carl Icahn School of Medicine at Mt Sinai
Bronx, New York

Today’s Goals

- Principles of elimination of Pediatric HIV/AIDS.
- Where are we now?
- Past challenges.
- Today’s failures.
- Will eradication always lie beyond our reach?
- Who will be the second cure?
Assumptions and Projections

- Based on informative diagnostic HIV testing of women.
- Benefits of maternal ARV treatment are no longer disputed.
- Potential teratogenesis of ARVs has been studied more than any other class of drugs in history.
- With almost 23,000 prospective reports to the Antiretroviral Pregnancy, no signal detected in APR to date.

APREGISTRY.COM

- Potential adverse fetal effects of ARVs are overwhelmed by benefits to maternal health and near 100% prevention of pediatric HIV/AIDS.

Current Principles of Elimination of Pediatric AIDS

- Identify women living with HIV before and during pregnancy.
- Universal opt-out HIV testing and re-testing in 3rd trimester.
- HIV Ab as part of newborn heel stick screen for metabolic diseases.
- Reproductive counseling (10sec – 10min) at every visit for women and men.
- Optimize parents’ health for all illnesses (diabetes, hypertension).
- Control maternal HIV-viremia by:
  - combination therapy for all
  - close monitoring of VL (every 1-2 months or more often)
  - honest communication in order to enhance adherence and achieve durable maternal viral suppression.
  - access to once-daily single pill formulations.
- enhancement of service coordination!

Antiretroviral Pregnancy Registry, 31 July 2018: Prevalence of Birth Defects (%), +/- 95% CI

Following First Trimester Exposure:

- CMV
- Toxoplasmosis
- Rubella
- Varicella
- Syphilis
- HIV
- Hepatitis B
- Hepatitis C
- HHV-6
- HHV-7
- EBV
- Adenovirus
- Cytomegalovirus
- HHV-6
- HHV-7
- EBV
- Adenovirus
- HCMV
- CMV
- Toxoplasmosis
- Rubella
- Varicella
- Syphilis
- HIV
- Hepatitis B
- Hepatitis C
- HHV-6
- HHV-7
- EBV
- Adenovirus
- Cytomegalovirus
- HHV-6
- HHV-7
- EBV
- Adenovirus

MACDP, Metropolitan Atlanta Congenital Defects Program; TBDR, Texas Birth Defects Registry

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- Adenovirus
- Cytomegalovirus
- HHV-6
- HHV-7
- EBV
- Adenovirus

MACDP, Metropolitan Atlanta Congenital Defects Program; TBDR, Texas Birth Defects Registry
**ARV in Common Use with < 1000 1st Trimester Reports**

<table>
<thead>
<tr>
<th>ARV</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darunavir</td>
<td>1/496</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>20/427</td>
</tr>
<tr>
<td>Etravirine</td>
<td>1/69</td>
</tr>
<tr>
<td>Indinavir</td>
<td>3/312</td>
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<tr>
<td>Maraviroc</td>
<td>1/30</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>7/289</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>3/254</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>5/213</td>
</tr>
<tr>
<td>Tobilixat</td>
<td>1/17</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>3/110</td>
</tr>
</tbody>
</table>

Prospective Registration is Urgently Needed!
APREGISTRY.COM

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**Dolutegravir Advisory: aidsinfo.nih.gov**

- NTDs occur within the first 28 days after conception or 6 weeks from the last menstrual period, before fetal heart motion can be detected on US.
- If other good options are available, women less than 8w from the LMP, switching to a non-DTG regimen is recommended. Do not stop DTG without replacement.
- Those 8w or greater pregnant may initiate or continue DTG.
- Pregnancy testing prior to initiating DTG. (Consider avoiding if good option available)
- Use of DTG late in pregnancy to enhance virologic control is not associated with NTDs
- FOLIC ACID offers significant protection against NTDs for everyone (!)
- Dolutegravir remains treatment of choice for acute/early HIV infection regardless of reproductive status.
- Final decision is patient's informed choice.

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**Cases #1 & #2, West Coast**

**“Low Risk for HIV”**

1996
- 18yo, married, G1P0, Early prenatal care. Good health.
- HIV testing not done.
- University provider at community clinic stated, “I didn’t offer testing because she was married, and our guidelines state it is single women who are at increased risk.”

1998
- 34yo G1P1 health care professional. Early prenatal care. Excellent health.
- Offered and declined HIV testing. Provider noted “no risk factors” and did not offer testing again.
- NSVD at term of 3200g healthy male.

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National Harbor, Maryland, December 9-11, 2018  Page 286
Women who are "known to be at high risk" for HIV infection should be tested as early as possible during each pregnancy.

Women in jurisdictions with elevated incidence of HIV or AIDS among women aged 15–49 years (not limited to pregnant women) should be tested as early as possible during each pregnancy.

Test women for HIV as early as possible during each pregnancy.

No additional process or written documentation of informed consent beyond what is required for other routine prenatal tests should be required for HIV testing.

Women who decline the test should be encouraged to be tested at later visits.

A second HIV test during the third trimester, preferably <36 weeks of gestation, is cost-effective even in areas of low HIV prevalence and may be considered for all pregnant women.

A second HIV test during the third trimester is recommended for women who meet one or more of the following criteria:

- Women in jurisdictions with elevated incidence of HIV or AIDS among women aged 15–49 years.
- Women who receive health care in facilities in which prenatal screening identifies at least one HIV-infected pregnant woman per 1,000 women screened (25 States).
- Women who are "known to be at high risk."
Repeat HIV testing in the third trimester:
1. preferably before 36 weeks of gestation
2. women with initial negative HIV antibody tests
3. known to be at high risk of acquiring HIV infection
4. receiving care in facilities with HIV incidence in pregnant women of at least 1 per 1,000 per year
5. incarcerated women
6. reside in jurisdictions with elevated HIV incidence
7. signs or symptoms consistent with acute HIV infection (eg, fever, lymphadenopathy, skin rash, myalgias, arthralgias, headache, oral ulcers, leukopenia, thrombocytopenia, or transaminase elevation) … When acute infection is possible, a plasma RNA test should be used in addition to standard testing for HIV antibodies.

Pregnant women at high risk of acquiring HIV include:
8. those who have been diagnosed with another sexually transmitted disease in the past year.
9. those who are injection drug users or whose sex partners are injection drug users.
10. those who exchange sex for money or drugs.
11. those women with a new sex partner.
12. more than one sex partner during this pregnancy, or
13. sex partners known to be infected with HIV or at high risk of HIV.

JUST RETEST!

But understand when to send a Viral PCR test, And/Or when to ask a colleague!

<<Anytime you think of acute or early infection>>
How are we doing?
Percent Re-tested During Prenatal Care: 38.4% of 1032
Johns Hopkins Hospital Deliveries, 2012

P<0.001 on adjusted multivariate analysis

PMTCT = 99%

1997: Routine newborn screening begins in New York. Maternal ARV Treatment or prophylaxis = 64%
1999: Expedited testing in obstetrical settings implemented.
2003: No reported perinatal transmission in children born to HIV-infected mothers.
2015: Maternal ARV Treatment or prophylaxis = 99%

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National Harbor, Maryland, December 9-11, 2018
Life Expectancy in the Bronx has increased 12.4% since 1980.
FIGURE 4.1: Poverty level, NYC 2011-2015

Poverty by ZIP code based on Federal Poverty Level (FPL)
- Low poverty (<150% below FPL)
- Medium (150% - <200% below FPL)
- High (200% - <300% below FPL)
- Very high poverty (300%+ below FPL)
- Non-residential areas.

2016 Median Household Income:
- South Bronx: $25,388
- Bronx County: $55,191
- New York State: $55,191

FIGURE 4.3: HIV prevalence, NYC 2014

PLWHA as a percent of population by ZIP code
- <1: 0.0%
- 1 - 4.9: 5.0%
- 5 - 9.9: 7.5%
- 10 - 19.9: 10%
- 20 - 49.9: 15%
- 50 - 99.9: 20%
- 100 or more: 25%

Bronx, 2016
- All: 1.8%
- Female: 1.1%

Bronx, 2016: Persons Living With Dx’d HIV Infection
Bronx, 2016: Persons Living With Dx’d HIV Infection

Case #3, 2009. Fever of Unknown Origin

- 24 yo G2P0 at 34 weeks by LMP c/w early US. Early prenatal care in general OB clinic, no visits missed.
- Admitted for persistent fever of unknown origin, flu-like symptoms.
- Co-managed by obstetric and infectious disease services. Work-up included PPD, CXR, TORCH, Legionella and HIV1/2 antibody testing. Entirely negative.
- Pt discharged home on HD#8 after being afebrile for 2 days. MFM service sent a HIV-1 VL on day of discharge.

Case #3, 2009. Fever of Unknown Origin

- Presented to L&D at 1:30 am at 37w2d.
- c/o labor pains for the past 12 hours, now every 5 minutes. Had been feeling much better prior to onset of labor.
- Routine admission labs unremarkable by on-call MD. Expedited HIV test not sent due to negative HIV-1/2 antibody test 3 weeks earlier.
- NSVD at 8:05 am, Live male, Apgar 7/9, 2950g.
- Home with mother on DOL #2 per routine.
Case #3, 2009.
Fever of Unknown Origin

- Pediatrics notified by NYS DOH of positive HIV-1/2 antibody screen on day of life 7.
- Infant HIV-1 pcr returned at 600,000 copies/mL on day of life 16.

WHAT DID WE MISS at our high volume, experienced hospital?
WHY?
WHAT OTHER TESTS COULD WE HAVE DONE?

Case #4, 2013.
Negative 3rd Trimester HIV-1/2 Ab Test

- 31yo G5P2022 at 34 weeks gestation. One partner of the last 12 months. Eight prenatal visits. HIV-1/2 Ab test negative at 16w registration and at 32w.
- Complained of strong contractions for 3h, found to be 5cm dilated. Allowed to deliver.

Case #4, 2013.
Negative 3rd Trimester HIV-1/2 Ab Test

- NSVD of live male, 1740g, Apgars 6/7.
- Admitted to NICU for mild RDS and r/o sepsis workup.
- CPAP discontinued d/ #5. Septic w/u negative, “Premie grower”.
- DOL18, call from NYS DOH with positive HIV1/2 Ab from newborn heel-stick screen.
- HIV-1 qTqPCR returned 7 days later: 120,000 copies/mL.
What have we changed?

- Since 2015, in addition to existing universal opt-out HIV testing, women are asked at their 1st prenatal visit if they know the HIV status of their partner.
- Pregnant women identified as at risk are tested with Expedited HIVAg/Ab test, HIV1/2 Ab screen and HIV-1 qPCR (viral load).
- PrEP and PEP are strongly recommended and paid for in pregnancy per New York State Guidelines.

Is this enough?

Case # 5, 2017: New to the Bronx

- 36y G6P4014 presented, as planned, in labor at term. She was referred from an outside clinic where she had been late to care.
- Recent arrival from West Africa with her 4 children, finally able to join her husband who had been living in the Bronx since 2010, visiting his family once every year.
- Prenatal labs: O+, Hb AA, Hb/Hct 11.2/34%.
  US c/w LMP, HIV-1/2 Ab negative x 2.

Initial exam: 4cm/Vtx/1-sta/100%, intact.
- Interviewed, PMHx unremarkable. Prenatal records available.
- Per 2015 protocol, pt asked if she knew her partner’s HIV status. She stated her husband was HIV-negative.
- L&D admission labs, including expedited HIVAg/Ab negative.
- NSVD 3620g female without complication 4h later; successful with exclusive breastfeeding.
- Home with infant PPD #2
- Uneventful newborn & postpartum f/u.
- No missed visits
- Newborn heel-stick screen unremarkable & negative.
- At 3mo post-partum, our patient presented to adult ED with the worst headache of her life with flu-like symptoms.
- Records reviewed. HIV testing not repeated.
- Evaluation, including head MRI was negative.
- Home with tamiflu, po hydration and tylenol.
- Symptoms improved over the following week.

---

- Three days later the 14 week old-infant presented to Peds ED with fever, irritability and poor feeding.
- Evaluation significant for persistent cough, CXR negative. Home on pedialyte.
- Infants did not improve over the following weeks. Parents presented to several different pediatric facilities over the following 2 months.

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- The family self-referred to another hospital where the infant was admitted and transferred to a University Hospital. Pediatric Infectious Diseases and Pulmonary Medicine were consulted.
- After transfer, the infant began to desaturate, deteriorated rapidly and required intubation.
- Aspirate from the ET tube was sent for analysis.
Smear from bronchoalveolar lavage. Methenamine silver stain.
Dr. Russell K. Brynes/CDC

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Case # 5: New to the Bronx

Infant admitted in respiratory failure. Intubated for 5 weeks.
Mother HIV infected.
Father HIV infected.

WHAT DID WE MISS at our high volume, experienced hospital? WHY?

WHAT OTHER TESTS COULD WE HAVE DONE?

<table>
<thead>
<tr>
<th>Birth Year</th>
<th>Maternal History</th>
<th>Delivery</th>
<th>Infant</th>
<th>Mat Del VL</th>
<th>Infant Del VL</th>
<th>Infant Dx by</th>
<th>Missed Opportunities</th>
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<tbody>
<tr>
<td>1996 (1)</td>
<td>18yo married G1P0</td>
<td>Normal</td>
<td>Female</td>
<td>Low birth weight</td>
<td>Unknown</td>
<td>Infant Dx: PCP</td>
<td>HIV testing offered per risk-based testing guidelines.</td>
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<tr>
<td>2009 (2)</td>
<td>34yo G1P0, Health care professional</td>
<td>Normal</td>
<td>Male</td>
<td>Healthy</td>
<td>Unknown</td>
<td>Infant Dx: PCP</td>
<td>HIV testing offered per risk-based testing guidelines.</td>
</tr>
<tr>
<td>2009 (3)</td>
<td>24yo G2P0 at 37w</td>
<td>Normal</td>
<td>Male</td>
<td>Infant</td>
<td>Unknown</td>
<td>Infant Dx: PCP</td>
<td>HIV testing offered per risk-based testing guidelines.</td>
</tr>
<tr>
<td>2013 (4)</td>
<td>31yo G5P2 at 34w</td>
<td>Normal</td>
<td>Male</td>
<td>Premature</td>
<td>Unknown</td>
<td>Infant Dx: PCP</td>
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<tr>
<td>2017 (5)</td>
<td>30yo G6P5 at 34w</td>
<td>Normal</td>
<td>Male</td>
<td>Infant</td>
<td>Unknown</td>
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And we have learned that...

- Even though we consider a vertical transmission event unacceptable, failure to prevent a case of pediatric HIV may not be our worst tragedy.
- Our inability to detect a case of Pediatric AIDS resulted in the unexpected return of a nightmare from 20 years ago.
- Breast milk transmission can occur anywhere in the world.
- **Primary maternal infection** carries markedly increased risk of MTCT.

While we must also acknowledge, **Risk** remains very difficult to assess accurately...

- Globally, more than 70% of new transmissions occur in long-term couples who don’t realize that one partner is HIV+ and the other is HIVneg. (S.Allen, 2008)
- Women identified as HIV positive, who are able to participate in care and take cART are at extraordinarily low risk of transmission to infants.
- Women “testing out” are at significant risk of transmitting HIV to their babies should they become infected during pregnancy or nursing.

![HIV infectivity per 1,000 sex acts](image)
So how can uninfected pregnant women at risk of HIV infection protect themselves?

- Known infected partners can maximize their adherence to treatment and protect their partners’ health at the same time (Early Treatment, U=U).
- Uninfected women who know or learn they are in an ongoing discordant relationship can begin nPEP if within <72 hours of last exposure.
- nPEP includes safer sex practices
- Ongoing antibody and viral testing. If negative at 28 days, switch to PrEP.

Couples Testing

Successful demonstration projects since the 1990s:
- India: Low seroprevalence, high risk of DV.
- Rwanda & Zambia: Studies of discordant couples
- Partners are easily tested for other illnesses in US prenatal clinics:
  - Blood typing, Kell status
  - Sickle cell testing, Karyotype, Microarrays

Allows for mutual disclosure
Blame free disclosure
Can only be effective if on-site and routine part of prenatal care and becomes NORMATIVE BEHAVIOR
Case #6, 2018.
HIV1/2 and p24 Negative at 10w

- Pt decided to begin nPEP. Prescriptions were given.
- 3d later results available:
  - HIV1/2Ab neg; RPR positive 1:2, FTA pending. H/H 8.2g/dL/26%
  - HIVplRNA 43 copies/mL. CD4=1498.
- 14d after initial visit, No c/o. FTA neg
- Repeat VL 30, expedited HIVAg/Ab Reactive.
- Pt queried regarding adherence. “I missed 2d of my pills.”
- 28d VL 340, pt reports missing 2nd raltegravir dose “half the time”.

Case #6, 2018.
Pregnant at 14 wk with hyperacute HIV-1 infection.

ARS Question 3: You and your colleagues disagree about the best ARV strategy in this setting. One infectious disease friend says, “Well, dolutegravir would be best but I don’t want to be responsible if this baby has a birth defect!”

You check references and talk to a few more colleagues. The best course now is to:
1. Transfer care completely to your colleague because he seems so sure of what he’s talking about.
2. Counsel patient patient about alternatives and recommend TDF/FTC once daily + lopinavir/ritonavir twice daily, or darunavir+ritonavir once then twice daily.
3. Tell the patient that she is going to have to get her act together and remember to take her pills or ACS will take this baby away too.
4. Counsel patient regarding timing of neural tube closure and offer her TDF/FTC+dolutegravir, all once daily, as per USPHS Guidelines.
5. Counsel patient and offer a switch to TAF/FTC/rilpivirine once daily.
Case #6, 2018.
Pregnant at 14 wk with hyperacute HIV-1 infection.

- Patient decided to switch to TDF/FTC plus Dolutegravir, all once daily.
- Two weeks later, at 42d VL target not detected, CD4 1641; HIV1Ab Interderm/Ag NR. qual DNA PCR positive. RPRNR/FTAneg.

Untreated vs. Treated Acute HIV Infection:
Projected viral load, CD4 cell count, reservoir seeding, and symptom duration


ARS Question 4: At this point, how has diagnosis during the hyperacute phase of primary HIV-1 infection changed the prognosis for mother and baby?

1. If infected, the infant is more likely to have resistance to integrase inhibitors.
2. There is not much change. It’s likely someone would have made the diagnosis before she delivered.
3. If uninfected, the baby will still be at risk for immune compromise.
4. If she is able to tolerate and continue ARVs, the mother will remain immune competent with an unusually low HIV-1 viral reservoir.
5. After a few years we can be certain that she will be able to stop ARVs with little chance of viral rebound.

Initiating cART during PHI represents a major opportunity to reduce HIV reservoirs and achieve optimal immune reconstitution.

HIV baseline pHIV RNA = 4-5.6 log_{10} copies/mL Henrich & Deeks (2017) = 2.3 log_{10} copies/mL vs patient 6: baseline = 1.6 log_{10} copies/mL

More likely to be the second "Cure"?

CDC: New Cases of Pediatric HIV/AIDS, 1985-2003, United States


"As long as there are new HIV infections in women of reproductive age, 100% "elimination" of HIV MCT cannot be achieved. In the current phase of the epidemic, with low numbers of infants infected annually, one could predict that prevention of the annual "residual" cases will become increasingly difficult."

But just because it may be tough, that doesn’t mean we can’t do it.

Real time casefinding must include uninfected exposed & infected women
Learning from Failures and even disaster

- Risk-based HIV re-testing strategies are confusing and difficult.
- Universal re-testing is straightforward and indicated in the majority of the United States.
- Asking women, especially when pregnant, about their partner’s STI Hx and HIV status can be informative. As it becomes more normative it becomes easier.
- Couples testing for HIV, especially in higher prevalence settings, could be straightforward if it becomes normative. Appropriate settings could include women’s health centers, prenatal care centers, and Labor and Delivery suites, especially when expedited testing is indicated.
- Even if partners opt out, their consciousness about HIV could be raised.
- PrEP and nPEP work! Diagnosis during acute infection will also create a pool of individuals most likely to reach a CURE first.
- Why can’t #2 be a woman?

We know how to prevent transmission of HIV to newborns.
We know how to prevent sexual transmission.
We know how to prevent transmission by IVDU.
But we can’t prevent what we cannot see.

Question-and-Answer
Learning Objectives

After attending this presentation, learners will be able to:

- Describe opioid use disorder
- Initiate treatment for opioid use disorders
- Describe the implications of opioid use disorders in people living with HIV infection
Addiction

- A state in which a person engages in compulsive behavior
  - The behavior is reinforcing (that is, pleasurable or rewarding)
  - There is a loss of control in limiting the intake of the substance

Why do people take drugs?

- To feel good
  - To have novel feelings, sensations, experiences AND to share them
- To feel better
  - To lessen anxiety, worries, fears, depression, hopelessness
Why do some people become addicted?

- Biology/genetics
- Environment
- Biology/Environment Interactions

Drugs Are Usurping Brain Circuits and Motivational Priorities

Diagram showing the functional state of a typical "normal" heroin user. Arrows show the repetitive injections of heroin in uncertain doses, usually 10 to 20 mg but sometimes much more. Note that the addict is hardly ever in a state of normal function ("straight").

Data from "Drugs of Abuse" by H. E. Hollister, M. S. Greenberg, and M. J. Bond, 1970, Archives of Neurology and Psychiatry 104, pp. 505-510.
People who use drugs still acquire HIV

- Even in the 21st Century, we have outbreaks of HIV infection among people who use drugs (e.g., Indiana).
- But there is treatment for opioid use disorders
  - Metzger, 1993:
    - 2 cohorts of patients
    - 103 out-of-treatment IDU opiate users
    - 152 subjects receiving methadone treatment
    - HIV antibody conversion, 18-months
    - 22% of those out-of-treatment
    - 3.5% of those receiving METHADONE

“But it isn’t really a problem”

- Transtheoretical Model of Change:
  - Helping patients to move along the stages of change
- Basics of Harm Reduction
  - Syringe exchanges
- When helping hurts
  - Enabling vs. boundaries

What is medication assisted treatment?

- Opioid substitution treatment and medication assisted treatment are the same, but what is it?
- Buprenorphine and methadone can
  - reduce injection related HIV risk behavior
  - decrease psychosocial & medical morbidity
  - increase access to and retention with ARV
  - improve overall health status
  - are associated with decreased criminal activity
Dose effect on mu-opioid receptor availability

![MRI images showing binding potential (Bmax/Kd) for different doses of buprenorphine (Bup 0 mg, Bup 0.2 mg, Bup 16 mg, Bup 32 mg)]

Bup 0 mg
Bup 0.2 mg
Bup 16 mg
Bup 32 mg

MRI Courtesy of Laura McNicholas, MD, PhD

Medications to treat opioid use disorder

- **Methadone**
  - Only in OTP
  - Efficacious, best retention

- **Buprenorphine**
  - Office based
  - Efficacious, retention less than methadone

- **Naltrexone**
  - Office based
  - Efficacious
  - Retention less than methadone & buprenorphine

Functional state

High
Straight
Sick

Stabilization of patient in state of normal function by blockade treatment. A single daily and dose of methadone prevents him from feeling symptoms of abstinence ("sick") or euphoria ("high"), even if he takes a shot of heroin. Critical time blockade occurs if methadone is omitted.


Slide 15 of 30

December 3, 2018
Best Practices in Treatment

- Provision of low threshold, rapid access, appropriately dosed methadone
- Culturally appropriate counseling for heroin addiction [can be simple (NA) to more complex (CBT)]
- Treatment of the medical issues associated with addiction (e.g., HIV, hepatitis B/C, and Tuberculosis)

Key themes for HIV and substance use

- People who use drugs and are infected with HIV have higher morbidity and mortality than the general population and others with HIV infection
- Discrimination is still evident among treating people who use drugs for HIV, Hepatitis C and tuberculosis treatments in the US and globally
- Adherence remains possible, even in the setting of ongoing substance use
In the Past, Bias: PWID without ART

- In the past, people who inject drugs (PWID) were denied HIV therapy until they ceased drug use
- While multifactorial, there was a bias against drug users and a failure to recognize addiction as a medical illness
- PLWHA with other medical illness were not denied treatment. In some settings (e.g., HIV/HCV; HIV/TB), having another medical illness with HIV makes ART access a priority.

In the Present: The Evidence

- Work from Evan Woods in British Columbia showed that in a cohort of 1191 ART naïve patients followed from ART initiation, resistance was found in 25% of the cohort during the first 30 months (PI and NNRTI resistance).
- No difference in resistance between people who inject drugs and people who do not inject who were started on ART.

This can be done anywhere

- In India, directly observed therapy of DAAs with buprenorphine in the field
- In Tanzania, adherence support for HIV and TB medications with methadone
- In New Haven, HIV and HCV treatment integrated into the methadone clinic
Practical Next Steps

- Screen patients for substance use disorders using standardized questions:
  - How many times in the past year have you had 5 or more standard drinks in a day?
  - How many times in the past year have you used an illegal drug or a prescription medication for nonmedical reasons?

Additional Next Steps

- People who use drugs can take medications and should be eligible for HIV, HBV, HCV, and TB care
- Prescribe naloxone and consider becoming a buprenorphine provider
- Review guidelines on the treatment of chronic pain and re-evaluate how you prescribe opioids and review

Useful websites:

- American Pain Society has resources available online: [http://www.americanpainsociety.org/resources/content/primary-care-practitioner.html](http://www.americanpainsociety.org/resources/content/primary-care-practitioner.html)
- Providers Clinical Support System (PCSS) for MAT at [https://pcssnow.org/resources/clinical-tools/](https://pcssnow.org/resources/clinical-tools/)
- Buprenorphine training: [https://www.samhsa.gov/medication-assisted-treatment/training-resources/buprenorphine-physician-training](https://www.samhsa.gov/medication-assisted-treatment/training-resources/buprenorphine-physician-training)