CO-CHAIRS

Laura W. Cheever, MD, ScM
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Michael S. Saag, MD
Professor of Medicine
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University of Alabama at Birmingham
Birmingham, Alabama
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General Information

WELCOME AND GOALS

Welcome to the 2019 Ryan White HIV/AIDS Program CLINICAL CONFERENCE. The goals of the 2019 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 2019 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.

The 2019 CLINICAL CONFERENCE is planned with and supported by the HIV/AIDS Bureau, Health Resources and Services Administration of the US Department of Health and Human Services (HRSA) and is sponsored and organized by the International Antiviral Society–USA (IAS–USA). This conference is coordinated through the RWHAP AIDS Education and Training Centers (AETC) clinician training network. A mix of lectures, case-based interactive presentations, and small-group meet-the-expert breakout sessions will be held during the 3 days of the 2019 CLINICAL CONFERENCE.

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 U1OHA28686.

Selected aspects of the conference are supported in kind by the IAS–USA.

The networking reception is supported in kind by the Hyatt Regency New Orleans.

MEALS AND INCIDENTALS

Attendees are responsible for their transportation expenses to and from the CLINICAL CONFERENCE, 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. Per diem meal options will be available onsite.

WEBSITE

For additional information about the 2019 CLINICAL CONFERENCE please visit the website at https://www.iasusa.org/events/rwcc2019/

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: meet-the-expert breakout sessions will not be recorded.

POSTCONFERENCE MATERIALS AND RESOURCES

As you know, an important goal of the 2019 CLINICAL CONFERENCE is to provide attendees with the resources to update their clinical colleagues who were not able to attend the conference. To that end, a Slide Training Guide with PowerPoint slides and webcasts of each plenary lecture will be available after the 2019 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 Hyatt Regency. Network information is as follows:

1. Your Internet Network ID is: RWCC19
2. Your password is: iasusa19 (case sensitive)

REGISTRATION AND INFORMATION DESK HOURS
The hours of the 2019 CLINICAL CONFERENCE registration and information desk, located on the outside the conference area are as follows:

- Wednesday, December 4: 3:00 PM – 6:30 PM
- Thursday, December 5: 7:30 AM – 6:30 PM
- Friday, December 6: 7:30 AM – 5:15 PM
- Saturday, December 7: 7:30 AM – 12:30 PM

BADGES
When you arrive at the 2019 CLINICAL CONFERENCE, please check in at the registration desk 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 in the meeting rooms. No flash photography is permitted in meeting rooms.

CLIMATE AND CLOTHING
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 New Orleans area.

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

NETWORKING RECEPTION AND SMALL MEETINGS
Networking space is located on Level 2 in Strand 11B, on Level 3 in the Celestin Foyer, and on Level 4 in Imperial 8. Tables are on a first-come, first-serve basis. The space cannot be reserved. Small meeting space is available on Level 4 in Imperial Boardrooms 4, 6, and 7. Sign-up to reserve rooms will be posted outside each room.
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.

International Antiviral Society–USA

**Mission**

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 or other viral infections and their associated health conditions through high-quality, relevant, balanced, and needs-oriented education and information for practitioners and scientists who are actively involved in medical care and research.

**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.

**HIV Prevention, Sexual Health, and Primary Care**

*Sexual Health, HIV Prevention, and Primary Care,* a new educational effort from the IAS–USA, addresses the rising epidemic of sexually transmitted infections (STIs) in the United States. Programs include a national course and webinars addressing issues in the management of sexual health among adolescents and adults with or at risk for HIV infection. Content is designed for primary care clinicians, HIV specialists, and other clinicians who are responsible for the prevention and management of STIs and HIV. Information is presented through a mix of didactic lectures and clinically relevant cases developed.

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

These one-day live 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.

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 infection prevention and management and the treatment of concomitant conditions. Archived webinars now offer CME credit for a year.

Conference on Retroviruses and Opportunistic Infections

The IAS–USA organizes 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, and years forward are available at www.CROIconference.org.

CROI 2020 will be held in Boston, Massachusetts, from March 8 to March 11, 2020.

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.

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.


Drug Resistance Mutations Project

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 July 2019, 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](http://www.iasusa.org/resources/podcasts) for details and a list of available presentations. Please note that these podcasts do not offer CME credit.

**Slides**

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

For information about any of these programs, please contact the IAS–USA.

Phone: (415) 544-9400

Email: registration@iasusa.org • Website: [www.iasusa.org](http://www.iasusa.org)

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**AIDS Education and Training Center National Coordinating Resource Center**

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.
## Conference Co-Chairs and Faculty

### CHAIRS

<table>
<thead>
<tr>
<th>Name</th>
<th>Title and Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laura W. Cheever, MD, ScM</td>
<td>Associate Administrator, Chief Medical Officer, HIV/AIDS Bureau, Health Resources and Services Administration, Rockville, Maryland</td>
</tr>
<tr>
<td>Michael S. Saag, MD</td>
<td>Professor of Medicine, Associate Dean for Global Health, Jim Straley Chair in AIDS Research, University of Alabama at Birmingham, Birmingham, Alabama</td>
</tr>
<tr>
<td>Steven C. Johnson, MD</td>
<td>Professor of Medicine, University of Colorado, Aurora, Colorado</td>
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### SPEAKERS AND WORKSHOP LEADERS

<table>
<thead>
<tr>
<th>Name</th>
<th>Title and Affiliation</th>
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<tbody>
<tr>
<td>Jean R. Anderson, MD</td>
<td>Professor of Gynecology and Obstetrics, Johns Hopkins University, Baltimore, Maryland</td>
</tr>
<tr>
<td>Sara Ginella-Weibel, MD</td>
<td>Assistant Professor of Medicine, University of California San Diego, La Jolla, California</td>
</tr>
<tr>
<td>John T. Brooks, MD</td>
<td>Chief Medical Officer, Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia</td>
</tr>
<tr>
<td>Tim Horn</td>
<td>Director, Medication Access and Pricing, National Alliance of State &amp; Territorial AIDS Directors, Washington, DC</td>
</tr>
<tr>
<td>R. Douglas Bruce, MD, MA, MS</td>
<td>Associate Clinical Professor of Medicine, Chief of Medicine, Cornell Scott-Hill Health Center, Yale University, New Haven, Connecticut</td>
</tr>
<tr>
<td>Jayme E. Locke, MD, MPH</td>
<td>Director, Comprehensive Transplant Institute, Chief, Division of Transplantation, University of Alabama at Birmingham, Birmingham, Alabama</td>
</tr>
<tr>
<td>Heidi M. Crane, MD, MPH</td>
<td>Professor of Medicine, University of Washington, Seattle, Washington</td>
</tr>
<tr>
<td>Hyman M. Scott, MD, MPH</td>
<td>Assistant Clinical Professor, HIV/ID and Global Medicine, University of California San Francisco, San Francisco, California</td>
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<tr>
<td>Rajesh T. Gandhi, MD</td>
<td>Professor of Medicine, Harvard Medical School, Boston, Massachusetts</td>
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<tr>
<td>David H. Spach, MD</td>
<td>Professor of Medicine, University of Washington, Seattle, Washington</td>
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Victor Valcour, MD, PhD
Professor of Medicine
Director, Global Brain Health Institute
University of California San Francisco
San Francisco, California

Kimberly A. Workowski, MD
Professor of Medicine
Emory University School of Medicine
Atlanta, Georgia

Linda Wesp, PhD, APNP, FNP-C
Adjunct Faculty
University of Wisconsin – Milwaukee
Milwaukee, Wisconsin
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 relationships with commercial interests discussed in the activity (eg, presentation or article) within the previous 12 months.

The ACCME defines financial relationships as “those relationships in which the individual benefits by receiving a salary, royalty, intellectual property rights, consulting fee, honoraria for promotional speakers’ bureau, ownership interest (eg, stocks, stock options or other ownership interest, excluding diversified mutual funds), or other financial benefit. Financial benefits are usually associated with roles such as employment, management position, independent contractor (including contracted research), consulting, teaching, membership on advisory committees or review panels, board membership, and other activities from which remuneration is received, or expected. ACCME considers relationships of the person involved in the CME activity to include financial relationships of a spouse or partner. The ACCME has not set a minimum dollar amount for relationships to be significant. Inherent in any amount is the incentive to maintain or increase the value of the relationship.”

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 Johnson has served on an advisory board for and received consultation fees to his institution from ViiV Healthcare. *(Updated 11/21/19)*

Dr Saag has received research grants and support awarded to his institution from Gilead Sciences, Inc, and ViiV Healthcare. *(Updated 11/21/19)*

**Speakers and Breakout Session Leaders**

Dr Anderson has received grants and research support from Gilead Sciences, Inc. Her spouse holds stock or stock options in Gilead Sciences, Inc. *(Updated 11/08/19)*

Dr Brooks has no relevant financial affiliations to disclose. *(Updated 11/21/19)*

Dr Bruce has no relevant financial affiliations to disclose. *(Updated 11/21/19)*

Dr Crane has no financial relationships with commercial entities related to the topic of her talk. Funding sources not related to topic area: ViiV Healthcare. *(Updated 11/21/19)*

Dr Gandhi has served as a consultant or advisor to Merck & Co, Inc. *(Updated 11/18/19)*

Mr Horn has no relevant financial affiliations to disclose. *(Updated 11/19/19)*

Dr Locke has no financial relationship with commercial entities to report. *(Updated 11/21/19)*

Dr Scott has no relevant financial affiliations to disclose. *(Updated 11/18/19)*

Dr Spach has no relevant financial affiliations to disclose. *(Updated 10/27/19)*

Dr Valcour has served as a consultant to Merk & Co, Inc and ViiV Healthcare. *(Updated 11/20/19)*

Dr Wesp has no relevant financial affiliations to disclose. *(Updated 10/15/19)*

Dr Workowski has received consulting or advisory fees paid through her institution for GSK and Jansen Therapeutics. *(Updated 11/22/19)*

Dr Gianella-Weibel has no relevant financial affiliations to disclose. *(Updated 11/18/19)*
## CLINICAL CONFERENCE Agenda

### WEDNESDAY, DECEMBER 4, 2019

**PRECONFERENCE SESSION: BASICS OF HIV MANAGEMENT SESSION FOR PRACTITIONERS WHO ARE NEW TO THE FIELD**

**Moderated by:** Laura W. Cheever, MD, ScM

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<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker(s)</th>
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<tr>
<td>4:00 – 6:00 PM</td>
<td>Fundamentals of Antiretroviral Therapy</td>
<td>Michael S. Saag, MD</td>
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<td></td>
<td>Initiating Antiretroviral Therapy: What to Start and How to Monitor</td>
<td>Steven C. Johnson, MD</td>
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<tr>
<td>6:00 – 6:15 PM</td>
<td>Question-and-Answer Period</td>
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### THURSDAY, DECEMBER 5, 2019

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker(s)</th>
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<tbody>
<tr>
<td>8:30 – 8:45 AM</td>
<td>Welcome to Day 1</td>
<td>Michael S. Saag, MD</td>
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<tr>
<td>8:45 – 9:05 AM</td>
<td>HRSA’s HIV/AIDS Bureau Updates</td>
<td>Laura W. Cheever, MD, ScM</td>
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<tr>
<td>9:05 – 9:20 AM</td>
<td>Question-and-Answer Period</td>
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<tr>
<td>9:20 – 9:50 AM</td>
<td>Investigational Approaches to Antiretroviral Therapy</td>
<td>Rajesh T. Gandhi, MD</td>
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<tr>
<td>9:50 – 10:05 AM</td>
<td>Question-and-Answer Period</td>
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<tr>
<td>10:05 – 10:20 AM</td>
<td>Short Break</td>
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<tr>
<td>10:20 – 11:20 AM</td>
<td>Treating HIV in 2019: Interactive Cases From the Clinic(ians) and Panel Discussion</td>
<td>Michael S. Saag, MD</td>
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<tr>
<td>11:20 – 11:35 AM</td>
<td>Question-and-Answer Period</td>
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<tr>
<td>12:05 – 12:20 PM</td>
<td>Question-and-Answer Period</td>
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<tr>
<td>12:20 – 1:50 PM</td>
<td>Lunch</td>
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<tr>
<td>1:50 – 2:20 PM</td>
<td>Best Practices in HIV Care: Providing Gender-Affirming Care for Transgender and Nonbinary People</td>
<td>Linda Wesp, PhD, APNP, FNP-C</td>
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<tr>
<td>2:20 – 2:35 PM</td>
<td>Question-and-Answer Period</td>
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<tr>
<td>2:35 – 3:05 PM</td>
<td>Opioid Use and Substance Abuse Disorder</td>
<td>R. Douglas Bruce, MD, MA, MS</td>
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<tr>
<td>3:05 – 3:20 PM</td>
<td>Question-and-Answer Period</td>
<td></td>
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<tr>
<td>3:20 – 3:40 PM</td>
<td>Break</td>
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Concurrent Meet-the-Expert Breakout Sessions (Session preregistration is required)

Investigational Antiretroviral Drugs and Strategies – Rajesh T. Gandhi, MD
This session will focus on new approaches to treating HIV, including emerging 2-drug regimens, long-acting antiretroviral medications, and new classes of HIV medicines that are nearing approval or are on the horizon.

Substance Abuse and HIV Infection – R. Douglas Bruce, MD, MA, MS
This session will provide an in-depth discussion of substance use disorders beyond opioids (eg, cocaine, marijuana, benzodiazepines, and club drugs). Specific cases that illustrate common themes in treating HIV infection among people with substance use disorders will be presented. Attendees are encouraged to bring cases for discussion.

Managing Older Patients with HIV Infection – Steven C. Johnson, MD
This session will focus on clinical issues in the care of older patients with HIV infection including late presentation, poor reconstitution, frailty, polypharmacy, and non-AIDS cancers.

Managing HIV Infection Among Transgender Adults – Linda Wesp, PhD, APNP, FNP-C
This session focuses on various aspects of gender-affirming and culturally safe care, covering the most common questions clinicians new to transgender health have. Attendees are encouraged to bring cases for discussion.

Management and Prevention of Common HIV-Related Complications – David H. Spach, MD
This session will focus on clinical issues in the care of persons with HIV infection including recognition and treatment of common clinical manifestations (including skin and oral manifestations), routine lab monitoring before and after starting antiretroviral therapy, immunizations, and updated recommendations for prevention of opportunistic infection.

Networking Reception
The Hyatt Regency New Orleans is offering a complimentary networking reception for attendees. Light hors d’oeuvres will be served and a cash bar will be available.
FRIDAY, DECEMBER 6, 2019

8:30 – 8:45 AM  Welcome to Day 2  
Steven C. Johnson, MD

8:45 – 9:15 AM  Inflammation and Its Role in HIV Pathogenesis and Aging  
Sara Gianella-Weibel, MD

9:15 – 9:30 AM  Question-and-Answer Period

9:30 – 10:00 AM  Neurocognitive Disorders in HIV  
Victor Valcour, MD, PhD

10:00 – 10:15 AM  Question-and-Answer Period

10:15 – 10:30 AM  Short Break

10:30 – 11:00 AM  Renal Disease and Kidney Transplant  
Jayme E. Locke, MD, MPH

11:00 – 11:15 AM  Question-and-Answer Period

11:15 – 11:45 AM  Cardiovascular Disease in HIV  
Heidi M. Crane, MD, MPH

11:45 – 12:00 PM  Question-and-Answer Period

12:00 – 1:30 PM  Lunch

1:30 – 2:30 PM  Common PrEP Questions: A Case-Based Discussion  
Hyman M. Scott, MD, MPH

2:30 – 2:45 PM  Question-and-Answer Period

2:45 – 3:15 PM  Drug Pricing and Generics: Impact on Ryan White HIV/AIDS Programs  
Tim Horn

3:15 – 3:30 PM  Question-and-Answer Period

3:30 – 3:50 PM  Break
3:50 – 4:50 PM

**Concurrent Meet-the-Expert Breakout Sessions (Session preregistration is required)**

**Antiretroviral Therapy: Managing Treatment Failure – Steven C. Johnson, MD**

This session will focus on the approach to treatment failure including definitions of treatment failure, the use of resistance testing, and antiretroviral agents useful in early failure and in salvage regimens. Attendees are encouraged to bring cases for discussion.

**Preexposure Prophylaxis (PrEP) – Hyman M. Scott, MD, MPH**

This session will focus on challenging PrPEvaluation and management scenarios, adherence, non daily PrEP, HIV and STI testing, and management of renal complications related to PrEP use.

**Renal Disease in HIV Infection – Jayme E. Locke, MD, MPH**

This session will focus on post-transplant care of people with HIV infection including viral, immune, infection, and metabolic control; malignancy risk and bone disease.

**Neurocognitive Disorders in HIV – Victor Valcour, MD, PhD**

This session is designed to review challenging clinical cases in a discussion format. Attendees are welcome to bring cases to the workshop for group discussion.

**Management and Prevention of Common HIV-Related Complications – David H. Spach, MD**

This session will focus on clinical issues in the care of persons with HIV infection including recognition and treatment of common clinical manifestations (including skin and oral manifestations), routine lab monitoring before and after starting antiretroviral therapy, immunizations, and updated recommendations for prevention of opportunistic infections.

**Prescription Drug Pricing and Cost Considerations in the Management of HIV Infection – Tim Horn**

This session will serve as an opportunity for participants to better understand and discuss key aspects of HIV treatment drug pricing and cost containment across the US healthcare system and within the Ryan White HIV/AIDS Program.
Saturday, December 7, 2019

8:30 – 8:45 AM  
**Welcome to Day 3**  
Laura W. Cheever, MD, ScM

8:45 – 10:00 AM  
**Ending the HIV Epidemic: Reaching the Unsuppressed and Out of Care Panel Discussion**  
Moderated by:  
Laura W. Cheever, MD, and John T. Brooks, MD

10:00 – 10:30 AM  
**Sexually Transmitted Infections on the Rise: Syphilis, Chlamydia, and Gonorrhea**  
Kimberly A. Workowski, MD

10:30 – 10:45 AM  
**Question-and-Answer Period**

10:45 – 11:05 AM  
**Break**

11:05 AM – 12:05 PM  
**Concurrent Meet-the-Expert Breakout Sessions (Session preregistration is required)**

  - **Antiretroviral Therapy: Managing Treatment Failure** – Michael S. Saag, MD  
    This session will focus on the approach to treatment failure including definitions of treatment failure, the use of resistance testing, and antiretroviral agents useful in early failure and in salvage regimens. Attendees are encouraged to bring cases for discussion.

  - **Diagnosing and Treating Chlamydia and Gonorrhea** – Kimberly A. Workowski, MD  
    This session will focus on the diagnosis and treatment of chlamydia and gonorrhea.

  - **Neurocognitive Disorders in HIV** – Victor Valcour, MD, PhD  
    This session is designed to review challenging clinical cases in a discussion format. Attendees are welcome to bring cases to the workshop for group discussion.

  - **Management and Prevention of Common HIV-Related Complications** – David H. Spach, MD  
    This session will focus on clinical issues in the primary care of persons with HIV infection including recognition and treatment of common clinical manifestations (including skin and oral manifestations), routine lab monitoring before and after starting antiretroviral therapy, immunizations, and updated recommendations for prevention of opportunistic infections.

  - **Ending the HIV Epidemic** – Laura W. Cheever, MD, ScM and John T. Brooks, MD  
    This will be an audience listening session moderated by Dr. Cheever and Dr. Brooks. This session will be an in-depth continuation of the correlating panel discussion, focusing on strategies regarding aspects of the care continuum.
The 2019 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 2019 CLINICAL CONFERENCE, participants will be able to:

- Describe the new aspects to the Ryan White HIV/AIDS Program
- Apply current data on HIV management that includes antiretroviral treatment strategies for medical care of people with established HIV infection and the consideration of special clinical circumstances, such as pregnancy
- Describe current data on investigational new drugs and approaches
- Determine which patients might benefit from prevention intervention strategies, including the use of preexposure prophylaxis (PrEP), and initiate and monitor uninfected patients at risk for HIV infection
- Describe the current epidemiology, clinical presentations, and management of the most common sexually transmitted infections (STIs) in patients with HIV infection
- Detect and manage common comorbidities occurring in the aging population of persons with HIV infection, including renal disease and those in need of transplant, cardiovascular disease, and neurocognitive disorders
- Identify individuals with chronic opioid dependency and develop treatment strategies for the management of these patients with opioid substitution therapy
- Identify best practices for ending the HIV epidemic

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.

Meet-the-expert breakout sessions 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 http://www.iasusa.org/events/rwcc2019/

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/

ASSESSMENT OF NEEDS

The goal of the 2019 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 2019 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 17.75 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 17.75 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.

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. Participants of the session who complete the evaluation and provide accurate NABP e-Profile information will have their credit for up to 17.75 contact hours (1.775 CEU) submitted to CPE Monitor as early as 14 days after the event and no later than 60 days after the event. Please know that if accurate e-Profile information is not provided within 60 days of the event, credit cannot be claimed after that time. The participant is accountable for verifying the accurate posting of CE credit to their CPE Monitor account within 60 days. UAN #s 0761-9999-19-310-L02-P; 0761-9999-19-311-L02-P; 0761-9999-19-312-L02-P; 0761-9999-19-313-L02-P

AMERICAN ACADEMY OF FAMILY PHYSICIANS (AAFP) CREDITS
This Live activity, 2019 Ryan White HIV/AIDS Program (RWHAP) CLINICAL CONFERENCE, with a beginning date of 12/04/2019, has been reviewed and is acceptable for up to 17.00 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.

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 up to 17.75 hours of continuing nursing education.

Educational Review Systems is also approved for nursing continuing education by the state of Florida and the District of Columbia.
Continuing Education Credits (Continued)

CLAIMING CME CREDITS OR A CERTIFICATE OF PARTICIPATION

Obtaining CME credit, American Board of Internal Medicine’s Maintenance of Certification (ABIM MOC) points, Nursing or Pharmacy credits, American Academy of Family Physicians (AAFP) credit, 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 if you will be claiming ABIM MOC points, which will require a passing grade of 70%
6. FINAL STEP: After completing the posttest, at the top of the Thank you page, click “online CME claim form”, where, once logged in, you will: a) answer “Yes” to the question “Are you a licensed physician?” b) enter the CME hours you wish to claim, and c) click Submit.

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. Follow steps 1 through 4 above.
2. When you get to the end of the evaluation, click Submit Form. Click Take the CE posttest to start the test.
3. FINAL STEP: After completing the posttest, at the top of the Thank you page, click “online CME claim form”, where, once logged in, you will: a) answer “No” to the question “Are you a licensed physician?” and b) click Submit.

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.

Educational Review Systems provides 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. Follow steps 1 through 4 above.
2. When you get to the end of the evaluation, click Submit Form. Click Take the CE posttest to start the test.
3. **FINAL STEP:** After completing the posttest, at the top of the Thank you page, click "online CME claim form", where, once logged in, you will: a) answer "No" to the question "Are you a licensed physician?" and b) click Submit.

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.

Educational Review Systems provides credit to nursing professionals, and your credit notification will be emailed directly from that organization.

How to Claim AAFP Credits

1. Login to your AAFP account.
2. Search for course title, "2019 Ryan White HIV/AIDS Program (RWHAP) CLINICAL CONFERENCE"
3. Claim your credits
How to Use Poll Everywhere

Here are the steps working with the audience-response system, Poll Everywhere.

Responding via the web (RECOMMENDED)

• When you are logged into the WiFi and the course begins, join Poll Everywhere by going to www.PollEv.com/iasusa334 on your device.
• To answer a multiple-choice question, enter or select your choice in the Response field and click Submit Response. You will have approximately 10 to 20 seconds to enter an answer.
• To cancel an answer, click on Clear response. This can only be done while the poll is open.

SMS text messaging instructions

• Text KEYWORD “IASUSA334” to “22333” once to join the session.
• Text your answer using: A, B, C, D, or etc.
• The initial KEYWORD you text in is remembered. For the next poll question, you only have to submit A, B, C, etc, in your SMS text message.
Fundamentals of Antiretroviral Therapy

Michael S. Saag, MD
Professor of Medicine
Associate Dean for Global Health
University of Alabama at Birmingham
Birmingham, Alabama

Financial Relationships With Commercial Entities

Dr. Saag has received research grants and support awarded to his institution from Gilead Sciences, Inc, and ViiV Healthcare. (Updated 11/21/19)

Learning Objectives

After attending this presentation, learners will be able to:
• Articulate the mechanisms of action of antiretroviral therapy
• Describe viral dynamics and how viral replication drives HIV pathogenesis
• Explain how antiretroviral drug resistance occurs and how to prevent it
ARS Question 1: How many HIV virions are produced a day in an HIV infected person?

A. 1
B. ~ 1000
C. 570,342
D. ~ 1 million
E. > 1 billion
ARS Question 2: At steady state, when an actively producing cell dies, it is replaced by how many newly infected cells?

A. One  
B. Twenty-Five  
C. One Hundred  
D. One Thousand  
E. It depends on the viral load
Viral Load

\[
\text{Weeks} \\
T_{1/2} = 1.1 \text{ days}
\]
ARS Questions 3: When should antiretroviral therapy be started? At a CD4 count of:

A. 200 cells/ul or less
B. 200 – 350 cells/ul
C. 350 – 500 cells/ul
D. 500 – 750 cells/ul
E. Any CD4 count
Co-morbid conditions common in HIV-infected adults
HIV-infected adults age 50-55 similar to uninfected adults > 65

T cell "activation" is lower in treated than untreated adults, but consistently higher than "normal"

Early ART Also Appears to Reduce Residual T Cell Activation during ART
Inverse Probability Weighted Cox Regression
Multivariate Analysis

<table>
<thead>
<tr>
<th>Relative Hazard (RH)</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deferral of HAART at 351-500</td>
<td>1.7</td>
<td>1.4, 2.1</td>
</tr>
<tr>
<td>Female Sex</td>
<td>1.1</td>
<td>0.9, 1.5</td>
</tr>
<tr>
<td>Older Age (per 10 years)</td>
<td>1.6</td>
<td>1.5, 1.8</td>
</tr>
<tr>
<td>Baseline CD4 count (per 100 cells/mm³)</td>
<td>0.9</td>
<td>0.7, 1.0</td>
</tr>
</tbody>
</table>

- Results were similar when restricting the analysis to the 77% of participants with baseline HIV RNA data
- Adjusted RH for deferral vs. immediate treatment was also 1.7 (95% CI 1.4, 2.2; p <0.001)
- HIV RNA was not an independent predictor of mortality

START: 57% Reduced Risk of Serious Events or Death With Immediate ART

- Serious AIDS or non-AIDS event or death: 4.1% vs. 3.8% in deferred vs. immediate ART (HR 0.4; 95% CI 0.30-0.62; P=0.001)

Cost-Effectiveness of Early vs. Deferred ART

- Markov modeling approach
- Johns Hopkins HIV clinic database

<table>
<thead>
<tr>
<th>ART Initiation</th>
<th>Incremental Lifetime Costs</th>
<th>Incremental Discounted QALY* Gained</th>
<th>Cost Per Life-Year Gained</th>
<th>Cost Per QALY* Gained</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 &gt;350 vs 200-350</td>
<td>$19,074</td>
<td>0.75 (0.61)</td>
<td>$25,567</td>
<td>$31,226</td>
</tr>
</tbody>
</table>

- “Starting ART earlier … rather than later … is a cost-effective strategy (by the generally accepted benchmark in the US).”


New Orleans, LA, December 4-7, 2019, Ryan White HIV/AIDS Program CLINICAL CONFERENCE
Relative Time on Treatment...

Relative Time on Treatment...

Improved Clinical Outcomes With Rapid ART Initiation

- Universal recommendations for treating all HIV-infected persons
- Systematic review of 22 studies of rapid ART initiation (including 4 RCTs)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ART start within 90 days</th>
<th>Retained in care at 12 mos</th>
<th>Viral suppression at 12 mos</th>
<th>LTFU at 12 mos</th>
<th>Died by 12 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (95% CI)</td>
<td>1.35 (1.13-1.62)</td>
<td>1.11 (0.90-1.36)</td>
<td>1.17 (1.07-1.27)</td>
<td>0.86 (0.42-1.04)</td>
<td>0.53 (0.28-1.00)</td>
</tr>
</tbody>
</table>

**Expedited 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>Outcome</th>
<th>Pre-REACH (n=117)</th>
<th>Post-REACH (n=111)</th>
<th>ORR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attended 1st scheduled appointment</td>
<td>85 (72)</td>
<td>73 (63)</td>
<td>1.63 (0.82; 3.22)</td>
</tr>
<tr>
<td>Achieved vRNA suppression*</td>
<td>87 (74)</td>
<td>62 (55)</td>
<td>0.77 (0.39; 1.55)</td>
</tr>
</tbody>
</table>

*Excludes for age, race, sex, and using ART alone

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**Timeline of ARV Approvals**

- 1987: 1st NRTI Approved
- 1995: 1st PI
- 1996: 1st NNRTI
- 2003: 1st Fusion Inhibitor
- The Future: Capsid inhibitors, Gag inhibitors, ntRTI

- 1987: Zidovudine
- 1995: Lamivudine, Saquinavir
- 1996: Nevirapine, Ritonavir, Indinavir
- 2003: T-20, Atazanavir, Emtricitabine, Fosamprenavir
- 2005: Tipranavir
- 2006: Darunavir
- 2007: 1st CCR5 Inhibitor
- 2008: 1st Integrase Inhibitor
- 2009: 1st entry inhibitor
- 2010: 1st CCR5 Inhibitor
- 2013: 2nd generation integrase inhibitors (IBI)
- 2014: 2nd generation entry inhibitors (IBI)
- 2015: 3rd generation integrase inhibitors (IBI)
- 2016: 4th generation integrase inhibitors (IBI)
- 2017: 5th generation integrase inhibitors (IBI)

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**Site of Action of ARV Drugs**

- Entry Inhibitors
- Nucleoside RTI
- Non Nucleoside RTI
- HIV Integrase
- Protease Inhibitors
What is Immunologic Failure?

Conclusions

- Understanding HIV viral life-cycle is critical to understanding basis of ARV therapy
- Viral replication is very dynamic (1-10 billion new viruses produced a day) and is the driving force of HIV pathogenesis
- ARV therapy interrupts HIV replication – completely, halting the most of the damage done by HIV
- ARV therapy protects uninfected cells from becoming infected and has no effect on cells already infected
- All ARV drugs target specific sites within the viral life-cycle

Question-and-Answer Period
Initiating Antiretroviral Therapy: What to Start and How to Monitor

Steven C. Johnson, MD
Professor of Medicine, Division of Infectious Diseases
University of Colorado School of Medicine
Aurora, Colorado

Learning Objectives
After attending this presentation, learners will be able to:
• Apply updated guidelines on the initiation of antiretroviral therapy (ART).
• Identify individual characteristics in persons with HIV infection that help to determine the choice of therapy.
• Develop an approach to the clinical and laboratory monitoring of persons on ART.

Financial Relationships With Commercial Entities
Dr Johnson has served on an advisory board for and received consultation fees to his institution from ViiV Healthcare. (Updated 12/04/19)
Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents: When to Start

- Antiretroviral therapy (ART) is recommended for all HIV-infected individuals to reduce the risk of disease progression.
- ART also is recommended for HIV-infected individuals for the prevention of transmission of HIV.
- Patients starting ART should be willing and able to commit to treatment and understand the benefits and risks of therapy and the importance of adherence.

Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Last updated July 10, 2019

Antiretroviral Therapy: Approved agents in Seven Mechanistic Classes

- Reverse Transcriptase Inhibitors: NRTIs (Nucleosides, Nucleotides) and NNRTIs
- Protease Inhibitors
- Entry Inhibitors: Target CD4, Fusion, or CCR5
- Integrase Inhibitors

Antiretroviral Timeline: 1987-2019
## New Antiretroviral Agents and Combinations: 2018-2019

<table>
<thead>
<tr>
<th>Agent/Regimen</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bictegravir-FTC-TAF</td>
<td>Single tablet regimen (STR)</td>
</tr>
<tr>
<td>3TC-TDF</td>
<td>Generic combination</td>
</tr>
<tr>
<td>Doravirine-3TC-TDF</td>
<td>New STR with NNRTI</td>
</tr>
<tr>
<td>Dolutegravir-3TC</td>
<td>New STR with 2 drugs</td>
</tr>
<tr>
<td>Darunavir</td>
<td>New NNRTI</td>
</tr>
<tr>
<td>Etavirine-3TC-TDF</td>
<td>Generic STR with etavirine</td>
</tr>
<tr>
<td>Efavirenz 400-3TC-TDF</td>
<td>STR with lower dose of EFV</td>
</tr>
<tr>
<td>Darunavir-COFI-HTC-TAF</td>
<td>First PI-based STR</td>
</tr>
<tr>
<td>Ibalizumab-uiyk</td>
<td>IV monoclonal antibody</td>
</tr>
<tr>
<td>IM Cabotegravir/rilpivirine and oral cabotegravir</td>
<td>Injectable regimen; pending FDA approval in late December 2019</td>
</tr>
</tbody>
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## Initiating Antiretroviral Therapy

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**Initiating Antiretroviral Therapy**

- Most of the guidelines for initial therapy are based on well-designed prospective randomized clinical trials.
- Current guidelines emphasize INSTI-containing regimens as the primary approach to initial therapy.
- Individual characteristics are important in choosing the most appropriate initial regimen.
- Many programs emphasize rapid initiation of antiretroviral therapy which will affect the choice of therapy.

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**Factors in the Timing and Choice of Initial Antiretroviral Therapy**

**Clinical Factors**
- Clinical trial results
- HIV disease stage
- Hepatitis B co-infection
- TB co-infection
- Presence of other OIs
- Substance use
- Mental health conditions

- Other co-morbidities (e.g. CVD)
- Drug-drug interactions
- Drug-food interactions
- Gender
- Plans for pregnancy
- HIV encephalopathy

---

**Factors in the Timing and Choice of Initial Antiretroviral Therapy**

**Laboratory Factors**
- CD4 cell count
- HIV RNA level
- HIV resistance testing
- HLA B*5701 testing
- Serum creatinine
- Urinalysis
- Liver enzyme testing
- Hepatitis B testing

**Other Factors**
- Patient preference
- Provider preference and beliefs
- Adherence potential
- Access to care
- Retention in care
- Financial/insurance issues
Recommendations are Graded Based on the Strength of Evidence

<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
<th>Quality of Evidence for Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Strong recommendation for the statement</td>
<td>I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints</td>
</tr>
<tr>
<td>B: Moderate recommendation for the statement</td>
<td>II: One or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes</td>
</tr>
<tr>
<td>C: Optional recommendation for the statement</td>
<td>III: Expert opinion</td>
</tr>
</tbody>
</table>

Recommended Initial Regimens for Most People with HIV

**DHHS Guidelines**

- INSTI plus 2 NRTIs
  - BIC/TAF/FTC (A1)
  - DTG/ABC/3TC (A1) - if HLA-B*5701 negative
  - DTG plus tenofovir/FTC or 3TC (A1)
  - RAL plus tenofovir/FTC or 3TC, BII for TDF/FTC

**IAS-USA Guidelines**

- INSTI plus 2 NRTIs
  - BIC/TAF/FTC (A1a)
  - DTG/ABC/3TC—only for persons who are HLA-B*5701-negative (A1a)
  - DTG plus TAF/FTC (A1a)

Dolutegravir plus 3TC: A new 2-drug Option

- 96 week data show that DTG/3TC has similar efficacy to DTG plus TDF/FTC
- Caveats with this regimen:
  - Baseline HIV RNA level > 500,000 copies/mL (because this regimen has not been studied adequately at high viral loads)
  - HIV genotype results unavailable (given the use of just two drugs, it is essential that the virus is susceptible to both)
  - Individuals with chronic Hepatitis B or if Hepatitis B infection status is unknown (3TC alone is not adequate treatment for Hepatitis B)
- This regimen will be discussed in greater detail during the conference
Individual Characteristics May Affect Initial Choice of ART

- Baseline CD4 < 200: Do not use rilpivirine-containing regimens.
- Baseline HIV viral load > 100K: Do not use rilpivirine-containing regimens or ABC/3TC with efavirenz or boosted atazanavir.
- HLA-B*5701 positive: Do not use abacavir-containing regimens.
- Starting ART before resistance test results: Do not use NNRTI-containing regimens.
- Psychiatric illness: Avoid efavirenz and rilpivirine-containing regimens.
- Hepatitis B co-infection: Use regimens that include TDF or TAF with 3TC or FTC.
- Chronic kidney disease: Avoid use of TDF. Consider not using atazanavir.

What Not to Use!

- Drugs not recommended: didanosine, stavudine, delavirdine, nelfinavir, indinavir
- Regimens not recommended: Monotherapy, Dual therapy with NRTIs, Triple therapy with NRTIs
- Components not recommended: Dual protease inhibitors, unboosted PIs, nevirapine in women with CD4 count above 250 cells/mm³ or in men with CD4 count above 400 cells/mm³

Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Last updated July 10, 2019

ARS Question 1

A 33-year-old man is diagnosed with HIV infection in the emergency department and comes to you on the same day, anxious to start antiretroviral therapy. The most appropriate ART regimen for a rapid start would be:

A. Bictegravir/tenofovir alafenamide/emtricitabine
B. Dolutegravir/abacavir/lamivudine
C. Dolutegravir plus emtricitabine
D. Efavirenz/tenofovir DF/emtricitabine
E. Something else
RAPID ART Program in San Francisco

- Citywide rapid initiative to link all new cases of HIV infection into care within 5 days of diagnosis and to start ART at the first visit.
- HIV providers trained through public meetings, medical rounds, and public health discussions.
- Community navigators linked persons with HIV to RAPID-trained clinicians.
- RAPID program initiated in 2015.

Coffey S, et al. AIDS 2019;33:825-832

RAPID ART Program in San Francisco

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</thead>
<tbody>
<tr>
<td>In Care within 1 year (%)</td>
<td>372(93%)</td>
<td>318(97%)</td>
<td>262(96%)</td>
<td>258(97%)</td>
<td></td>
</tr>
<tr>
<td>Diagnosis to care in days</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>5</td>
<td>-38%</td>
</tr>
<tr>
<td>1st Care Visit to ART in days</td>
<td>27</td>
<td>17</td>
<td>6</td>
<td>1</td>
<td>-96%</td>
</tr>
<tr>
<td>ART to VL &lt; 200 c/mL in days</td>
<td>70</td>
<td>53</td>
<td>50</td>
<td>38</td>
<td>-46%</td>
</tr>
<tr>
<td>Diagnosis to VL &lt; 200 c/mL in days</td>
<td>134</td>
<td>92</td>
<td>77</td>
<td>61</td>
<td>-54%</td>
</tr>
</tbody>
</table>

Bacon O, et al, Abstract 93, 25th CROI, Boston, March 4-7, 2018

Benefits of Rapid Initiation of ART

- Faster time to viral suppression and immunologic recovery
- Faster time for person to move to good health
- Less chance for the person to transmit the infection to others
- Improved engagement in care
- Sends a clear message that treatment is needed in everyone throughout the course of the infection
Regimens for Rapid Start

Bictegravir/tenofovir alafenamide/emtricitabine
Dolutegravir plus tenofovir alafenamide/emtricitabine
Darunavir plus ritonavir plus tenofovir/FTC
Darunavir/cobicistat plus tenofovir/FTC

- These regimens are likely safe and effective in the setting of active Hepatitis B or some pre-existing HIV drug resistance, and don’t require HLA-B*5701 testing.

ARS Question 2

A 27-year-old woman with newly diagnosed HIV infection presents for care. CD4 count: 420 cells/mm³. HIV RNA level: 150,000 copies/ml. Testing reveals no evidence of Hepatitis B or HIV resistance. She is sexually active and reports inconsistent use of birth control. She is anxious to start ART. Which regimen would you choose:

A. Bictegravir/tenofovir alafenamide/emtricitabine
B. Dolutegravir/abacavir/lamivudine
C. Dolutegravir plus emtricitabine
D. Raltegravir plus TDF/FTC
E. Something else

Dolutegravir in Pregnancy

- Tsepamo: Neural tube defects were initially detected in 4 out of 429 (0.9%) of infants born to mothers on dolutegravir at conception.
- Recent data indicate a risk of approximately 0.3%. Ongoing studies will define the risk with more certainty.
- Dolutegravir appears to be safe when started after 12 weeks of pregnancy.
- There are no data on bictegravir.
- Raltegravir appears to be safe in pregnancy.
- This issue will be addressed more during the conference.
Limitations of ART

- Drug toxicity
  - Safety in pregnancy
- Drug interactions
- Drug resistance
- Need for adherence
- Cost
- Not curative

Potential Adverse Effects of Commonly Used Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Potential Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir DF</td>
<td>Renal toxicity. Osteopenia.</td>
</tr>
<tr>
<td>Tenofovir AF</td>
<td>Weight gain.</td>
</tr>
<tr>
<td>Abacavir</td>
<td>Hypersensitivity. Possible CV risk.</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>Weight gain. Safety in early pregnancy.</td>
</tr>
<tr>
<td>Bictegravir</td>
<td>Weight gain.</td>
</tr>
</tbody>
</table>

- Weight gain will be discussed more during the conference.

Abacavir Hypersensitivity

Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by signs or symptoms in 2 or more of the following groups:
- Fever
- Rash
- Gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain)
- Constitutional (including malaise, fatigue, or achiness)
- Respiratory (including shortness of breath, cough, or sore throat)
**Abacavir Hypersensitivity**

- Individuals who are HLA-B*5701 positive have approximately a 50% risk of an abacavir hypersensitivity reaction.
- Individuals who are HLA-B*5701 negative have a less than 1% risk of an abacavir hypersensitivity reaction.
- Testing for HLA-B*5701 is relatively inexpensive and is done once in the life of a patient.
- Those who test positive for HLA-B*5701 should have abacavir added to the allergy section of the electronic health record.
- Recommended prior to abacavir use in federal treatment guidelines.

**Drug-Drug Interactions**

- Protease inhibitors, including atazanavir or darunavir boosted by either ritonavir or cobicistat, tend to inhibit cytochrome p450 enzymes and may lead to higher levels of co-administered drugs.
- This can also be seen with the INSTI, elvitegravir, that is boosted with cobicistat.
- Nevirapine and efavirenz, through induction of cytochrome p450 enzymes, may reduce levels of co-administered drugs.
- A number of other drug-drug interactions are important; many are reviewed in the DHHS antiretroviral treatment guidelines or through on-line drug interaction databases.

**Drug-Drug Interaction Example: Atazanavir Trough Concentrations with Co-administered Drugs**

ATV = atazanavir, RTV or r = ritonavir, RIF = rifampin
OMP = omeprazole, TDF = tenofovir
Drug Resistance

- Acquired drug resistance
  - Develops in a patient while on therapy
  - Prescribing errors can lead to resistance
  - Nonadherence can lead to resistance
- Primary drug resistance
  - Acquired from a person with resistant virus
- Assessed by one of two technologies
  - HIV genotyping
  - HIV phenotyping


<table>
<thead>
<tr>
<th>Any TDRM</th>
<th>NNRTI</th>
<th>NRTI</th>
<th>PI</th>
<th>INSTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TDRM</td>
<td>NNRTI</td>
<td>NRTI</td>
<td>PI</td>
<td>INSTI</td>
</tr>
</tbody>
</table>

HIV Resistance Tests

- Standard RNA Resistance Tests
- DNA Archive Resistance Tests
Adherence to ART is critical. Fixed dose combinations have helped.

How to Monitor Antiretroviral Therapy
## Baseline Laboratory Testing

- CBC with differential: screening primarily for leukopenia, anemia, and thrombocytopenia
- Chemistry panel: screening primarily for renal disease, hyperglycemia, or evidence of hepatitis
- Fasting lipid panel: dyslipidemia can be a complication of HIV/AIDS and its treatment
- Urinalysis: to screen primarily for pyuria, hematuria, or proteinuria

## Baseline Laboratory Testing

- CD4 lymphocyte count
- HIV RNA level (AKA HIV viral load)
- HIV resistance testing
  - HIV genotyping is preferred over HIV phenotyping
  - Testing is typically for protease and reverse transcriptase resistance unless INSTI-resistance is suspected
- Other tests to consider
  - HLA B*5701 testing (if planning to use the drug abacavir)
  - HIV tropism testing (if planning to use the drug maraviroc)

## Baseline Laboratory Testing: Screening for Co-Infections

- GC and Chlamydia (urine, throat, and rectum, based on exposure)
- Hepatitis A: Total Hepatitis A antibody
  - Hepatitis B core antibody, surface antibody, and surface antigen
  - Hepatitis B DNA level (in selected circumstances)
- Hepatitis C:
  - Hepatitis C antibody
  - Hepatitis C RNA level (if HCV AB+ or suspect false negative)
- Syphilis: Treponemal antibody screen or RPR
- Toxoplasmosis: Toxoplasma IgG
- Tuberculosis: PPD or interferon gamma release assay
Laboratory Tests to Monitor HIV Infection:
HIV RNA Level and CD4 Lymphocyte Count

Source: CDC/Public Health Image Library

Virologic Response Definitions

- **Virologic Suppression**: A confirmed HIV RNA level below the lower limit of detection of available assays.
- **Virologic Failure**: The inability to achieve or maintain suppression of viral replication to an HIV RNA level <200 copies/mL.
- **Incomplete Virologic Response**: Two consecutive plasma HIV RNA levels ≥200 copies/mL after 24 weeks on an ARV regimen in a patient who has not yet had documented virologic suppression on this regimen.
- **Virologic Rebound**: Confirmed HIV RNA level ≥200 copies/mL after virologic suppression.

Virologic Response Definitions

- **Virologic Blip**: After virologic suppression, an isolated detectable HIV RNA level that is followed by a return to virologic suppression.
- **Low-Level Viremia**: Confirmed detectable HIV RNA level <200 copies/mL.
- **Potential causes of blips and low-level viremia**:
  - Intermittent adherence
  - Laboratory error
  - Release of virus from latent reservoirs
  - Early virologic failure
ARS Question 3

Your patient has well-controlled HIV infection with an HIV viral load < 20 copies/mL. He is sexually active with his HIV-negative partner. How often would you monitor HIV viral load in order to ensure that there is no risk of HIV transmission?

A. Monthly  
B. Every 3 months  
C. Every 6 months  
D. Once a year  
E. I have a different answer

---

Laboratory Monitoring on ART: CD4 and HIV RNA

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Viral Load Monitoring</th>
<th>CD4 Count Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Initiating ART</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After Initiating ART</td>
<td>2-4 weeks into ART; every 4-8 weeks until VL und</td>
<td>3 months after initiation of ART</td>
</tr>
<tr>
<td>During the first 2 years of ART</td>
<td>Every 3-4 months</td>
<td>Every 3-6 months</td>
</tr>
<tr>
<td>After 2 years, consistently suppressed, CD4 300-500</td>
<td>Every 6 months</td>
<td>Every 12 months</td>
</tr>
<tr>
<td>After 2 years, consistently suppressed, CD4 &gt; 500</td>
<td>Every 6 months</td>
<td>Optional</td>
</tr>
<tr>
<td>Change in clinical status (e.g., new HIV clinical symptom or initiation of chronic systemic corticosteroids, or anti-neoplastic therapy)</td>
<td>Every 3 months</td>
<td>Perform CD4 count and repeat as clinically indicated</td>
</tr>
</tbody>
</table>

---

The “U = U” Campaign Underscores the Importance of Regular HIV Viral Load Measurement

---
Potential Savings by Reduced CD4 Monitoring in Stable Patients Receiving Antiretroviral Therapy

- Estimation of cost and savings with different CD4 monitoring strategies
- Population level costs estimated for 3 different CD4 intervals: q 3 months, q 6 months, q 12 months
- Potential annual savings of $10.2 million with annual CD4 testing ($225.7-615.1 million over the lifetime of patients in care)


Other Laboratory Monitoring Tests

- CBC with differential
- Basic Chemistry: Na, K, HCO3, BUN, creatinine, glucose (preferably fasting), creatinine-based GFR, serum phosphorous in patients with CKD who are on TAF- or TDF-containing regimens
- ALT, AST, Total Bilirubin
- Fasting glucose or hemoglobin A1C
- Fasting lipids

Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Last updated October 25, 2018.

Learning Objectives Revisited

After attending this presentation, learners will be able to:
- Apply updated guidelines on the initiation of antiretroviral therapy (ART)
- Identify individual characteristics in persons with HIV infection that help to determine the choice of therapy
- Develop an approach to the clinical and laboratory monitoring of persons on ART
Useful Internet Resources

- **www.aidsinfo.nih.gov**: The definitive guidelines on ART, OI management, PrEP, and perinatal HIV management
- **www.iasusa.org**: Alternative ART guidelines, charts of resistance mutations, other HIV content
- **www.idsociety.org**: Multiple guidelines on HIV management including primary care guidelines
- **www.hiv-druginteractions.org**: Excellent site on drug interactions from the University of Liverpool
- **www.hiv.uw.edu**: The National HIV Curriculum

Question-and-Answer Period
HIV/AIDS Bureau Updates
Ryan White HIV/AIDS Program Clinical Conference

December 5, 2019
Dr. Laura Cheever, MD, ScM
Associate Administrator
HRSA/AIDS Bureau (HRSA)

Vision: Healthy Communities, Healthy People

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 with HIV and their families.

2018 Client-Level Data
Continued Progress
Recently Released Data & Reports

- RWHAP AIDS Drug Assistance Program (ADAP) Annual Client-Level Data Report
- Oral Health Data Report
- 2019 Ryan White HIV/AIDS Program Highlights: Advancing Innovation to End the HIV Epidemic
- 2017 Ryan White HIV/AIDS Program State Profiles

Viral Suppression among Clients Served by the Ryan White HIV/AIDS Program (non-ADAP), 2010–2018—United States and 3 Territories

Viral Suppression among RWHAP Clients, by State, 2010 and 2018—United States and 2 Territories
Viral Suppression among Key Populations Served by the Ryan White HIV/AIDS Program, 2010 and 2018—United States and 3 Territories

Responding to Challenges:
Focus on People with HIV over 50

- Policy Clarification Notice: Ryan White funds can pay Medicare premiums and cost sharing
- CROI Poster Presentation: Projected growth and needs of older adults in the Ryan White Program
- AETC National Coordinating Resource Center Toolkit: Care of People Aging with HIV
- CHAC Recommendations Letter: Develop a tool to support HIV providers’ care for people with HIV as they age
- HIV.gov Blog: Growing Ryan White Client Population Over 50 Years Old on HIV.gov
- ACE TA Center: Training on how to leverage Medicare for people with HIV
- Technical Expert Panel: In planning stages

Ending the HIV Epidemic
Identifying and Addressing Challenges
Four Pillars of Ending the HIV Epidemic

1. **Diagnose**
   - All people with HIV as early as possible.

2. **Treat**
   - People with HIV rapidly and effectively to reach sustained viral suppression.

3. **Prevent**
   - New HIV transmissions by using proven interventions, including pre-exposure prophylaxis (PrEP) and syringe services programs (SSPs).

4. **Respond**
   - Quickly to potential HIV outbreaks to get needed prevention and treatment services to people who need them.

Geographic Locations of Ending the HIV Epidemic Initiative

Efforts focused in 48 counties, Washington, DC, and San Juan, PR, where more than 50% of HIV diagnoses occurred in 2016 and 2017, and seven states with substantial rural HIV burden.

Ending the HIV Epidemic – Overlap of RWHAP Parts A and B and Identified Counties and States
HRSA HAB Ending the HIV Epidemic (EHE) Resources

- Ryan White HIV/AIDS Program Parts A and B
- Technical Assistance Provider
- Systems Coordination Provider
- Plan to supplement Ryan White HIV/AIDS Program Part F AIDS Education and Training Center (AETC) Program for workforce capacity development

Identifying the Challenges Ahead

**People with HIV in care**
- Improve viral suppression rates
- Decrease disparities

**People newly diagnosed with HIV**
- Enhance linkage to care
- Enhance engagement in care

**People with HIV out of care**
- Expand re-engagement in care
- Improve retention in care

Responding to Challenges:
**Recent Changes to HRSA HAB Policies**
- People in care: Improve viral suppression and decrease disparities
  - CQM updates reduce administrative burden with focus on improving high-utilization services
- Newly diagnosed: Enhance linkage to and engagement in HIV care
  - Rapid eligibility determinations increase opportunities to engage newly diagnosed people with HIV in care
- People out of care: Expand re-engagement and retention for those diagnosed
  - Clarifications on providing HRSA RWHP services in correctional settings facilitate engagement and retention in care for people who are justice-involved
Responding to Challenges: HRSA HAB Strategies and Activities

- Apply Implementation Science
  - Capacity Building in the Ryan White HIV/AIDS Program (RWHAP) to Support Innovative Program Model Replication
  - HRSA HAB Compilation of Best Practice Strategies and Interventions
  - Using Evidence-Informed Interventions to Improve Health Outcomes (E2i)
- Engage Community & Experts
  - Building Leaders of Color (BLOC)
  - Evaluation of RWHAP Eligibility and Recertification
  - Reimagining RWHAP Part D
  - Technical Expert Panels: Housing; People who are Justice-Involved; Women; People Over 50
- Address Co-occurring Conditions
  - Enhancing Linkage of Sexually Transmitted Infection (STI) and HIV Surveillance Data in the RWHAP
  - Strengthening Systems of Care for People with HIV and Opioid Use Disorder
  - Improving STI screening and Treatment among People with HIV

HRSA EHE Listening Sessions – Key Themes

- Addressing mental health, substance use, incarceration, transportation, and homelessness is critical to reach people not in care
- Planning for EHE needs to include community-based organizations, community health centers, people with HIV, and new partners
- Supporting training for clinic staff to ensure that culturally responsive and supportive experiences happen for clients (for testing, care, and PrEP)
- Addressing stigma, health education, and criminalization laws

HRSA EHE Listening Sessions – Key Themes (2)

- Addressing workforce shortages for medical providers, and mental health and substance use providers
- Leveraging community strengths by hiring community health workers, peer navigators, peer specialists, etc.
- Assessing eligibility and intake processes and forms for testing and care
- Allowing jurisdictions to be innovative and to adapt and adjust as they learn
Thank You!

Laura Cheever, MD, ScM
Associate Administrator
HIV/AIDS Bureau (HAB)
Health Resources and Services Administration (HRSA)
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Twitter: twitter.com/HRSAgov
Facebook: facebook.com/HHS.HRSA

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Question-and-Answer Period
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December 5, 2019
Dr. Laura Cheever, MD, ScM
Associate Administrator
HIV/AIDS Bureau (HAB)
Investigational Approaches to Antiretroviral Therapy

Rajesh T. Gandhi, MD
Massachusetts General Hospital
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Financial Relationships With Commercial Entities

Dr Gandhi has served as a consultant or advisor to Merck & Co, Inc. (Updated 11/11/19)

Learning Objectives

After attending this presentation, learners will be able to:
• Describe investigational approaches for treating people with HIV infection
• Discuss the pipeline for novel antiretroviral agents
Investigational Approaches to Antiretroviral Therapy

- Have we moved into the era of 2-drug therapy? New, emerging and investigational 2-drug regimens.
- What are the ART options in someone who has difficulty taking daily drugs? Long-acting ART.
- What about new medicines for treating someone with multi-drug resistant HIV?
- What’s on the horizon?

What to Start in Most People with HIV: Integrase Inhibitor + 2 NRTI

<table>
<thead>
<tr>
<th>DHHS (10/2018) Recommended for Most People with HIV</th>
<th>IAS-USA (7/2018) Recommended Initial Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bictegravir/TAF/FTC</td>
<td>Bictegravir/TAF/FTC</td>
</tr>
<tr>
<td>Dolutegravir/abacavir/3TC</td>
<td>Dolutegravir/abacavir/3TC</td>
</tr>
<tr>
<td>Dolutegravir + TAF/FTC or TDF/FTC</td>
<td>Dolutegravir + TAF/FTC</td>
</tr>
<tr>
<td>Raltegravir + TAF/FTC or TDF/FTC</td>
<td></td>
</tr>
</tbody>
</table>

- If substantial cost difference, TDF (with FTC or 3TC) is effective and generally well-tolerated, esp. if patient not at high risk for bone, renal disease
- Differences between TAF and TDF accentuated when TDF is used with ritonavir or cobicistat

GEMINI-1 and -2: DTG + 3TC vs DTG + TDF/FTC in Treatment Naïve People with HIV

- International, double-blind phase III noninferiority studies

Who was in GEMINI?
- Valve: 20%
- Age: 32-33 years
- Black: 12%
- HIV RNA level: Mean: 4.4 log_{10} c/mL, >100K: 20% (C4 level: Mean: 462, ≤200-5%
- CD4 count: Mean: 462, ≤200-8%

- No major RT or PI resistance
- No HIV infection

- ART-naive adults
- No 1,000-500,000

Week 24          Week 48          Week 96

• ART-naive adults
  • No major RT or PI resistance
  • No HIV infection
  • N = 1433

• Bictegravir/TAF/FTC
  • Dolutegravir/abacavir/3TC
  • Dolutegravir + TAF/FTC or TDF/FTC
  • Raltegravir + TAF/FTC or TDF/FTC
Other 2-drug options for treatment of HIV

- **Initial therapy**
  - DRV/r + RAL: but not as good as 3-drug therapy when CD4 <200, VL >100K
  - Maintenance therapy (once VL suppressed on 3-drug therapy)
    - DTG/RPV (SWORD)\(^1\) INI/NRTI
    - LPV/r + 3TC/FTC (OLE)\(^2\)
    - ATV/r + 3TC (SALT, ATLAS-M)\(^3, 4\)
    - DRV/r + 3TC (DUAL)\(^5\)

- **Second-line therapy**
  - DRV/r + DOR (vs. 2 NRTI + DRV/r or DTG) [D2EFT], N=1010. Ongoing.\(^2\)
  - Maintenance therapy (once VL suppressed on 3-drug therapy)
    - DRV/r + RPV (n=48)\(^2\)
    - DRV/r + DOR (DUALUS): similar 48 wk results as 3-drug therapy (n=265)\(^4\)
    - LA Cabotegravir/Rilpivirine (ATLAS, FLAIR, ATLAS-2M)\(^1\)

Emerging and investigational 2-drug options for treatment of HIV

- **Initial therapy**
  - DRV/r + 3TC (ANDES): promising in small randomized trial\(^1\)
  - Istalavir + Doravirine: investigational

Emerging and investigational 2-drug options for treatment of HIV

- **Second-line therapy**
  - DRV/r + DOR (vs. 2 NRTI + DRV/r or DTG) [D2EFT], N=1010. Ongoing.\(^2\)
  - Maintenance therapy (once VL suppressed on 3-drug therapy)
    - DRV/r + RPV (n=48)\(^2\)
    - DRV/r + DOR (DUALUS): similar 48 wk results as 3-drug therapy (n=265)\(^4\)
    - LA Cabotegravir/Rilpivirine (ATLAS, FLAIR, ATLAS-2M)\(^1\)
ART Options in Someone Who Has Difficulty Taking Daily Drugs

- 55 yo M with HIV, achalasia, dysphagia
- Long-standing difficulty swallowing pills
- Virologically suppressed on dolutegravir and rilpivirine
- He asks whether there are long-acting HIV medicines that he can take instead of a daily oral regimen

How do you respond?
A. Yes
B. No
C. Not yet
D. I don’t know

Long-acting Cabotegravir and Rilpivirine

- Cabotegravir (CAB), an INSTI, and rilpivirine (RPV), an NNRTI, available in long-acting nanosuspension formulations; half-lives of months

Phase 3 Clinical Trials: ATLAS/FLAIR Week 48

- ATLAS: virologically suppressed; switch to monthly IM LA CAB/RPV vs. continue oral ART
- FLAIR: Treatment naïve; suppress with oral ART; switch to monthly IM LA CAB/RPV vs. continue oral ART
ATLAS/FLAIR Week 48 Pooled Results

Virologic outcomes

<table>
<thead>
<tr>
<th></th>
<th>Adjusted treatment difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary Endpoint: La noninferiority to CAB (HIV-1 RNA ≥50 c/mL) at Week 48</td>
</tr>
<tr>
<td></td>
<td>Key Secondary Endpoint: La noninferiority to CAB (HIV-1 RNA &lt;50 c/mL) at Week 48</td>
</tr>
</tbody>
</table>

Virologic Nonresponse (≥50 c/mL)

<table>
<thead>
<tr>
<th></th>
<th>CAB + RPV LA (n=591)</th>
<th>CAR (n=591)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic Success (&lt;50 c/mL)</td>
<td>93.1%</td>
<td>94.4%</td>
</tr>
<tr>
<td>No Virologic Data</td>
<td>1.7%</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Difference (%)</th>
<th>-10</th>
<th>-8</th>
<th>-6</th>
<th>-4</th>
<th>-2</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAB + RPV LA</td>
<td>-1.4</td>
<td>1.4</td>
<td>-1.4</td>
<td>1.7</td>
<td>0.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAR</td>
<td>4%</td>
<td>10%</td>
<td>8%</td>
<td>6%</td>
<td>4%</td>
<td>2%</td>
<td>0%</td>
<td>2%</td>
<td>4%</td>
<td>6%</td>
<td>8%</td>
</tr>
</tbody>
</table>

<table>
<thead>
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</tr>
</tbody>
</table>

Treatment Emergent Resistance (CAB/RPV Groups)

<table>
<thead>
<tr>
<th>Site/HIV subtype</th>
<th>Baseline Resistance (HIV DNA)</th>
<th>Resistance at Virologic failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Russia/A1</td>
<td>E138A/L74I</td>
<td>E138A/L74I</td>
</tr>
<tr>
<td>France/A1</td>
<td>V108I/E138K, E138K</td>
<td>None</td>
</tr>
<tr>
<td>Russia/A1</td>
<td>None</td>
<td>E138K/L155K, L74I</td>
</tr>
<tr>
<td>Russia/A1</td>
<td>L74I</td>
<td>K101E/L74I, G140R</td>
</tr>
<tr>
<td>Russia/A1</td>
<td>E138K/L74I</td>
<td>E138K/L74I, Q148R</td>
</tr>
<tr>
<td>FLAIR</td>
<td>L74I more common in people with HIV subtype A but did not affect treatment response.</td>
<td></td>
</tr>
<tr>
<td>CAB, RPV conc at time of failure below population means but within range for majority who maintained suppression.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LA CAB/RPV: Questions

- Is the 4-week oral lead-in needed? What about direct to inject?
- What about the long tail in people who stop the drugs? CAB detectable up to 48 wks after single injection, longer in women
- Will the drugs be useful in people who have difficulty adhering to oral ART?
- Can LA CAB/RPV be used in someone who is viremic?
  - Case: person with bowel resection; not able to absorb oral ART; suppressed on IM CAB/RPV
- What will the cost of the drugs be? Will the cost of the administration be reimbursed?
### Ongoing CAB/RPV Studies

- **2 monthly IM: ATLAS 2M** (n=1049)
  - Phase 3 open-label 48 wk results in persons suppressed on oral ART or on every 4 wk CAB/RPV LA
  - Randomized 1:1 to CAB/RPV LA every 4 weeks or every 8 weeks
  - Every 8 wk therapy was non-inferior
- **Poor Adherers ACTG 5359** (n=350)
  - VL >200 at entry
  - No RPV or INSTI mutations
  - Phase 1: 24 weeks of standard of care oral ART (conditional financial incentives)
  - Then open label switch CAB/RPV 48 weeks

### Practical Aspects of Using CAB/RPV

- **Loading dose:** CAB LA 600 mg (one 3-mL injection) and RPV LA 900 mg (one 3-mL injection)
- **Monthly maintenance:** CAB LA 400 mg (one 2-mL injection) and RPV LA 600 mg (one 2-mL injection)
- **RPV LA requires cold chain**
- Injection into gluteus medius (upper outer quadrant of buttock)
- Need a private place for injections
- What about people with buttock implants?

### Practical Aspects of Using CAB/RPV: Continued

- **Staffing and physical space to deliver injections**
  - In 3000 patient clinic, if 10% want injections: 15 visits/day, 30 injections/day (if monthly)
- Are there alternative places to deliver injections? Pharmacies? Home healthcare?
- How will people remember to come in for visits? How will we remind people to come in for visits? Might pharmacies play a role?
- If people are late in coming in, will need oral ARV bridging

---

New Orleans, LA, December 4-7, 2019, Ryan White HIV/AIDS Program CLINICAL CONFERENCE
My take on LA Cabotegravir/Rilpivirine

- For most people, oral daily ART will remain effective and convenient option
- LA CAB/RPV may be good option for people who struggle with taking daily oral regimen (e.g., swallowing difficulties; stigma – external or internal)
- In people who struggle with adherence with oral ART, LA CAB/RPV may be helpful as long as the person comes back for appointments
- Combining visits with other appointments may be helpful, e.g., when picking up methadone refills, psychiatrist/psychologist/support group visits
- Every 8 wk dosing (if safe and effective) will make LA CAB/RPV more attractive but adherence, long pharmacokinetic tail, oral bridging for missed injections, reminders, administration logistics, and cost will still be important considerations

New Drugs for Multi-drug Resistant HIV

Case Scenario

- 60 yo F diagnosed with HIV in 1990.
  Multiple previous regimens
- HIV RNA 20,000; CD4 cell count 150
- HIV phenotype: resistance to NRTI, NNRTI, PIs. Sensitive to INSTI
ARS Question

- Which of the following classes are in or have completed phase 3 trials for treatment?
  
  A. Entry/attachment inhibitors  
  B. Maturation inhibitors  
  C. Capsid inhibitors  
  D. Broadly neutralizing antibodies

HIV Entry Inhibitors

- Fostemsavir
- Ibalizumab*

* FDA approved

Ibalizumab: Post-Attachment Inhibitor

- Humanized monoclonal Ab: binds CD4 on host cells; blocks HIV entry (post attachment inhibitor)
- Active against CCR5 and CXCR4 tropic HIV
- In phase 3 clinical trial (n=40), 50% of those who received ibalizumab + optimized background regimen achieved VL <200
- IV infusion: 2,000 mg loading dose then 800 mg every 2 wks
- Duration of infusion: 15-30 min
**Fostemsavir (FTR): Oral HIV Attachment Inhibitor**

- Prodrug of temsavir: binds to gp120, inhibits HIV attachment to CD4
- Phase 3 trial in heavily treatment experienced patients with virologic failure (BRIGHTE)
- Randomized- 272 pts with ≥1 fully active drug in 1 or 2 classes. 8 days blinded therapy (FTR or placebo), then FTR + OBT
- Non-Randomized- 99 pts with no fully active approved drug. FTR + OBT

**BRIGHTE: Most Common ARVs in Initial Optimized Background Therapy (OBT)**

<table>
<thead>
<tr>
<th>OBT Class</th>
<th>20%</th>
<th>30%</th>
<th>40%</th>
<th>50%</th>
<th>60%</th>
<th>70%</th>
<th>80%</th>
<th>90%</th>
</tr>
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<tbody>
<tr>
<td>FTR</td>
<td></td>
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<td></td>
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<td>NVP</td>
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<td></td>
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<td>AZT</td>
<td></td>
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</tr>
</tbody>
</table>

**BRIGHTE: ITT-E Virologic Response Through Wk 96**

ITT-E: Efficacy through Wk 96.

*Regulatory submissions are currently anticipated to take place in 2019/2020 timeframe*
On the Horizon

- Islatravir
- Capsid inhibitor
- CD4 antibody
- CCR5 antibody
- Broadly neutralizing Ab
- Other novel agents
- Novel delivery systems

Islatravir (MK-8591)

- Nucleoside RT translocation inhibitor (NRTTI)
- Potent at low doses: single oral dose as low as 0.5 mg suppressed HIV RNA for >7 days
- High barrier to resistance
- Long half-life (about 120 h)
  - Potential for once daily, once weekly or less frequent dosing

Phase 2b study for treatment: DRIVE2Simplify: ISL + DOR vs. DOR/3TC/TDF

Participants initially received ISL+DOR+3TC; then switched to ISL+DOR during week 24-48 after achieving virologic suppression. Week 48 virologic outcomes (FDA Snapshot)

- All participants with protocol-defined virologic failure had confirmatory VS <80
- No participants met criteria for resistance testing
ISL + DOR

- Phase 3 treatment program being launched:
  - Trial for treatment-experienced participants.
  - Two trials for participants switching therapy.
  - Trial for treatment naïve participants.

Future possibilities:
- Based on pharmacokinetics (PK), ISL has potential for once weekly dosing for treatment.
- Also being considered for PrEP (promising PK results with ISL implant).

HIV Capsid Inhibitor: Sustained levels for >24 weeks after single subcutaneous injection

HIV Capsid Inhibitor: Antiviral activity after single subcutaneous dose in people with HIV

- Mean reduction of HIV RNA: -1.4 to 2.2 log_{10} c/mL over 10 days

Recently announced:
- Phase 2/3 study in treatment-experienced/multi-drug resistant HIV
- Phase 2 trial in treatment naïve
- Capsid inhibitor: two-week oral lead-in followed by subcutaneous injection every 6 mo.
**HIV Entry Inhibitors: Novel Antibodies**

**UB-421: Antibody against CD4**

- 29 people with virologic suppression on oral ART
- Received up to 8 infusions of UB-421
  - Weekly: cohort 1
  - Every 2 wks: cohort 2
- Oral ART stopped after first infusion
- All participants remained virologically suppressed during infusions
- Rash: 52%: mild and transitory; 1 person stopped Ab because of more severe rash
- Approval in China for a phase 3 ART substitution trial

**Leronlimab (PRO 140)**

- Monoclonal antibody against CCR5
- Weekly subcutaneous injection
- Being studied as a single agent for maintenance of suppression and for people with drug resistant HIV
- Single agent for maintenance of suppression
  - Participants with virologic suppression and R5 tropic HIV (Trofile DNA)
  - Virologic failure rate: 14-66%
  - Participants who had virologic failure re-suppressed on baseline ART
  - No tropism shifts
Leronlimab (PRO 140) in people with drug-resistant HIV

- Treatment-experienced people with multi-drug resistant R5-tropic HIV
- Randomized to receive PRO140 + baseline ART vs. placebo + baseline ART
- All participants then start open label PRO140 + optimized background regimen
- Results:
  - >0.5 log reduction in VL after single injection: 64% in PRO 140 treated group vs. 23% in placebo group
  - Week 25: 81% of participants with VL <50

Broadly Neutralizing Antibodies against HIV

Combination of 2 Antibodies Maintained HIV suppression in Absence of ART in Some People

- 15 participants received a combination of 2 bNAb and then stopped ART after first dose
- Combination of 2 bNAb maintained viral suppression for median of 15 wk after last dose
- 2 participants maintained HIV suppression > 24 weeks

Will need to combine antibodies with multiple specificities
Antibodies with improved potency and breadth: Reduction in VL after VRC01LS or VRC07-523LS Infusion

- **VRC01LS**
  - Day 7: 5/7 decrease of at least 0.9 log10
  - Day 14: 2/7 decrease of at least 1.6 log10

- **VRC07-523LS**
  - Day 7: 6/8 decrease of at least 1.2 log10; 2/7 decrease of at least 1.6 log10
  - Day 14: 2/7 decrease of at least 0.6 log10

**Study of LA cabotegravir + VRC07-523 LS being launched (ACTG)**

**Selected other investigational drugs in the pipeline**

- **Long acting injectables**:
  - Eltuvstravine (NNRTI); raltegravir; atazanavir/ritonavir; combifectin (entry inhibitor)
  - Considerations: managing toxicities if they develop; what to do if recipients become pregnant; what happens if doses missed

- **Implants**:
  - Islatravir: NRTTI
  - TAF: NRTI
  - Biodegradable, removable, polymer-based implants with multiple drugs

- **Patches**

- **Oral once-weekly delivery system**

- **Novel antibody delivery systems**: viral vectors; synthetic DNA

**New Delivery Systems (in development)**

- **Long acting injectables**:
  - Eltuvstravine (NNRTI); raltegravir; atazanavir/ritonavir; combifectin (entry inhibitor)
  - Considerations: managing toxicities if they develop; what to do if recipients become pregnant; what happens if doses missed

- **Implants**:
  - Islatravir: NRTTI
  - TAF: NRTI
  - Biodegradable, removable, polymer-based implants with multiple drugs

- **Patches**

- **Oral once-weekly delivery system**

- **Novel antibody delivery systems**: viral vectors; synthetic DNA
Investigational Approaches to Antiretroviral Therapy

- Have we moved into era of 2-drug therapy? → Dolutegravir/3TC is an approved option; new & investigational regimens under evaluation.
- What are the ART options in someone who has difficulty taking daily drugs? → Long-acting IM cabotegravir/rilpivirine may be approved soon.
- What do you give to someone with highly drug resistant HIV? → Ibalizumab approved; fostemsavir (attachment inhibitor): promising results in phase 3 trial.
- What’s on the horizon? → Ilatravir, capsid inhibitor, antibodies against CCR5 or CD4, broadly neutralizing antibodies, new delivery systems, and more!

Question-and-Answer Period
Treating HIV in 2019: Interactive Cases From the Clinic(ians) and Panel Discussion

Michael S. Saag, MD
Professor of Medicine
Associate Dean for Global Health
University of Alabama at Birmingham
Birmingham, Alabama

Panelists

• Rajesh Gandhi, MD
• Michelle Iandiorio, MD
• Jesse Moore, MD
• Paula Seal, MD
• Phillip Bolduc, MD
• Steven Johnson, MD

Financial Relationships With Commercial Entities

Dr Saag has received research grants and support awarded to his institution from Gilead Sciences, Inc, and ViV Healthcare. (Updated 11/21/19)
Learning Objectives

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

- Are starting initial therapy
- Are Elite Controllers
- Are debating between starting TDF or TAF
- Have persistent low level viremia
- Have End-Stage Renal Disease
- Have a slow CD4 count response to ART

Question

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

Case 1

- 30 yo Male was diagnosed with HIV infection 4 hours ago in the ER
- Asymptomatic
- Initial: No Viral Load, CD4, Resistance Data, or HLA-B57 neg
- Other labs are normal
  - WBC 3800 / Lymphocytes 20%
- No prior medical history.
- Ok to start therapy if you think he should
ARS Question 1: When would you choose to start therapy?

A. Right now in the ED  
B. Within 1 or 2 days (outpatient Clinic)  
C. In the next 2 weeks (outpatient Clinic)  
D. Within 2 to 4 weeks  
E. Some other option

ARS Question 2: At this point, which regimen would you choose?

A. TDF / 3TC / low dose (400mg) EFV (fdc; generic)  
B. ABC / 3TC / DTG (fdc)  
C. TAF / FTC (fdc) + DTG  
D. DTG + 3TC  
E. TAF / FTC / ELV / cobi (fdc)  
F. TAF / FTC / BIC (fdc)  
G. TAF / FTC (fdc) + RAL (once daily)  
H. TAF / FTC / RPV (fdc)  
I. TAF / FTC (fdc) + DRV/r (or cobi / fdc)  
J. Some other option (e.g., DRV/r + DTG or …)
Question

What regimen should I use as initial therapy?

Case 2

- 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

ARS Question 3: At this point, which regimen would you choose?

A. TDF / 3TC / low dose (400mg) EFV (fdc; generic)
B. ABC / 3TC / DTG (fdc)
C. TAF / FTC (fdc) + DTG
D. TAF / FTC / ELV / cobi (fdc)
E. TAF / FTC / BIC (fdc)
F. TAF / FTC (fdc) + RAL (once daily)
G. TAF / FTC / RPV (fdc)
H. TAF / FTC (fdc) + DRV/r (or cobi / fdc)
I. Some other option (e.g., DRV/r + DTG or …)
ARS Question 4: Would you use DTG / 3TC as initial therapy?

A. Yes
B. No
C. Not sure

GEMINI: Initial ART with DTG/3TC

DTG + 3TC is non-inferior to DTG + TDF/FTC in Snapshot HIV-1 RNA <50 c/mL at Week 96

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

<table>
<thead>
<tr>
<th>Baseline viral load strata</th>
<th>DTG + TDF/FTC</th>
<th>DTG + 3TC</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤100,000 c/mL</td>
<td>90/101</td>
<td>92/96</td>
</tr>
<tr>
<td>&gt;100,000 c/mL</td>
<td>50/50</td>
<td>52/52</td>
</tr>
<tr>
<td>&gt;250,000 c/mL</td>
<td>4/4</td>
<td>6/6</td>
</tr>
<tr>
<td>&gt;500,000 c/mL</td>
<td>3/3</td>
<td>2/2</td>
</tr>
</tbody>
</table>

Difference in proportion, % (95% CI)

<table>
<thead>
<tr>
<th>Baseline viral load strata</th>
<th>DTG + TDF/FTC</th>
<th>DTG + 3TC</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤100,000 c/mL</td>
<td>2 (95% CI 0.2 to 4.8)</td>
<td>2 (95% CI 0.2 to 4.8)</td>
</tr>
<tr>
<td>&gt;100,000 c/mL</td>
<td>0 (95% CI -0.8 to 0.8)</td>
<td>0 (95% CI -0.8 to 0.8)</td>
</tr>
<tr>
<td>&gt;250,000 c/mL</td>
<td>0 (95% CI -2.8 to 2.8)</td>
<td>0 (95% CI -2.8 to 2.8)</td>
</tr>
<tr>
<td>&gt;500,000 c/mL</td>
<td>0 (95% CI -5.0 to 5.0)</td>
<td>0 (95% CI -5.0 to 5.0)</td>
</tr>
</tbody>
</table>
**Recommended Initial Regimens: InSTI Plus 2 nRTIs**

- Bictegravir/TAF/emtricitabine
- Dolutegravir/abacavir/lamivudine
- Dolutegravir plus (TAF/emtricitabine)

---

**ARS Question 5: Would you use TAF or TDF with an InSTI?**

A. TAF  
B. TDF  
C. Either

---

**Virological Suppression**

<table>
<thead>
<tr>
<th>Boosted</th>
<th>Unboosted</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAF/FTC</td>
<td>94%</td>
</tr>
<tr>
<td>TDF/FTC</td>
<td>92%</td>
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</table>

*P = 0.0004  
P = n.s.*
Renal Toxicity

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<th>TDF</th>
<th>Un-boosted</th>
<th>Boosted</th>
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<tbody>
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<td>Events</td>
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<td>200</td>
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<td>Total</td>
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<td>850.03</td>
<td>852.53</td>
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<tr>
<td>% in treatment</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Bone Toxicity

<table>
<thead>
<tr>
<th></th>
<th>TDF</th>
<th>Un-boosted</th>
<th>Boosted</th>
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<tbody>
<tr>
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<tr>
<td>Total</td>
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<tr>
<td>% in treatment</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Question

Seems like we are now starting ARV therapy for about everyone, what about starting therapy for an **Elite Controller**?

Case 3

• 30 yo Male was diagnosed with HIV infection 7 years ago
• Asymptomatic
• **Initial**: HIV RNA < 50 c/ml (HIV DNA positive)
  CD4 count 870 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

ARS Question 6: Would you choose to start therapy at this time?

A. Yes  
B. No  
C. Maybe
T cell "activation" is lower in treated than untreated adults, but consistently higher than "normal"


Question

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

Case 4

- 55 yo male referred to you for evaluation
- Diagnosed 18 years ago with HIV infection
  - Initial: HIV RNA 936,000c/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 (tc).
  - Now DTG / DRV/c / 3TC
- No historical resistance tests are available
ARS Question 7: Should you change ARV therapy now?

A. Yes  
B. No  
C. Not sure
Does InSTI therapy cause weight gain?

Case 4

- 47 year old woman starts on BIC/FTC/TAF 12 months ago from her original ARV regimen (TDF/FTC/DRV/r)
- Diagnosed 4 years ago
- Initial: HIV RNA 28,000 c/ml (Wildtype virus)
  CD4 count 450 cells/ul
- Current: HIV RNA <20 c/mL / CD4+ count 930 /uL
- Since starting her current regimen her weight has increased from 145 lbs to 171 lbs

Case 5

- 47 year old woman starts on BIC/FTC/TAF 12 months ago from her original ARV regimen (TDF/FTC/DRV/r)
- Diagnosed 4 years ago
- Initial: HIV RNA 28,000 c/ml (Wildtype virus)
  CD4 count 450 cells/ul
- Current: HIV RNA <20 c/mL / CD4+ count 930 /uL
- Since starting her current regimen her weight has increased from 145 lbs to 171 lbs

ARS Question 8: At this point you would

- A. Keep her on her current Rx (TAF/FTC/BIC)
  or Switch her to:
- B. TDF/ FTC (fdc) / DRV/r
- C. TAF/ FTC / DRV/c (fdc)
- D. TDF / FTC / RPV (fdc)
- E. DTG / RLP (fdc)
- F. TAF / FTC / ATV/c
- G. Some other option
Long-term weight gain (mean 2.0 years)

Weight gain after ~2 years, comparing ART regimens in adjusted analyses

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Years on regimen</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV (ref)</td>
<td></td>
<td>-0.38 to -0.00</td>
<td>0.001</td>
</tr>
<tr>
<td>RPV</td>
<td>0.38</td>
<td>0.10 to 0.66</td>
<td>0.01</td>
</tr>
<tr>
<td>ATV</td>
<td>0.62</td>
<td>0.20 to 1.44</td>
<td>0.14</td>
</tr>
<tr>
<td>DRV</td>
<td>1.07</td>
<td>0.53 to 1.61</td>
<td>0.00</td>
</tr>
<tr>
<td>RAL</td>
<td>0.55</td>
<td>-0.13 to 1.23</td>
<td>0.11</td>
</tr>
<tr>
<td>EVG/TDF</td>
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<td>-0.10 to 0.58</td>
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<tr>
<td>DTG/TDF+a</td>
<td>0.64</td>
<td>0.12 to 1.17</td>
<td>0.02</td>
</tr>
<tr>
<td>DTG/ABC</td>
<td>0.75</td>
<td>0.37 to 1.14</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Note: All new drugs were analyzed vs. EFV, RPV, ATV, DRV; all new TDF regimens were analyzed vs. DTG/TDF.

* TAF regimens not included as mean follow up time is shorter due to more recent approval.

Source: Bourgi et al. CROI 2019
GAM plot: change in weight in kg over time

ADVANCE: Weight Gain

Cabotegravir vs Placebo for PrEP

Primary Outcome: Changes in weight
CAB vs. PBO

New Orleans, LA, December 4-7, 2019, Ryan White HIV/AIDS Program CLINICAL CONFERENCE
Question

Do I change ARV regimen in a patient with a discordant CD4 count response?

Case 6

- 48 yo man presents with newly diagnosed HIV infection
- Asymptomatic except for weight loss / fatigue
- Initial: HIV RNA 860,000 c/ml
  CD4 count 24 cells/ul
- Started on ARV Rx
- One year later his HIV RNA < 20 c/ml but his CD4 is 65 cells/ul
ARS Question 9: Should you change ARV therapy now?

A. Yes
B. No
C. Not sure

What is Immunologic Failure?

![Graph showing CD4 and viral load over time.]

Question

What do I do with a patient who has persistently detectable viremia?
Case 7

- 55 yo man referred to you for evaluation
- Diagnosed 18 years ago with HIV infection
- Initial: HIV RNA 936,000c/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 (tsc)
  - Now DTG / DRV/c / 3TC
- No historical resistance tests are available

ARS Question 10: Should you change ARV therapy now?

A. Yes
B. No
C. Not sure

Virologic Responses on Antiretroviral Therapy

Virologic Suppression

**Virologic Responses on Antiretroviral Therapy**

**Virologic Blip**


After virologic suppression, an isolated detectable HIV RNA level followed by return to virologic suppression.

**HIV RNA (copies/mL)**

- **Antiretroviral Therapy Started**
- **Weeks**
- **HIV RNA (copies/mL)**

**Virologic Failure**

**Question**

What regimen should I use (or not use) in a patient with End-Stage Kidney Disease?

---

**Case 8**

- 57 year old man is referred to you for care; newly diagnosed with HIV
- Diagnosed when he presented for care at a local FQHC after years of not seeing a provider
- Initial Labs:
  - HIV RNA 147,000
  - CD4 Count 370 cells / ul
  - Serum creatinine 5.6 mg/dl
  - Estimated CrCl < 30 cc/min
  - Wild type virus
  - HLA B5701 negative

---

**ARS Question 11: At this point which regimen would you choose?**

A. DOR + TAF + 3TC (renally adjusted)
B. ABC/3TC / DTG (fdc)
C. TAF/ FTC / BIC (fdc)
D. TAF/ FTC (fdc) + DTG
E. DTG + abacavir + 3TC (renally adjusted)
F. DTG + 3TC (renally adjusted)
G. RAL (once daily) + abacavir + 3TC (renally adjusted)
H. DTG + rilpiviren
I. DTG + DRV/r (or cobi / fdc)
J. Some other option (e.g., DRV/r + DTG or …)
At this point which regimen would you choose?

- A. DOR + TAF + 3TC (renally adjusted)
- B. ABC/3TC/DTG (fdc)
- C. TAF/FTC/BIC (fdc)
- D. TAF/FTC (fdc) + DTG
- E. DTG + abacavir + 3TC (renally adjusted)
- F. DTG + 3TC (renally adjusted)
- G. RAL (once daily) + abacavir + 3TC (renally adjusted)
- H. DTG + rilpivine
- I. DTG + DRV/r (or cobi / fdc)
- J. Some other option (e.g., DRV/r + DTG or …)

---

Summary of ARVs in ESRD

<table>
<thead>
<tr>
<th>No Dose Adjustment</th>
<th>Dose Adjustment Required</th>
<th>Do Not Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>3TC</td>
<td>MOST FDCs</td>
</tr>
<tr>
<td>TAF (on hemodialysis)</td>
<td>FTC</td>
<td>- ELV (fdc)</td>
</tr>
<tr>
<td>EFV</td>
<td>(TDF)</td>
<td>- BIC (fdc)</td>
</tr>
<tr>
<td>DOR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NVP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RPV / ETV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRV / r or ATZ / r</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

Question

What regimen should I start when a patient returns after a long absence?
Case 9
- 55 yo male returns after being “Lost to Follow Up” for 2 years
- Diagnosed 7 years ago with HIV infection
- Initial Rx: TDF / FTC / RPV (Tolerated well)
- Initial: HIV RNA 86,000 c/ml (wildtype virus)
  CD4 count 70 cells/ul
- Status at last visit (2 years ago):
  HIV RNA 26 c/ml / CD4 count 325 cells/ul
- Now returns and wants to re-engage in care
- Lab results pending

ARS Question 12: What ARV therapy should you use now?
A. Same regimen as originally on
B. Start an InSTI-based regimen
C. Start a PI-based regimen
D. Wait for repeat resistance test, then choose regimen based on results
E. Some other answer

Question
How do I manage a heavily experienced patient who is experiencing virologic failure?
Prevalence of Patients with Limited Treatment Options

![Graph showing prevalence over time.]

Virologic Success in Those with or without LTO

![Graph showing virologic success.]

Discussion

- Confirm the virologic failure
- Explore all prior regimens and resistance tests
- Identify 2 fully active drugs (if possible)
  - Use Dolutegravir (50 mg) twice daily
  - Some form of Tenofovir (as long as no K65R)
  - Boosted darunavir
  - 3TC or FTC (despite resistance)
- Ibalizumab
- Compassionate Use Drug
## Conclusions

- ARV therapy should be initiated with an InSTI-based regimen (unless otherwise indicated), as close to time of Dx as possible
- Do not change Rx in setting of low-level viremia
- Do not change Rx in setting of low CD4 count response
- Avoid Fixed Dose Combination Therapy in patients with ESRD
- Weight gain is associated with initiation of ARV Rx, with more weight gain observed in InSTI regimens
- As a rule, restart the last successful regimen for those who were lost to care and now return

## Question-and-Answer Period
Antiretroviral Therapy and Pregnancy in 2019: Current Recommendations and Controversies

Jean R. Anderson, MD
Professor of Gynecology and Obstetrics
Johns Hopkins University
Baltimore, Maryland

Financial Relationships With Commercial Entities

Dr Anderson’s spouse holds stock or stock options in Gilead Sciences, Inc. (Updated 11/21/19)

Learning Objectives

After attending this presentation, learners will be able to:

• Describe the current state of perinatal transmission of HIV infection
• Discuss current recommendations regarding the use of antiretroviral therapy (ART) regimens in pregnant women or those desiring pregnancy
• Describe current recommendations for preexposure prophylaxis (PrEP) in pregnancy and breastfeeding
ARS Question #1

A 24-year-old woman presents at 7 weeks gestational age on DTG/3TC/ABC. Her CD4 count is 430 cells/µL and HIV-RNA is <20 copies/ml. She is tolerating this regimen well. After appropriate counseling, which of the following is the most appropriate management of her ART during pregnancy?

A. Continue her current regimen
B. Stop all ARVs until 14 wks gestation and then restart current regimen
C. Change to BIC/FTC/TAF
D. Change to EVG/COBI/FTC/TDF

ARS Question #2

A 36-year-old woman presents at 24 week gestational age with a new diagnosis of HIV. Her CD4 count is 246 cells/µL and HIV-RNA is 21,000 copies/ml. She is also found to be HBsAg+. Which would be the most appropriate regimen to start?

A. EVG/COBI/FTC/TDF
B. DTG/ABC/3TC
C. DTG + TDF/FTC
D. BIC/TAF/FTC

ARS Question #3

A 34 year old is in her 2nd pregnancy. She delivered her first infant in Zambia 4 years ago and did not breastfeed because of her HIV diagnosis. She states that she never bonded with him and states her intention to breastfeed after this pregnancy. She is currently on TDF/FTC + ATV/r. Which of the following should you consider?

A. Tell her she cannot breastfeed her infant and threaten to call Child Protective Services
B. Counsel that BF is not recommended and offer only formula as option
C. Discuss importance of continuous viral suppression throughout pregnancy and BF
D. Recommend that breastmilk be mixed with formula to reduce risk
**Change in MTCT in Resource-Rich Countries**

<table>
<thead>
<tr>
<th>Year</th>
<th>Transmission (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993: WITS</td>
<td>24.5</td>
</tr>
<tr>
<td>1994: PACTG 076</td>
<td>7.4</td>
</tr>
<tr>
<td>1997: PACTG 185</td>
<td>5.0</td>
</tr>
<tr>
<td>1999: WITS</td>
<td>3.3</td>
</tr>
<tr>
<td>2001: PACTG 247</td>
<td>2.0</td>
</tr>
<tr>
<td>2002: PACTG 316</td>
<td>1.5</td>
</tr>
<tr>
<td>2003: WITS</td>
<td>0.5</td>
</tr>
<tr>
<td>2011: UK</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

**Perinatal Cascade: 2005-2014**

<table>
<thead>
<tr>
<th>Step</th>
<th>HIV Exposed/Uninfected</th>
<th>HIV-Infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>No/Inadequate prenatal care</td>
<td>21-31%</td>
<td>45-58%</td>
</tr>
<tr>
<td>Prenatal ARVs</td>
<td>86-93%</td>
<td>40-52%</td>
</tr>
<tr>
<td>Intrapartum ARVs</td>
<td>80-90%</td>
<td>50-62%</td>
</tr>
<tr>
<td>Elective C-section</td>
<td>40%</td>
<td>20-40%</td>
</tr>
<tr>
<td>Neonatal ARVs</td>
<td>93-98%</td>
<td>67-92%</td>
</tr>
<tr>
<td>Breastfed</td>
<td>1.5%</td>
<td>10%</td>
</tr>
<tr>
<td>Maternal HIV dx before pregnancy</td>
<td>75-82%</td>
<td>~50%</td>
</tr>
<tr>
<td>Maternal HIV dx at/after delivery</td>
<td>&lt;10%</td>
<td>21-29%</td>
</tr>
</tbody>
</table>

Overall perinatal HIV testing rate has not exceeded 76% since 2006.
7-24% infants with perinatal HIV born to women with acute HIV in pregnancy.
Rating Scheme for Recommendations

<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
<th>Quality of Evidence for Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Strong</td>
<td>I: One or more RCTs with clinical outcomes and/or validated lab endpoints</td>
</tr>
<tr>
<td>B: Moderate</td>
<td>II: One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes</td>
</tr>
<tr>
<td>C: Optional</td>
<td>III: Expert opinion</td>
</tr>
</tbody>
</table>

General Principles for the Use of ARVs in Pregnancy

- ART is recommended for all pregnant women to prevent perinatal transmission and to optimize the health of the mother (AI)
  - Perinatal transmission is directly related to HIV viral load
    - Undetectable VL (<50 c/ml) at time of delivery associated with 0.09% transmission (UK/Ireland, Townsend 2014)
    - Early initiation of ART increases viral suppression by time of delivery and further reduces risk of transmission
      - French Perinatal Cohort: with NDVL at delivery: 0% transmission with preconception ART, 0.2% with 1st trimester, 0.5% with 2nd trimester, 0.9% with 3rd trimester (Mandelbrot 2015)
  - HIV drug resistance tests should be performed but ART initiation should not be delayed while waiting for results (AII)
  - ARV drugs further reduce transmission risk through infant pre- and post-exposure prophylaxis

- Choice of ART regimen should be informed by current adult treatment guidelines but there are special considerations in pregnancy:
  - Risk of birth defects or other adverse pregnancy outcomes
  - Availability of pregnancy-specific pharmacokinetic data
  - Maternal factors (e.g., nausea/vomiting, comorbid conditions)
- Women who become pregnant on ART should continue their regimen during pregnancy, provided the regimen is safe, effective in suppressing viral replication and tolerated (AII)
  - Drugs not recommended due to toxicity (e.g. d4T, ddi) should be stopped and women switched to another ART regimen (AIII)
- EVG/COBI, ATV/COBI, DRV/COBI regimens: consider switching due to PK concerns in 2nd/3rd trimester (BIII)
Lack of Viral Suppression in Pregnancy

- HIV Outpatient Study (2005-2013): 28% of women had HIV RNA >500 c/ml at end of pregnancy
- Adherence issues: systematic review/meta-analysis: 73.5% pregnant women had >80% adherence (Nacenga 2012)
- Pharmacologic issues/food requirements
- Treatment interruption
- Inadequate time on ART
- ART resistance
- Perinatally-infected
- Acute infection
- Associated with higher viral load and lower likelihood of diagnosis
- May represent significant proportion of residual perinatal transmission in US (Hedsen et al 2013)
- Maintain high level of suspicion with clinical sx/sx—obtain plasma HIV-RNA
- 3rd trimester repeat screening

Integrase Strand Transfer Inhibitors (InSTIs) and Neural Tube Defects

Birth Defect Surveillance Uganda – Neural Tube Defects

Barlow-Musha et al. CROI 2019, Seattle Abs. 743

- 4 hospital defect surveillance: 69,766 births (6,494 to HIV+ women, 80% on TDF-3TC-EVF (no DTG used in country yet)

<table>
<thead>
<tr>
<th></th>
<th>HIV-</th>
<th>HIV+</th>
<th>NTD% births HIV- women</th>
<th>NTD% births HIV+ women</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTD</td>
<td>71</td>
<td>66</td>
<td>5.11% (0.08-0.13)</td>
<td>0.07% (0.03-0.17)</td>
</tr>
</tbody>
</table>

Tsepano NTD prevalence:
- HIV- women: 0.09% (95% CI 0.07-0.12%)
- HIV+ EFV preconception: 0.05% (95% CI 0.02-0.15%)

Phenotypes of the 71 NTD:
- Spina Bifida: 41 (58%)
- Anencephaly: 19
- Encephalocele: 12

New Orleans, LA, December 4-7, 2019, Ryan White HIV/AIDS Program CLINICAL CONFERENCE
Merck Review of Raltegravir-Exposed Pregnancies

- Merck review of database on 2426 pregnancies with RAL exposure, including data from:
  - Merck safety database, including APR
  - UK/Ireland National Surveillance HIV in Pregnancy and Childbirth (NSHPC)
  - French Perinatal Cohort (includes data from abstract 774)
- Prospective: 1991 cases, with 456 periconception RAL: no NTD
- Retrospective: 435 retrospective reports (no denominator), 4 NTD cases – 1 with periconception exposure; also 1 encephalocele with periconception exposure (APR)
- Merck safety database, including APR
- UK/Ireland National Surveillance HIV in Pregnancy and Childbirth (NSHPC)
- French Perinatal Cohort (includes data from abstract 774)

Dolutegravir in Pregnancy

- Use at conception:
  - May 2018: unplanned interim analysis of observational surveillance study of pregnant women on ART in Botswana: 4/426 (0.94%) NTD among women who conceived on DTG-based regimen (Zash et al. NEJM 2018)
  - July 2019: update – DTG exposure at conception associated with slightly higher rate of NTDs compared to other types of ARV exposure (3/1000 deliveries vs 1/1000 deliveries) (Zash et al NEJM 2019)
- DTG started in pregnancy: (Zash. Lancet Global Health 2018;6:e804)
  - 1st trimester >4-6 wk GA: 0/280 birth defects
  - 2nd, 3rd trimester: 0/729 birth defects

Recommendations of Perinatal Guidelines Panel: DTG (November 2019)

- DTG is a preferred INSTI for ART-naive women irrespective of trimester
  - For pregnant women receiving DTG and present to care in 1st trimester, counsel about risks/benefits of continuing DTG vs switch to alternative regimen. In most cases, continuation of DTG is recommended (AIII)
  - NTDs may have already occurred
  - Additional risk of NTD may be small, depending on current GA
  - Background risk of NTD (0.06% in US)
  - Changes in ART, even in 1st trimester, may increase risk of viral rebound
- DTG +TDF/FTC is recommended with acute HIV in pregnancy
- DTG is an alternative agent for women trying to conceive
**Antiretroviral Pregnancy Registry (APR):**

**Integrase Inhibitors (InSTI) and Neural Tube Defects (NTD)**

Albano J et al.  CROI 2019 Seattle, WA Abs. 747

- Evaluation of the prevalence of NTD with InSTI exposure in prospective and retrospective components of the APR (through 31 Jul 2018).
- Prospective APR: primary analysis. Clinicians register pregnant women (no identifiers) with prenatal ARV exposures before pregnancy outcome is known, report data on exposure throughout pregnancy, and provide birth outcome data.
- Retrospective APR: secondary review. Reports of exposed pregnancies after pregnancy outcome is known; no denominator.
- APR reports come from North America (75%), Europe (8%), Africa (7%), South America (6%) and Asia (4%).
- Through 31 Jul 2018: includes 20,064 pregnancies with 20,413 fetal outcomes including 19,005 live births.

**APR Methods**

- **Prospective APR**
  - Clinicians register pregnant women (no identifiers) with prenatal ARV exposures before pregnancy outcome is known, report data on exposure throughout pregnancy, and provide birth outcome data.
- **Retrospective APR**
  - Reports of exposed pregnancies after pregnancy outcome is known; no denominator.
- APR reports come from North America (75%), Europe (8%), Africa (7%), South America (6%) and Asia (4%).
- Through 31 Jul 2018: includes 20,064 pregnancies with 20,413 fetal outcomes including 19,005 live births.

**Prospective Antiretroviral Pregnancy Registry (APR):**

Integrase Inhibitors (InSTI) and Neural Tube Defects (NTD)

Albano J et al.  CROI 2019 Seattle, WA Abs. 747

- 1,193 live births with InSTI exposure at any time in pregnancy: 604 periconceptional exposure, including 174 DTG, 186 EVG, 244 RAL.
- 2 CNS defect cases were reported with InSTI exposure at any time (both DTG, one 1st trimester, one 2nd/3rd trimester).
- There were no NTD among prospective cases for any InSTI drug.

<table>
<thead>
<tr>
<th>Exposition to any InSTI</th>
<th>1st trimester</th>
<th>2nd/3rd trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG</td>
<td>6/174 (3.4%)</td>
<td>2/55 (3.6%)</td>
</tr>
<tr>
<td>EVG</td>
<td>5/186 (2.7%)</td>
<td>0/27 (0%)</td>
</tr>
<tr>
<td>RAL</td>
<td>5/244 (2.0%)</td>
<td>4/68 (5.9%)</td>
</tr>
<tr>
<td>Renal</td>
<td>5/199 (2.5%)</td>
<td>3/97 (3%)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>8/617 (1.3%)</td>
<td>13/290 (4.5%)</td>
</tr>
<tr>
<td>Chromosome abnl</td>
<td>2/168 (1.2%)</td>
<td>12/194 (6.2%)</td>
</tr>
<tr>
<td>Other organ systems</td>
<td>1/168 (0.6%)</td>
<td>12/194 (6.2%)</td>
</tr>
<tr>
<td>1st-trimester defect</td>
<td>2/168 (1.2%)</td>
<td>12/194 (6.2%)</td>
</tr>
<tr>
<td>2nd/3rd-trimester defect</td>
<td>1/168 (0.6%)</td>
<td>12/194 (6.2%)</td>
</tr>
</tbody>
</table>

No Neural Tube Defects

CNS: 2: 1 (lissencephaly – neural migration disorder) with preconception DTG; 1 (ventriculomegaly) with 2nd/3rd trimester DTG exposure.

Face, ear, face, neck: 2

Cleft lip/palate: 2

Respiratory: 1

Cardiac/circulatory: 11

Lower GI: 1

Renal: 4

Musculoskeletal: 8

Chromosome abnl: 2

Other organ systems: 1

Specify syndromes 1

**Integrase Strand Transfer Inhibitors (InSTIs) in Late Pregnancy**

Integrase Inhibitors (InSTIs) in Late Pregnancy

Albano J et al.  CROI 2019 Seattle, WA Abs. 747

- Through 31 Jul 2018: includes 20,064 pregnancies with 20,413 fetal outcomes including 19,005 live births.

- APR reports come from North America (75%), Europe (8%), Africa (7%), South America (6%) and Asia (4%).

- Through 31 Jul 2018: includes 20,064 pregnancies with 20,413 fetal outcomes including 19,005 live births.
Integrase Inhibitors (InSTIs)

- Rapid viral decay after initiation (approx. 2 log reduction in VL by wk 2-RAL in naïve pts) and good placental passage
- Acute infection-InSTI associated with shorter time to viral suppression than PI-based regimen (median 12 vs 24 wk) (un就好)
- Use of an InSTI-based regimen has been suggested in late pregnancy in the following circumstances:
  - Women presenting late and not on ART, especially with high VL
  - As part of new regimen for women on failing regimen—consider after review of treatment history and resistance testing
  - Women on failing regimen with high VL or incomplete suppression as 4th ARV
  - Efficacy and safety of this approach have NOT been evaluated in clinical trials
- If failing regimen, intensification with addition of single agent may risk loss of future effectiveness

Randomized Trial of RAL vs EFV-Based ART

Mirochnick M et al. CROI, 2019 Seattle Abs. 39LB

- Randomized trial of RAL+2NRTI vs EFV+2NRTI in 408 pregnant ART-naïve women S America, Africa, Thailand and US presenting to ANC at ≥28-36 weeks (later expanded to ≥ 20 weeks) gestation. Primary endpoint is virologic response (VL <200) at delivery.

<table>
<thead>
<tr>
<th></th>
<th>Delivery</th>
<th>EFV + 2 NRTI</th>
<th>RAL + 2 NRTI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VL &lt;200</td>
<td>84% (151/179)</td>
<td>94% (174/183)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Enrolled 20 to &lt;28 wks</td>
<td>97% (87/90)</td>
<td>96% (85/88)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Enrolled 28 to &lt;37 wks</td>
<td>71% (64/89)</td>
<td>93% (89/95)</td>
<td>0.05</td>
<td></td>
</tr>
</tbody>
</table>

Median Time to VL <200 copies/mL:
- RAL: 8 days
- EFV: 15 days

More Rapid VL Decline with RAL than EFV

Mirochnick M et al. CROI, 2019 Seattle Abs. 39LB

- VL decline was greater in raltegravir arm than efavirenz arm at study weeks 2, 4 and 6.
- Both regimens well-tolerated; no difference AE, stillbirth, preterm.
- 1 raltegravir and 6 efavirenz infants were infected (p=0.06).
DTG vs EFV When Starting ART in Late Pregnancy

Khoo S et al. CROI 2019 Seattle, WA Abs. 40LB

- Open-label randomized trial of DTG+2NRTI vs EFV+2NRTI in 268 pregnant ART-naïve women presenting to antenatal clinic at ≥28-36 weeks gestation in Kampala and Cape Town.
- Primary endpoint is virologic response (VL<50) at delivery.
- Analysis at delivery (ITT): 122 DTG, 115 EFV
  - Median gestation age at enrollment, 31 weeks
  - No difference in baseline VL (median 4.4 log), CD4 (median 445), prior obstetric history, gestation, BMI

- Open-label randomized trial of DTG+2NRTI vs EFV+2NRTI in 268 pregnant ART-naïve women presenting to antenatal clinic at ≥28-36 weeks gestation in Kampala and Cape Town.
- Primary endpoint is virologic response (VL<50) at delivery.
- Analysis at delivery (ITT): 122 DTG, 115 EFV
  - Median gestation age at enrollment, 31 weeks
  - No difference in baseline VL (median 4.4 log), CD4 (median 445), prior obstetric history, gestation, BMI

More Rapid VL Decline with Dolutegravir than Efavirenz

Khoo S et al. CROI 2019 Seattle, WA Abs. 40LB

- Primary outcome – Time on medication before delivery, median 55 days

<table>
<thead>
<tr>
<th></th>
<th>Delivery</th>
<th>Dolutegravir</th>
<th>Efavirenz</th>
<th>aRR DTG vs EFV*</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VL&lt;50</td>
<td>73.8%</td>
<td>92.6%</td>
<td>0.80 (1.0, 2.1)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>VL&lt;1000</td>
<td>92.6%</td>
<td>92.6%</td>
<td>1.01 (0.9, 1.2)</td>
<td>0.5513</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age, country, VL (< 100,000), CD4 (<=200), GA at start ART

Pharmacokinetics in Pregnancy

- EVG/COBI: lower drug levels in 3rd trimester [P1026]; only 74% of women maintained viral suppression at delivery
- DRV/COBI: low drug levels in late pregnancy and high rates of virologic failure in late pregnancy; once daily dosing of DRV not recommended in pregnancy
- ATV/COBI: PK data not yet available, but anticipated to be similar to DRV/COBI
- LPV/r: dose adjustment recommended in 2/3 trimester
- ATV/r: consider dose adjustment in 2/3 trimester
**Initial ART Regimens for ARV-Naive Pregnant Women (December 2019)**

**Preferred**
- NRTI backbone: ABC/3TC or TDF/FTC or TDF/3TC
  - INSTI: DTG/ABC/3TC or DTG + preferred 2-NRTI backbone, or RAL + preferred 2-NRTI backbone
  - PI: ATV/r + preferred 2-NRTI backbone or DRV/r + preferred 2-NRTI backbone

**Alternative**
- NRTI backbone: 2D4/3TC
  - PI: LPV/r + preferred 2-NRTI backbone

**Insufficient Data**
- BIC/TAF/FTC; DOR; IBA; TAF/FTC; RPV/TAF/FTC

**Do Not Use**
- Not recommended in pregnancy due to concerns about maternal or fetal safety or inferior efficacy:
  - ATV/COBI; DRV/COBI; DRV/COBI/FTC/TAF; EVG/COBI/FTC/TDF/TAF

**Not recommended in ARV-naive pregnant women due to limited data on PK, safety and efficacy:**
- MVC; ETR; NVP (potential for adverse events, low resistance barrier); T20

**Not recommended in pregnancy:**
- ddI; d4T; FPV; FPV/r; IDV; IDV/r; NFV; RTV; SQV; SQV/r; TPV; TPV/r; DTG/RPV; ABC/3TC/3TC

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**Table 7. Situation-specific Recommendations for Use of Antiretroviral Drugs in Pregnant Women and Nonpregnant Women Who Are Trying to Conceive**

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New Orleans, LA, December 4-7, 2019, Ryan White HIV/AIDS Program CLINICAL CONFERENCE
USPHS Perinatal Guidelines: Breastfeeding

- Breastfeeding is NOT RECOMMENDED for women living with HIV in the US (AII).
- However, women who have questions about breastfeeding or a desire to breastfeed should receive patient-centered, evidence-based counseling on infant feeding options (AII).
- When a woman with HIV chooses to breastfeed after counseling, a harm-reduction approach should be taken to help minimize the risk of HIV transmission to their infant.
Why is breastfeeding (BF) not recommended in US?

- Maternal ART reduces but does not fully eliminate the risk of HIV transmission via breastmilk.
- Safe and affordable infant feeding alternatives and safe water are readily available.
- Little safety data on most modern ART regimens during breastfeeding.
- Potential differential diffusion of ARV drugs into breast milk, so that infant may be exposed to incomplete regimen, which could increase risk of resistance if transmission occurs.
- U=U: BF represents an area of uncertainty.
- In PROMISE study there were 2 postnatal transmissions in BF women with nondetectable HIV RNA.

Why would a woman with HIV want to breastfeed?

- Women from some areas of the US may face challenges that are similar to women in developing countries: cost limits access to formula, inadequate quantities of formula, lack of access to clean water.
- May face environmental, social, familial and personal pressure to consider breastfeeding.
- Patients will often cite not wanting to disclose their HIV status to their families that may be closely interacting with them following delivery.
- There may be safety concerns for interpersonal violence if HIV status is disclosed to close relatives or extended family or partners.
- Increasing number of immigrants living with HIV from countries where HIV stigma is greater and cultural expectations are to breastfeed.

Non-judgmental counseling is key

- Offer joint problem solving and shared decision making.
- Recommended harm-reduction measures:
  - Document consistent viral suppression prior to delivery and throughout breastfeeding.
  - Breastfeed exclusively for up to 6 months postpartum, followed by breastfeeding in combination with the introduction of complementary foods.
  - Develop a plan for weaning with input from the family and provider. Rapid weaning over a few days is not recommended.
  - Neonatal prophylaxis: ZDV +/- NVP for 6 wks.
    - ZDV alone would not be effective prophylaxis for 1 mo after complementary foods and formula.
  - Promptly identify and treat maternal mastitis and infant thrush.
  - Monitor the infant for HIV acquisition via breastfeeding.
  - If infant transmission does occur, it is critical to immediately start fully suppressive ART regimen, perform in resistance testing.
PrEP in Pregnancy or Breastfeeding

- Pregnancy is associated with an increased risk of HIV acquisition
- Women whose partners have HIV infection with sustained VL suppression are at effectively no risk for sexual acquisition of HIV
- Clinicians providing preconception or pregnancy care to women whose partners have HIV may not have access to partner’s medical records documenting viral suppression
- HIV testing should be offered to partners of women receiving preconception or pregnancy care when their HIV status is unknown
- TDF/FTC used extensively in pregnancy in setting of HIV and no evidence of adverse effects; recommended by WHO for all pregnant/BF women with HIV in low resource areas
- Use of PrEP for HIV-uninfected but at risk pregnant or breastfeeding US women is recommended after appropriate counseling
- TAF/FTC not recommended at this time in pregnancy or BF

Postpartum Considerations

- Only 37-39% of postpartum women are retained in care (Rana 2010; Adams 2015)
- Systematic review and meta-analysis estimated adequate adherence (>80%)75.7% in pregnancy but only 53% postpartum (Nachega 2012)
- Viral suppression achieved by 30-61% of postpartum women (Adams 2015; Sha 2011)
- South Africa (n=4,311): after viral suppression in pregnancy, VL obtained over a total of 4185 woman-months (wm) of observation postpartum
- May consider simplification of ART regimen postpartum
- Remember potential drug-drug interactions with hormonal contraception

Summary

- Elimination of perinatal transmission is within reach, but...There remain missed opportunities to identify HIV infection in pregnant women and treat appropriately
- The strongest predictor of prevention of perinatal transmission is viral load suppression
- DTG is a preferred INSTI for ART-naïve women irrespective of trimester
- There may be a role of INSTIs in women presenting in late pregnancy to lower viral load more rapidly
- Several ARV agents have lower blood levels in 2nd/3rd trimesters with consideration to increase dose or increase frequency of VL monitoring
- The postpartum period is a time of special risk for nonadherence to ART and to care
For Further (and Ongoing) Guidance

• DHHS Clinical HIV Guidelines: aidsinfo.nih.gov: Perinatal Guidelines—these are updated regularly and recommendations may change as more data becomes available

• National Perinatal HIV Hotline/Clinician Consultation Center: (888)448-8765—for consultation 24 hr/7 days per week

Question-and-Answer Period
Best Practices in HIV Care: Providing Gender-Affirming Care for Transgender and Nonbinary People

Linda Wesp, PhD, APNP, FNP-C
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University of Wisconsin – Milwaukee
Milwaukee, Wisconsin

Financial Relationships With Commercial Entities

Dr Wesp has no relevant financial affiliations to disclose. (Updated 11/25/19)

Learning Objectives

After attending this presentation, learners will be able to:
• Recognize culturally safe gender-affirming patient-provider interactions and their impact on health outcomes
• Discuss gender-affirming interventions (hormones and surgery) and considerations for HIV management
• Implement gender-affirming care best practices in HIV clinical settings
ARS Question 1

How many transgender adults (>age 18) are estimated to be living in the U.S. today?

A. 250,000  
B. 500,000  
C. 1.4 million  
D. 4 million

Background

• “Transgender” refers to individuals with a gender identity/expression that does not align with sex assigned at birth  
• Myriad of terms and identities under the “trans umbrella”  
• Sexual orientation is NOT gender identity  
• 1.4 million transgender adults in US  
  ◦ More than # of adults and children with type 1 diabetes

Flores et al, 2015

Stressful realities

• Shape environment where live, learn, work, and seek healthcare  
• Unsafe public spaces  
• When compared to US adult population  
  ◦ 2x as likely to be living in poverty  
  ◦ 3x as likely to be homeless  
  ◦ 3x as likely to be unemployed  
  ◦ 9x higher suicide rate  
  ◦ Higher rates of sexual/physical assaults

James et al, 2016; Miller & Orlutman, 2015; Reissner et al, 2016; Sevelius et al., 2014; White Hughto, Reissner, & Pachankis, 2015
National Transgender Discrimination Survey

Lack of provider knowledge
- 50% reported having to teach their providers about trans health care

Negative experiences in healthcare
- 19% were refused care
- 28% were subjected to harassment in healthcare settings
- 28% postponed care due to discrimination by healthcare providers
- 33% delayed or did not try to get preventative healthcare due to discrimination by healthcare providers.

James et al., 2016

HIV and Transgender People

HIV Diagnoses in the US, 2009-2014
3,351 transgender people received an HIV diagnosis. Of these:
- 54% were transgender women
- 15% were transgender men
- About half lived in the South

CDC, 2019

HIV Diagnoses Among Transgender People in US by Race/Ethnicity, 2009-2014

Clark et al., 2017
HIV Estimates: Trans Women

  - Prevalence in US: 22% (OR=34); highest prevalence among trans women of color
  - Transfeminine individuals have some of the highest concentrated HIV epidemics in the world with laboratory-confirmed prevalence up to 40%.

HIV Estimates: Transgender Men

- Systematic review (2012 – 2015); 6 U.S. prevalence studies
  - 1 self-report: 0.4%
  - 5 laboratory-tested: 0.5% – 4.3% (n=1)
- Possible underestimated high risk for trans men who have sex with men – have not been focus of research or data collection

Gender Affirmation & HIV Continuum of Care

- Transgender women had lower proportions of retention in care compared to cisgender women and cisgender men, with little change over time.2
  - Transgender women engaged in care had similar proportions of VS
- N=400 transgender women in 9 demonstration SPNS sites2
  - 47.5% used hormones within previous 6 months
    - If HIV primary care provider was hormone prescriber, trans women were 3 times more likely to have VS and to be engaged in care (HIV primary care visit in past 6 mos)
- Among transgender women of color living with HIV, gender affirmation and healthcare empowerment significantly and fully mediated the total effect of discrimination on VS.
Framework of Cultural Safety

- Making health care safe and free from harm
- Caring for the unique experience of each individual
- Becoming aware of our own individual biases and assumptions to avoid perpetuating harm
- Understanding structural inequalities and dynamics of power that impact health encounters

(Ramsden, 1990)

Managing Uncertainty (Poteat et al., 2013)

- Grounded theory study of trans health providers
- Power dynamic impacts care
  - Providers' authority is challenged when we are uncertain
  - Uncertainty is managed with stigmatizing responses towards patients
  - Blaming, shaming, othering, discriminating

Self-reflection...

Where am I resistant to relinquishing power in health care encounters?

How do I react when I’m uncertain and uncomfortable?

Where have I responded (consciously or unconsciously) with stigmatizing actions/reactions?
Gender Affirming Care Model

Affirming and recognizing authentic gender across 4 domains:

- Social: Name, pronoun, interpersonal, institutional acknowledgement
- Psychological: Self-actualization, preventing internalized negative beliefs, behavioral health services
- Medical: Gender-affirming medical interventions and other body modifications, primary and preventative healthcare
- Legal: Name and gender markers on identity documents, health insurance

Approach to Creating Gender Affirming Clinical Care

Clinical Environment
Patient-Centered Care
Advocacy

Changes to Clinical Environment

- Intake forms:
  - Name and pronouns
  - Name/gender as printed on insurance card w/explanation about why
  - Two-step data collection: current gender + sex assigned at birth
- Ensure EMR has names/pronouns visible
- Bathrooms
- Training all staff
- Making your org a safe place & hire trans people
Two-Step Gender Identity Data Collection:

- 97% of respondents at large FQHCs were able to answer without problems
- (Cahill et al, 2014)

Patient Centered Care

- Care which is respectful of and responsive to patient preferences, needs, and values
- Ensure patient values guide care
- Prioritize community engagement & leadership
  - Learn what trans/nonbinary people want/need!

   (Institute of Medicine, 2001)

Establishing Trust

Trust = “Choosing to risk making something I value vulnerable to another person’s actions”

Distrust = “What is important to me is not safe with this person in this situation (or any situation)”

(From The Thin Book of Trust: An Essential Primer for Building Trust at Work by Charles Feltman)
ARS Question 2

The following would be an example of gender affirming communication and language:

A. Hello my name is Linda and I use she/her pronouns. What name and pronouns may I use for you?
B. Thank you, sir.
C. A sign that says: Welcome to Women’s Health Clinic
D. Do you have sex with men, women, or both?

Communication and Language

- Protocol for asking and documenting name and pronouns
- Avoid language that assumes binary gender – strive for gender neutral or non-gendered language
- Medical terminology may be different than how patients experience or describe their gender/body parts

Advocacy

- Disrupting status quo, getting creative
  - EMR, policies/procedures, bathrooms, pharmacy, lab, insurance
  - Find/facilitate referrals to affirming providers and surgeons
  - Provide documentation for legal affirmation of gender
    - Schools, employers, housing, etc
  - Complete prior authorizations or appeals to insurance
  - Advocate via legal system (expert testimonies)
Ongoing Process

- Clinical Environment
- Patient-Centered Care
- Advocacy
- Self-reflection

Current Best Practices

- Incongruence between gender identity and physical characteristics can lead to distress
- DSM V diagnosis “Gender Dysphoria”
- New WHO diagnosis will be “Gender Incongruence”
- Gender affirming hormone and/or surgical interventions are shown to relieve gender dysphoria and are considered medically necessary
- World Professional Association of Transgender Health Standards of Care Version 7: www.wpath.org

Recommended Clinical Guidelines

Long term clinical trials are lacking; Guidelines compile evidence-based and expert opinion to provide graded recommendations

Deutsch et al, 2016 - UCSF Transgender Care Guidelines
https://transcare.ucsf.edu/guidelines

Hembree et al, 2017 - Endocrine Society Guidelines
Clinical Support: TransLine
https://transline.zendesk.com/hc/en-us

- Hormone Prescriber Protocols
- Office set up, billing and coding, legal, surgical, and other resources
- Consultation Services – submit request and receive feedback within 24 hours

Medical Gender Affirmation

- Guided by patient goals, highly individualized
- Hormone Therapy:
  - Masculinization – use testosterone formulations and doses similar to hypogonadism in cisgender men
  - Feminization – use estrogen alone in combination with anti-androgen usually spironolactone

Medical Gender Affirmation (cont’d)

- Guided by patient goals, highly individualized
- Surgeries
  - Multiple surgical options
  - May have mental health, hormone, BMI requirements
  - Pre-op clearance: consider immune function/VL
  - Consider social factors as well for post op recovery
Potential Comorbidities

- Osteoporosis
  - Trans women may have lower BMD prior to feminizing hormone therapy due to reduced physical activity, lower muscle mass, lower vitamin D levels
  - Additional risk for people who have had gonadectomy or use of androgen blockers alone/without sufficient estrogen

  Radix et al, 2016

Potential Comorbidities (cont’d)

- Cardiovascular Disease
  - Possible increased risk related to hormone therapy, more research is needed
  - Transdermal estrogens safest for those with CV history or many risk factors
  - Minority stress and trauma

  Radix et al, 2016

ARS Question 3

Feminizing hormone therapy for gender affirmation is contraindicated with most ARVs due to severe drug drug interactions.

A. True
B. False
Estrogen and Antiretroviral Agents

- Data lacking: mostly based on studies with ethinyl estradiol – we DO NOT use in gender affirming tx
- Metabolism of estrogens occurs via cytochrome P450
  - Several ARVs also metabolized by cytochrome P450 (PI, NNRTI, cobicistat)
  - If at all, more likely to lower estradiol levels than ARV levels

Radix et al. 2016

<table>
<thead>
<tr>
<th>Estrogen and Antiretroviral Agents</th>
<th>Table 1: Interactions between antiretroviral therapy and estrogen therapy</th>
<th>Key Points:</th>
</tr>
</thead>
</table>

Key Points:

- HIV is not a contraindication to gender-affirming medical interventions
- Most ARVs and single tablet regimens unlikely to have major drug-drug interactions
- Combining hormone therapy into the HIV clinical care streamlines management and increases access to care
- Several comorbidities that we monitor more closely in HIV should also be monitored in people on hormone therapy or post-gonadectomy
- HIV providers are well-equipped to provide comprehensive gender affirming care within HIV clinical settings!

Radix et al. 2016

Table 1: Interactions between antiretroviral therapy and estrogen therapy

<table>
<thead>
<tr>
<th>Antiretroviral drug class</th>
<th>Estrogen therapy</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI</td>
<td>Estradiol</td>
<td></td>
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<tr>
<td>PI</td>
<td>Estradiol</td>
<td></td>
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<tr>
<td>Cobicistat</td>
<td>Estradiol</td>
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<tr>
<td>Zidovudine</td>
<td>Estradiol</td>
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<tr>
<td>Lamivudine</td>
<td>Estradiol</td>
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<td>Abacavir</td>
<td>Estradiol</td>
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<tr>
<td>Tenofovir</td>
<td>Estradiol</td>
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<tr>
<td>Emtricitabine</td>
<td>Estradiol</td>
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</tbody>
</table>

Radix et al. 2016
Ongoing Educational Opportunities

- Attend local community events
- Trans Health ECHO Program: transecho@fenwayhealth.org
- Documentaries and Films
- Trans Health Conferences
  - Philadelphia Trans Wellness
  - USPATH/WPATH
  - Chicago LGBTQ Symposium
- Online webinars, CME modules, etc:
  - Center of Excellence for Transgender Health
  - National LGBT Education Center

Recommended Reading


UCSF Guidelines for Transgender Care [https://transcare.ucsf.edu/guidelines](https://transcare.ucsf.edu/guidelines)
Opioid Use and Substance Use Disorders

R. Douglas Bruce, MD, MA, MS
Chief of Medicine, Cornell Scott-Hill Health Center
Associate Clinical Professor of Medicine
Yale University
New Haven, Connecticut

Financial Relationships With Commercial Entities

Dr. Bruce has no relevant financial affiliations to disclose. (Updated 11/21/19)

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
▪ Describe stimulant use disorders and treatments for these disorders
ARS Question 1

According to CDC data, from 1999 to 2017, how many people have died in the United States from drug overdose?

A. 150,000  
B. 250,000  
C. 450,000  
D. 550,000  
E. More than 700,000

ARS Question 2

Please rate your current confidence in managing addiction in people with HIV.

A. Very Confident  
B. Confident  
C. Neutral  
D. Little Confidence  
E. Not Confident at All
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/genes

Environment

Biology/ Environment

Interactions
Drugs Are Usurping Brain Circuits and Motivational Priorities

Consequences: Sex and Drugs - "Chemsex"

Chemsex drugs & HIV risk

- MACS Cohort (HIV Neg)
- AURAI study (HIV Neg)
- AURAI study (HIV Pos)

General Principles
General Principles

- Treat all patients with dignity and respect
- People who use drugs are people
- Malingering, manipulation, etc. are all survival mechanisms people who use drugs use for survival. Don't take it personally.

Practical Initial Step: Screening

- Inquire openly with all patients regarding past personal & family substance use
  - Include use of alcohol and over the counter drugs
- Particular screening tools include: ASSIST, AUDIT, DAST, CAGE-AID, but we use a 2 question initial screen (don't worry, on the next slide)
- Screen ALL patients for substance use to avoid profiling

Practical Initial Step: Screening

1. 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?
Practical Next Step: Think about systems

- Provision of low threshold, rapid access, appropriately dosed treatment (e.g., buprenorphine, methadone, or other treatments)
- Culturally appropriate counseling for addiction [can be simple (NA) to more complex (CBT)]

Practical Steps: Treat everyone

Treatment of the medical issues associated with addiction (e.g., HIV, hepatitis B/C, and Tuberculosis)
- There are NO data to support denying or waiting to start patients on ART or any other treatment.
- Prescribe naloxone and consider becoming a buprenorphine provider
- Review guidelines on the treatment of chronic pain and re-evaluate how you prescribe opioids

Case 1

- You inherit a new patient: A 45 year old male comes in for his refill of oxycodone of 30 mg tablets, two tablets every 6 hours for a total of 240 tablets for the month. You notice there hasn’t been a urine toxicology in 5 years, but notice that there have been a few recent Emergency Department visits for methamphetamine intoxication. The patient today is agitated, struggling to sit still, and wondering why the refill is taking so long….
ARS Question 3: Your next steps:

A. Curse the prior provider who left you a mess
B. Give the refill and find a way never to see the patient again
C. Call social work (or anyone) to try and diffuse the situation and get the patient into treatment
D. Talk with the patient about the ED visits and methamphetamine use to gauge interest in treatment, and refill the medication
E. D, but do not refill the medication

“But it isn’t really a problem” – change is a process

- Transtheoretical Model of Change:
  - Helping patients to move along the stages of change
  - MI – “Roll with resistance”
- Harm Reduction
  - Syringe exchanges
  - Naloxone
- When helping hurts
  - Enabling vs. boundaries

Why isn’t it a problem? The Lifecycle of a Heroin User

[Diagram: Lifecycle of a Heroin User]

Repetitive injection of heroin in uncertain dose, usually 10 to 30 mg but sometimes much more. Note that the addict is hardly ever in a state of normal function (“straight”).

---

New Orleans, LA, December 4-7, 2019, Ryan White HIV/AIDS Program CLINICAL CONFERENCE
It's Friday at 4PM …

- 30 year old comes into clinic and, through much creative and interesting conversations, you conclude that the oxycodone you were giving for back pain is not in the urine toxicology, but morphine is.....

ARS Question 4: Your next step:

A. Refuse to refill the medication and call someone else to deal with the upset patient
B. Agree with the patient that it was a one time thing and give all or some of the oxycodone
C. Discuss treatment for opioids and start buprenorphine
D. Discuss treatment for opioids and refer to methadone
E. Discuss treatment for opioids and start naltrexone
Treatment

- Pharmacological Treatment
  - Buprenorphine, Methadone, Naltrexone

- Behavioral Treatment (Therapy)
  - Motivation Interviewing – getting you motivated to do treatment
  - Cognitive Behavioral Therapy – getting you to think differently about drug use

Medication: BUP and mu-opioid receptors

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
Methamphetamine Treatments

Structural Changes: Methamphetamines

Ending the Mind. Researchers have mapped brain decay caused by methamphetamine use (left). The damage affected memory, emotion, and the reward system. Notice the similarity to the brain decay caused by Alzheimer’s Disease (right).
Methamphetamines and Dopamine Effects

- Normal Control
- Methamphetamine Abuser


Motor Task
Loss of dopamine transporters in the meth abusers may result in slowing of motor reactions.

HIV Specific Methamphetamine Effects

- Neurocognitive effects and HIV may result in permanent neurobiological changes.
- Methamphetamine increases HIV replication and expression of CCR5 on macrophages and these events may contribute to the immunopathogenesis of HIV-infected methamphetamine users.
- Reduced neurocognitive performance can severely compromise HIV clinical care and is associated with HIV nonadherence and the development of HIV resistance.

Treatment

- Pharmacological Treatment
- Behavioral Treatment (Therapy)
  - Motivation Interviewing – motivated to do treatment
  - Cognitive Behavioral Therapy – getting you to think differently about drug use
Medications that do not work

<table>
<thead>
<tr>
<th>Medication</th>
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</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
</tr>
<tr>
<td>Mirtazapine</td>
</tr>
<tr>
<td>Baclofen</td>
</tr>
<tr>
<td>Modafinil</td>
</tr>
<tr>
<td>Bupropion</td>
</tr>
<tr>
<td>Ondansetron</td>
</tr>
<tr>
<td>Dextroamphetamine</td>
</tr>
<tr>
<td>Risperidone</td>
</tr>
<tr>
<td>Gabapentin</td>
</tr>
<tr>
<td>Sertraline</td>
</tr>
</tbody>
</table>

Putting it all together.

Jim is a 47 year-old male living with HIV who has a history of heroin injection, is on methadone maintenance, and is receiving opioids from his primary HIV provider for back pain.

He starts complaining of more back pain. Members of his care team believe this is drug seeking behavior, deny his request, and refer Jim to you to address his complaints.

ARS Question 5: Your next step is....

A. Pretend to be sick and avoid seeing the patient.
B. Take a history and do a physical examination.
C. Inform the patient that he already has someone giving him opioids, and to go see that person.
D. Because he is on methadone, regardless of the cause of pain, no additional medications are available.
You take a history

You take a history and find out that Jim has had a lumbar back pain for years, but that in the last six weeks he has developed a new pain. You ask him to point to where it is and he points to a region in his thoracic vertebrae.

On examination, he has pinpoint tenderness in his thoracic spine which prompts you to order a MRI which shows…

Discitis/osteomyelitis

HIV, Pain and Addiction
Useful websites:

- American Pain Society has resources available online: http://www.americanpainsociety.org/resources/content/primary-care-practitioner.html
- Providers Clinical Support System (PCSS) for MAT at https://pcssnow.org/resources/clinical-tools/
- Buprenorphine training: https://www.samhsa.gov/medication-assisted-treatment/training-resources/buprenorphine-physician-training

Questions?

- Email: robert.bruce@yale.edu
Inflammation and Its Role in HIV Pathogenesis and Aging

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University of California San Diego
San Diego, California

Financial Relationships With Commercial Entities

Dr Gianella Weibel has no relevant financial affiliations to disclose. (Updated 11/18/19)

Learning Objectives

Upon completion of this webinar, learners will be able to:

• Describe the changing face of the HIV epidemic
• Describe the complexity of older adults with HIV
• List factors that contribute to unsuccessful aging
• List the main factors associated with inflammation
• Describe how to best care for aging PWH
Describe the Changing Face of the HIV Epidemic

"We just felt it was time that people saw the truth about AIDS" Kay Kirby

Photography by Therese Frare, 1990, no copyright infringement intended

Background

The development of antiretroviral therapy (ART) for the treatment of HIV is one of the greatest achievements of modern medicine.
Projected Age Distribution of PWH

Describe the Complexity of Older Adults with HIV

Multi-Morbidity is Increasing

70-80% people aging with HIV (50 years and older) have at least one co-morbidity other than HIV


Accelerated Aging in PWH

Pathai et al, J of Gerontology, 2013

Includes Geriatric Syndromes

Greene JAIDS 2015
Contributes to Disability

- HAILO (observational study of ACTG A5322) evaluated 1015 participants with median age 51 years
- At least 1 IADL impairment was reported in 18%

<table>
<thead>
<tr>
<th>Type of Impairment</th>
<th>1 Impaired (n=189)</th>
<th>Median Comparator</th>
<th>10 Impaired (n=1015)</th>
<th>Median Comparator</th>
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<tbody>
<tr>
<td>Housekeeping</td>
<td>16%</td>
<td>3%</td>
<td>4%</td>
<td>11%</td>
</tr>
<tr>
<td>Transportation</td>
<td>36%</td>
<td>13%</td>
<td>25%</td>
<td>40%</td>
</tr>
<tr>
<td>Shopping</td>
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<td>15%</td>
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<td>35%</td>
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<td>4%</td>
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</tr>
<tr>
<td>Finance Management</td>
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<td>13%</td>
<td>21%</td>
<td>26%</td>
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<tr>
<td>Cooking</td>
<td>13%</td>
<td>7%</td>
<td>23%</td>
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</tr>
<tr>
<td>Difficulty using the phone</td>
<td>12%</td>
<td>2%</td>
<td>20%</td>
<td>17%</td>
</tr>
<tr>
<td>Difficulty with medications</td>
<td>5%</td>
<td>2%</td>
<td>11%</td>
<td>11%</td>
</tr>
</tbody>
</table>

John CS 2017

... And Medical Cost

- Study examining Medicare expenditures for 9767 PWH aged 40+ in California in 2010
- 89.3% male, 56.9% white, 52.4% were >50 years
- Average cost $47,036 for Californian with HIV and medications account of 2/3 of that cost

<table>
<thead>
<tr>
<th>Number of conditions</th>
<th>Mean Expenditure</th>
<th>Median Expenditure</th>
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<tbody>
<tr>
<td>1</td>
<td>$16,260</td>
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<td>2</td>
<td>$19,128</td>
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<tr>
<td>11-12</td>
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<td>$18,700</td>
</tr>
</tbody>
</table>

Zagajewski Plot One 2017

List Factors that Contribute to Unsuccessful Aging
Possible Reasons for “Unsuccessful Aging” among PWH

Adapted from: Deeks and Phillips, BMJ, 2009

Genetics and Lifestyle
ART Toxicity
Persistent Inflammation
Unsuccessful Aging

SMART Study: Interrupting ART Increases the Risk of Heart Disease

El-Sadr, NEJM, 2006

T Cell Activation Declines with ART

An Important Clue from Nature

Sooty Mangabey
- Infect with SIV
- High Levels of Viral Replication
- No AIDS, normal lifespan
- Minimal Immune Activation

Rhesus Macaque
- Infect with SIV
- High Levels of Viral Replication
- AIDS and death
- Massive Immune Activation

Inflammation Can Cause Lymphoid Tissue Fibrosis

- Associated with low %naive T cells and poor CD4+ T cell recovery
- May impair functional immune responses

High T Cell Activation Associated with Blunted CD4 Recovery

Spearman's rho: -0.40
P<0.001

Hunt et al, JID, 2003 (see also Goicoechea, JID, 2006; Gandhi, JAIDS, 2006)
**SMART: Inflammatory Markers Strongly Associated with Mortality and CVD Events**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>All-Cause Mortality (N=85)</th>
<th>Fatal or Non-fatal CVD (N=136)</th>
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<tr>
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<td>1.6 0.20</td>
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<tr>
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<td>2.6 0.003</td>
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<td>Amyloid A</td>
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<td>2.8 0.002</td>
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<td>D-dimer</td>
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<td>2.0 0.06</td>
</tr>
<tr>
<td>F1.2</td>
<td>1.3 0.64</td>
<td>0.8 0.56</td>
</tr>
</tbody>
</table>


**Inflammation Predicts Disease in Treated HIV**

- Cardiovascular Disease  (Duprez, Atherosclerosis, 2009)
- Cancer  (Bjerk, Cancer 2012; Rys, JAIDS, 2015)
- Venous Thromboembolism  (Buzzetti, AIDS, 2013)
- Type II Diabetes  (Buzzetti, Diabetes Care, 2013)
- COPD  (Alba, Chest, 2014)
- Bacterial Pneumonia  (Rys, PLoS One, 2014)
- Cognitive Dysfunction  (Buzzetti, AIDS, 2013; Lathe, CID 2012)
- Depression  (Alba, JAIDS, 2013)
- Frailty  (Bjerk, JAIDS, 2013)

**List the Main Factors Associated with Inflammation**

New Orleans, LA, December 4-7, 2019, Ryan White HIV/AIDS Program CLINICAL CONFERENCE
**Model of Inflammation**

![Diagram of Model of Inflammation]

**Low-level Viremia <20 cp/ml is Common During ART**

- 80% Patients had detectable viremia
- Median 3.1 copies/ml

**HIV RNA Is Detectable in GUT During ART**

Unspliced HIV RNA per 10^6 CD4+ T Cells

- Median: 2500
- Maximum: 6044

*Yakhi et al., JID 2010*
Microbial Translocation

Healthy GI tract

Damaged GI tract during HIV infection

Microbial Translocation Decreases with ART but Persists for Years

P = 0.003

P < 0.001

Microbial Translocation is Associated with Inflammation

New Orleans, LA, December 4-7, 2019, Ryan White HIV/AIDS Program CLINICAL CONFERENCE
CMV Associated with CD8 Expansion and Inflammation in HIV Infection

Freeman, JD, 2014 (see also: Sacre, AIDS, 2011; Mudd, JD, 2016; Mussethila, AIDS 2011 and many Gianella papers)

CD8+ T Cell Counts

\[
P = 0.007
\]

\[
P = 0.002
\]

sTNF-RII

\[
P = 0.002
\]

Valganciclovir Reduces Inflammation

What can we do to reduce Inflammation?
Early ART can Greatly Reduce T Cell Activation

- Jain et al, JID, 2013

Statins Decrease Monocyte Activation in Treated HIV Infection (SATURN-HIV Trial)

Funderburg, 2014 CID

Diet and Exercise

- High fat or carbohydrate meal ↑ inflammation (Deopurkar, Diabetes Care, 2010).
- RCTs of exercise in elderly have been shown to:
  - Decrease inflammation (Nichols, J Am Ger Soc, 2008)
  - Increase functional status (Kirdoris, Geriatrics, 1992)
  - Decrease insulin resistance (Diabetes Care, 2002)
  - Improve cognitive function (Mascarin, Int J Ger Psych, 2010)
- Studies in HIV?
Summary

• Despite optimal ART, HIV is associated with shorter life expectancy and an increase in several age-associated morbidities.
• Immune activation / inflammation persist despite ART and may predict these morbidities.
• Earlier initiation of ART decreases persistent immune activation.
• Statins, diet, and exercise may hold promise and need to be studied.
• Targeted interventions directed at the underlying causes of inflammation may hold promise
  -- HIV reservoirs, co-infections/CMV, microbial translocation.

Recommendations for Patients

• Follow-up with your medical provider regularly.
  -- Follow guidelines for checking and controlling vascular risk factors (cholesterol, blood pressure, diabetes).
• Stop smoking.
• Exercise regularly, eat healthy diet, maintain healthy weight.
• Get regular cancer screening.
• Assess Polypharmacy, Safety at home, Quality of life
• Avoid or treat co-infections.
  -- Viral hepatitis, syphilis, tuberculosis
  -- Vaccinations
  -- No current recommendations for CMV

Acknowledgments

• Peter Hunt, Maile Karris for sharing their slides.
• Dilip Jeste, David Moore, Scott Letendre, Davey Smith, Sanjay Metha for helpful discussion.
Question-and-Answer Period
Neurocognitive Disorders in HIV

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San Francisco, California

Financial Relationships With Commercial Entities

Dr Valcour has served as a consultant to Merck & Co, Inc, and ViiV Healthcare. (Updated 11/20/19)

Learning Objectives

After attending this presentation, learners will be able to:
• Recognize signs and symptoms of cognitive problems in aging people living with HIV infection
• Describe the challenges in diagnosing Alzheimer’s disease in aging people living with HIV infection
• Describe the inflammatory phenotype of cognitive issues in the setting of HIV infection
ARS Question #1

In studies designed to understand the frequency of HIV-associated Neurocognitive Disorders (HAND), which statement is true?

A. The frequency of HAND is similar now to what it was before the introduction of combination antiretroviral therapy.

B. The frequency of cognitive impairment among people with sustained viral suppression in blood is < 5%.

C. Progression of cognitive impairment is the most common course for people with HIV-related cognitive impairment with suppressed plasma HIV RNA.

Key Points

- Impaired cognition remains an important challenge in the era of cART
  - Effects 1/3 of patients despite successful plasma viral suppression
  - Etiology is complex
  - Chronic inflammation underpins this continued mild/moderate fluctuating encephalopathy for many
  - Comorbidity is common
  - Cerebrovascular disease is a common comorbidity in older age
  - Co-occurrence of Alzheimer’s disease and other age-associated neurodegeneration is a reality
  - Distinguishing AD from HAND is one of the greatest clinical challenge in geriatric neuroHIV

Estimates of cognitive impairment

- Switzerland (2010): 69% (aviremic for median of 48 months)
- Botswana (2010): 38% (98% on cART)
- Thailand (2010): 38% (2NN Cohort)
- US Military cohort (early treatment): 19%

- Concern: Many studies continue to publish rates of cognitive impairment that include individuals not optimally treated
- CHARTER, for example, possibly representative at the time, but under-treated
Prevalence of HIV-associated Neurocognitive Disorder (HAND)

* Caveat: Post-cART rate is from a prevalence-type study and includes people without viral suppression - ? Truly representative of today's clinics

Modified from Nat Rev Neurosci 2007

Clinical presentation

Cognition
- Memory loss
- Concentration
- Mental slowing

Behavior
- Apathy
- Depression
- Agitation, Mania

Motor
- Unsteady gait
- Poor coordination
- Tremor

Clinical Features – Cognitive Profile

- Multiple cognitive domains can be involved, including memory
- Common to see attentional deficits
  - Re-reading, use of lists
- Information processing may be impaired
  - Keeping up with banter
- Course does not tend to be progressive in the setting of cART but may fluctuate
Progressive atrophy in older HIV+

Despite persistent suppression of plasma HIV RNA

- Seen largely in subcortical regions, including asymptomatic suppressed participants
- Seen in cerebellum, caudate, frontal lobe, total cortical gray matter, brainstem, and pallidum
- During acute HIV despite immediate therapy, reduced volumes over 2 years in putamen and caudate
- Brain volume reductions seen during primary HIV (not on ART) including putamen despite treatment
- Two contrasting studies among younger individuals compared to demographically matched controls and a study where individuals with substantial cerebrovascular disease were excluded

The Role of Inflammation Despite Viral Suppression

Numerous studies demonstrate correlations to chronic inflammation
Among individuals optimally treated with plasma viral suppression

- In vivo brain imaging using ligands (PET)
  - TPSO binding (microglial activation) increased in HIV compared to controls and inversely associated with cognitive performance
  - Plasma markers and immunological markers
    - sCD163 and global performance
    - CD4+CD103+ and CD8+CD103+ (% CD14) and progressive worsening of memory performance
- Additionally:
  - Chronic inflammation persists even when ARV started during acute HIV
  - CD163 links to brain pathology at autopsy

1. Rubin et al; AIDS 2018;
2. Vera et al; Neurology 2016;
3. Imp et al; JID 2017;
4. Fabbiani M JAIDS 2017;
5. Sereti et al; CID 2017;
6. Bryant et al; AIDS 2017
Imaging studies show damaged integrity linked to inflammation
Further linked to cognitive impairment

- MCP-1 and neopterin broadly linked to abnormal brain integrity by diffusion tensor imaging (DTI)
- These DTI abnormalities link to worse cognitive performance

1. Chang et al, JAIDS 2019

The Role of Cerebrovascular Disease

Small Vessel Ischemic Disease in HIV

- Autopsy series in the US between 1993 to 2011
  50% of cases
White matter lesion burden in aging with HIV

- Two patterns seen
  - (1) Periventricular confluent lesions that are often described in small vessel ischemic disease (top)
  - (2) Discrete lesions (bottom)

Studies demonstrating contribution of cerebrovascular disease to cognition in HIV

- White matter hyperintensities link to abnormalities on diffusion tensor imaging and are accelerated in HIV\(^1\) as well as to cognitive performance (age > 60)\(^2\)
- Some contrasting studies exist (no added burden due to HIV in age >50)\(^3\)
- May be particularly important for HIV over age 60 years
  - In HIV, the burden of white matter hyperintensities was predicted by age > 60 vs. < 60 years\(^4\)


Increased risk of symptomatic dementia associated with co-morbidity

Theoretical increased risk associated with cerebrovascular disease (CVD)
Other potential contributors

- Co-morbidities – Infectious and non-infectious
- Psychiatric illness
- Medication effects
- Recreational drug use
- Others...

Distinguishing Alzheimer's disease from HIV-related cognitive impairment

Increased risk of symptomatic dementia associated with co-morbidity
Overlap between HAND and AD

- HAND (30-50%)
- Neurodegenerative disorders (e.g., AD, FTD, PSP)

80 years old

- HAND?
- AD?

Hand (HAND)

- Increased risk?
- Altered phenotype?
- Accelerated course?

Why bother figuring out if it is HIV or AD?

- Sense of futility with each disease
- Few effective pharmacological adjunctive treatments
- Planning for care
- Clinical course vastly different between the two
- Clarity of diagnosis and optimal care

Why bother figuring out if it is HIV or AD:

- Currently, individuals living with HIV are at high risk for delayed diagnosis of Alzheimer’s disease and other age-associated neurodegenerative disorders.

Course of AD in People Living with HIV

- Whether the course, features or timing of onset differ in HIV is unknown
- Pathology data worrisome that the course could be affected since multiple proteins have been reported to accumulate in brain tissue with HIV. These are also seen in neurodegenerative disorders
  - TDP-43 seen in fronto-temporal dementia (Ellis Nature Reviews 2008)
  - Alpha-synuclein seen in Lewy Body Dementia (Khanlou JNV 2008)
ARS Question #2

When an older patient living with HIV presents with new cognitive problems, which will be most helpful in distinguishing HIV-related impairment from Alzheimer’s disease?

A. Brain imaging with distinct atrophy patterns that differentiate the two diseases
B. Cerebrospinal fluid analysis of HIV RNA levels
C. The pattern of neuropsychological testing with more clear deficits in ‘subcortical’ pattern in HIV
D. Cerebrospinal fluid Alzheimer’s disease markers of amyloid and tau

A Case Report

- 75 year-old right-handed man with 16 years of education
- Sought evaluation due to memory changes and because a brother died of Alzheimer’s disease at age 79 with symptoms “just like his”
- HIV History:
  - Diagnosed with HIV in the mid 1980s; nadir CD4 > 200 cells, no opportunistic infections
  - On integrase-based regimen for years, current, CD4 = 850 cells; UD plasma HIV RNA
Case Report – Cognitive Presentation

- Cognitive Symptoms
  - Subtle, insidious decline in his memory and executive functioning
  - Started 5-10 years ago and he feels they are progressing
  - Reports no functional problem currently

- Has had depression since age 40, on treatment and both mild and stable
- Comorbidities:
  - Hyperlipidemia, hypertension, osteoarthritis, gout, and CAD with past MI

Case Report – Clinical Assessment

- Neurological exam:
  - Slow motor serial sequencing (Luria)
  - Lower extremity neuropathy – longstanding

- Neuropsychological testing
  - Montreal Cognitive Assessment (MoCA) Score of 24/30
  - Impaired visuospatial & executive functioning
  - Inefficient registering with reasonable memory

Case Report - MoCA

- Marked dysfunction in executive performance and/or visual processing
- Unexpected error in confrontation naming
- Inefficient learning/registration, achieving only 4 of 5
- Retention of learned material supportive of proper encoding
Neuropsychological testing – mixed picture

<table>
<thead>
<tr>
<th>Domain</th>
<th>Score</th>
<th>Standard Deviation</th>
<th>Frascati Domain</th>
<th>Score</th>
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Manual dexterity and speed decreased, often seen in HIV

Case Report - Neuroimaging

Read as normal for age

Case Report - Next Steps?

- Modification of ARVs for greater CNS penetration?
  - No evidence to support this approach for a 10-year course
  - Most people are undetectable – thus CSF HIV RNA seldom linked to impairment
- Initiation of cholinesterase inhibitors for Alzheimer’s disease?
  - Would be empiric and possibly wrong
- Watch and wait
  - Natural longitudinal course is likely to distinguish the two over 3 years
  - Could implement broad recommendations without diagnostic clarity
  - Reasonable, but would you want this for yourself?
- CSF assessment for neurodegenerative biomarkers or referral to a specialist?
Neuropsychological Testing

- Considerable overlap between HAND and Alzheimer’s disease\(^1\),\(^2\)
- Cannot rely on cortical vs. subcortical pattern
- Memory is one of many domains that can be perturbed in HAND\(^3\)
- Encoding vs. retrieval of information may help distinguish
- Error-prone/impulsive in HAND confounds recognition memory


Structural Brain Imaging

- Machine learning approach to differentiate 15 HAND vs. 80 Mild Cognitive Impairment due to Alzheimer’s disease
- Eight regions show promise to differentiate HAND from MCI (machine learning was >90% accurate)

Zhang et al, Haman Brain Mapping 2016

CSF Alzheimer’s disease biomarkers

- Insufficient to differentiate HAND from AD
- Patients with HIV dementia have abnormailities in a-beta, t-tau, and p-tau similar to AD\(^1\)
- Some a-beta and tau alterations in HIV dementia\(^2\)

- Amyloid-beta alterations in HAND similar to mild AD, total tau measures may help differentiate\(^3\)
- Substantial overlap in a-beta and t-tau, p-tau measures may help differentiate\(^4\)

Case Report - Next Steps?

- Modification of ARVs for greater CNS penetration?
  - No evidence to support this approach for a 10-year course
  - Most people are undetectable – thus CSF HIV RNA seldom linked to impairment
- Initiation of cholinesterase inhibitors for Alzheimer's disease?
  - Would be empiric and possibly wrong
- Watch and wait
  - Natural longitudinal course is likely to distinguish the two over 3 years
  - Could implement broad recommendations without diagnostic clarity
  - Reasonable, but would you want this for yourself?
- CSF assessment for neurodegenerative biomarkers or referral to a specialist?

Summary Points

- Impaired cognition remains an important and frequent challenge in the era of cART
- Cognitive impairment affects one-third to one-half of patients despite successful plasma viral suppression
- Chronic inflammation underpins this continued mild/moderate fluctuating encephalopathy
- Cerebrovascular disease is a common comorbidity among older people living with HIV and it contributes to the cognitive burden
- Due to advancing age of people living with HIV, the likelihood for Alzheimer's disease (AD) will increase
- Like people without HIV, the rate of AD is likely to increase exponentially with age – whether the overall rate is higher in people living with HIV is unknown
- Distinguishing AD from HAND is an urgent issue with few data to define a clinical approach
- Alzheimer's disease biomarkers including PET imaging and brain imaging are not likely to be enough, used individually. CSF AD biomarkers may add clarity
- Patterns of neuropsychological testing deficits overlap between the two diseases
What can we do now?

To screen or not screen

- Controversy exists
- Screening tools are not great
  - International HIV Dementia Scale is not useful – WOULD NOT USE
  - Mini Mental State Exam (MMSE) does not target HIV-related changes (more designed for AD) – WOULD NOT USE
  - Montreal Cognitive Assessment test (MoCA) has some association
  - Computer or tablet based measures may hold promise, particularly for longitudinal patterns

Treatment recommendations

1. Adherence to antiretroviral medications with persistent plasma viral suppression
2. Referral to a specialist if Alzheimer’s disease or other age-associated neurodegenerative disorders is considered
3. Consideration for CSF escape (rare), particularly in more rapid and progressive presentations
4. Minimize polypharmacy and address medications that can impact cognition
   - Beers criteria available online
Treatment recommendations

- Compensatory measures
  - Given an underlying attentional and speed component, many patients respond to use of lists, reminders, alerts
  - Limiting multitasking
- Disclosing to friends when possible
  - Re: challenges keeping up with conversation/banter
- Reassurance on likely trajectory
- Empowerment with knowledge that symptoms are due to HIV and occur in others

The Lancet Commission: Potentially modifiable risk factors

- Up to 35% of dementia risk is potentially modifiable
  - Hearing loss
  - Hypertension
  - Obesity
  - Smoking
  - Depression
  - Physical inactivity
  - Social isolation
  - Diabetes

Thank you
Renal Disease and Kidney Transplant

Jayme E. Locke MD, MPH
Director, Comprehensive Transplant Institute
Chief, Division of Transplantation
University of Alabama at Birmingham
Birmingham, Alabama

Financial Relationships With Commercial Entities

Dr Locke has no financial relationship with commercial entities to report. (Updated 11/21/19)

Learning Objectives

• Describe risk for acute kidney injury among people living with HIV (PLWH)
• Describe chronic kidney disease and end-stage renal disease in PLWH
• Describe the role for kidney transplant among PLWH
Acute Kidney Injury (AKI)

Risk Factors and Common Etiologies

Risk factors for AKI
- Male gender, CD4<200, VL>10,000, HCV co-infection, ART use (not traditional)

Most common etiologies
- 38% Prerenal (due to infection, predominantly OIs)
- 46% Intrinsic (ischemic ATN or nephrotoxic medications)

AKI in HIV - Incidence

Ambulatory patients (Francheschini et al. KI 2002)
- Prospective cohort study of 754 HIV+ patients followed for 2 years
- Mean age 40, 61% black, 68% on ART, 3% have GFR<60ml/min at enrollment
- ARF defined as increase in Scr
- Etiologies categorized: prerenal, intrinsic, obstructive
- 111 episodes AKI in 71 subjects; incidence rate 5.9 per person years

Hospitalized patients (Wyatt et al. AIDS 2006)
- AKI is a strong predictor of in hospital mortality in the general population
- Examine hospital discharge billing data/codes for NYS in 2003
- 25,114 patients admitted with HIV compared with 2,010,847 non-HIV admissions
- Risk factors for AKI?
- HIV+ increased risk of AKI – OR 2.82
- HIV+ increased risk of hospital mortality – OR 2.95
- HIV+ with AKI had higher hospital mortality (27% vs. 4.5%) with adjusted OR 5.83
- Risk factors for AKI among HIV+ patients: older age, black race, DM, CKD, HCV (traditional)

<table>
<thead>
<tr>
<th>AKI in HIV - Incidence</th>
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</tr>
<tr>
<td>Acute</td>
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<tr>
<td>Chronic</td>
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</table>

p<0.001

Wyatt et al. AIDS 2006

Similar results were found in an observational cohort study from the VA
- Even mild AKI is associated with a significant increase in risk for ESRD and death (37%)
- Those who do not recover to their baseline renal function do worse

Choi et al JASN 2010

Causes of AKI in HIV

**Prerenal causes**
- Hypovolemia

**Intrinsic renal injury**
- ATN (ischemic v. nephrotoxic)
- Parenchymal infection (TB, CMV, fungus)
- Interstitial nephritis
- Glomerular disease

**Postrenal causes**
- Tubular obstruction
- Ureter/bladder obstruction
Prerenal
- Most common etiology
- Hypovolemia due to GI losses
- Poor oral fluid intake
- Adrenal insufficiency/hypoaldosteronism
- Sepsis
- CHF
- Cirrhosis

Acute Tubular Necrosis (ATN)
- Hypoperfusion injury (ischemic)
- Medications (most common)
  - NSAIDs
  - Amphotericin B
  - Pentamidine
  - Cidofovir, foscarnet
  - Aminoglycides
  - AIN: bactrim, rifampin, β-lactam antibiotics

Parenchymal infection
- Fungal infections
- Granuloma formation from TB
- CMV, EBV, BK – cause interstitial nephritis
Glomerular Diseases

HIVAN

HIV associated immune complex GN
  - Lupus-like nephritis, IgAN, MPGN, MN

Thrombotic microangiopathy

AA Amyloid

HCV co-infection
  - MPGN, fibrillary GN, immunotactoid GN

Non-HIV associated renal disease
  - Diabetic nephropathy

HIV Associated Nephropathy (HIVAN)

- First described in the 1984 as a series of patient with advanced AIDS and RPGN
- Almost exclusively found in African Americans (90%) or mixed ethnicity Hispanics (10%)
- Third leading cause of ESRD in African Americans ages 20-64

Rao TK et al NEJM 1984

HIVAN- Presentation

- Rapidly progressive renal failure
- Moderate-nephrotic range proteinuria
- Bland urinary sediment
- Enlarged, echogenic kidneys on renal US
- Progression to ESRD and/or death nearly universal
- Associated with end-stage AIDS, but there are reports of HIVAN with seroconversion or asymptomatic HIV infection
- Diagnosis - renal biopsy; clinical predictors?
**HIVAN – Pathology**

- Pattern of focal segmental glomerular sclerosis on LM, often with global sclerosis of affected glomeruli
- Podocyte hypertrophy and hyperplasia
- Visceral epithelial cells form pseudocrescents
- Tubular atrophy, simplification, microcystic changes and proteinaceous casts
- Inflammatory interstitial infiltrate of lymphocytes, plasma cells and monocytes
ARS Question 1: Which of the following is an effective treatment for HIVAN?
A. Prednisone
B. HAART
C. ACE inhibitor
D. All of the above

HIVAN treatment
- HAART
- ACEI
- Prednisone

HAART
- Incidence of HIVAN and HIVAN-related ESRD has declined since the introduction of HAART in 1996
- In a retrospective study of 42 patients with bx proven HIVAN ART use delayed progression to ESRD Szczech et al. KI 2004
- Similar results were found in a study of 36 patients from Johns Hopkins Atta et al. NDT 2006
- In a prospective cohort study from Baltimore HAART use was estimated to reduce HIVAN risk by 60% Lucas et al. AIDS 2004
- HIVAN is an indication to start HAART
**ACEI**

- No RCTs exist; usage extrapolated from other proteinuric kidney diseases
- Series of 22 patients with HIVAN, fosinopril use was associated with preservation of renal function at 12 wks (Scr 1.7–2.0) improvement of proteinuria (5.4–2.5g/day) compared with untreated patients. Burns et al. JASN 1997
- A small case-control series of 44 patients with HIVAN demonstrated decreased progression to ESRD (479 v. 146 days) in patients treated with fosinopril. Wei et al. KI 2003
- ACEI usage is likely beneficial; monitor for increases in Scr and hyperkalemia

---

**Both kidney and patient survival were improved by ACEI use**

---

**Prednisone**

- No RCT data; standard FSGS treatment
- May diminish the inflammatory infiltrate noted on HIVAN biopsies
- Case report of 4 patients treated with prednisone 60mg qd x6wks. Mean Scr decreased from 9.3mg/dl but proteinuria was unchanged; increased OIs. Smith et al. Am J Med 1994
- Series of 21 patients, 13 treated with prednisone. Proteinuria decreased in all and renal function was preserved in 50% of treated patients at 2 years. Eustace et al. KI 2003
- Prednisone may ameliorate renal function but risk of infection needs to be considered
Immune Complex Renal Disease

- Not all renal disease in HIV is HIVAN
- In a multicenter observational study of 89 HIV patients with a renal bx, 50% had a disease other than HIVAN
- Non-HIVAN patients: better renal outcome, Caucasian, higher CD4, more often co-infected with HCV

Obstruction

Intrarenal:
- Due to drug precipitation out of the urine and formation of crystals in the tubules
- Associated with: Sulfadiazine, acyclovir, indinavir, foscarinet, atazanavir
- Risk factors: volume depletion, hypoalbuminemia and CKD

Extrarenal:
- Atazanavir nephrolithiasis
- Retroperitoneal fibrosis
- Pelvic lymphadenopathy - Lymphoma, histoplasmosis, MAC
- Fungus balls - Candida, aspergillus

Indinavir Crystals
Chronic Kidney Disease (CKD)

CKD in HIV
- CKD is an important complication of HIV infection and treatment
- As patients live longer and HIV spreads among populations at high risk for renal disease, it is expected the number of patients with HIV related ESRD will increase
- ART decreased HIVAN related ESRD but is itself nephrotoxic
- Although only a small percentage of patients may progress to ESRD, proteinuria has been shown in 30% of HIV patients, indicating widespread occult kidney injury

CKD negatively affects delivery of HIV care

In a retrospective observational study from the VA:
- 9% of patients had CKD stage III or higher
- HAART exposure was 14-49% less as GFR declined
- 15% of patients did not have HAART adjusted for renal dysfunction
- Undereposure and inappropriate dosing was associated with a 35% excess mortality

CKD stage III + also predicted mortality in the WIHS

Choi et al. CID 2007
HIV and ESRD

- Mortality rates for HIV+ patients on dialysis were initially very high
- In a review of the USRDS, 1 year survival of HIV+ dialysis patients improved from 56% in 1990 to 74% in 1999; attributed to introduction of ART
- Race did not predict survival

Ahuja et al. JASN 2002

HIV and ESRD

- Higher mortality rates on dialysis among HIV+ compared to uninfected
- Highest dialysis mortality among co-infected and non-Caucasian

Sawinski & Locke et. al. KI 2017, accepted publication.

Kidney Transplantation

New Orleans, LA, December 4-7, 2019, Ryan White HIV/AIDS Program CLINICAL CONFERENCE
**Long-term Outcomes among Mono-infected**

A National Study of Outcomes among HIV-infected Kidney Transplant Recipients

Mono-infected HIV outcomes similar to matched HIV-counterfactuals

**Long-term Outcomes among Co-infected**

A National Study of Outcomes among HIV-infected Kidney Transplant Recipients

Co-infected HIV outcomes worse than matched HIV-HCV+ counterfactuals

**Kidney Transplantation is Associated with a Significant Survival Benefit among HIV+ Candidates**

Kidney transplantation is associated with a significant survival benefit among HIV+ candidates. Benefit achieved 194 days post-transplant.

Kidney Transplantation is Associated with a Significant Survival Benefit among Co-infected HIV+ Candidates


Can Increased Risk Associated with HCV Infection be Mitigated among HIV+ Candidates?

YES!

1. Avoid high degrees of HLA mismatching
2. Antiviral therapy to eradicate HCV (pre vs. post-transplant referral?)

ARS Question 2: What is the optimal timing for HCV treatment?

A. Always pre-transplant
B. Depends only on fibrosis stage
C. Depends only on waiting time
D. Depends on both fibrosis stage and waiting time
Pre vs. Post Transplant HCV Treatment?

Panel A (Life Years):
- Red: pre-transplant treatment yields fewer life years — do not treat.
- Green: pre-transplant treatment yields more life years — treat now.

Panel B (QALYs):
- Red: pre-transplant yields fewer quality-adjusted life years — do not treat.
- Green: pre-transplant yields more quality-adjusted life years — treat now.

Panel C (ICERS):
- Red: pre-transplant treatment yields fewer quality-adjusted life years and is not cost-effective (dominated) — do not treat.
- Yellow: pre-transplant provides more quality-adjusted life years but is not cost-effective (ICER ≥$100,000/QALY) — consider delaying treatment.
- Green: pre-transplant treatment provides more quality-adjusted life years and is cost-effective (ICER <$100,000/QALY) — treat now.

ART/DAA/IS interactions must be considered
- LDV/SOF and GLE/PIB compatible with most contemporary ART regimens and TAC based IS
- ELB/GRZ and GLE/PIB should not be given with CYA
- ELB/GRZ and GLE/PIB have no GFR restrictions
- ART should only be modified in consultation with an ID specialist
- Consultation with Hepatology is advised

High Rates of Acute Rejection


No. at Risk: HIV-collected (this study) 63 41 19

Sawinski Seminars in Dialysis 2019
Potential Etiologies for High Rates of Acute Rejection

1. Reluctance to use lymphocyte depleting agents

<table>
<thead>
<tr>
<th>Induction Immunosuppression</th>
<th>HIV Negative (%)</th>
<th>HIV Positive (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>21.4</td>
<td>35.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anti-thymocyte globulin</td>
<td>43.5</td>
<td>25.8</td>
<td>0.028</td>
</tr>
<tr>
<td>Anti-interleukin 2</td>
<td>23.8</td>
<td>19.5</td>
<td>0.249</td>
</tr>
<tr>
<td>Maintenance Immunosuppression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid</td>
<td>0.8</td>
<td>0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cyclosporine + basiliximab</td>
<td>9.3</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>9.5</td>
<td>7.0</td>
<td></td>
</tr>
</tbody>
</table>


Lower Risk of Acute Rejection at 1-year with ATG Induction among HIV-infected Recipients

<table>
<thead>
<tr>
<th>Induction</th>
<th>Reference</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0.36</td>
<td>0.19-0.67</td>
<td>0.02</td>
</tr>
<tr>
<td>ATG</td>
<td>1.11</td>
<td>0.90-1.36</td>
<td>0.77</td>
</tr>
<tr>
<td>Maintenance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid</td>
<td>2.35</td>
<td>1.2-4.57</td>
<td>0.01</td>
</tr>
<tr>
<td>Cell-based</td>
<td>1.25</td>
<td>0.68-2.34</td>
<td>0.6</td>
</tr>
</tbody>
</table>

The factors evaluated for association with rejection were: type of induction, donor type, age, race, PRA, and number of positive donor-recipient HLA mismatches and human leukocyte antigen (HLA) antibodies. The incidence of rejection was defined using the Banff classification system. Locke JE, James N, Mehta S, et al. Induction immunosuppression and the risk of acute rejection in HIV-infected kidney transplant recipients. Transplantation 2014; 97: 446-50.

No Difference in Risk of Acute Rejection among ATG Induced HIV+ & HIV- Recipients

<table>
<thead>
<tr>
<th>Induction</th>
<th>Rejection within 1-year (RR)</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-HIV infected</td>
<td>1.16</td>
<td>0.41, 3.31</td>
<td>0.77</td>
</tr>
<tr>
<td>HIV-infected</td>
<td>1.16</td>
<td>0.41, 3.31</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Matched Control analysis among HIV-infected and non-HIV-infected antithymocyte globulin induced kidney transplant recipients.

Progressive radius matching (1:1):
- Donor factors: type of donor, race
- Recipient factors: age, sex, PRA, number of positive HLA mismatches, prior transplant, HCV

• Infection common > 50% first year (AIDS-defining ~10%)
• Neither ATG or IL2 associated with higher infection risk
• ATG associated with lower risk of CMV, CDI, pneumonia

Potential Etiologies for High Rates of Acute Rejection
2. Drug interactions resulting in altered exposure to IS

- Pharmacokinetic curve of tacrolimus in HIV patients receiving protease inhibitors does not show the normal peak-and-trough pattern
- Resembles a flat line with half-life of up to 20 days secondary to strong inhibition of CYP3A
- Trough levels of tacrolimus in patients receiving protease inhibitors should be higher to achieve AUCs equal to patients not on protease inhibitors
  - 17.5 ng/mL at 1-month
  - 10 ng/mL at 1-year

Antiretroviral Therapy & Risk for Graft Loss

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protease inhibitors</td>
<td>1.48 (1.02-2.17)</td>
<td>0.04</td>
</tr>
<tr>
<td>Male</td>
<td>1.28 (0.93-0.55)</td>
<td>0.06</td>
</tr>
<tr>
<td>Hispanic American</td>
<td>1.98 (1.16-3.40)</td>
<td>0.002</td>
</tr>
<tr>
<td>HIV antibody+</td>
<td>2.41 (1.18-5.04)</td>
<td>0.01</td>
</tr>
<tr>
<td>HCV antibody+</td>
<td>1.45 (0.81-2.63)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Donor Characteristics</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>KDPI</td>
<td>1.97 (1.29-3.00)</td>
<td>0.002</td>
</tr>
<tr>
<td>&gt;85%</td>
<td>1.93 (0.95-3.89)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

HIV transplants

<table>
<thead>
<tr>
<th>Proportion</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-365 days post-transplant</td>
<td>4.48 (1.75-11.48)</td>
<td>0.002</td>
</tr>
<tr>
<td>&gt;365 days post-transplant</td>
<td>1.40 (1.64-2.32)</td>
<td>0.20</td>
</tr>
</tbody>
</table>
Why are Integrase Inhibitors preferred?

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Effect on CNI/mTOR levels</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td>none</td>
<td>Non-CYP3A4</td>
</tr>
<tr>
<td>NNRTIs</td>
<td>Decrease*</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>PIs</td>
<td>Increase</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Fusion Inhibitors</td>
<td>none</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Integrase Inhibitors</td>
<td>none</td>
<td>Non-CYP3A4</td>
</tr>
</tbody>
</table>

*exceptions: darunavir and raltegravir (no effect)
Ritonavir has the greatest effect of PIs

---

TDF use posttransplant

- 104 HIV+ KTx 2001-2014
- 3yr graft loss: 26% TDF vs 28% non-TDF
- TDF associated with AKI and CKD
- Fanconi's syndrome – mitochondrial toxicity
- TAF – produg, intracellular conversion to TDF in lymphocytes, lower plasma exposure

---

HIV control does not prevent renal infection

- 68% of HIV+ recipients with undetectable VL had HIV detectable in their kidneys
- Infection had 2 forms: podocyte and tubular
- Podocyte infection was associated with more rapid decline in renal function and graft loss
- Urine HIV RNA and DNA screening test developed – correlates with biopsy
- Rationale for protocol biopsies?
Access to Kidney Transplantation among HIV+ Waitlist Candidates

<table>
<thead>
<tr>
<th>Rate per 100 PY</th>
<th>HIV+ Candidates</th>
<th>HIV- Candidates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waitlist Mortality</td>
<td>5.61</td>
<td>6.62</td>
</tr>
<tr>
<td>Transplantation</td>
<td>14.32</td>
<td>26.70</td>
</tr>
</tbody>
</table>


Access to Kidney Transplantation among HIV+ Waitlist Candidates

South African Experience – HIV to HIV KT

Patient Survival
1-year 86%
3-year 73%

Graft Survival
1-year 91%
3-year 81%
HOPE Act Signed into Law – November 21, 2013

- Mandate for research on the use of HIV-infected deceased donors (HIVOD)
- Guidelines for research in November 2015
- Specifically, develop and publish criteria for the conduct of research relating to transplantation of organs from donors infected with HIV to HIV-end stage patients
**Summary**

- AKI is prevalent in HIV and a risk factor for both CKD and death.

- HIV confers a risk of CKD that can rival DM.

- Renal transplant is a good option for HIV+ patients with outcomes comparable to HIV- recipients

- Continued efforts are needed to realize full potential of HOPE Act
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Recommended additional reading

Question-and-Answer
Cardiovascular Disease and HIV

Heidi M. Crane, MD, MPH
Professor of Medicine
University of Washington
Seattle, Washington

Learning Objectives

After attending this presentation, learners will be able to:

- Describe importance of cardiovascular disease (CVD) among people living with HIV (PLWH)
- Describe myocardial infarction types among PLWH
- Describe the changing epidemiology of HIV and CVD

Financial Relationships With Commercial Entities

Dr. Crane has no financial relationships with commercial entities related to the topic of her talk. Funding sources not related to topic area: ViiV Healthcare. (Updated 11/21/19)
**Roadmap**

- Why do we care?
  - HIV-infected vs. uninfected, incidence
- MI types in HIV
  - Universal MI definition
  - CNICS MI adjudication
  - Type 1 vs. Type 2 MIs
- Why increased risk
- Other CVD
- What do we do?
  - Risk scores
- Summary

---

**Why do we care about CVD and HIV**

- CVD risk is significantly higher among those with HIV
- The impact of CVD is substantial in terms of both morbidity and mortality
- The impact will likely continue to increase with the aging of the population of those with HIV
- Traditional risk factors play an important role in CVD and HIV
- Non-traditional risk factors play an important role in CVD and HIV
- Does understanding the role of inflammation and HIV factors teach us about HIV itself, other comorbidities of HIV, or CVD?

---

**CVD risk and impact among PLWH by country**

- PLWH twice as likely to develop CVD
- Global burden of HIV-associated CVD has tripled over the last two decades

---

*Shah et al. Circulation, 2018*
Risk compared to HIV-uninfected individuals

<table>
<thead>
<tr>
<th>Author</th>
<th>Cohort</th>
<th>Study Period</th>
<th>End Point</th>
<th>IRR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silverberg</td>
<td>Kaiser California</td>
<td>1996-2009</td>
<td>MI</td>
<td>1.4 [1.3, 1.6]</td>
</tr>
<tr>
<td>Freberg</td>
<td>Veterans Affairs</td>
<td>2003-2009</td>
<td>MI</td>
<td>0.49 [1.04, 1.72]</td>
</tr>
<tr>
<td></td>
<td>Virtual Cohort</td>
<td></td>
<td></td>
<td>50-95 [1.47-2.11]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25-39 [2.16, 1.81-2.58]</td>
</tr>
<tr>
<td>Trant</td>
<td>Partners Boston</td>
<td>1996-2004</td>
<td>MI</td>
<td>1.75 [1.51-2.02]</td>
</tr>
</tbody>
</table>

Proportionate CVD mortality, US, 1999-2013

MI rate ratios (95% CI) for HIV status over time

<table>
<thead>
<tr>
<th>Year</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996-1999</td>
<td>2.0 (1.5, 2.8)</td>
<td>1.8 (1.3, 2.6)</td>
</tr>
<tr>
<td>2000-2003</td>
<td>2.0 (1.6, 2.5)</td>
<td>1.7 (1.4, 2.1)</td>
</tr>
<tr>
<td>2004-2007</td>
<td>1.5 (1.2, 1.9)</td>
<td>1.3 (1.0, 1.6)</td>
</tr>
<tr>
<td>2008-2009</td>
<td>1.5 (1.1, 2.0)</td>
<td>1.3 (0.9, 1.7)</td>
</tr>
<tr>
<td>2010-2011</td>
<td>1.2 (0.9, 1.6)</td>
<td><strong>1.0 (0.7, 1.4)</strong></td>
</tr>
</tbody>
</table>
HIV as a model

Roadmap
- Why do we care?
  - HIV infected vs. uninfected, incidence
- MI types in HIV
  - Universal MI definition
  - CNICS MI adjudication
  - Type 1 vs. Type 2 MIs
- Why increased risk
- Other CVD
- What do we do?
  - Risk scores
- Summary

Universal MI definition

Plaque rupture with thrombus
Type 1 / Primary

Vasospasm
Type 2 / Secondary

Supply demand mismatch
What percentage of MIs among PLWH are type 2 vs type 1?

- <1%
- 1-10%
- 10-40%
- 40-60%
- >60%
- 3.14159265359

What is the most common cause of type 2 MI among PLWH?

- Sepsis
- Cocaine-induced vasospasm
- Politics
- GI bleed

CNICS MI Central Adjudication Protocol

- Based on traditional MI protocols (e.g., MESA) to facilitate comparisons with HIV-uninfected populations, 2-step protocol
- Ascertainment: Potential events identified centrally including diagnoses, cardiac enzymes, cardiac procedures such as CABG
- Site assembled de-identified packets: notes, ECGs, procedures, labs
- Exposures (ARVs) redacted from packets
- Central Adjudication: 2 reviewers per packet, 3rd if discrepancies
- Enter standardized data required to define an MI into a web application enabling application of multiple operational definitions of MI
- Identify events that were likely falsely positive rather than true events: Most often isolated troponin elevations with a reason for a falsely positive troponin value such as renal failure or pericarditis
- Categorize each probable or definite MI event as 1° (Type 1) vs. 2° (Type 2), and identify causes for each 2° MI event
### Clinical and demographic characteristics of PLWH with Type 1 vs. Type 2 MI

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>T1MI*</th>
<th>T2MI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=362</td>
<td>56%</td>
<td>288</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>324</td>
<td>207</td>
<td>0.006</td>
</tr>
<tr>
<td>Female</td>
<td>38</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>32</td>
<td>47</td>
<td>0.01</td>
</tr>
<tr>
<td>40-49</td>
<td>152</td>
<td>106</td>
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</tr>
<tr>
<td>50-59</td>
<td>125</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>≥60</td>
<td>43</td>
<td>22</td>
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</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>171</td>
<td>65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>African American</td>
<td>156</td>
<td>202</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>19</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Other/unknown</td>
<td>16</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>HIV Transmission Risk Factor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterosexual</td>
<td>101</td>
<td>93</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MSM</td>
<td>166</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>IDU</td>
<td>78</td>
<td>107</td>
<td></td>
</tr>
<tr>
<td>Other/unknown</td>
<td>17</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>CD4 count closest to event (cells/µl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-200</td>
<td>96</td>
<td>130</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>201-350</td>
<td>71</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>&gt;350</td>
<td>194</td>
<td>102</td>
<td></td>
</tr>
<tr>
<td>CD4 cell count nadir (cells/µl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-200</td>
<td>215</td>
<td>201</td>
<td>0.03</td>
</tr>
<tr>
<td>201-350</td>
<td>77</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>&gt;350</td>
<td>69</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA closest to event (copies/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;400</td>
<td>217</td>
<td>127</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>400-10,000</td>
<td>47</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>10,001-100,000</td>
<td>63</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>&gt;100,001</td>
<td>34</td>
<td>53</td>
<td></td>
</tr>
</tbody>
</table>

### Cardiovascular disease risk factors among PLWH with Type 1 vs. Type 2 MI

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>T1MI*</th>
<th>T2MI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=362</td>
<td>56%</td>
<td>288</td>
<td></td>
</tr>
<tr>
<td>Lipid Levels mean (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td>40</td>
<td>42</td>
<td>0.2</td>
</tr>
<tr>
<td>LDL</td>
<td>108</td>
<td>87</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-HDL</td>
<td>149</td>
<td>125</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>190</td>
<td>167</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>227</td>
<td>208</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>204</td>
<td>197</td>
<td>0.01</td>
</tr>
<tr>
<td>No</td>
<td>119</td>
<td>157</td>
<td></td>
</tr>
<tr>
<td>Body Mass Index mean (kg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>26</td>
<td>24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Risk Score mean (CHD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Framingham CHD</td>
<td>10</td>
<td>8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Rates of Type 1 and Type 2 MI per 1000 person-years of follow-up

<table>
<thead>
<tr>
<th>Age category</th>
<th>Type 1 MI</th>
<th>Type 2 MI</th>
<th>Type 2 vs. Type 1 MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>0.14 (0.04-0.50)</td>
<td>1.41 (0.91-2.19)</td>
<td>10.0 (2.43-38.24)</td>
</tr>
<tr>
<td>50-69</td>
<td>0.75 (0.52-1.07)</td>
<td>1.15 (0.69-1.93)</td>
<td>1.55 (0.95-2.52)</td>
</tr>
<tr>
<td>70-89</td>
<td>2.37 (2.01-2.72)</td>
<td>2.11 (1.79-2.46)</td>
<td>0.89 (0.70-1.14)</td>
</tr>
<tr>
<td>≥90</td>
<td>4.15 (3.60-4.65)</td>
<td>3.31 (2.81-3.93)</td>
<td>0.80 (0.63-1.00)</td>
</tr>
<tr>
<td>≥100</td>
<td>0.95 (0.42-2.23)</td>
<td>3.71 (2.74-6.82)</td>
<td>0.95 (0.45-1.94)</td>
</tr>
</tbody>
</table>

* All comparisons were made using Chi squared test.
Mortality after MI by type

Roadmap

- Why do we care?
  - HIV infected vs. uninfected, incidence
  - MI types in HIV
    - Universal MI definition
    - CNICS MI adjudication
    - Type 1 vs. Type 2 MIs
- Why increased risk
  - Other CVD
  - What do we do?
    - Risk scores
- Summary

Why?
Causes of HIV-associated inflammation

MI risk 1.5-2.5 times greater in PLWH across CVD risk strata

ART and MI risk
Roadmap

- Why do we care?
  - HIV infected vs. uninfected, incidence
- MI types in HIV
  - Universal MI definition
  - CNICS MI adjudication
  - Type 1 vs. Type 2 MIs
- Why
- Other CVD
- What do we do?
  - Risk scores
- Summary

Strokes more common among PLWH

- 75% Ischemic
  - Small vessel 31%
  - Cardiembolic 30%
  - Atheroembolic 23%
  - Other/unknown 16%
- 12% Hemorrhagic
- 9% Case fatality rate
- 19% Current illicit drug use
- 20% Infection

Chow FC, et al. JAIDS, 2012

Strokes in HIV

- 75% Ischemic
  - Small vessel 31%
  - Cardiembolic 30%
  - Atheroembolic 23%
  - Other/unknown 16%
- 12% Hemorrhagic
- 9% Case fatality rate
- 19% Current illicit drug use
- 20% Infection

New Orleans, LA, December 4-7, 2019, Ryan White HIV/AIDS Program CLINICAL CONFERENCE
Clinical and demographic characteristics by stroke status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ischemic stroke not due to drugs/infection</th>
<th>Ischemic stroke due to drugs or infection</th>
<th>No ischemic stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male: 76</td>
<td>Female: 72</td>
<td>75</td>
</tr>
<tr>
<td>Age (years)</td>
<td>&lt;40: 22</td>
<td>40-49: 26</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>50-59: 28</td>
<td>60-69: 15</td>
<td>2</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td>White: 36</td>
<td>Black: 19</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>Hispanic: 4</td>
<td>50-60: 10</td>
<td>10</td>
</tr>
<tr>
<td>Risk Factor</td>
<td>IDU: 42</td>
<td>Heterosexual: 27</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>MSM: 37</td>
<td>50-60: 15</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Other: 27</td>
<td>≥60: 3</td>
<td>3</td>
</tr>
<tr>
<td>CD4 Count</td>
<td>0-200: 39</td>
<td>201-350: 25</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>&gt;350: 43</td>
<td></td>
<td>54</td>
</tr>
<tr>
<td>HCV</td>
<td>CDC: 26</td>
<td></td>
<td>54</td>
</tr>
</tbody>
</table>

Risk factors for ischemic strokes

- Ischemic strokes associated with traditional risk factors such as age, diabetes, HTN
- Ischemic strokes associated with HIV-specific risk factors such as CD4 count, HCV

<table>
<thead>
<tr>
<th>Covariate</th>
<th>aHR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>1.06</td>
<td>1.04-1.08</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Female</td>
<td>0.96</td>
<td>0.67-1.38</td>
<td>0.8</td>
</tr>
<tr>
<td>White Race/Ethnicity</td>
<td>Ref</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>1.78</td>
<td>1.24-2.55</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hispanic</td>
<td>Ref</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0.78</td>
<td>0.24-2.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Viral load: time updated (&gt;400)</td>
<td>1.29</td>
<td>0.91-1.84</td>
<td>0.1</td>
</tr>
<tr>
<td>CD4 count: time updated (per 100 cells/mm³)</td>
<td>0.86</td>
<td>0.80-0.91</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.69</td>
<td>1.04-2.74</td>
<td>0.03</td>
</tr>
<tr>
<td>Treated hypertension</td>
<td>2.28</td>
<td>1.00-5.26</td>
<td>0.05</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>1.91</td>
<td>1.09-3.36</td>
<td>0.02</td>
</tr>
<tr>
<td>Mean age</td>
<td>1.1</td>
<td>0.87-1.43</td>
<td>0.3</td>
</tr>
</tbody>
</table>

In analyses restricted to ischemic strokes not secondary to infection or illicit-drug use
- HCV was no longer significantly associated with stroke
- The impact of CD4 count was smaller
- Diabetes and HTN associations with risk of ischemic stroke were larger

VTEs in HIV

- DVT most common
- Mean age 49
- Predisposing conditions
  - Infections 27%
  - Hospitalizations 21%
  - Malignancy 17%
  - IDU 13%
  - Immobilization 12%
Roadmap

- Why do we care?
  - HIV infected vs. uninfected, incidence
- MI types in HIV
  - Universal MI definition
  - CNICS MI adjudication
  - Type 1 vs. Type 2 MIs
- Why
- Other CVD

- What do we do?
  - Risk scores
  - Summary

Traditional risk factor modification

- Smoking cessation
- Diabetes
- Hypertension
- Dyslipidemia: lots of rosuvastatin
- ART choices
- Risk scores

Risk calculators

- Framingham Risk Score
- AHA/ACC ASCVD Pooled Risk Calculator
- D:A:D – includes some ART medications

- Most risk predictors developed in the general population, do they predict risk in HIV? Type 1 vs. Type 2 vs. all MI?
- Do we want an HIV specific calculator?
  - Should an HIV specific risk model include inflammatory/immunologic parameters?
- Some of the general population models likely underestimate risk in HIV
Risk score comparisons

<table>
<thead>
<tr>
<th></th>
<th>Framingham</th>
<th>CVD</th>
<th>Type 1</th>
<th>ASCVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>0.725</td>
<td>0.69</td>
<td>0.70</td>
<td>0.77</td>
</tr>
<tr>
<td>CI</td>
<td>0.69, 0.77</td>
<td>0.65</td>
<td>0.70, 0.78</td>
<td>0.70, 0.78</td>
</tr>
<tr>
<td>AUC</td>
<td>0.741</td>
<td>0.70</td>
<td>0.72</td>
<td>0.75</td>
</tr>
<tr>
<td>CI</td>
<td>0.70, 0.78</td>
<td>0.70</td>
<td>0.72, 0.79</td>
<td>0.72, 0.79</td>
</tr>
<tr>
<td>AUC</td>
<td>0.735</td>
<td>0.70</td>
<td>0.72</td>
<td>0.77</td>
</tr>
<tr>
<td>CI</td>
<td>0.70, 0.78</td>
<td>0.70</td>
<td>0.72, 0.79</td>
<td>0.72, 0.79</td>
</tr>
<tr>
<td>AUC</td>
<td>0.750</td>
<td>0.71</td>
<td>0.73</td>
<td>0.79</td>
</tr>
<tr>
<td>CI</td>
<td>0.71, 0.79</td>
<td>0.73</td>
<td>0.74, 0.80</td>
<td>0.77, 0.81</td>
</tr>
</tbody>
</table>

- Some variations across risk measures to be expected given differences in the outcome (i.e., predicted CVD vs. MI).
- Adding HIV-specific variables to the DAD score did not improve discrimination compared with ASCVD.
- Could inclusion of different HIV-specific measures improve discrimination?
- ASCVD performed as well or better than others across all MI events and had superior performance for Type 2 MI.
- While there is room for improvement, does not mean they cannot be used to improve for clinical care.

ASCVD in PLWH

- Harrell’s C = 0.76
- GND = 6.4 (P = 0.50)
- Slope = 0.857
- Intercept = 0.009

- Harrell’s C = 0.64
- GND = 12.9 (<0.01)
- Slope = 0.442
- Intercept = 0.012

- Harrell’s C = 0.74
- GND = 10.3 (0.24)
- Slope = 0.589
- Intercept = 0.046

- Harrell’s C = 0.74
- GND = 8.0 (0.24)
- Slope = 0.553
- Intercept = 0.077

Feinstein MJ, et al. JAMA Cardiology

Roadmap

- Why do we care?
  - HIV infected vs. uninfected, incidence
  - MI types in HIV
  - Universal MI definition
  - CNICS MI adjudication
  - Type 1 vs. Type 2 MIs
- Why
  - Other CVD
- What do we do?
  - Risk scores
- Summary
Interesting future directions

- Many interesting biomarker studies underway to determine the best biomarkers to predict CVD and other non-AIDS related outcomes in HIV
- Studies focused on inflammatory markers as potential targets for atherosclerotic therapies
- New lipid lowering agents (PCKS9) and diabetes agents (oral rather than injectable semaglutide)
- Impact of treatments to lower HIV-related inflammation on CVD?
- Role of newer agents (e.g. integrase inhibitors) and CVD?
- Are we seeing smaller increases in CVD risk today than just a few years ago?
- Will moving forward thinking about MI type help understand some of the differences between PLWH and uninfected

Summary

- Not a comprehensive summary of all relevant studies, in particular whole day sessions could be done on imaging studies; inflammation and other biomarkers, etc.
- CVD in HIV is an important outcome with substantial morbidity and mortality
- Endpoint ascertainment, central adjudication, and identifying MI types is key in defining risk and mechanism in HIV for research
- Type 2 MI are a much larger proportion of events than in the general population and almost half of all MIs in PLWH
- Traditional CVD risk factors common: focus on traditional risk prevention but additional targets also needed
- Focus on ART treatment
- Many many questions remain unanswered regarding inflammation and the role and potential intervention targets
Common PrEP Questions: A Case-Based Discussion
Hyman Scott, MD, MPH
Assistant Clinical Professor, HIV/ID and Global Medicine
University of California San Francisco
San Francisco, California

Financial Relationships With Commercial Entities
Dr Scott has no relevant financial affiliations to disclose.
(Updated 11/18/19).

Learning Objectives
After attending this presentation, learners will be able to:
▪ Identify US populations at highest risk of HIV infection
▪ Counsel patients about how to take different Preexposure prophylaxis (PrEP) regimens
▪ Describe the impact of sexually transmitted infections (STIs) on PrEP and PrEP on STIs
▪ Explain U=U
**Diagnoses of HIV Infection among Adults and Adolescents, by Transmission Category, 2017—United States and 6 Dependent Areas**

*Note:* Data for the year 2017 are considered preliminary and based on 6 months reporting delay. Data have been statistically adjusted to account for missing transmission category. "Other" transmission category not displayed as it comprises less than 1% of cases.

**Rates of Diagnoses of HIV Infection among Adults and Adolescents by Sex and Race/Ethnicity, 2017—United States**

*Note:* Data for the year 2017 are considered preliminary and based on 6 months reporting delay. Hispanics/Latinos can be of any race.

**Diagnoses of HIV Infection among Adults and Adolescents by Age at Diagnosis, 2017—United States**

*Note:* Data for the year 2017 are considered preliminary and based on 6 months reporting delay.
Rates of Diagnoses of HIV Infection among Adults and Adolescents
2017—United States and 6 Dependent Areas
N = 38,640  Total Rate = 14.0

Note: Data for the year 2017 are considered preliminary and based on 6 months reporting delay.

ARS Question 1
Do you start PrEP on the same day, or wait for test results before prescribing PrEP?
A. Same day
B. Wait for lab results
C. Something else

Same day starts in NYC

Figure 1: PrEP Initiation Among Caudets of NYC HIV by PrEP model (PrEP vs. ARV) and Medical Contraindications: January 2017 - June 2018.

New Orleans, LA, December 4-7, 2019, Ryan White HIV/AIDS Program CLINICAL CONFERENCE
ARS Questions 2

When you prescribe PrEP, how do you prescribe it?

A. 1 month of PrEP, require patient to return before giving refills
B. 3 months of PrEP, require patient to return before giving refills
C. 3 months of PrEP, with refills
D. 12 months of PrEP
E. Something else

PrEP prescribing: The Goldilocks problem

• Want to give enough PrEP to ensure coverage of risk, but not so much that PrEP users don’t come in for q 3 month HIV/STI testing
• Analysis of data from San Francisco primary care clinics found that prescriptions of < 30 days were associated with higher rate of PrEP discontinuation (OR 1.5, 95% CI: 1.1-2.2)
• However, only 2/3 of PrEP intervals had HIV/STI testing done, even when allowing for intervals of 4 months
• Panel management associated with better adherence to follow-up HIV/STI testing

ARS Question 3 – Case 1

A 21 year old woman asks you to prescribe PrEP. She states that she always uses condoms with her multiple sexual partners but would like to stop using them.

What do you recommend?

A. You don’t offer PrEP because condoms have worked well for her up to this point, and you don’t want to risk STIs
B. You don’t offer PrEP because it doesn’t work well in women
C. You offer PrEP but tell her it works less well if she has bacterial vaginosis
D. You offer PrEP and counsel that only condoms will prevent STIs, but leave the condom decision up to her
CDC Guidelines for PrEP among HTW

- It can be challenging to identify HIV risk among HT women.
- Risk assessment should also consider sexual networks and male partners’ HIV risk.

Table 1: Summary of Guidance for PrEP Use

<table>
<thead>
<tr>
<th>Men Who Have Sex with Men</th>
<th>Heterosexual Men and Women</th>
<th>Persons Who Inject Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-positve sexual partner</td>
<td>HIV-positve sexual partner</td>
<td>HIV-positve sexual partner</td>
</tr>
<tr>
<td>Recent heterosexual</td>
<td>Recent heterosexual</td>
<td>Recent heterosexual</td>
</tr>
<tr>
<td>Sex partners</td>
<td>Sex partners</td>
<td>Sex partners</td>
</tr>
<tr>
<td>History of low risk sex</td>
<td>History of low risk sex</td>
<td>History of low risk sex</td>
</tr>
<tr>
<td>or no condom use</td>
<td>or no condom use</td>
<td>or no condom use</td>
</tr>
<tr>
<td>History of high risk sex</td>
<td>History of high risk sex</td>
<td>History of high risk sex</td>
</tr>
<tr>
<td>or no condom use</td>
<td>or no condom use</td>
<td>or no condom use</td>
</tr>
<tr>
<td>In high HIV prevalence area or network</td>
<td>In high HIV prevalence area or network</td>
<td>In high HIV prevalence area or network</td>
</tr>
</tbody>
</table>

CDC. 2017 PrEP Clinical Guideline update

PrEP Works if You Take It — Effectiveness and Adherence in Trials of Oral and Topical Tenofovir-Based Prevention

Does TDF/FTC for PrEP work for cis women?

Yes, if they take it regularly

- Tenofovir concentrates at 10-100 fold higher in rectal than vaginal tissue
- Tenofovir also cleared more rapidly from vaginal than rectal tissue
- PK suggests women need to take daily TDF/FTC 6-7 days/week to maximize effectiveness

BUT:

- Tenofovir concentrates at 10-100 fold higher in rectal than vaginal tissue
- Tenofovir also cleared more rapidly from vaginal than rectal tissue
- PK suggests women need to take daily TDF/FTC 6-7 days/week to maximize effectiveness
ARS Question 4 – Case 2

A 34 year-old MSM has sex with new partners approximately twice per month. He doesn’t want to take a daily pill because his sexual exposures are relatively infrequent, but he doesn’t always use condoms.

What would you do?

A. Encourage him to use condoms
B. His exposure is relatively low, so don’t worry about PrEP
C. Encourage him to take daily PrEP
D. Have him start PrEP 7 days before sexual episodes
E. Prescribe “on-demand” or “2-1-1” PrEP, even though this is not FDA approved
Ipergay Results

**HIV Incidence (mITT Analysis)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Follow-up</th>
<th>HIV Incidence per 100 py</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Py-years</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Placebo (double-blind)</td>
<td>212</td>
<td>6.60 (3.60-11.1)</td>
</tr>
<tr>
<td>TDF/FTC (double-blind)</td>
<td>219</td>
<td>0.81 (0.11-3.30)</td>
</tr>
<tr>
<td>TDF/FTC (open-label)</td>
<td>515</td>
<td>0.19 (0.01-1.08)</td>
</tr>
</tbody>
</table>

Median Follow-up in Open-Label Phase 18.4 months (IQR:17.5-19.1)

97% relative reduction vs. placebo

Molina et al, Lancet HIV 2017;4:e402-10

What about less frequent sex?

- An analysis of IPERGAY study evaluating 269 patients (134 person-years) who took on-demand TDF/FTC PrEP less frequently (<15 pills/month) AND reported using PrEP systematically or often during sexual intercourse

<table>
<thead>
<tr>
<th>Person years</th>
<th># HIV infections</th>
<th>HIV Incidence rate/100 py (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>64.8</td>
<td>6</td>
<td>9.3 (3.4-20.1)</td>
</tr>
<tr>
<td>TDF/FTC</td>
<td>68.9</td>
<td>0</td>
<td>0.0 (0.0-5.4)</td>
</tr>
</tbody>
</table>

Antoni et al, AIDS 2017

Recommendations for 2-1-1 TDF/FTC PrEP

- CDC continues to recommend daily TDF/FTC PrEP only
  - only licensed indication by FDA
- IAS-USA guidelines recommend 2-1-1 TDF/FTC PrEP as alternative to daily PrEP for MSM
  - Use if can plan ahead for pre-dose, can take post-doses, use with all partners
  - Does not avoid adverse events
- Daily TDF/FTC PrEP is the only recommended option for cis- and transgender women and PWID
Considerations of 2-1-1 vs Daily TDF/FTC PrEP

<table>
<thead>
<tr>
<th>2-1-1 PrEP</th>
<th>Daily PrEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Who can use it</td>
<td>Only studied in MSM</td>
</tr>
<tr>
<td>Chronic HBV</td>
<td>Can trigger a flare</td>
</tr>
<tr>
<td>Planning</td>
<td>Need to plan sex at least 2hrs in advance</td>
</tr>
<tr>
<td>“Forgiveness”</td>
<td>Not forgiving of missed doses</td>
</tr>
</tbody>
</table>

ARS Question 5 – Case 3

A 48 year-old MSM with hypertension comes in requesting PrEP. He has multiple partners, frequent sex, and frequent STIs. His creatinine is 1.7, creatinine clearance is 61 ml/min.

What would you do?

A. Prescribe daily TDF/FTC
B. Prescribe daily TAF/FTC
C. Prescribe every other day TDF/FTC
D. Prescribe 2-1-1 TDF/FTC
E. Tell him he should use condoms. PrEP won’t work well because of multiple STIs.

Modest TDF/FTC renal effects in older persons

- In iPrEx OLE and SF Kaiser (Marcus JAIDS 2016), risk of eGFR<70 if:
  - Baseline eGFR<90
  - >40-50 years old
- In Partners PrEP and Partners Demo (Mugwanya, JAIDS 2016)
  - Same as above or weight < 55kg
  - >75% of creatinine increases unconfirmed on repeat test
  - No difference in picking up true renal effects if q 3 vs 6 month testing
- In Thai IDU study (Marin, CID 2014)
  - No effect of recent IDU on creatinine
  - More likely to have renal effects with increased age
- All studies
  - Creatinine reverts to near baseline after trial
  - Re-challenge has been used successfully
In IPERGAY, fewer pills had less renal effect

<table>
<thead>
<tr>
<th></th>
<th>Univariate model</th>
<th>P</th>
<th>Adjusted analysis</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of pills per month in the last two months</td>
<td>15 pills (n=1941)</td>
<td>250</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 pills (n=2259)</td>
<td>330</td>
<td>-1.31 (+0.30)</td>
<td>&gt;0.001</td>
</tr>
<tr>
<td>Renal toxic plasma concentration at the time of eGFR assessment</td>
<td>4-8 mg/mL (n=5741)</td>
<td>231</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2-4 mg/mL (n=227)</td>
<td>30</td>
<td>-1.27 (+0.30)</td>
<td>-0.48 (+0.49)</td>
</tr>
<tr>
<td></td>
<td>10 to 50 mg/mL (n=512)</td>
<td>80</td>
<td>-1.42 (+0.32)</td>
<td>-0.26 (+0.42)</td>
</tr>
<tr>
<td></td>
<td>&gt;50 mg/mL (n=2233)</td>
<td>33</td>
<td>2.08 (+0.30)</td>
<td>&gt;0.001</td>
</tr>
</tbody>
</table>

Notes on slide:
- Liangon, CROI 2019, Abstract 960

DISCOVER Primary Endpoint Analysis: HIV Incidence

- FTAIF is noninferior to PIPID for HIV prevention

Renal Safety at Week 48

- FTAIF, n=2; PIPID, n=4
- FTAIF, n=2; PIPID, n=4

Notes on slide:
- Hare, CROI 2019, Abstract 104H
4 Doses/Week has Similar Efficacy to Daily TDF/FTC for MSM

<table>
<thead>
<tr>
<th># Doses/week</th>
<th>Estimated efficacy</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>76%</td>
<td>56-96%</td>
</tr>
<tr>
<td>4</td>
<td>96%</td>
<td>90%-99%</td>
</tr>
<tr>
<td>7</td>
<td>99%</td>
<td>96%-99%</td>
</tr>
</tbody>
</table>


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Do STIs modulate the efficacy of PrEP?

- No evidence STIs lower PrEP efficacy in RCTs
  - iPrEx: Syphilis incidence of 7.3/100 py; no interaction with PrEP efficacy (Solomon, CID 2014)
  - Partners PrEP: No difference in PrEP efficacy among those with STIs (Murnane, AIDS 2013)
- No evidence in open label studies
  - PROUD in UK: 73% with baseline STI & 86% effectiveness of PrEP (McCartney, Lancet 2015)
  - Partners PrEP: No difference in PrEP efficacy among those with STIs (Murnane, AIDS 2013)
- No evidence in open label studies
  - US MSM PrEP Demo study: 90/100 p-y STI incidence & 0.43/100 p-yrs HIV incidence (Li, JAMA Int Med 2015)

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Effect of PrEP on STIs

- Rates of bacterial STIs increasing over time, however, rises pre-PrEP use
- High rates of STIs in many studies of PrEP users
- Mixed results about whether PrEP increases rate of STIs and interpretation complicated by association of PrEP use with high-risk sexual practices
- PrEP users should be screened every 3 months for STIs

Traeger et al, CID 2018

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ARS Question 6 – Case 4

A 29 year old MSM in a serodifferent relationship with an HIV positive partner comes in requesting PrEP. When you ask him, he explains that his partner is fully virally suppressed and has been for over a year, but he would feel more comfortable being on PrEP.

What do you do?
A. Prescribe PrEP
B. Prescribe PrEP for now, with the hope of eliminating PrEP in the future if his partner remains suppressed
C. Tell the patient that he doesn't need PrEP because U=U
D. What’s U=U??

HPTN 052: Immediate vs. Delayed ART

1763 sexually active serodiscordant couples, HIV positive partner CD4+ 350-550 cells/mm³

Randomized to
• Immediate ART vs.
• Delayed ART (CD4+ < 250 cells/mm³ or AIDS defining illness)

Efficacy 93%

Observational Data: 3 couples studies

<table>
<thead>
<tr>
<th>Number of couples</th>
<th>Partner 1</th>
<th>Partner 2</th>
<th>Opposites Attract</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>888</td>
<td>793</td>
<td>343</td>
</tr>
<tr>
<td>Risk</td>
<td>Heterosexual, MSM</td>
<td>MSM</td>
<td>MSM</td>
</tr>
<tr>
<td># Condomless sex acts</td>
<td>58,000</td>
<td>77,000</td>
<td>17,000</td>
</tr>
<tr>
<td># Unlinked infections</td>
<td>11</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td># Linked infections</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Rodger et al, JAMA 2016;316:171-181
Bavinton et al, Lancet HIV 2018; 5(8) e438-e447
Rodger et al AIDS 2016; 30(14): 171-181
Policy statements on U=U

On September 27, 2017, the US CDC sent out a “Dear Colleague” letter stating:

“... people who take ART daily as prescribed and achieve and maintain an undetectable viral load have effectively no risk of sexually transmitting the virus to an HIV-negative partner.”

Condom Effectiveness

Heterosexuals (Giannou et al, Expert Rev Pharmacoecon Outcomes Res 2016)
- Meta-analysis of 25 studies, >10,000 couples
- Overall effectiveness: 71-77%

MSM (Smith et al, JAIDS 2015;68:337-344)
- Data from 2 large cohorts
- 70% effective

Underutilization of PrEP in Partners of HIV positive MSM

10% of MSM HIV patients with HIV-negative partners reported having a partner taking PrEP

Among all reported HIV-negative partners...

- 6% taking PrEP
- 67% not taking PrEP and patient was virally suppressed
- 27% not taking PrEP and patient not virally suppressed

Beer et al, CROI 2018, #1052
Self-reported vs. actual VL among men stating VL undetectable

Teran, CROI 2018, #997

ARoS Question 7 – Case 5

A 28 year old HIV negative woman is in a serodifferent relationship with an HIV positive man. He is newly diagnosed, and not yet stably virally suppressed. The couple wants to have a baby.

What do you recommend?

A. Wait for the male partner to become fully virally suppressed for at least 6 months before attempting pregnancy
B. Use PrEP – it’s safe peri-conception and in pregnancy
C. Don’t use PrEP – its safety is unknown. Use sperm washing instead
D. Something else

HIV risk increases during pregnancy

• 2,751 HIV-uninfected females in African HIV serodiscordant couples followed for ≤48 mos in 2 HIV prevention studies between 2004-2012
• Frequent HIV and pregnancy testing
• Genetic linking of HIV infections

References: 28

Trotman KA et al. JID 2018

New Orleans, LA, December 4-7, 2019, Ryan White HIV/AIDS Program CLINICAL CONFERENCE
**PrEP safety in pregnancy**

- Study of 30 women who became pregnant while on PrEP (compared with 96 women not exposed to PrEP)
  - No difference in miscarriage, congenital anomalies, or growth through 1 year of infancy
  - Slightly lower z-scores for length (-1.73 v. -0.79, p=0.05) and head circumference (0.24 v. 1.07, p=0.04) at 1 month, but NS at 1 year.

Heffron et al AIDS 2018

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**ARS Question 8 – Case 6**

A 35 year old MSM in a serodifferent relationship comes in seeking PrEP. He states that his partner has been unsuppressed, and is just starting a new treatment regimen. The partner had to change his regimen because of antiretroviral resistance, and he’s pretty sure his partner mentioned M184V. He doesn’t like using condoms.

What do you recommend?

A. They should continue to use condoms until the partner has been fully virally suppressed for at least 6 months.
B. You prescribe TDF/FTC or TAF/FTC
C. You prescribe 3-drug PEP
D. Something else

---

**Breakthrough infections**

- PrEP Breakthrough infections despite documented high adherence

<table>
<thead>
<tr>
<th>Location</th>
<th>Duration on PrEP before HIV diagnosis</th>
<th>Resistance Mutations</th>
<th>Adherence Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen et al</td>
<td>US</td>
<td>13 months</td>
<td>M184V, L74V</td>
</tr>
<tr>
<td>Knox et al</td>
<td>Canada</td>
<td>24 months</td>
<td>M41L, D67G, T69D, K70R, M184V, Y115E</td>
</tr>
<tr>
<td>Markowitz et al</td>
<td>US</td>
<td>6 months</td>
<td>K65R, M184V</td>
</tr>
<tr>
<td>Hoornenborg et al</td>
<td>Amsterdam</td>
<td>8 months</td>
<td>No major resistance</td>
</tr>
<tr>
<td>Thaden et al</td>
<td>US</td>
<td>14 months</td>
<td>M184V, K70T, K65R</td>
</tr>
<tr>
<td>Colby et al</td>
<td>Thailand</td>
<td>8 weeks</td>
<td>M184V</td>
</tr>
</tbody>
</table>

DBS=Dried Blood Spot

Cohen et al Lancet HIV 2018
ARS Question 9 – Case 7

A 29 year old woman in a serodifferent relationship would like to stop using condoms. Her partner is not virally suppressed. She wants to know how long she has to take daily PrEP before she is protected. What do you tell her?

A. 3 days
B. 7 days
C. 21 days
D. 28 days
E. I have no idea

How long do you need to take PrEP before protected?

In blood (PBMCs)
• 89% achieve EC90 after 7 doses
• 98% by 13th dose

Recommended for MSM:
• Start TDF/FTC PrEP 7 days before
• Continue 28 days after (based on animal data)

Recommended for Women
• CDC recommends 21 days before, but growing consensus that 7 days may be adequate
• Women need 6-7 doses/week while men only need 4-7 doses for maximal protection

Proportion achieving EC90 of tenofovir in PBMCs

Cottrell et al. CID 2015;60:804-810

ARS Question 10 – Case 8

A 35 year old transgender woman reports that she has infrequent condomless sex and is reluctant to start PrEP because she believes PrEP will interfere with her gender-affirming hormones. How do you counsel her?

A. You tell her we have data that PrEP does not affect hormone levels and encourage PrEP use
B. You tell her we don’t know if PrEP affects hormone levels but encourage PrEP use
C. You tell her we don’t know if PrEP affects hormone levels, nor do we know if it works for trans women and encourage condoms
D. You recommend 2-1-1 PrEP so that she has less PrEP exposure
Pharmokinetic study of men and trans women

- Design: Open label, one way (estrogen on TFV/FTC) study
- Subjects: 8 cis men, 8 trans women (HIV-Neg; 18-65 years)
- Inclusion: Screening estradiol > 100 pg/mL (TGW only)
- Creatinine Clearance (CrCl) > 70 mL/min
- No contraindication to TDF/FTC

Findings: Lower intracellular TFV-DP and FTC-TP among TGW, but NS

<table>
<thead>
<tr>
<th></th>
<th>PBMC</th>
<th>PBMC</th>
<th>Colon Cell</th>
<th>PBMC</th>
<th>PBMC</th>
<th>Colon Cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Reduction (TGW/CGM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TFV-DP</td>
<td>C&lt;sub&gt;0&lt;/sub&gt; AUC</td>
<td>C&lt;sub&gt;0&lt;/sub&gt; AUC</td>
<td>C&lt;sub&gt;0&lt;/sub&gt; AUC</td>
<td>C&lt;sub&gt;0&lt;/sub&gt; AUC</td>
<td>C&lt;sub&gt;0&lt;/sub&gt; AUC</td>
<td></td>
</tr>
<tr>
<td>FTC-TP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>0.30</td>
<td>0.12</td>
<td>0.44</td>
<td>0.98</td>
<td>0.28</td>
<td>0.38</td>
</tr>
<tr>
<td>% Reduction (TGW/CGM)</td>
<td>16%</td>
<td>24%</td>
<td>36%</td>
<td>-1%</td>
<td>12%</td>
<td>44%</td>
</tr>
<tr>
<td>p value</td>
<td>0.30</td>
<td>0.12</td>
<td>0.44</td>
<td>0.98</td>
<td>0.28</td>
<td>0.38</td>
</tr>
<tr>
<td>% Reduction (TGW/CGM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Does PrEP work for trans women?

In iPrEx, 339 participants were identified as trans women
- No infections in women with detectable tenofovir in blood, but only 18% had detectable levels
- Trans women express concern about interaction of TDF/FTC with hormones
  - In iPrEx, women on hormones less likely to take PrEP
- Studies planned or underway to evaluate interaction of TDF/FTC on hormones
  - Several studies suggest small reductions in TDF levels

Bottom line: limited data, TDF/FTC likely works in trans women but more data needed

ARS Question 11 – Case 9

Your 31 year old patient on PrEP comes in for his routine quarterly lab tests. His 4<sup>th</sup> generation antibody test comes back positive, but the confirmatory test and viral load come back negative.

What do you do?

A. Repeat the tests but continue PrEP, as you assume the 4<sup>th</sup> gen test is a false positive
B. Repeat the tests and stop PrEP, but start ART for acute HIV infection
C. Repeat the tests and stop PrEP until you can determine what the infection status is
D. Something else
How to manage ambiguous HIV Test Results

1. **Ambiguous or Discrepant HIV Tests**
   - Confirm the presence or absence of infection
     - Repeat serologic or RNA tests (DNA tests not validated)
     - Use a test from another manufacturer

2. **Manage antiretroviral drugs**
   - Stop PrEP, reassess HIV Status
   - Continue PrEP if adherent
   - Start ART if not adherent to PrEP

**Maintenance Protection**
- Risk of Resistance
- Risk of Infection
- Drug Related AEs
- Confirm Diagnosis

More experience needed to manage ambiguous test results for false-positive results:
- Repeat HIV testing, discuss with clinicians and virologists. Seek expert opinion and potentially additional research testing (ultrasensitive HIV VL testing).

PrEPline: 855-448-7737 (11am-6pm PST)

Smith et al OFID 2018; Stekler JD et al OFID 2018; Saag M et al JAMA 2018
ARS Question 12

What is most exciting to you in the future of PrEP?

A. Long-acting injectable cabotegravir
B. Long-acting injectable rilpivirine
C. Oral EtdA (MK-8591)
D. Broadly neutralizing antibodies
E. Vaginal rings
F. Maraviroc

What’s happening with topical PrEP?

Dapivirine ring studies
• Early efficacy: ~30%
• Open label extension: 54%
• Undergoing regulatory review

Multipurpose technology
• Possibility of combining with contraception or anti-STD interventions

Rectal douches also under development

Systemic approaches

• Long-acting ARVs
  ◦ Cabotegravir (INSTI) being evaluated
  ◦ Challenges: oral lead-in, long pharmacologic tail needs coverage
  ◦ Other agents, other methods of delivery (e.g., implants)

• Active vaccination
  ◦ 2 efficacy trials in sub-Saharan Africa: 1 planned in the Americas/Europe
  ◦ Use viral vectors with protein sub-unit boost

• Passive vaccination
  ◦ 1 efficacy trial in SSA, 1 in North/South America
  ◦ Use broadly neutralizing antibody infused or injected
Implantable devices

Drug must be extremely potent, as total mass dose to be loaded is small:
- E.g., estradiol implant: 50mg/day

Formulation PK profiles compared

Question-and-Answer Period
Financial Relationships With Commercial Entities

Mr. Horn has no relevant financial affiliations to disclose. (Updated 11/11/19)

Learning Objectives

After attending this presentation, learners will be able to:
• Describe the 340B Drug Pricing Program and its role in achieving cost containment and program income for Ryan White HIV/AIDS Programs
• Describe the challenges associated with high antiretroviral drug pricing
• Assess the impact of generic drugs on program cost containment and 304B program income
RWHAP Core Medical and Support Services

AIDS Drug Assistance Program Treatments - AIDS Pharmaceutical Assistance + Early Intervention Services (EIS) + Health Insurance Premium and Cost Sharing Assistance for Low-Income Individuals + Home and Community-Based Health Services + Home Health Care + Hospice Services + Medical Nutrition Therapy + Medical Case Management, including Treatment Adherence Services + Oral Health Care + Outpatient Ambulatory Health Services + Substance Abuse Outpatient Care + Child Care Services + Emergency Financial Assistance + Food Bank/Home Delivered Meals + Health Education/Risk Reduction + Housing + Linguistic Services + Medical Transportation + Non-Medical Case Management Services + Outreach Services + Professional Services + Psychosocial Support Services + Referral for Health Care and Support Services + Rehabilitation Services + Respite Care + Residential Substance Abuse Services

The 340B Drug Pricing Program helps Ryan White HIV/AIDS Programs, including ADAPs, to achieve both cost containment and revenue, "to stretch scarce federal resources as far as possible, reaching more eligible patients and providing more comprehensive services."

H.R. No. 102-384, Part II, Pg. 12, 102nd Congress, Second Session

New Orleans, LA, December 4-7, 2019, Ryan White HIV/AIDS Program CLINICAL CONFERENCE
HIV Drug Cost Considerations

**ARS QUESTION 1**

Over the past 10 years, list prices of DHHS Guidelines “preferred” single-tablet regimens have increased by how much?

A. 10% to 50%
B. 50% to 100%
C. 100% to 150%
D. 150% to 200%
E. More than 200%
Payer and Access Considerations

- Total undiscounted spending on ARVs in 2018: $22.8 billion\(^1\)
- HIV among the top five therapeutic classes in non-discounted spending in 2018, after medications for diabetes, autoimmune diseases, cancer and respiratory diseases\(^2\)
- ARVs are No. 1 Medicaid outpatient drug expenditure (No. 5 and 4 for commercial and ACA plans, respectively)\(^3\)
- Public and private payers: increasing formulary restrictions, utilization management (e.g., prior auth)
- Out-of-pocket spending is an issue; copay assistance programs in crosshairs

---

\(^{1}\) IQVIA. Medicine Use and Spending in the U.S. 2018 April.
\(^{3}\) CMS, Medicare Part D Spending in the U.S. 2018 April.
Generic ARV Options (2019)

Multi-Source "Generic" Drugs
• abacavir, abacavir/lamivudine, atazanavir, didanosine, fosamprenavir, lamivudine, nevirapine, ritonavir, stavudine, tenofovir disoproxil fumarate

Multi-Source "Quasi-Generic Brand" Drugs
• Mylan: EFV/TDF/3TC, EFV(400)/TDF/3TC, TDF/3TC
• Celltrion: TDF/3TC

Pending Generics
• September 2020: TDF/FTC
• Mid-2020s: darunavir, raltegravir

ARS QUESTION 2

Can generic drugs be used in DHHS Guidelines-recommended regimens?
A. No
B. Only "Initial Regimens in Certain Clinical Situations"
C. Both "Initial Regimens for Most People With HIV" and "Initial Regimens in Certain Clinical Situations"

Generics in the HHS Guidelines

Recommended for Regimens for Most People With HIV
- EFV/TDF/3TC
- EFV(TDF+3TC)
- TDF/FTC
- TDF/3TC
- 3TC/FTC

Recommended for Regimens in Certain Clinical Situations
- Darunavir
- Raltegravir
- HIV-1 integrase inhibitor
- Raltegravir dispersible tablets
- TDF/FTC, 400 mg/200 mg
- TDF/FTC, 200 mg/100 mg
- TDF/FTC, 300 mg/150 mg

Approved for Use in Therapy in Adults and Adolescents
- EFV/TDF/3TC
- EFV(TDF+3TC)
- TDF/FTC
- TDF/3TC
- 3TC/FTC
U.S. Drug Pricing: It’s Complicated

Nonfederal Average Manufacturer Price (Non-FAMP)
Federal Supply Schedule (FSS) Price
Federal Ceiling Price
Federal Ceiling; “Big 4” Price
Private sector prices
Rebates to PBMs
Copay assistance
Other price concessions
Supplemental discounts negotiated (VA and DoD)

U.S. Drug Pricing: It’s Complicated

Generics
Average Wholesale Price (AWP)
Wholesale Acquisition Cost (WAC)
Average Manufacturer Price (AMP)
Best Price
Medicaid Price
340B Price
Unit rebate: 23.1% / 13% of AMP or AMP – Best Price plus additional discounts
Supplemental rebates and discounts negotiated (including ADAPs)
Federal Upper Limit
State Maximum Allowable Cost
Commercial Payer MAC
24% of non-FAMP plus additional discounts
Negotiation on most favored commercial customer price

340B and the Ryan White HIV/AIDS Program

340B Background

- The 340B Drug Pricing Program was developed to allow manufacturers to continue offering discounted drugs to safety net entities, following the introduction of the Medicaid Drug Rebate Program
- Medicaid required manufacturers to calculate average and best prices for the Medicaid program, and any discounts to safety net entities would reduce Medicaid reimbursement
- The 340B Program was established to allow manufacturers to exclude these discounts from their Medicaid calculations
Manufacturers and 340B

- Why do manufacturers participate in 340B (and Medicaid)?
  - Manufacturers are not required to participate – they choose to participate and offer discounts
  - Participation is the only way to receive Medicare Part B and Medicaid reimbursement

340B and RWHAP

- RWHAP grantees are essential public health care programs and therefore eligible for 340B Drug Pricing Program
- RWHAPs also subject to extensive restrictions on how 340B can be used: program-eligible PLWHIV, "additive" use consistent with grant terms
- HRSA Policy Clarification Notice (PCN) 15-03
- Most RWHAP programs – or their contract pharmacies – access up-front discounts
- ADAPs, under RWHAP Part B, may choose up-front discounts and/or rebates paid by manufacturer
- ADAP Crisis Task Force negotiates supplemental discounts/rebates with manufacturers – agreements with all ARV manufacturers on behalf of all ADAPs

340B Discount and Program Income Basics

- 340B entities subject to a minimum discount of 23.1% off the Average Manufacturer Price; "Best Price" adjustment also possible
- When manufacturer takes a price increase that exceeds the Consumer Price Index for All Urban Costumers (CPI-U), an additional rebate – or "inflation penalty" – is added to base discount
- Achieves prescription drug cost containment
- Revenue, or "program income," is generated when clinics are able to purchase the drug at a discounted rate but are reimbursed by third-party payers at a higher usual and customary rate
340B Discount and Program Income Basics

- DISCOUNT or REBATE FROM MANUFACTURER
- PROGRAM INCOME

ADAPs

- 340B Ceiling Price
- Voluntary Sub-ceiling ADAP Price

RWHAP Providers

- WAC/AMP Price
- Insurance Payment

340B Program Income Over Time

- LAUNCH: $100.00
- YEAR 5: $140.00
- YEAR 10: $175.00

Challenges to 340B Program Income

- Any legislation or regulations that directly or indirectly lower “AMP” or “Best Price”
- Legislation or regulations that alter 340B Drug Pricing Program, including entity and patient definitions
- Legislation, regulations, or policies allowing payers to reimburse 340B discounted drugs at lower rates
- Competition that lowers list prices, AMP, or Best Price
- Patent cliffs and commercialization of generic drug products
A Word About PrEP

- Generic TDF/FTC
- TAF/FTC
- LA-CAB
- USPSTF
- Payer Cost Containment

340B Savings

Summary

- The era of cost containment and generic competition has arrived; clinician knowledge/engagement increasingly important
  - Payers asking the same critical questions of data as clinicians: TAF vs. TDF, STRs vs. MTRs, added value of LA ARVs
- 340B has been a lifeline to US HIV programs, including RWHAP clinics and AIDS Drug Assistance Programs (ADAPs)
- ARV market (e.g., generics) and policy dynamics may impact 340B as savings source
- The big question: How do we make lower drug prices work to the advantage of people with, or at risk for, HIV?

THANK YOU!

thorn@NASTAD.org
Question-and-Answer Period
Ending the HIV Epidemic: Reaching the Unsuppressed and Out of Care Panel Discussion

John T. Brooks, MD
Chief Medical Officer
Division of HIV/AIDS Prevention
Centers for Disease Control and Prevention
Atlanta, Georgia

Laura W. Cheever, MD, ScM
Associate Administrator
Chief Medical Officer
HIV/AIDS Bureau
Health Resources and Services Administration
Rockville, Maryland

Dr Brooks and Dr Cheever have no financial affiliations to disclose. (Updated 11/26/19)

30 years of Innovating Care, Optimizing Public Health, Ending the HIV Epidemic

• Clinical Conference: August 9-11, 2020
• National Conference: August 11-14, 2020
• Marriott Marquis Washington, DC
• Abstract Submissions Open: November 18, 2019, through December 20, 2019

2020 National Ryan White Conference on HIV Care & Treatment

Ending the HIV Epidemic: Presenters and Panel Members

• Two-Pronged Attack: HIV Testing in a South Florida Healthcare System
  Elizabeth Sherman, Memorial Healthcare System
• CrescentCare’s Immediate ART Continuum
  Lorna Seybolt, CrescentCare
• The Undetectables Project
  Andre Brutus, Brooklyn-Plaza Medical Center, Inc.
• A Multidisciplinary Intervention to Address Patients in Care who are Not Virally Suppressed
  Paula Seal, Louisiana State University Health Sciences Center
• Implementing Tailored Interventions to Improve Retention and Viral Suppression in a Rural Ryan White Clinic
  Michelle Collins-Opie, Warren-Vance Community Health Center, Inc.
Four Pillars of Ending the HIV Epidemic

- **Diagnose**: All people with HIV as early as possible.
- **Treat**: People with HIV rapidly and effectively to reach sustained viral suppression.
- **Prevent**: New HIV transmissions by using proven interventions, including pre-exposure prophylaxis (PrEP) and syringe services programs (SSPs).
- **Respond**: Quickly to potential HIV outbreaks to get needed prevention and treatment services to people who need them.

Identifying the Challenges Ahead

<table>
<thead>
<tr>
<th>People with HIV in care</th>
<th>People newly diagnosed with HIV</th>
<th>People with HIV out of care</th>
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<tbody>
<tr>
<td>• Improve viral suppression rates</td>
<td>• Enhance linkage to care</td>
<td>• Expand re-engagement in care</td>
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<tr>
<td>• Decrease disparities</td>
<td>• Enhance engagement in care</td>
<td>• Improve retention in care</td>
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PrEP Medication Access for Uninsured Patients

**HOW CAN PATIENTS PARTICIPATE?**

- If PrEP medication is a good option for your patients, they can choose the application process that is most convenient:
  - GetYourPrEP.com
  - By phone: 855.447.8450
  - In person at a healthcare provider’s office, including a community health center where trained staff can assist.

**READY, SET, PrEP** makes PrEP medications available at no cost.

+ FIND OUT IF YOU QUALIFY

- Patients can receive PrEP medication through a pharmacy of their choice.
Thank You!

Laura Cheever, MD, ScM  
Associate Administrator  
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Brooklyn Plaza Medical Center, Inc.

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FOLLOW US:
Ending the HIV Epidemic

Test and Link to Care
Rapid Start
Retention in Care
Viral Suppression
Re-Engagement in Care

Ending the HIV Epidemic

Test and Link to Care
HIV Testing
Retention in Care
Viral Suppression
Re-Engagement in Care

Two-Pronged Attack: HIV Testing in a South Florida Healthcare System

Elizabeth Sherman, PharmD
Memorial Healthcare System

Dr. Sherman has received grant support from Gilead. (11/13/2019)
**Goals: Memorial’s HIV Testing Program**

- The Miami-Ft. Lauderdale-West Palm Beach metropolitan area (MSA) leads USA in new HIV diagnoses and prevalence of diagnosed HIV.
- Ft. Lauderdale (Broward county) #1 in new HIV diagnoses and HIV prevalence.
- Memorial Healthcare System is the public healthcare system of south Broward county and one of the largest public healthcare systems in USA.
- Approximately 80% of new HIV transmissions from persons with undiagnosed HIV or those not in care.
- Memorial’s large-scale HIV testing program identifies patients who are undiagnosed, or diagnosed and not retained in care, and links them to medical services including our RWHAP-funded clinic.


**Methods: 2-Pronged Approach to HIV Testing**

1. Opt-out 4th generation HIV testing for all patients in emergency department (ED)

2. Point-of-care testing (POCT) for patients in the 9 primary care clinics, aboard the adult mobile health center (AMHC), and for partners/caregivers/family members of patients in clinics/ED

- Collaboration with the Gilead Sciences’ FOCUS program and Florida Department of Health
- Physician champions: Dr. Randy Katz and Dr. Paula Eckardt

**Results: July 2018 - June 2019**

1. Opt-out 4th generation HIV testing for all patients in ED
   - 22,067 patients tested
   - 121 positive (0.5% reactive rate)
   - 83 previously diagnosed (53% were engaged in care)
   - 38 new diagnoses
   - 104 linked to/retained in care (86% of positives)

2. POCT for patients in primary care clinics, aboard AMHC, and for partners/caregivers/family members
   - 11,389 persons tested
   - 31 positive (0.2% reactive rate)
   - 30 (97%) linked to care
Lessons Learned: HIV Testing Program Expansion

1. Opt-out 4th generation HIV testing for all patients in ED
   • Frontline ED staff require ongoing training
   • Stigma remains a challenge: patients and providers afraid to say "HIV"
     • 83 patients previously diagnosed – but did not disclose status
     • ED treated 96,016 patients – yet only 54,932 were screened

2. POCT for patients seen in the primary care clinics, aboard AMHC, or community members
   • Testing can impact patient throughput time
   • Decreasing number of POCT performed as HIV testing is routinized

Further Applications

• The Memorial Healthcare System HIV testing program demonstrates an effective HIV testing initiative working to end the HIV epidemic
• Knowledge of serostatus is the first step in accessing HIV treatment, reducing transmission, and mitigating public health challenges
• HIV testing programs can be rapidly expanded within healthcare systems and can serve to increase testing in communities
• If you test them, you will find them!
## CrescentCare’s Immediate ART Continuum

Lorna Seybolt, MD  
CrescentCare

**Dr Seybolt has no relevant financial affiliations to disclose. (11/13/2019)**

---

### CrescentCare Start Initiative (CCSI):
Patients newly diagnosed with HIV seen by a provider within 72 hours (optimally same-day) and provided 30 days of ART

### Early Intervention Services (EIS):
Same protocol but patients contacted clinic over 72 hours after diagnosis  
Range: 4 days – 25 years

---

### Procedure/Methods

**Medical Provider Visit:**
- HIV Lifecycle, importance of adherence, U=U discussed
- Comorbidities assessed
- Physical Examination
- Provider option to not rx, alter medications if suspected resistance
- 30 day-supply of TAF/FTC/DTG
- DOT – first dose in clinic

**Post-Provider Visit:**
- Enroll in insurance programs
- Intake Labs obtained
- Social Work services for those with urgent needs

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New Orleans, LA, December 4-7, 2019, Ryan White HIV/AIDS Program CLINICAL CONFERENCE
Results

<table>
<thead>
<tr>
<th>Category</th>
<th>Median Time to Suppression (days)</th>
<th>Mean Time to Suppression (days)</th>
<th>Number of patients</th>
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<tbody>
<tr>
<td>CCSI</td>
<td>28</td>
<td>40.4</td>
<td>227</td>
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<tr>
<td>EIS</td>
<td>27</td>
<td>51.28</td>
<td>141</td>
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</tbody>
</table>

2. Time from Diagnosis to First Viral Load Suppression: CCSI
2. Time from Linkage to Care to First Viral Load Suppression: EIS

Key Facilitators of RAPID Intervention

- Same-day appointments
- Flexible provider scheduling (on call backup)
- ART-regimen preapproval prior to genotyping or lab testing
- Availability of ART starter packs
- Accelerated process for health insurance initiation
- Observation of first ART dose in clinic (recommended)
- Guarantee sustained access to ART

Concluding Comments

- Both cohorts demonstrate that starting patients on the day of diagnosis or linkage, before labs are obtained, is highly accepted, safe and well tolerated
- Rapid entry/initiation improves
  - Time to viral suppression
  - Viral suppression at 12 months
  - Retention in care at 10–12 months
  - Survival at 12 months (international studies)
- Rapid entry/initiation is feasible in a variety of settings
- There are differences between newly diagnosed patients (viral suppression 90%) and those who deferred immediate linkage (viral suppression 77%) P = 0.0071
- Immediate ART leading to rapid viral suppression will be a key component of ending the HIV epidemic
Ending the HIV Epidemic

The Undetectables Project

Andre Brutus, MD
Brooklyn Plaza Medical Center, Inc.

Dr. Brutus has served as a speaker for Gilead Sciences, Inc., ViiV Healthcare, and Janssen. (Updated 12/2/18)

GOALS

In 2018, viral load suppression among new patients dropped 16% from the previous year.

Increase viral load suppression by 15% among New Patients (newly diagnosed & new to care) by December 31, 2019.

METHODS – Data Driven

- When comparing 2017 data, we learned that our New Patients (particularly those New to Care) significantly impacted the clinic’s overall VLS rate in 2018. 16% drop in new patients VLS in 2018.
- In Quarter 1, 2019, the Quality Improvement Team reviewed 2018 viral load suppression data in the electronic medical record by comparing 2018 VLS among New patients versus VLS among Existing Patients.
- To address this gap in care, the Quality Improvement Team:
  A. Conducted a monthly review of the data during QI Meetings to assess which patients’ VL had increased over 500
  B. Through reports generated in the EMR, assessed which patients missed clinic or case management appointments
  C. Ensured Case management staff follow up with patients & the pharmacy to ensure patients picked up their medication.
METHOD - The Undetectables Project

The Undetectables Project is an evidence-based HIV intervention designed to help clients achieve and maintain viral suppression.

Funded by both HRSA (RWPC) and NYC DOH (RWPA), the Rising Heights Program was able to provide increased outreach, and offer incentives (through special funding from DSRIP) to engage, retain and promote treatment adherence among PLWHA disproportionately impacted by social determinants of health such as:

- Homelessness/housing instability
- Behavioral/mental health issues
- Substance use
- Poverty
- Marginalization due to sexual orientation or gender identity

Primary Methods to Increase Viral Load Suppression

- Robust follow up via phone calls & home visits
- Integrate case conferences
- Interprofessional care planning (IPCP) & refers to the SW
- Behavioral health assessment & referrals to the SW
- Adherence sessions (pill boxes, blister packs)
- Motivational interviewing
- Adherence support groups
- DOT for ARV meds
- $100 gift card (Funded through DSRIP)

RESULTS - Viral Load Indicators

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<tr>
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<th>Baseline (2017)</th>
<th>2018</th>
<th>2019</th>
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<tr>
<td>Total Clients</td>
<td>267</td>
<td>255</td>
<td>264</td>
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<tr>
<td># of Clients Suppressed</td>
<td>81%</td>
<td>85%</td>
<td>86%</td>
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<tr>
<td># of Clients with VL &gt;200</td>
<td>16%</td>
<td>11%</td>
<td>9%</td>
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<tr>
<td># of Clients &lt;20</td>
<td>65%</td>
<td>67%</td>
<td>66%</td>
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<tr>
<td># of Clients w VL &lt;200</td>
<td>81%</td>
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<td># of Clients Suppressed</td>
<td>65%</td>
<td>50%</td>
<td>64%</td>
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<tr>
<td># of Clients with VL &gt;200</td>
<td>2%</td>
<td>3%</td>
<td>19%</td>
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<td># of Clients &lt;20</td>
<td>42%</td>
<td>50%</td>
<td>56%</td>
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<tr>
<td># of Clients w VL &lt;200</td>
<td>65%</td>
<td>50%</td>
<td>64%</td>
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LESSONS LEARNED

- Robust follow up via phone calls & home visits bolsters patient adherence to medication;
- Financial incentives are extremely helpful as a tool in helping the provider and staff maintain engagement with fragile patients;
- Adherence groups are a useful forum in receiving feedback from patients on their adherence barriers; (Pill fatigue, Disclosure – family does not know status, care of family, depression)
- Monthly monitoring of VLS Reports provided enhanced structure for staff in using data as a reference to perform targeted outreach & engagement of fragile patients
- Through the use of data & proven HIV intervention strategies, viral load suppression among New Patients increased by 14% as of November 30, 2019.
Ending the HIV Epidemic

A Multidisciplinary Intervention to Address Patients in Care who are Not Virally Suppressed

Paula Seal, MD, MPH
Louisiana State University Health Sciences Center

Dr. Seal has no relevant financial affiliations to disclose. (11/13/19)

Background

- Setting: HIV Outpatient Program at University Medical Center New Orleans, serves over 1650 people living with HIV
- Provides comprehensive, interdisciplinary HIV primary care
- On-site services include psychology, psychiatry, dentistry, pharmacy, social work, health education, and patient navigation
- Receives Ryan White Parts A and C
- VL suppression was 86% in 2018
Inclusion

• All patients with 2 viral loads >1000 in the last 6 months were included in the intervention.
• The goal was to increase to viral suppression from 0% to 85% at one year.
• Began in February 2019

Intervention

Patient Navigation contacted the patient 3 days prior for an appointment reminder

At the scheduled visit, Patient Navigation and Health Education met with the patient.

Health Education scheduled an adherence follow-up appointment with the patient to review adherence to ART, and assist with pill boxes, etc.

After the visit, Patient Navigation followed up by phone with the patient to confirm receipt of antiretroviral therapy and assess motivations and barriers.

Health Education engaged patients at adherence appts and by phone.

Barriers and other adherence issues were directed to the appropriate providers and team members for further intervention and additional visits as needed.

Results

• 54 patients met the inclusion criteria (~3% of clinic)
  – 49% had a psychiatric diagnosis
  – 36% had substance abuse
  – 36% had one or more hospitalizations in the last year
  – 30% had difficulty understanding medication instructions
  – 90% were African American (versus 76% in the clinic)
  – 42% were women (versus 33% in the clinic).
• At six months, viral suppression was 56%.
• 33% had issues with transportation and 17% with medication acquisition.
Conclusions

• While time intensive, an interdisciplinary intervention can improve viral suppression among patients in care but not virally suppressed.
• Intervention is ongoing, and we will reassess viral suppression in January 2020.
Retention Initiatives and the National HIV/AIDS Strategy

National HIV / AIDS Strategy (NHAS)

- Reducing New HIV Infections
- Increasing Access to Care and Improving Outcomes
  - Improving linkage into care and retention to achieve viral suppression that can reduce transmission risk
  - Increase a diverse workforce trained to provide specialty care
  - Support comprehensive, coordinated, patient-centered care
- Reducing HIV Related Disparities and Health Inequities
- Achieve A More Coordinated National Response

Patient Care and Retention Program
Assessment for Patient Care and Retention Intervention

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<td>Inconsistent Transportation</td>
<td>Stable Transportation</td>
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<td>Unstable Housing / Homeless</td>
<td>Inconsistent Housing / Homeless</td>
<td>Stable Housing / Homeless</td>
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<tr>
<td>Food Insecurity / Resources</td>
<td>Food Insecurity / Resources</td>
<td>Adequate Food / Nutrition</td>
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<td>Increased VL or not virally suppressed</td>
<td>Virally suppressed but admits stigma, fear, accepting dx.</td>
<td>Virally Suppressed</td>
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High Risk Patient Care And Retention Program Demographics 2014-2018

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Patient Care And Retention Program (PCARP)  

Conclusion  

- Identifying patients at highest risk for not being retained is important to target intervention efforts to those groups.
- Invalid contact information, food insecurity, lack of nutritional resources and not being virally suppressed are strong predictors of retention.
- Other important factors more specific to rural communities are inconsistent transportation and lack of a family based support network.
- Characteristics associated with retention will necessarily vary between urban and rural clinics. Rurality of HIV in the deep south becomes important when prioritizing interventions for improvement.
- We highlight the importance of addressing social determinants of health on patient retention, including case management, transportation, use of social media, food and nutrition.

Discussion: Attendee Innovations and Implementations  

Ending the HIV Epidemic
A Multidisciplinary Intervention to Address Patients in Care Who Are Not Virally Suppressed

Paula Seal, MD, Louisiana State University Health Sciences Center, New Orleans, Louisiana

Established in 1987, the HIV Outpatient Program (HOP) is part of University Medical Center and is one of the largest clinics serving people living with HIV (PLWH) in New Orleans. Our mission is to support and promote the health and well-being of PLWH by providing high-quality health care services regardless of socioeconomic status. HOP provides comprehensive, interdisciplinary HIV primary care delivered by a team of infectious disease specialists from Louisiana State University and Tulane Schools of Medicine. A full complement of services are available onsite and include psychology, psychiatry, dentistry, pharmacy, social work, health education, and patient navigation, among others. HOP receives Ryan White HIV/AIDS Program Part A and C funds. Viral load suppression at HOP was 86% in 2018, but a subset of patients remained in care who were not suppressed.

The intervention used an interdisciplinary team that included the medical practitioner, health educators, patient navigators, and social workers and was designed by the quality improvement committee. The intervention went as follows: 3 days prior to the scheduled visit, the patient navigator called the patient to remind them of the visit. At the visit, the patient navigator or health educator (or both) met with the patient face to face. Health educators scheduled an adherence follow-up appointment with the patient to review adherence to prescribed antiretroviral therapy (ART) and assist with pill boxes. After the visit, the navigator followed up by phone to ensure the patient received the ART and assessed motivations and barriers. Health educators engaged patients at adherence appointments and subsequently followed up by phone. Barriers and other adherence issues were directed to the appropriate practitioner for intervention and additional visits as needed. The intervention began in February 2019. All patients with 2 viral load measurements above 1000 copies/mL in the last 6 months were included in the intervention. The goal was to increase to viral suppression from 0% to 85% at 1 year.

Fifty-four patients met the inclusion criteria for the intervention out of approximately 1650 patients who receive primary HIV care on our clinic (~3%). About half (49%) had a psychiatric diagnosis, 36% had substance abuse, 36% had 1 or more hospitalizations in the last year, and 30% had difficulty understanding medication instructions. Ninety percent were African American (compared with 76% in the clinic overall) and 42% were women (compared with 33% in the clinic overall). At 6 months into the intervention, viral suppression was 56%. A third of the patients had issues with transportation and 17% with medication acquisition. The plan is to continue with the intervention until January 2020 and reassess viral suppression.

Although time intensive, an interdisciplinary intervention can improve viral suppression among patients in care but not virally suppressed. Often additional barriers persist for these patients, who need individual assessment and attention.
The Miami-Ft Lauderdale metropolitan area is at the epicenter of an HIV hotbed, leading the nation in new HIV diagnoses. In response, the Memorial Healthcare System (Memorial; the public healthcare system of south Broward county and one of the largest public healthcare systems in the nation), in collaboration with the Florida Department of Health and Gilead Sciences’ FOCUS program, implemented a 2-pronged approach to HIV testing: 1) opt-out 4th generation HIV testing for all patients seen in the emergency department (ED), and 2) opt-in point-of-care testing (POCT) for patients seen in the 9 primary care clinics, aboard the adult mobile health center (AMHC), or for partners/caregivers/family members of patients seen in the clinics or ED. The AMHC provides scheduled medical services at several sites, including community centers, homeless shelters, halfway houses, churches, and outpatient substance abuse rehabilitation centers. Memorial’s large-scale HIV testing program aims to identify patients who are undiagnosed, or diagnosed and not retained in care, and link them to medical services, including our Ryan White HIV/AIDS Program-funded multidisciplinary hospital-based clinic’s rapid ART initiation program. Our testing program has demonstrated tremendous success.

In the past 12 months, 22,067 patients were tested in the ED using an opt-out approach, with 121 patients’ test results yielding a confirmed HIV diagnosis (0.5% reactive rate); 104 of these patients (86%) were linked to and retained in care. In the same time frame, 11,389 persons received a POCT in one of the primary care clinics or on the AMHC, with 31 patients’ test results yielding a reactive result (0.2% reactive rate) and 30 of these patients (97%) linked to care. In addition to the large-scale HIV testing program described, Memorial has also routinized age- and risk-based hepatitis C screening in the primary care clinics, expanded preexposure prophylaxis prescribing in the primary care clinics, implemented an HIV test-and-treat program in the Ryan White clinic, and spearheaded an inpatient antiretroviral stewardship program. HIV testing programs can be rapidly expanded within healthcare systems and can serve to increase testing in communities. Knowledge of serostatus is the first step in accessing HIV treatment, reducing transmission, and mitigating public health challenges. The Memorial Healthcare System HIV testing program demonstrates an effective HIV testing initiative designed to end the HIV epidemic.
The US Department of Health and Human Services proposed a plan to end the HIV epidemic within 10 years. The plan calls for the Centers for Disease Control and Prevention (CDC) to work with “partners and providers to quickly link people who test positive for HIV to care, so that HIV treatment can begin as soon as possible after diagnosis.” Rapid Start is an innovation that does just this, ideally starting HIV medications on the day of diagnosis. CrescentCare, a Federally Qualified Health Center (FQHC), partnered with the New Orleans Office of Health Policy to implement a city-wide linkage and same-day antiretroviral treatment (ART) program in December 2016. We studied 2 cohorts: those newly diagnosed and started on ART within 72 hours of diagnosis (CrescentCare Start Initiative [CCSI]), and ART-naive individuals who were linked and started on ART within 72 hours, but were diagnosed beyond 72 hours of clinic contact (Early Intervention Services [EIS]). We present a continuum of care for both cohorts.

The CCSI and EIS cohorts were enrolled from 12/2016 through 5/2018. Laboratory and practitioner visits were reviewed through 10/2019. Outcomes measured include achieved viral suppression, median time to viral suppression, sustained viral suppression (first viral load 12 months after linkage less than 200 copies/mL), and engagement in care (completed practitioner appointment beyond 12 months after linkage). For CCSI, 124 patients were linked within 72 hours of diagnosis. All patients chose to start ART, and none stopped due to adverse effects. The median age for CCSI was 29 years. Seventy-two percent identified as male, 22% as female, and 6% as transfemale. Sixty percent identified as African-American, 21% as white, and 6% as Latinx. Viral suppression was achieved in 98% in a median of 28 days, 90% remained virally suppressed beyond 12 months, and 98% were engaged in care beyond 12 months.

For EIS, 68 patients were linked within 72 hours of contacting our clinic. In total 67 of 68 patients chose to start ART on the day of linkage and no one stopped due to adverse effects. The median age for EIS was 29 years; 84% identified as male, 13% as female, and 3% as transfemale. Seventy-four percent identified as African-American, 21% as white, and 6% as Latinx. Viral suppression was achieved in 96% in a median of 29 days from linkage, 79% remained virally suppressed beyond 12 months, and 91% were engaged in care beyond 12 months.

This rapid start strategy at an FQHC in New Orleans shows high rates of immediate and sustained viral suppression. Differences do exist between those started within 72 hours of diagnosis and those linked to care after 72 hours. Resources are still required for retention programming. Both cohorts demonstrate that starting patients on the day of diagnosis or linkage, before laboratory test results are obtained, is a safe, well-tolerated, and effective intervention. Interventions that harness the power of virologic suppression to end the epidemic are urgently needed.
Implementing a Program to Improve Patient Retention and Viral Suppression in a Community-Based Ryan White Clinic

Michelle Ogle, MD, Warren-Vance Community Health Center, Inc

Warren-Vance Community Health Center, Inc, understands that maximizing sustained viral suppression (VS) is a vital tool to End the Epidemic (EtE). Retention in medical care among people living with HIV (PLWH) is also vital as this maximizes viral suppression, reduces the risk of disease progression, and reduces viral transmission. Implementing interventions and measuring retention presents unique challenges in rural HIV clinics. One goal in EtE is to increase access to HIV care and improve VS. Our tailored intervention addresses access, engagement, and retention in care among PLWH in rural communities in the southern region of the United States. We implemented 3 tailored interventions targeting transgender youth and men (men who have sex with men [MSM] and heterosexual men) to determine if specific methods are associated with improved retention in care. Patients who never achieved VS and those who were not durably suppressed were enrolled in the Patient Care And Retention Program (PCARP). The main objective was to address barriers to retention unique to rural communities. Implementing and measuring retention interventions presents unique challenges in rural HIV clinics. Rural RWHAP are implementing to improve Parts B and C outreach and unique individualized retention measures. A focus on retention efforts for vulnerable sub-groups, namely transgender youth will be highlighted in this innovative project. Retention in Care Measure: Scheduled Medical visits kept versus "no shows" Outcome Measure: Did the patient achieve viral load suppression at the 6-month interval visit? PCARP Results 2013 to 2018: Overall VS prior to interventions 69%. VS after implementation; 12 months, 72%; 24 months, 79%; 36 months, 83%; 48 months, 84%; and 60 months, 92%.

Identifying patients at highest risk for not being retained is important to target intervention efforts to those groups. Invalid contact information, food insecurity, lack of nutritional resources, and absence of VS are strong predictors of retention. Other important factors more specific to rural communities are inconsistent transportation and lack of a family-based support network. Characteristics associated with retention will necessarily vary between urban and rural clinics. Rurality of HIV in the deep south becomes important when prioritizing interventions for improvement. We highlight the importance and positive impact of supportive service programs on patient retention, including case management, transportation, use of social media, food, and nutrition.
The Undetectables Project

Andre Brutus, MD, Brooklyn Plaza Medical Center, Brooklyn, New York

In 2018 Brooklyn Plaza Medical Center implemented Part A, Care Coordination & DSRIP (Delivery System Reform Incentive Payment) funding through the New York City Department of Health & Mental Hygiene. Through this funding, Rising Heights, the HIV Program at Brooklyn Plaza Medical Center, improved our intervention efforts with fragile patients by using a client-centered, holistic approach through team-based management. The program uses patient navigation to identify, advocate, and coordinate resources for people living with HIV (PLWH) to ensure improved health outcomes.

To date, the clinic serves 308 patients. We are able to outreach patients who have not returned for their HIV test results, aggressively follow up with patients who are lost to care, conduct health education groups, home visits and modified directly observe therapy to support treatment adherence. In 2019, we implemented a quality improvement project targeting our new patients; New patients include newly diagnosed and patients new to the clinic with known HIV status. This population was selected based on our 2018 data, which demonstrated 50% viral load suppression for NEW patients – a 15% decrease from the previous year. To address this gap in care, the HIV Quality Improvement Committee implemented the interventions listed above & the Undetectable Project (DSRIP funding) which consisted of peer support, and a $100 voucher for unsuppressed patients who enrolled in the project, reaching and maintaining viral suppression. As the 4th quarter of 2019 comes to an end, Brooklyn Plaza is currently at 64% viral load suppression among our New patients, a 14% increase from 2018 data. We are expected to exceed our 65% viral load suppression goal for new patients by December 31, 2019. Our overall viral load suppression, including existing patients, is 86%.
Sexually Transmitted Infections on the Rise: Syphilis, Chlamydia, and Gonorrhea

Kimberly A. Workowski, MD
Professor of Medicine
Emory University School of Medicine
Atlanta, Georgia

Financial Relationships With Commercial Entities

Dr Workowski has received grant support from GlaxoSmithKline. (Updated 11/22/19)

Learning Objectives

After attending this presentation, learners will be able to:

- Describe the increases in bacterial sexually transmitted infections (STIs)
- Identify unusual presentations of chlamydia and syphilis
- Discuss forthcoming changes in treatment recommendations
Limitations of case report data
- Not all STIs are nationally notifiable
- 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 Known HIV Status, STD Surveillance Network (SSuN), 2018

STI Screening

Women and Heterosexual Men
- Chlamydia, Gonorrhea
- Women <25 or older women (increased risk) annually
  - Self-collected vaginal swab
  - No extragenital testing
- HIV (bimanual, pap smear)
- Heterosexual men
  - Consider chlamydia screening (Atlanta,或其他, STD clinic)
  - Population-based gonorrhea screening not recommended
- Retest 3 mo after treatment

Men who Have Sex with Men
- HIV, Hepatitis B
- Syphilis serology (RPR/treponemal)
- Chlamydia, Gonorrhea
- Urethral infection (NAAT)
- Rectal infection (NAAT)
- Pharyngeal infection gonorrhea (NAAT)

USPSTF, JAMA 2016; USPSTF 2014, Ann Int Med CDC, MMWR, STD Treatment Guidelines 2015

Retest 3 mo after treatment
### Rectal Gonorrhea vs Pharyngeal Gonorrhea

<table>
<thead>
<tr>
<th>Study</th>
<th>Rectal Gonorrhea</th>
<th>Pharyngeal Gonorrhea</th>
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<tbody>
<tr>
<td>Chan et al 2016</td>
<td>0.20% - 24.0%</td>
<td>0 - 16.5%</td>
</tr>
<tr>
<td>Dewart et al 2018</td>
<td>6.1% (weighted average)</td>
<td>4.6%</td>
</tr>
<tr>
<td>NHBS MSM 2017</td>
<td>3.6%</td>
<td>4.6%</td>
</tr>
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</table>

### Rectal Chlamydia vs Pharyngeal Chlamydia

<table>
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<tr>
<th>Study</th>
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</thead>
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<tr>
<td>Chan et al 2016</td>
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<td>0 - 3.6%</td>
</tr>
<tr>
<td>Dewart et al 2018</td>
<td>9.0% (weighted average)</td>
<td>1.4%</td>
</tr>
<tr>
<td>NHBS MSM 2017</td>
<td>7.9%</td>
<td>1.4%</td>
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ARS Question #1: 49 yo male HIV+, DM, CKD, CVA, HBV, HDV

- Lip pain, weight loss, anorexia, dysphagia
- CD4 453, HIV VL 275,000, HBV VL 177,000,000, Cr 2

**Diagnostic testing?**
- A) Darkfield microscopy
- B) HSV PCR
- C) Treponemal EIA
- D) Chlamydia/GC
- E) RPR

### Syphilis

Syphilis...
Syphilis Continues to Increase

Primary and Secondary Syphilis — Reported Cases by Sex and Sex of Sex Partners and HIV Status, United States, 2018

Proportion of P&S Syphilis Cases that Reported Meth or Heroin Use or Sex with a PWID, 2012–2016
Public Health Implications

- Two epidemics
  - MSM networks
  - Heterosexual networks
- Historic success in heterosexual epidemics
  - Intensive partner services, contact tracing
  - Targeted community outreach, screening, treatment to reach at-risk individuals
- Less success addressing MSM epidemics
  - MSM in smaller metropolitan areas and South and Midwest more commonly linked to heterosexual women and less likely to identify (Oster, STD, 2014)

Primary Syphilis

- Chancre appears 10-90 days after infection
  - Single, painless, indurated, with rolled edges
  - Multiple or persistent lesions
  - Most are asymptomatic
- Regional adenopathy (painless)
- Primary urethritis
  (Chambers, CID 2019)

Secondary Syphilis

- "≈3-6 weeks after primary"
  - Rash
    - Generalized lymphadenopathy
    - Constitutional symptoms
  - Mucous patches
  - Condylomata lata
  - Patchy alopecia
Unusual presentations

- *T. pallidum* PCR+ 1° anogenital lesions (Stoens et al. STI 2016)
  - Anal lesions were more common in HIV+ (34.2%) vs. HIV- (11.6%).
  - 48.2% of 1° anal or genital lesions were painful, 37.7% were multiple. Of n=37 with painful and multiple lesions, only 8% had concurrent HSV.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical characteristics of <em>T. pallidum</em> PCR+ positive primary anogenital syphilis lesions among men by HIV status</th>
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<td>excl</td>
<td>TPD excl</td>
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Syphilis serologic screening algorithms

<table>
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<th>RPR (Sensitivity)</th>
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<tr>
<td>Primary: 62–78%</td>
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<tr>
<td>Secondary: 97–100%</td>
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<tr>
<td>Tertiary: 47–64%</td>
</tr>
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</table>

- Traditional
  - Reverse sequence
    - Early primary requires RPR (active), false +
Can enhanced screening impact syphilis rates?

- Screening of MSM populations at increased risk for syphilis is suboptimal.
- Increased screening of MSM may be reducing infectious (primary and secondary) syphilis (Australia).
- More frequent screening (q3 to 6mo) of high risk MSM was more cost effective than increased screening coverage in controlling incident syphilis (modeling).

Evaluation of CNS Involvement

- Initial spirochetal invasion during early syphilis
  - Reversible or progress
  - Neurologic symptoms/signs
  - CSF examination
    - Auditory disease, cranial nerve dysfunction, meningitis, stroke, altered mental status, loss of vibration, iritis, uveitis Neurologic or ophthalmic symptoms/signs
    - Tertiary disease
      - aortitis, gumma
    - Serologic treatment failure
  - CNS invasion in early syphilis is common
  - CSF abnormalities of unclear significance in the absence of signs/symptoms
  - Neurosyphilis = CSF tests + reactive RPR + signs/symptoms
### Ocular Syphilis

- Every part of the eye can be involved during any stage of the infection
- Secondary syphilis or late stage
- Serologic tests +
  - Late ocular syphilis, 30% NEGATIVE serum RPR but + Triposistral test
  - Rarely, early syphilis (primary stage) negative (Treponemal and RPR) + eye symptoms
- 30-40% of persons with ocular syphilis will have a normal CSF examination

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### Cardiovascular Syphilis

- Aortitis (thoracic aorta)
  - Endarteritis obliterans vasa vasorum
  - Disruption of media - dilation
  - Aortic regurgitation
- Surgical evaluation for symptoms or diameter > 5.5 cm
  - Rupture may occur in 15-30% of cases
  - 47-year-old HIV + man V1 < 10
  - 10 years after secondary syphilis: RPR 1:1, TPPA +
  - Wide pulse pressure, systolic and diastolic murmur
  - Echo - moderate to severe AR
  - 6.8-cm fusiform aneurysm proximal aorta.
  - Histology - inflammation with plasma cells, gummas/histiocytes/giant cells with calcified plaques.

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### ARS #2: 32 yo HIV + man on arvs VL < 20 with sore throat, blurry vision. +anterior uveitis, RPR 1:128, LP (nl protein, glucose, VDRL neg)

**Treatment Options:**

- Benzathine PCN 2.4 mu IM x1
- Benzathine PCN 2.4 MU IM X 3 wkly
- Penicillin G 24 mu IV daily x 14 days
- Doxycycline 100 mg bid x 14 days
- Amoxicillin 3 grams daily + probenecid 500 mg qid x 14 days
Syphilis Treatment

- Benz Pcn 2.4 mu IM x 1 early syphilis
- Role of enhanced therapy
  - Rolfs (2001)
  - Observational > 500 HIV+ no difference in serologic outcomes at 12 months 1 vs 3 (Ganne 2001, Rolfs 2001)
  - Andrade R et al. CID 2017 RCT, 64 HIV+ patients with grade 1 or 2 infection
  - RCT Benz 1 vs 3 early syphilis (NCT 03637950)
- PCN alternatives (early, latent, NS)
  - Doxycycline (6 observational)
  - Ceftriaxone 1 g x 10d, HIV+ (Cas, CID 2017)

Monitoring

- Serologic nonresponse: lack of a four fold decline in nontreponemal antibody titers 12 (Early) or 24 (Late) months after therapy depending on the stage of syphilis
- Nontreponemal test titers might decline more slowly for persons previously treated for syphilis
- Serologic associated with several factors
  - Stage of syphilis
  - Initial nontreponemal titers
  - Age (older patients less likely to decline fourfold)

STI PEP/PrEP with Doxycycline

Bolan RK, STD 2015
  - 30 HIV+ MSM ≥2 episodes syphilis
  - Doxycycline-PEP 200mg po daily x 35 weeks (N=15) vs. incentive based STI-free (N=15)
  - Doxycycline-PEP decreased risk of incident syphilis, GC or CT (OR: 0.27, CI: 0.09-0.38).

Molina, Lancet ID 2018
  - 233 high risk MSM (IPERGAY)
  - Doxycycline PEP 200mg 24-72 hours after high risk sex (n=116) vs. no PEP (n=116)
  - Doxycycline PEP associated with lower occurrence of first episode of syphilis (HR 0.27, CI: 0.07-0.98), followed: median 8.7 mos.
  - Five studies underway or in development (Canada, Australia, France, United States)

Concerns and challenges
- Efficacy not determined, small sample sizes
- Which MSM would benefit most?
- Risk compensation
- Dose, regimen, and formulation (monohydrate versus hyclate)
- Effect on microbiome
- Antimicrobial resistance (23+% GC resistance)
Chlamydia

Proportion of STD Clinic Patients Testing Positive by Age Group and Sex and Sex of Sex Partners, STD Surveillance Network (SSuN), 2018

Chlamydia & Gonorrhea Diagnostic Tests

- Nucleic acid amplification tests (NAAT) recommended for women & men
- Optimal specimen: vaginal swabs in women and first-catch urine in men
- NAAT optimal for rectal and pharyngeal testing (MSM)
- Recently FDA approved at extragenital sites
- Limitations: no antibiotic resistance testing with NAAT
- NAAT POC tests

http://www.cdc.gov/mmwr

Recommendations for the laboratory-based detection of Chlamydia trachomatis and Neisseria gonorrhoeae — 2014
Chlamydia Treatment

• Azithromycin vs Doxycycline
  • RCT data - CT urethritis treatment with azithro has a cure rate of <95% (Schwebke, Marhorn, Kissinger, Grulier)
  • Meta-analysis (Kong 2014)
    - Doxy > Azi 3% (unilateral)
    - Doxy > Azi 7% (ix urethral)

• Rectal Infection
  • Several retrospective studies (doxy-azi)
  • Retest in 3mo (reinfection)

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Chlamydia Treatment

• Doxy is highly efficacious - all sites in men and women
• Azithromycin
  • efficacious in women and asymptomatic men
  • lower efficacy in urethritis, poor efficacy in rectum, 7pharynx
• RCT (asymptomatic) - US, UK, Australia
• CDC Guidelines Draft recommendations
  • Doxycycline 100 mg bid
  • Azithromycin 1 gm alternative regimen

LGV Inguinal syndrome

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

Proctocolitis in MSM or GUD + tender inguinal lymphadenopathy +/-1 perianal ulcers
• Compatible clinical syndrome
• + CT test at the anatomic site
• Exclusion of HSV, gonorrhea, syphilis
• Genotyping LGV
• Tx: Doxycycline 100 mg bid x 21 d (meta-analysis: 98.5% cure)
  • Short course therapy 7-14 d GUM clinic in UK (Simon, STD 2018)
  • Empiric tx for HSV + ulcers
  • Asymptomatic infection can occur

How likely is a patient with proctitis to have LGV?

• No routine surveillance in U.S.
• 2 studies of patients with anorectal symptoms and + CT
  • NYC, 2012-15: 23% had +LGV PCR
  • San Francisco, 2016-18: 48% had +LGV PCR
• Epi associations: HIV+, older age, Black or Hispanic
• Clinical characteristics: anal discharge, bleeding, >=10 WBC on rectal gram stain
• Asymptomatic infection can occur
  • Wide range in European studies (10-90%)
  • NYC, 2012-15: 6% of ax CT cases had +LGV PCR
• Treatment: 49 yo male with HIV off ART, IDDM, CKD, CVA, HBV, HDV
  • Evaluation:
    • RPR, GS, HSV cx, HSV serology +, CT Naat
    • Empiric tx with doxy + valtrex
    • Ulcer + CT with genotyping L2b
  • Second case:
    • 25 MSM HIV + (CD4 73, VL 300,000)
    • >30 oral sex partners
    • Painful ulcers, adenopathy
    • Ulcer + CT with genotyping L2b
    • 7 published cases

Diagnostic testing?

A) Darkfield microscopy
B) HSV PCR
C) Treponemal EIA
D) Chlamydia/GC
E) RPR

49 yo male with HIV off ART, IDDM, CKD, CVA, HBV, HDV
Gonorrhea

Gonorrhea — Rates of Reported Cases by Sex, US, 2009–2018

![Graph showing rates of gonorrhea cases by sex from 2009 to 2018.]

Gonorrhea Clinical Manifestations

<table>
<thead>
<tr>
<th>Anatomic Site</th>
<th>Syndrome</th>
</tr>
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<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, pharyngitis</td>
</tr>
<tr>
<td>Rectum</td>
<td>Asymptomatic, Proctitis</td>
</tr>
<tr>
<td>Eye</td>
<td>Conjunctivitis</td>
</tr>
<tr>
<td>Systemic (i.e., joint, blood, other sterile site)</td>
<td>Disseminated Gonococcal Infection (DGI)</td>
</tr>
<tr>
<td>Females</td>
<td></td>
</tr>
<tr>
<td>Cervix</td>
<td>Cervicitis</td>
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<tr>
<td>Fallopian tube</td>
<td>Salpingitis/Pelvic Inflammatory Disease (PID)</td>
</tr>
<tr>
<td>Urethra</td>
<td>Urethritis</td>
</tr>
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<td>Infants</td>
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<td>Pharynx</td>
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<td>Eye</td>
<td>Conjunctivitis (Neonatal Ophthalmia)</td>
</tr>
</tbody>
</table>
Disseminated Gonococcal Infection (DGI)

- 0.5-3% of gonococcal infections
- Risk factors: female/menses/pregnancy, terminal complement deficiency
- Clinical presentation
  - Mono-articular septic arthritis
  - Skin lesions (petechial or pustular)
  - Perihepatitis, endocarditis, meningitis
  - Mucosal site asymptomatic (NAAT)
- Antimicrobial susceptibility (AST) culture
- DGI infection associated with eculizumab
- FDA adverse event reporting system (June 2018)

Changing Patterns of DGI

DGI Cases Surveillance, 2015 – 2018
- GC Sterile site isolate (CA, GA)
- 2015-16 (retrospective), 2017-prospective
- 52 cases
- Demographics: 59% male (MSM 16%), 15-29 yo (34%), >45yr (34%)
- 25% septic arthritis
- 13% HIV+
- Underestimate of true burden of DGI
- Surveillance area ~4% of US population

Neisseria gonorrhoeae — GISP, 2000–2018

Figure 29. Neisseria gonorrhoeae — Percentage of Isolates with E elevated Minimum Inhibitory Concentrations (MIC)< 1 mg/L as of 2017

Table 2. Epidemiologic, clinical, and microbiologic characteristics of 21 French patients with DGI

<table>
<thead>
<tr>
<th>Year</th>
<th>Patients</th>
<th>GC sterile site isolate</th>
<th>GC sterile site isolate, Carryover GA</th>
<th>2015–16 (retrospective); 2017-prospective</th>
<th>52 cases</th>
<th>Demographics</th>
<th>59% male (MSM 16%), 15-29 yo (34%), &gt;45yr (34%)</th>
<th>25% septic arthritis</th>
<th>13% HIV+</th>
<th>Underestimate of true burden of DGI</th>
<th>Surveillance area ~4% of US population</th>
</tr>
</thead>
</table>

Figure 31. Neisseria gonorrhoeae — Prevalence of Tetracycline, Penicillin, or Macrolidone Resistance* or Elevated Ciprofloxacin, Chloramphenicol, or Azithromycin MICs for 10 Project Years — Neisseria gonorrhoeae Isolate Surveillance Project (GISP), 2000–2018

*Resistance = Fluorescent Yellow/Orange (MIC 1.0 mg/L), Penicillin: 1.0 mg/L, Chloramphenicol: 2.0 mg/L, Azithromycin: 1.0 mg/L, Tetracycline: 1.0 mg/L, Ciprofloxacin: 2.0 mg/L, Vancomycin: 1.5 mg/L, Erythromycin: 2.0 mg/L, Gentamicin: 2.0 mg/L, Kanamycin: 2.0 mg/L, Rubribactin: 0.5 mg/L, Spectinomycin: 2.0 mg/L, Tobramycin: 2.0 mg/L.
Neisseria gonorrhoeae — Percentage of Urethral Isolates with Elevated Minimum Inhibitory Concentrations (MICs) to Azithromycin* and Ceftriaxone† by Sex and Sex of Sex Partners, Gonococcal Isolate Surveillance Project (GISP), 2009–2018

* Elevated Azithromycin MIC: ≥2.0 μg/mL.
† Elevated Ceftriaxone MIC: ≥0.125 μg/mL.

Gonorrhea

- United States
  - Ceftriaxone 250 mg IM in a single dose
  - 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
  - Azithromycin 2 gm orally in a single dose
- Japan
  - Ceftriaxone 1 gm IV/IM in a single dose

- Optimize therapeutic regimen
- PK/PD, bacterial burden
- Treatment Failures
- Reinfection
- Failure-culture/AST + partner treatment
- Novel Agents (Zoliflodacin, Gepotidacin)
- WGS for genomic epidemiology
- Identification of mutations conferring resistance
- Characterizing outbreaks and spread of resistant strains

GC Treatment Draft Recommendations

Ceftriaxone 500 mg IM once*

*for persons weighing 150 kg or more, use 1g IM Ceftriaxone

Anti-chlamydial therapy when chlamydia has not been ruled out

- Azithromycin resistance is widespread and increasing
- Wide inter-individual pharmacokinetics
- Resistance prevention concentration unknown, likely higher than dose for cure
- Pharyngeal gonorrhea is common/un-screened (test of cure 7-10 d)
STIs on the Rise

- Syphilis
  - Heterosexual, MSM
  - Painful ulcers, ocular, CV
  - Screen frequently
- Chlamydia
  - Extra-gential infection (MSM)
  - Urethral and rectal
  - Doxycycline
- Gonorrhea
  - Reappearance of DGI
  - Antimicrobial resistance
  - Ceftriaxone
- Pharynx test of cure

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Question-and-Answer Period