The Medical Management of HIV/AIDS and Hepatitis

COURSE CHAIRS
Diane V. Havlir, MD
Professor of Medicine
Chief, HIV, ID and Global Medicine Division
University of California, San Francisco
Zuckerberg San Francisco General Hospital and Trauma Center

Meg D. Newman, MD, FACP
UCSF Senate Emeritus – Medicine
HIV, ID and Global Medicine Division
Zuckerberg San Francisco General Hospital and Trauma Center

Annie Luetkemeyer, MD
Associate Professor of Medicine
HIV, ID and Global Medicine Division
Zuckerberg San Francisco General Hospital and Trauma Center
Upcoming CME Courses

Infectious Diseases in Clinical Practice:
Update on Inpatient and Outpatient Infectious Diseases
Monday, February 15 – Saturday, February 21, 2020
Hilton Hawaiian Village, Honolulu, Hawaii

Integrative Mental Health for the Pediatric Provider
Friday, February 21 – Sunday, February 23, 2020
1440 Multiversity, Scotts Valley, California

Being an Occupational and Environmental Health "Detective" and
Updates in Occupational and Environmental Medicine
Wednesday, March 4 – Saturday, March 7, 2020
Marriott Fisherman’s Wharf, San Francisco, California

Diabetes Update and Advances in Endocrinology and Metabolism
Thursday, March 12 – Friday, March 14, 2020
Marine’s Memorial Club and Hotel, San Francisco, California

FACES 2020: An Interdisciplinary Approach
Thursday, March 26 – Saturday, March 28, 2020
Park Central Hotel, San Francisco, California

Primary Care Medicine: Update 2020
Monday, April 5 – Saturday, April 10, 2020
Wailea Beach Resort by Marriott, Wailea, Maui, Hawaii

International Symposium on Incisional Hernia Prevention
Friday, May 28 – Saturday, May 29, 2020
InterContinental San Francisco, San Francisco, California

53rd Annual Advances and Controversies in Clinical Pediatrics
Thursday, May 28 – Saturday, May 30, 2020
Park Central Hotel, San Francisco, California

Neurosurgery Update 2020
Thursday, July 30 – Saturday, August 1, 2020
Silverado Resort and Spa – Napa, California

All Courses Managed by:
UCSF Office of Continuing Medical Education
3333 California Street, Room 450, San Francisco, CA 94118
For attendee information call: 415-476-4251
For exhibitor information: 415-476-4253
Visit the web site at www.cme.ucsf.edu
HIV, ID and Global Medicine Division
Zuckerberg San Francisco General Hospital and Trauma Center
Department of Medicine
University of California, San Francisco, School of Medicine
presents

31st Annual
The Medical Management of
HIV/AIDS and Hepatitis

December 12-14, 2019
Park Central Hotel
San Francisco, California

Course Chairs
Diane V. Havlir, MD
Meg D. Newman, MD, FACP
Annie Luetkemeyer, MD
University of California, San Francisco
Acknowledgement of Commercial Support

This CME activity was supported in part by educational grants from the following:

Gilead Sciences

Janssen Therapeutics

Merck & Co., Inc

ViiV Healthcare
Exhibitors

AbbVie Pharmaceuticals
AIDS Clinical Trials Group
AHF Pharmacy (AIDS Healthcare Foundation)
Alto Pharmacy
Antares Pharmaceuticals
UCSF Clinician Consultation Center
Dynavax
EMD Serono, Inc.
EndHepCSF
Gilead Sciences
HIVE
Janssen Therapeutics
Merck Virology
Mission Wellness Pharmacy
Monogram Biosciences
Pacific AIDS Education and Training Center
The Ihangane Project
ViiV Healthcare
The Medical Management of HIV/AIDS and Hepatitis

This course provides the active intermediate-to-advanced clinician with a comprehensive review of the science of HIV and infectious hepatitis, as well as updates on the application of HIV, HCV and HBV therapies. For ambitious newer clinicians who want a challenge, we continue offer our New Clinicians’ Track (NCT), which provides five additional lectures; antiretroviral therapy (ART), basic pharmacology, ART resistance, opportunistic infections and IRIS.

The course lecturers are leading clinicians and researchers who are also dedicated to teaching in their areas of expertise. Dr. Diane Havlir will frame the conference in the opening plenary with her keen take on the ‘Top Ten Issues’ in HIV medicine. Dr. Susan Buchbinder will provide the underpinnings of prevention efforts and explore future efforts, followed by Drs. Hyman Scott and Jonathan Volk, who will highlight the clinical expansion and nuances of successful PrEP administration. Days 1 and 3 will be filled with important teachings in regard to effective administration of ART beginning with Dr. Monica Gandhi’s talk on the ‘State of the Art of Antiretroviral Use’. A lively debate will follow on controversial ART questions including metabolic and weight complications of ART. Dr. Susan Philip will provide an update on STI’s for 2019 and Dr. Priscilla Hsue rejoins the program to bolster our knowledge base on HIV Cardiology.

Day 2 begins with Dr. Annie Luetkemeyer covering Hepatitis C care and cure, followed by Dr. Danielle Brandman covering the evolving topic of NALFD and NASH. Dr. Jenny Price will address the quandaries in HBV and cirrhosis treatment. All of these talks have case-based formats and address the issues that arise in the care of chronically infected and/or cirrhotic patients and the safe administration of efficacious therapies.

Dr. Toby Mauer will conclude the morning by revisiting the common and evolving dermatological manifestations of HIV. The afternoon opens with Dr. Deborah Cohan updating us on HIV and Reproductive Health followed by Dr. Joel Palefsky who rejoins the program this year to cover anal disease and HIV. Small group sessions will occupy the remainder of Day 2.

On Day 3 we will continue to explore how to manage complications common in HIV medicine, with Dr. Vivek Jain speaking on hyperlipidemia and Dr. Oliver Bacon will build on our STI knowledge base and bring interesting cases from the SF City Clinic and beyond. Dr. Steven Deeks will share the progress we have made toward a cure for HIV/AIDS. Dr. Kathleen (Kat) Grieco will address the evolution of available therapies and strategies in her talk on “Addiction Medicine”.

In the afternoon on Day 3, you’ll be able to privately test your antiretroviral knowledge and judgment and compare your clinical choices to those of the master clinicians on our
ART panel led by Dr. Oliver Bacon. Dr. Kelly Wentworth will join the faculty this year and cover Endocrinology with a focus on “Diabetes and Osteoporosis and HIV”.

This 3-day conference will provide the breadth and depth of topics necessary to effectively practice in the field of HIV Medicine.

This symposium is offered by the HIV, ID and Global Medicine Division, Zuckerberg San Francisco General Hospital and Trauma Center, Department of Medicine, University of California, San Francisco, and the School of Medicine.

**Educational Objectives**

Upon completion of this program, attendees will be able to:

- Diagnose, treat, and prevent important conditions in HIV medicine and HIV medicine subspecialties for improved patient outcomes;
- Apply in practice the latest treatment guidelines and recommendations for the prevention of HIV transmission and the appropriate use of PrEP; Apply new recommendations for initiating and timely switching of antiretroviral combinations in appropriate patients;
- Apply new recommendations for appropriate treatment of both Hepatitis C and/or Hepatitis B and HIV co-infection;
- Identify the new developments and apply treatment recommendations in HIV related STI’s, dermatologic disease, reproductive medicine, anal disease, cardiac and addiction medicine, as well as the endocrine issues of diabetes and osteoporosis.

**ACCREDITATION**

The University of California, San Francisco School of Medicine (UCSF) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

**Physicians**

UCSF designates this live activity for a maximum of 21.50 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This CME activity meets the requirements under California Assembly Bill 1195, Continuing Education and Cultural and Linguistic Competency.

**Nurses**

For the purpose of recertification, the American Nurses Credentialing Center accepts AMA PRA Category 1 Credit™ issued by organizations accredited by the ACCME.

**Physician Assistants**

AAPA accepts category 1 credit from AOACCME, Prescribed credit from AAFP, and AMA PRA Category 1 Credit™ from organizations accredited by the ACCME.

**Pharmacists**

The California Board of Pharmacy accepts as continuing professional education those courses that meet the standard of relevance to pharmacy practice and have been approved for AMA PRA Category 1 Credit™.
American Board of Internal Medicine (ABIM) MOC:
Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 21.50 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.

General Information

Attendance Verification/Sign-In Sheet / CME Certificates
Please remember to sign-in on the sign-in sheet when you check in at the UCSF Registration Desk on your first day. You only need to sign-in once for the course, when you first check in.

After the meeting, you will receive an email from Qualtrics@ucsf.edu with a link to complete your online Course Evaluation/Electronic CME Certificate. Please make sure that you add this email to your safe senders list. The Qualtrics system will send you reminders to complete your CME Certificate Claiming until you complete it.

Upon completing the Electronic CME Certificate, your CME certificate will be automatically generated to print and/or email yourself a copy. For smartphone users, you may want to take a photo of your certificate as some settings prevent you from emailing the certificate.

The link will be available for 30 days after the last day of the course. However, after that date the link will expire and you will no longer be able to claim your credits online. You must then contact the Office of CME at registration@ocme.ucsf.edu to receive your certificate and a $15 administrative fee may be applied.

Speaker Survey – Electronic
On Thursday, December 12th, you should receive an email from Qualtrics@ucsf.edu with a personalized link to access the Speaker Survey. Please make sure that you add this email to your safe senders list. This year the survey will be completed online for added convenience. If you did not receive the link, please see the UCSF Registration Desk. The Speaker Survey is to be completed in real time during the course and is separate from the Evaluation/CME Certificate.

Security
We urge caution with regard to your personal belongings and syllabus books. We are unable to replace these in the event of loss. Please do not leave any personal belongings unattended in the meeting room during lunch or breaks or overnight.

Exhibits
Industry exhibits will be available outside the ballroom during breakfasts and breaks, and lunches.

Final Presentations
A link to PDF versions of the final presentations will be sent via e-mail approximately 3 weeks post course. Only presentations that have been authorized for inclusion by the presenter will be included.
Federal and State Law
Regarding Linguistic Access and Services for Limited English Proficient Persons

I. Purpose.
This document is intended to satisfy the requirements set forth in California Business and Professions code 2190.1. California law requires physicians to obtain training in cultural and linguistic competency as part of their continuing medical education programs. This document and the attachments are intended to provide physicians with an overview of federal and state laws regarding linguistic access and services for limited English proficient (“LEP”) persons. Other federal and state laws not reviewed below also may govern the manner in which physicians and healthcare providers render services for disabled, hearing impaired or other protected categories.

The Federal Civil Rights Act of 1964, as amended, and HHS regulations require recipients of federal financial assistance (“Recipients”) to take reasonable steps to ensure that LEP persons have meaningful access to federally funded programs and services. Failure to provide LEP individuals with access to federally funded programs and services may constitute national origin discrimination, which may be remedied by federal agency enforcement action. Recipients may include physicians, hospitals, universities and academic medical centers who receive grants, training, equipment, surplus property and other assistance from the federal government.

HHS recently issued revised guidance documents for Recipients to ensure that they understand their obligations to provide language assistance services to LEP persons. A copy of HHS’s summary document entitled “Guidance for Federal Financial Assistance Recipients Regarding Title VI and the Prohibition Against National Origin Discrimination Affecting Limited English Proficient Persons – Summary” is available at HHS’s website at: http://www.hhs.gov/ocr/lep/.

As noted above, Recipients generally must provide meaningful access to their programs and services for LEP persons. The rule, however, is a flexible one and HHS recognizes that “reasonable steps” may differ depending on the Recipient’s size and scope of services. HHS advised that Recipients, in designing an LEP program, should conduct an individualized assessment balancing four factors, including: (i) the number or proportion of LEP persons eligible to be served or likely to be encountered by the Recipient; (ii) the frequency with which LEP individuals come into contact with the Recipient’s program; (iii) the nature and importance of the program, activity or service provided by the Recipient to its beneficiaries; and (iv) the resources available to the Recipient and the costs of interpreting and translation services.

Based on the Recipient’s analysis, the Recipient should then design an LEP plan based on five recommended steps, including: (i) identifying LEP individuals who may need assistance; (ii) identifying language assistance measures; (iii) training staff; (iv) providing notice to LEP persons; and (v) monitoring and updating the LEP plan.

A Recipient’s LEP plan likely will include translating vital documents and providing either on-site interpreters or telephone interpreter services, or using shared interpreting services with other Recipients. Recipients may take other reasonable steps depending on the emergent or non-emergent needs of the LEP individual, such as hiring bilingual staff who are competent in the skills required for medical translation, hiring staff interpreters, or contracting with outside public or private agencies that provide interpreter services. HHS’s guidance provides detailed examples of the mix of services that a Recipient should consider and implement. HHS’s guidance also establishes a “safe harbor” that Recipients may elect to follow when determining whether vital documents must be translated into other languages. Compliance with the safe harbor will be strong evidence that the Recipient has satisfied its written translation obligations.

In addition to reviewing HHS guidance documents, Recipients may contact HHS’s Office for Civil Rights for technical assistance in establishing a reasonable LEP plan.

The California legislature enacted the California’s Dymally-Alatorre Bilingual Services Act (Govt. Code 7290 et seq.) in order to ensure that California residents would appropriately receive services from public agencies regardless of the person’s English language skills. California Government Code section 7291 recites this legislative intent as follows:

“The Legislature hereby finds and declares that the effective maintenance and development of a free and democratic society depends on the right and ability of its citizens and residents to communicate with their government and the right and ability of the government to communicate with them.

The Legislature further finds and declares that substantial numbers of persons who live, work and pay taxes in this state are unable, either because they do not speak or write English at all, or because their primary language is other than English, effectively to communicate with their government. The Legislature further finds and declares that state and local agency employees frequently are unable to communicate with persons requiring their services because of this language barrier. As a consequence, substantial numbers of persons presently are being denied rights and benefits to which they would otherwise be entitled.

It is the intention of the Legislature in enacting this chapter to provide for effective communication between all levels of government in this state and the people of this state who are precluded from utilizing public services because of language barriers.”

The Act generally requires state and local public agencies to provide interpreter and written document translation services in a manner that will ensure that LEP individuals have access to important government services. Agencies may employ bilingual staff, and translate documents into additional languages representing the clientele served by the agency. Public agencies also must conduct a needs assessment survey every two years documenting the items listed in Government Code section 7299.4, and develop an implementation plan every year that documents compliance with the Act. You may access a copy of this law at the following url: http://www.spb.ca.gov/bilingual/dymallyact.htm
# Faculty List

## Course Chairs

<table>
<thead>
<tr>
<th>Name</th>
<th>Title and Affiliations</th>
</tr>
</thead>
</table>
| **Diane V. Havlir, MD**     | Professor of Medicine  
Chief, Division of HIV, Infectious Diseases, and Global Medicine Division  
University of California, San Francisco  
Zuckerberg San Francisco General Hospital and Trauma Center |
| **Meg D. Newman, MD, FACP** | UCSF Senate Emeritus – Medicine  
Division of HIV, Infectious Diseases, and Global Medicine Division  
Zuckerberg San Francisco General Hospital and Trauma Center |
| **Annie Luetkemeyer, MD**   | Professor of Medicine  
Division of HIV, Infectious Diseases, and Global Medicine Division  
Zuckerberg San Francisco General Hospital and Trauma Center |

## Course Faculty

(Division of HIV, Infectious Diseases, and Global Medicine, Zuckerberg San Francisco General Hospital and Trauma Center unless indicated)

<table>
<thead>
<tr>
<th>Name</th>
<th>Title and Affiliations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oliver M. L. Bacon, MD, MPH</strong></td>
<td>Associate Professor of Medicine</td>
</tr>
</tbody>
</table>
| **Danielle Brandman**       | Director, UCSF Fatty Liver Clinic  
Associate Professor of Medicine  
Division of Hepatology and Liver Transplantation |
| **Susan Buchbinder, MD**     | Director, Bridge HIV Population Health Division  
San Francisco Department of Public Health  
Clinical Professor of Medicine and Epidemiology |
| **Jehan Budak, MD**          | Action Assistant Professor of Medicine  
Department of Allergy and Infectious Diseases  
University of Washington, Seattle, WA |
| **A. Asa Clemenzi-Allen, MD** | Director, HIV & Integrated Services CoE,  
San Francisco Department of Public Health  
Assistant Professor of Medicine |
| **Susa Coffey, MD**          | Professor of Medicine                                                                 |
| **Deborah Cohan, MD, MPH**   | Professor Department of Obstetrics, Gynecology, and Reproductive Sciences  
Medical Director, HIV/EM |
| **Steven Deeks, MD**         | Professor of Medicine                                                                 |
Monica Gandhi, MD, MPH
Professor of Medicine,
Medical Director, Ward 86 Clinic

Katherine Grieco, DO FASAM
Medical Director of HAVEN
Health Assistance InterVention Education Network
State of Connecticut

C. Bradley Hare, MD
Chief, Infectious Diseases, HIV and Travel Medicine
Kaiser Permanente
San Francisco, CA

Matthew Hickey, MD
Clinical Fellow

Priscilla Hsue, MD
Processor of Medicine
Division of Cardiology

Vivek Jain, MD, MAS
Associate Professor of Medicine

Harry Lampiris, MD
Professor of Medicine
Chief, Infectious Disease Section
San Francisco VA Medical Center

Carina Marquez, MD, MPH
Assistant Professor of Medicine

Toby A. Maurer, MD
Professor and Chief of Dermatology
Zuckerberg San Francisco General

Joel Palesfsky, MD, FRCP (C)
Professor of Medicine
Division of Infectious Diseases

Susan Philip, MD, MPH
Deputy Health Officer
Director, Disease Prevention and Control Branch, Population Health Division
San Francisco Department of Public Health

Sarah Puryear, MD, PhD
UCSF Infectious Diseases
Clinical Fellow
Jennifer Price, MD  
Associate Professor of Medicine  
Division of Hepatology and Liver Transplantation

Parya Saberi, PharmD, MAS  
Assistant Professor of Medicine  
UCSF Center of AIDS Prevention Studies

Hyman Scott, MD  
Medical Director, Clinical Research  
Bridge HIV, San Francisco Department of Public Health  
Assistant Clinical Professor, Division of HIV, ID, and Global Medicine

John Szumowski, MD  
Attending Physician, Division of Infectious Diseases, Santa Clara Valley Medical Center  
Clinical Assistant Professor (Affiliate)  
Division of Infectious Diseases and Geographic Medicine  
Stanford University School of Medicine

Jonathan E. Volk, MD, MPH  
Infectious Diseases & Internal Medicine  
Kaiser Permanente  
San Francisco, CA

Kelly Wentworth, MD  
Assistant Adjunct Professor  
Division of Endocrinology

Lisa G. Winston, MD  
Professor of Medicine
Disclosures

The following individuals have disclosed they have no financial interest/arrangement or affiliation with any commercial interests who provide products or services relating to their presentation(s) in this continuing medical education activity:

Annie Luetkemeyer, MD  Harry Lampiris, MD
Oliver M. L. Bacon, MD, MPH  Toby A. Maurer, MD
Jehan Budak, MD  Joel Palefsky, MD, FRCP (C)
A. Asa Clemenzi-Allen, MD  Sarah Puryear, MD, PhD
Susa Coffey, MD  Jennifer Price, MD
Deborah Cohan, MD, MPH  Parya Saberi, PharmD, MAS
Monica Gandhi, MD, MPH  Hyman Scott, MD
Katherine Greico, DO  Jonathan E. Volk, MD, MPH
Matthew Hickey, MD  Kelly Wentworth, MD
Vivek Jain, MD, MAS  Lisa G. Winston, MD

The following individuals have disclosed having a financial interest/arrangement or affiliation during the past twelve months with a commercial interest who provides products or services relating to their presentation(s) in this continuing medical education activity. All conflicts of interest have been resolved in accordance with the ACCME Standards for Commercial Support:

<table>
<thead>
<tr>
<th>Danielle Brandman, MD, MAS</th>
<th>Allergan</th>
<th>Gilead</th>
<th>Grant/Research Support</th>
<th>Grant/Research Support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steven Grant Deeks, MD</td>
<td>Gilead</td>
<td>Merck</td>
<td>Grant/Research Support</td>
<td>Grant/Research Support</td>
</tr>
<tr>
<td></td>
<td>ViiV</td>
<td>AbbVie</td>
<td>Grant/Research Support</td>
<td>Grant/Research Support</td>
</tr>
<tr>
<td></td>
<td>Eli Lilly</td>
<td>ByroLogyx</td>
<td>Advisor or Reviewer</td>
<td>Advisor or Reviewer</td>
</tr>
<tr>
<td></td>
<td>Enochian</td>
<td>Biosciences</td>
<td>Stock Shareholder (excluding mutual funds)</td>
<td>Board Member</td>
</tr>
<tr>
<td>Priscilla Hsue, Md</td>
<td>Gilead</td>
<td>Metck</td>
<td>Honorarium Recipient</td>
<td>Honorarium Recipient</td>
</tr>
<tr>
<td>Annie Luetkemeyer, MD</td>
<td>AbbVie</td>
<td>Gilead</td>
<td>Grant/Research Support</td>
<td>Grant/Research Support</td>
</tr>
<tr>
<td></td>
<td>Gilead</td>
<td>ProteusMerck</td>
<td>Grant/Research Support</td>
<td>Grant/Research Support</td>
</tr>
<tr>
<td></td>
<td>GSK</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>toby maurer, MD</td>
<td>Medweb</td>
<td></td>
<td>Consultant</td>
<td></td>
</tr>
<tr>
<td>Jol Palefsky, MD</td>
<td>Merck and Co.</td>
<td></td>
<td>Grant/Research Support</td>
<td>Board Member</td>
</tr>
<tr>
<td></td>
<td>Ubiome</td>
<td></td>
<td>Grant/Research Support</td>
<td>Advisor or Reviewer</td>
</tr>
<tr>
<td></td>
<td>Vir</td>
<td></td>
<td>Grant/Research Support</td>
<td>Advisor or Reviewer</td>
</tr>
<tr>
<td></td>
<td>Biotechnology</td>
<td></td>
<td>Stock Shareholder (excluding mutual funds)</td>
<td>Grant/Research Support</td>
</tr>
<tr>
<td></td>
<td>Antiva</td>
<td>Biociences</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jennifer C Price, MD, PhD</td>
<td>Gilead</td>
<td>Grant/Research Support</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------</td>
<td>------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Merck</td>
<td>Honorarium Recipient</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surrozen</td>
<td>Grant/Research Support</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Advisor or Reviewer</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This UCSF CME educational activity was planned and developed to: uphold academic standards to ensure balance, independence, objectivity, and scientific rigor; adhere to requirements to protect health information under the Health Insurance Portability and Accountability Act of 1996 (HIPAA); and, include a mechanism to inform learners when unapproved or unlabeled uses of therapeutic products or agents are discussed or referenced.

This activity has been reviewed and approved by members of the UCSF CME Governing Board in accordance with UCSF CME accreditation policies. Office of CME staff, planners, reviewers, and all others in control of content have disclosed they have no relevant financial relationships.
# COURSE PROGRAM

**Thursday, December 12, 2019**

<table>
<thead>
<tr>
<th>Time</th>
<th>Event Description</th>
<th>Presenter(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7:00 am</td>
<td>Registration and Continental Breakfast</td>
<td>Drs Diane Havlir, Meg Newman, and Annie Luetkemeyer</td>
</tr>
<tr>
<td>8:00 am</td>
<td>Introduction</td>
<td></td>
</tr>
<tr>
<td>8:10 am</td>
<td>Top Ten Issues in HIV Medicine</td>
<td>Dr. Diane Havlir</td>
</tr>
<tr>
<td>8:50 am</td>
<td>Great Cases from the Bay</td>
<td>Drs. Ayesha Appa, Annie Luetkemeyer, Carina Marquez, Hyman Scott</td>
</tr>
<tr>
<td>9:30 am</td>
<td>The Foundation of Prevention</td>
<td>Dr. Susan Buchbinder</td>
</tr>
<tr>
<td>10:10 am</td>
<td>Break</td>
<td></td>
</tr>
<tr>
<td>10:40 am</td>
<td>PrEP 2019: Cases from the Clinics</td>
<td>Drs. Hyman Scott and Jonathan Volk</td>
</tr>
<tr>
<td>11:20 am</td>
<td>The State of the Art of ART</td>
<td>Conference Faculty</td>
</tr>
<tr>
<td>12:00 pm</td>
<td>Lunch on your Own</td>
<td></td>
</tr>
<tr>
<td>12:20 - 1:20</td>
<td>Optional Lunch Workshop: Additional Fee and Pre-registration Required</td>
<td>Dr. Vivek Jain</td>
</tr>
<tr>
<td>1:30 pm</td>
<td>Tipping the Scales: Is ART adding pounds to our patients?</td>
<td>Dr. Matthew Hickey</td>
</tr>
<tr>
<td>2:05 pm</td>
<td>The Great Debate About ART- Panel Style</td>
<td>Moderator: Dr. Annie Luetkemeyer, Panel Drs. Bradley Hare, Susa Coffey, John Szumowski</td>
</tr>
<tr>
<td>3:15 pm</td>
<td>Break</td>
<td></td>
</tr>
<tr>
<td>3:45 pm</td>
<td>*Update in STI's 2019</td>
<td>Dr. Susan Philip</td>
</tr>
<tr>
<td>4:30 pm</td>
<td>*Complicated Cases in HIV Cardiology</td>
<td>Dr. Priscilla Hsue</td>
</tr>
<tr>
<td>5:15 pm</td>
<td>Adjourn</td>
<td></td>
</tr>
</tbody>
</table>
Friday, December 13, 2019

7:00 am  Continental Breakfast

**PLENARY SESSION V: Viral Hepatitis and Care of the Liver Patient**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Title</th>
<th>Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00</td>
<td>G</td>
<td>Case-based Approach to HCV Care and Cure: the 2019 Perspective</td>
<td>Dr. Annie Luetkemeyer</td>
</tr>
<tr>
<td>8:35</td>
<td>G</td>
<td>*Making Sense of NALFD and NASH: Diagnosis and Management</td>
<td>Dr. Danielle Brandman</td>
</tr>
<tr>
<td>9:15</td>
<td>Break</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9:45</td>
<td>G</td>
<td>*10 Brilliant HBV Medicine and Cirrhosis Questions and 10 Brilliant Answers</td>
<td>Dr. Jennifer Price</td>
</tr>
<tr>
<td>10:20</td>
<td></td>
<td>Hepatitis Panel</td>
<td>Moderator: Dr. Susa Coffey Drs. Annie Luetkemeyer, Jennifer Price and Danielle Brandman</td>
</tr>
</tbody>
</table>

**PLENARY SESSION VI: Dermatology**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Title</th>
<th>Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>11:10</td>
<td></td>
<td>HIV Dermatology: The Common Diagnosis Revisted</td>
<td>Dr. Toby Maurer</td>
</tr>
<tr>
<td>12:00</td>
<td></td>
<td>Lunch on your Own</td>
<td></td>
</tr>
<tr>
<td>12:00</td>
<td>Optional Lunch Workshop: Additional Fee &amp; Pre-registration Required</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>New Clinicians’ Workshop: the Building Blocks of HIV Therapy – Intro to HIV Pharmacology</td>
<td>Dr. Parya Saberi</td>
</tr>
</tbody>
</table>

**PLENARY SESSION VII: Reproductive Health and STI’s**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Title</th>
<th>Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:20</td>
<td></td>
<td>HIV and Reproductive Health</td>
<td>Dr. Deborah Cohan</td>
</tr>
<tr>
<td>2:00</td>
<td></td>
<td>*Anal Disease and HIV in 2019</td>
<td>Dr. Joel Palefsky</td>
</tr>
<tr>
<td>2:45</td>
<td></td>
<td>Break and Transition to Breakout Sessions</td>
<td></td>
</tr>
</tbody>
</table>

**PLENARY SESSION VIII: Small Group Sessions (Select either Option A or B)  No Additional Fees**

**Option A:**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>3:10 – 4:00</td>
<td>NCTNew Clinicians’ Workshops  (No Additional Fee &amp; Pre-registration Required)</td>
<td>Dr. Susa Coffey</td>
</tr>
<tr>
<td>4:10 – 5:00</td>
<td>NCTIRIS and Opportunistic Infections</td>
<td>Dr. Carina Marquez</td>
</tr>
</tbody>
</table>

**Option B:**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>3:10 - 4:00</td>
<td>Update in ID Relevant to HIV Care</td>
<td>Dr. Lisa Winston</td>
</tr>
<tr>
<td>4:10 - 5:00</td>
<td>Incarceration and HIV in 2019</td>
<td>Dr. A. Asa Clemenzi-Allen</td>
</tr>
</tbody>
</table>

5:00 pm  Adjourn
Saturday, December 14, 2019

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>7:00 am</td>
<td><em>Continental Breakfast</em></td>
</tr>
</tbody>
</table>

**PLENARY SESSION VIII: Optimizing Care of the HIV Patient**

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00</td>
<td>G Lipids, Statins and HIV: Topics in Clinical Management</td>
<td>Dr. Vivek Jain</td>
</tr>
<tr>
<td>8:35</td>
<td>Moving Toward a Cure: Where are We Now?</td>
<td>Dr. Steven Deeks</td>
</tr>
<tr>
<td>9:15</td>
<td>*Interesting STI Cases from the Clinic</td>
<td>Dr. Oliver Bacon</td>
</tr>
<tr>
<td>10:00</td>
<td>Break</td>
<td></td>
</tr>
<tr>
<td>10:30</td>
<td>P G Addiction Medicine Update for the HIV Primary Care Clinician</td>
<td>Dr. Katherine Grieco</td>
</tr>
<tr>
<td>11:20</td>
<td>*Interesting Cases in HIV Medicine?</td>
<td>Dr. Jehan Budak</td>
</tr>
<tr>
<td>12:00</td>
<td>Questions for speakers</td>
<td></td>
</tr>
<tr>
<td>12:15</td>
<td>Lunch On Your Own</td>
<td></td>
</tr>
</tbody>
</table>

**PLENARY SESSION IX: ART Management, TB, and Endocrinology Updates**

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Speaker</th>
</tr>
</thead>
</table>
| 1:45  | ART Panel: Integrating Your Knowledge: What Would You Recommend for These Patients? | Moderator: Dr. Oliver Bacon  
Drs. Jehan Budak  
Harry Lampiris,  
Annie Luetkemeyer |
| 2:40  | What's New with Tuberculosis in 2019                                  | Dr. Sarah Puryear     |
| 3:20  | Break                                                               |                       |
| 3:45  | G *Endocrine Update 2019: A Focus on Diabetes and Osteoporosis       | Dr. Kelly Wentworth   |
| 4:30  | Closing Remarks                                                       | Drs. Diane Havlir,  
Meg Newman, and  
Annie Luetkemeyer |
| 4:35 pm | Adjourn                                                                |                       |

*New Topics for 2019

P = Pain Credit  
G = Geriatric Credit  
T = Trauma Credit
Diane Havlir, MD
Professor of Medicine
University of California, San Francisco

Top 10 Stories in HIV Medicine

Disclosures
- Receive funding for research from NIH
- Gilead sciences provides antiretroviral therapy for NIH funded SEARCH research study

Story 1: ART Guidelines

AR1: In 2019, new ART Guidelines recommend which of these 2-drug regimens in initial therapy for “most persons living with HIV?”

A. Dolutegravir + lamivudine (DTG + 3TC)
B. Dolutegravir + rilpivirine (DTG + RPV)
C. Darunavir(boosted) + DTG
D. All of the above
E. None of the above
Answer: None
2019: What to start in “most patients”

<table>
<thead>
<tr>
<th>CLASS</th>
<th>REGIMEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>INSTI</td>
<td>BIC/TAF/FTC</td>
</tr>
<tr>
<td>INSTI</td>
<td>DTG/ABC/3TC</td>
</tr>
<tr>
<td>INSTI</td>
<td>DTG/TAF/FTC</td>
</tr>
<tr>
<td>INSTI*</td>
<td>RTG/TAF/FTC*</td>
</tr>
</tbody>
</table>

*HHS Guidelines only

Some options TDF or TAF recommended

IAS-USA Guidelines, JAMA, July 2018
HHS guidelines, October 2018

2019 Updates

- Start ART for HIV-1 upon diagnosis and use INSTI (integrase strand inhibitor)
- Address substance use disorders when screening and treating persons for HIV infection
- Provide gender affirmative care for transgender population

Summary

- This past year, there were some new recommendations but not “transformative” changes in specific ART regimens
- We anticipate guideline changes in the coming year upon approval of long-acting injectable cabotegravir/rilpivirine and as more information is forthcoming on combinations and agents

Story 2: ART imperfections
Association of Neural Tube Defects (NTD) and Dolutegravir during conception: less, but detectable

Taepamo Study, Botswana

- 0.9 NTD with DTG at conception
- 0.3 NTD non-DTG at conception
- 0.08 NTD HIV-negative

Zash, NEJM, 2019

HHS Recommendations for women of childbearing potential

- DTG should not be prescribed for individuals:
  - Who are pregnant and within 12 weeks post-conception
  - Who are of childbearing potential and planning to become pregnant
  - Who are of childbearing potential, sexually active, and not using effective contraception

- For those who are using effective contraception, a DTG-based regimen can be considered after weighing the risks and benefits of DTG

- Similar recommendations for bictegravir
- Elvitegravir not recommended (pharmacokinetics); little data on raltegravir

HHS guidelines, July 2019

Weight Gain and ART
Large Randomized Study: “ADVANCE”

South Africa
Treatment naive
No TB or pregnancy
Primary endpoint: viral suppression
Secondary endpoints: renal, bone, metabolic

1053 Participants

1053 Participants

54 Weeks

Recipients of DTG/TAF/FTC:
- 10 kg mean weight increase in women
- 5 kg mean weight increase in men

Venter, IAS and NEJM, 2019

Large weight gains over time: greatest in DTG/TAF/FTC arm

Venter, IAS and NEJM, 2019
Increasing proportion of obesity: greatest in TAF/FTC + DTG

Summary
- Integrase strand inhibitors (INSTIs) remain the cornerstone of HIV therapy but
  - were associated with small risk for neural tube defects in Botswana
  - were associated with unplanned weight gain in randomized studies conducted in Africa
- As providers we must discuss evolving information with our patients for decision making in optimal ART regimens

Story 3: To TANGO or not? “2-Drug Regimens”

Stage Setting
- One of the most dynamic areas in ART management is “2-drug therapy”
- Why?
  - We now have several proven “2-drug” potent drug combinations to maintain viral suppression
  - Toxicity can potentially be reduced with these combinations
- Why not?
  - Unwise use of these regimens can lead to drug resistance of agents we want to preserve
  - Requires both drugs are fully active
  - Data are mostly from tightly controlled clinical trials where prior resistance can be identified and adherence may be higher
Start: ART Naïve: DTG + 3TC vs DTG + 3TC + TDF are comparable

- Gemini Study N=1441
- DTG + 3TC vs DTG + TDF/FTC
- Inclusion: ART naïve, no resistance, no hep B or C
- HIV RNA <50 c/mL at 48 weeks similar; 3 drug appears better if VL>100K, CD4 <200
- Adverse events: 24% (3 drug) vs 18% (2 drug)

3 drug better when HIV RNA > 100K and CD4 < 200

Cahn, Lancet 2019

Switch: ART experienced with viral suppression

- Randomize 741 patients on 3-drug ART to switch to 2 drug ART or stay on 3-drug ART

TANGO study

Switch to 2-drug regimen was comparable to staying on 3-drug regimen

- HIV viral load suppression 48 weeks 93.2% vs 93%
- Similar adverse events both arms
- No new drug resistance

Wyk, IAS 2019.

Switching to a 2-drug regimen – A Cohort “Experience”

- Spanish Cohort 2016-2019
- Any switch to INSTI regimen
  - Switch to 2 DR N= 617
  - Switch to 3 DR N= 5047
- Over 2-fold higher virologic failure with 2 DR vs 3 DR
- Over 2-fold higher virologic failure vs 3 DR among those with viral suppression at time of switch

Teira, EAC, 2019
Summary

- There are excellent data and options for 2-drug therapy for persons starting or switching therapy
- However, use carefully!
  - 2-Drug Therapy should be applied for patients that are similar to those in the clinical trials
  - Do not use in those with resistance to a regimen drug, poor adherence, low CD4, or starting “same day”
- Depending on your clinical practice, the proportion of your patients that qualify for 2-drug switches may vary
- This is a rapidly evolving field that will change with anticipated approval of 2-drug injectable therapies

Story 4: Two New Drugs under study

GS-6207: Long Acting Capsid Inhibitor

- Novel mechanism of action
- Active against ART resistant virus in vitro studies
- Sub-cutaneous regimen
- Long acting

GS-6207: Long half-life

- Supports a 3-6 month SQ dosing interval
- Potent antiviral activity: 2 log HIV RNA reduction at 10 days
MK-8591 (Islatravir) + Doravirine dose finding study

- Translocation deficient RTI (TDRTI)
- Blocks RT through multiple steps
- Oral formulation for treatment

GS-6207 and MK-8591 are promising new agents in development with unique mechanisms of action.

Current planned studies are pairing these drugs with other oral drugs for new combination regimens.

Summary
AR2: What country has 160,000 persons living with HIV and a recent outbreak among children?

A. Swaziland  
B. Ukraine  
C. Honduras  
D. Pakistan

Answer: Pakistan

- April 2019: Media alerted government officials about a surge of HIV cases in the Larkana District in Pakistan
- 872/30,192 persons tested were HIV+: 719 were less than 15 years of age
- Risk Factors: unsafe needle use, unsafe deliveries, blood banking, hospital infection control

Public Health Response

- Open a new HIV/ART clinic for children
- Close down unauthorized labs, blood transfusion centers, clinics with infection control violations
- Continue testing to identify scope of infected persons
- Support country efforts to improve overall prevention and care

Summary HIV epidemic in children

- 160,000 new HIV infections in children in 2018
  - Gaps in ART during pregnancy and increasingly during breastfeeding
  - Outbreak in Pakistan is a wake-up call for another important transmission route often overlooked
- 1.8 million children living with HIV globally, only 940,000 children accessing ART
- In high burden countries children are 5% of HIV population but account for 15% of deaths
- Gaps between adults and children are widening in prevention and treatment and need urgent attention
AR3: How many persons over the age of 55 years are living with HIV in the United States?

A. 100,000
B. 200,000
C. 300,000
D. 400,000
E. 500,000

Answer: 300,000

US HIV epidemic is aging

- 327,000 persons over 55 yrs. living with HIV
- Of these, 60% have viral suppression

Aging and HIV Equity or Disparity?

- No 2 people age the same
- Heterogeneity in prior exposures of HIV + persons
- Gaps in knowledge on HIV and aging

Source: CDC
Aging: Cancer Risk

- Risk higher in HIV+ vs HIV- after 50 years of age for anal, lung, liver, oral cancers
- Acceleration in risk in general population after 60 years
- What will be impact in HIV population?

Aging: Long-term care

- Considerations of prior history including “triggers” living with other ill persons
- Stigma and discrimination from extended care providers and residents
- Medical treatments that call for agents that may interact with HIV medications

Story 7: Yellow Brick Road to HIV Cure

AR4: How many case reports of HIV cure or prolonged remission in adults are in the medical literature?

A. One
B. Two
C. Three
D. Four
E. Five
Two “Berlin” and “London” patients

“Berlin Patient”: HIV infected 1995, AML 2007 treated with 2 allogeneic stem cell transplants with CCR5 mutated donor cells, total body radiation and intensive chemotherapy
- No evidence HIV replication more than 10 years later of antiretroviral therapy
- Questions:
  - Which part of his intense regimen was critical for outcome?
  - Can his outcome be replicated in other patients?
  - Can his outcome be replicated in other patients with a less intensive regimen?

Questions:
- Which part of his intense regimen was critical for outcome?
- Can his outcome be replicated in other patients?
- Can his outcome be replicated in other patients with a less intensive regimen?

“The London” patient
- 2003 HIV+, CD4 290, VL 180,000
- 2012 ART EFV/TDF/3TC
- 2012 Stage IVb Hodgkin’s Lymphoma
  - Refractory to first and second-line chemotherapy with treatment using over 9 agents
  - HIV therapy switched to RTG/TDF/FTC, treatment interruption with VL rebound, K65R and S157Q, resuppressed with DTG/RPV/3TC
- 2017 Allogeneic stem cell transplant (conditioning regimen) with cells with CCR5 mutation
- 2019 No viral replication detected

“London Patient” Viral Replication and Chimerism of Donor Cells

Gupta, Nature, 2019
Summary

- Second HIV remission/cure achieved with CCR5 stem cell transplant
- Less “intensive” regimen– no whole-body radiation
- However, therapy was very intense and not practical
- Bright spot: Supports cure strategies blocking CCR5 receptor

Story 8: Discovering more about PrEP

Results: 7 infections with F/TAF; 15 infections with F/TDF
HIV Rate Comparison at Discover sites

- Comparison of background HIV incidence rates in cities where the study was conducted suggest high levels of protection with both regimens

Other observations

- Resistance: Unlikely different - 4 persons with FTC resistance in TDF/FTC (suspected baseline infection)
- Safety: Both regimens were very well tolerated; less bone mineral density loss in spine with F/TAF
- Pharmacokinetic analysis showed faster onset of action and sustained duration of protection with F/TAF

Summary

- FTC/TAF adds a new option for PrEP for MSM
- May be better for those with renal/bone disease
- Suggestion of faster onset and durability
- Challenges/Issues for F/TAF
  - Access for F/TAF
  - Access for women
  - Weight gain, lipids, Use for 2-1-1 regimen
  - "Persistence" in the real world

*F/TAF approved by FDA for adults >35 kg at risk for HIV infection. Not approved for use by women who have vaginal receptive intercourse*

Story 9: HIV+ organ transplants
AR5: What is the HOPE act?

A. Allows HIV- donors for HIV+ transplant recipient
B. Allows HIV+ donors for HIV+ transplant recipient
C. Places HIV+ persons at top of transplant waiting lists
D. Reduces the number of “clicks” needed to write an EPIC note

Answer: The Hope Act allows HIV+ to HIV+ transplants

- HIV- to HIV+ recipient: In hospital outcomes and survival for kidney transplants are = between HIV+ recipients and HIV- recipients
- Number of HIV+ persons in need of a transplant is increasing, but for kidneys, they spend more time on dialysis while waiting
- HIV+ to HIV+ transplant: Starting in 2010, 27 done successfully in South Africa
- Hope Act opens the door for the US in 2013, implemented in 2015

Wilk, Am J Transplant, 2019
Summary

- The HOPE act increased the eligibility pool for donors for HIV+ persons
- However, it appears to be underutilized to date
  - 56 donors recovered, 50 donors transplanted 102 organs
  - 212 HIV+ on the waiting list
  - Estimated 600 HIV+ potential donors annually
  - Most programs accepting HIV+ organs on east or west coast
- No concerning safety signals, but need more follow-up

Wilk, Am J Transplant, 2019

Story 10: Living in the USA

United States “End the HIV Epidemic” in Ten Years

- February 5, 2019: President announces the “End the HIV Epidemic” in the State of the Union Address
- Goal: Reduce new HIV infections by 90% over 10 years

- Diagnosing: all individuals with HIV as early as possible after infection.
- Treating: HIV rapidly and effectively after diagnosis to achieve sustained viral suppression.
- Protecting: individuals at risk for HIV using proven prevention approaches.
- Responding: rapidly to detect and respond to growing HIV clusters and prevent new infections.

Fauci, JAMA, 2019

HIV Epidemic in the United States

- US has the most new HIV infections annually ~ 40,000 -- of any high-income nation in the world
- Decrease in new HIV infections has stalled
- Highest % of new cases in the South among blacks
**HIV Epidemic Snapshot**

- 1.1 persons living with HIV
- 86% aware of their HIV diagnosis
- 51% have viral suppression

**US lagging in overall viral suppression**

CDC, 2019

**What can we do?**

- Optimally treat our patients with multi-disease approach
- Support HIV testing and expansion of PrEP
- Participate in municipal or regional activities that respond to epidemics
- Be a resource to colleagues

**Some of the highest rates of population level viral suppression with universal test and treat in Sub-Saharan Africa**

El-Sadr, NEJM, 2019; Hayes, NEJM, 2019; Havlir, NEJM, 2019

**Country level**

- 75% in South Africa, 65% in Lesotho, 60% in Malawi, 50% in Uganda, 30% in Zambia, and 25% in Tanzania.

**Universal Test and Treat**

- 75% in South Africa, 65% in Lesotho, 60% in Malawi, 50% in Uganda, 30% in Zambia, and 25% in Tanzania.
Acknowledgments

Special thanks to:

Meg Newman
Monica Gandhi
Annie Luedtke-Meyer
Susan Buchbinder
Gabe Chamie
Vivek Jain
Moses Kamya
Maya Petersen
Colleagues at WHO
UNAIDS and the Global Fund
SF Getting to zero consortium
Fascinating Cases from HIV Clinic

Ayesha Appa, MD
Annie Luetkemeyer, MD
Hyman Scott, MD
Carina Marquez, MD

Division of HIV, Infectious Diseases, and Global Medicine
University of California, San Francisco
Zuckerberg San Francisco General Hospital

Disclosures

• Drs Appa, Scott, and Marquez do not have disclosures.

• Dr. Luetkemeyer reports research grant support to UCSF from AbbVie, Gilead, Merck, Viiv.

Note for syllabus

To avoid spoilers, we have moved slides that refer to the patient’s diagnosis to the end of the syllabus.
58 yo man with HIV (CD4 284, suppressed VL) and R eye pain, drainage, vision loss.

HPI
- Ground-level fall 3 days ago
- Denies overt eye trauma
- Rapid progression of symptoms

PMH
- HIV – on ABC/3TC/DTG
- Schizophrenia

SN
- Veteran, lives with dog in single-room occupancy
- Sexually active with women
58 yo man with HIV (CD4 284, suppressed VL) and rapidly progressive R eye pain, drainage, vision loss after a fall.

Hospital Course
- Immediately taken to the operating room: “Massively purulent keratoconjunctivitis with corneal melt, leading to panophthalmitis.”
- Required enucleation (surgical removal of globe).

**Ocular Anatomy Basics**

**Anterior Segment VS. Posterior Segment**

- **Anterior Segment**
  - Keratoconjunctivitis Sicca
  - HSV keratitis
  - VZV keratitis
  - Bacterial/ fungal keratitis
  - Microsporidia keratopathy
  - Rifampin-induced anterior uveitis

- **Posterior Segment**
  - HIV retinopathy
  - CMV retinitis
  - VZV retinitis
  - Toxoplasma chorioretinitis
  - TB choriorretinitis

**Use This Approach for HIV-Related Eye Infections!**
CASE 2 OF 2

HIV/AIDS
(VL 70K + CD 112, 12%)

AND

RIGHT EYE PAIN, DRAINAGE, AND VISION LOSS FOLLOWING TRAUMA

62 yo man with HIV (CD4 112, 12% + VL 70K), with R eye pain, drainage, and vision loss.

HPI
• When gardening 5 days ago, thinks tree branch struck his eye.

PMH
• HIV/AIDS – off ARVs x 2 years

SH
• Lives in suburbs with husband, only sexually active with him.

Ophthalmology describes as:
Purulent Keratoconjunctivitis with Corneal Ulcer
CASE SUMMARY

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middle-aged African-American veteran with history of schizophrenia who lives alone in a single-room occupancy</td>
<td>Middle-aged affluent Caucasian man who enjoys gardening and lives in the suburbs with his husband.</td>
</tr>
<tr>
<td>HIV VL suppressed</td>
<td>HIV/AIDS VL 7%</td>
</tr>
<tr>
<td>CD4 384, 20%</td>
<td>CD4 112, 13%</td>
</tr>
<tr>
<td>&quot;I got something in my eye...&quot;</td>
<td></td>
</tr>
</tbody>
</table>

Purulent keratoconjunctivitis with corneal melt
Purulent keratoconjunctivitis with corneal ulcer

Dramatically purulent inflammation of anterior surface that rapidly progressed to involve the entire globe.

DIFFERENTIAL AUDIENCE RESPONSE

What is the causative organism for both cases?

A. Staphylococcus aureus
B. Pasteurella multocida
C. Neisseria gonorrhoeae
D. Treponema pallidum
E. Sporothrix schenckii

DIFFERENTIAL!

ANTERIOR SEGMENT

Purulent keratoconjunctivitis

POSTERIOR SEGMENT

Clinical pearl from Ophthalmology: Only 3 bacterial pathogens that have ability to penetrate an intact cornea...

Neisseria gonorrhoeae
Listeria
Corynebacterium

*People living with HIV may have other reasons for corneal ulceration.
Case

- 48 year old Eritrean man, presented to ED with abdominal pain, back pain, fevers, and 30 pound weight loss over several months
- New diagnosis of HIV, CD4 68 (7%) in ED
- Physical Exam
  - No lymphadenopathy
  - Mild abdominal tenderness
  - No palpable hepatosplenuomegaly, no spine tenderness
  - No skin lesions
  - Admitted for further evaluation

Patient history

- Sexually active with women, thinks this was his route of HIV infection
- Currently works as a taxi driver.
- Travels back to Eritrea every few years for several months at a time to a rural area with goats, cows, dogs, cats
- Eats raw beef (Eritrean delicacy) occasionally
- No alcohol, drugs, tobacco
Additional Evaluation

- Chest imaging: no thoracic aortic involvement. Normal lungs
- Labs
  - CBC: Hematocrit 26.7
- Microbiology
  - RPR -, TPPA inconclusive
  - Toxoplasma IgG (+)
  - Quantiferon (-), AFB blood cultures: smear negative, cultures no growth
  - Blood cultures: no growth
  - Fungal serologies: Cryptococcus, Histoplasmosis, Cocci all negative

ARS question: What is your diagnosis?

A. Salmonella
B. Mycobacterial (TB or MAC)
C. Bartonella
D. Syphilis
E. Parasitic infection from beef or goats

ARS: What would you do to make the diagnosis?

A. Biopsy the aorta
B. Are you crazy? You can’t biopsy the aorta- provide empiric treatment for TB/MAC, monitor closely for anything else to biopsy and wait for mycobacterial cultures

FNA Biopsy:
"Occasional rod-like structures. Rare atypical AFB".

AFB staining & culture in microbiology lab: Negative
Initial Treatment Plan

- ART already started on admission
- Initiated empiric MAC/TB therapy
- Pain significantly improved after several weeks
- Path sent to UW for Molecular Diagnostics to determine TB vs. MAC by PCR returns:

Case 4: Patient with Fever and Bone Lesions
Presented by: Hyman Scott, MD

Case Presentation

- 52 yo man with HIV (CD4 534, HIV VL <40) developed sore throat and odynophagia, as well as nasal congestion and rhinorrhea.

- Diagnosed and treated for strep throat (culture positive). He was treated with Clindamycin 10days with complete resolution of symptoms.

- Subsequently developed subacute weakness, headache, malaise, and approximately 10lb weight loss, fevers, drenching night sweats, and malaise.

Objective

Ill appearing and febrile (102.6). Exam WNL, No LAN

All labs and imaging normal except:

**Microbiology**
- Influenza A – Positive
- RPR – 1:16 (serofast)

**Imaging**
- CT Chest – Scattered areas of GGO, and tree-in-bud nodularity in RUL, and RLL>LLL.
- CT Abd – Large lytic lesion in left iliac crest, other nonspecific lucency throughout the bony pelvis
Course

- During his inpatient stay:
  - He was treated with Tamiflu for Influenza A
  - Bone biopsy: “skeletal muscle with focal new woven bone formation and crushed cells”
- Clinic follow-up with some improvement in symptoms
- Another laboratory test was sent and repeat bone biopsy

ARS

What would be highest on your DDx for this patient’s lytic lesion?

1. This is a malignancy, just not sure which one yet.
2. Syphilis
3. TB
4. Sarcoid

Syphilis testing

<table>
<thead>
<tr>
<th>Date</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/15</td>
<td>1:16</td>
</tr>
<tr>
<td>1/26</td>
<td>1:1024</td>
</tr>
</tbody>
</table>
Bone Biopsy Results

- Pathology:
  - Reactive woven bony with osteonecrosis, and necrotizing granulomatous inflammation.
  - No evidence of carcinoma or melanoma

- Fungal, Bacterial, and AFB smear and Cxs negative

- University of Washington universal PCR.
  - No bacterial, fungal, non TB Mycobacteria, or MTB complex detected

Case 5
Hands the size of mitts

Presented By: Carina Marquez, MD
44 year old man with HIV/AIDS presents to clinic with painful, erythematous, and swollen hands for 2 weeks. Symptoms began two months after starting ART, at the time of ART start his CD4 was 8 and viral load was 80,000.

Physical Exam

• My hand

Patient’s Hand

More history...

• Born in the Yucatan Peninsula, Mexico

• Currently works as a prep-cook in a Mexican restaurant. He notes finger trauma from opening metal cans and from cutting shrimp.

• Off ART for last 4 years while in Mexico, re-started ART 2 months prior to presentation. CD4 8 at ART start.

Physical Exam (cont.)

• Afebrile with normal vitals

• MSK: Thickened flexor tendons and dactylitis were present bilaterally with stiffness and severely limited flexion and extension of his fingers.

• Skin: Erythematous nodules on R wrist and L knee.

• CD4: 63, VL: undetectable
**Imaging**

L hand radiograph indicating degree of soft tissue swelling. No fractures, no osteomyelitis.

**Skin biopsy**

- Granulomatous dermatitis and panniculitis, with negative stains for organisms.
- Polymerase chain reaction and immunohistochemical stains for mycobacteria were negative.

---

Audience Response: What would you think is the most likely diagnosis?

Treat empirically for:

A. M. Tuberculosis
B. Non-tuberculous mycobacterium (NTM)
C. Staphylococcus Aureus
E. Lymphoma
F. Tuberculosis and NTM

---

Case: 44 yo man with AIDS (CD4 63, VL: Undetectable), re-started on ART a month ago, found to have bilateral dactylitis and tenosynovitis.

**Hospital Course**

- Started initially on Vancomycin and Zosyn.
- Intermittent fevers, no clinical response to broad spectrum antibiotics.
- Started on empiric MAC + TB treatment with: Rifampin, Isoniazid, Pyrazinamide, Ethambutol and Azithromycin. ART continued.
- Deep tissue cultures grew on chocolate agar incubated at 30°C and AFB blood cultures grew 4 weeks after admission.
9 months later....

Case 6: The language teacher who lost his speech over 6 months

History
72 yo man presents for functional and cognitive decline over 6 months and a new diagnosis of HIV.

- He immigrated from the Philippines in his 20's. At baseline he lives alone in Marin and teaches Tagalog.
- Over the last 6 months increasingly dependent on ADLs, limited short term memory, living with daughter, decreased speech -only yes/no answers to questions, requiring a diaper and assistance with ADLs.
- Multiple visits to primary care undergoing dementia and anemia work up.
- Diagnosed with HIV during hospital admission for 'failure to thrive'

History (cont.)
**Exam**

**General:** Cachectic, poor attention

**Neuro:** Cranial nerves intact, full strength and sensation.

**Mental status exam:**
- Alert and oriented to name only.
- Not able to state why he was hospitalized, minimal speech output and prolonged speech latency. Follows simple commands, but difficulty with 3-step commands.
- Unable to complete the MOCA.

**Labs**

- CD4: <18 (1%), VL: 216,000
  - Toxo IgG negative, serum CrAg negative
  - PPD positive

- Lumbar Puncture: 1 WBC, 2 RBC, nl protein and glucose, CSF CrAg negative

**Imaging**

- Brain MRI: global atrophy, no leptomeningeal enhancement, no masses.

**What do you think is the most likely diagnosis?**

A. TB meningitis

B. Progressive Multifocal Leukoencephalopathy

C. Neurosyphilis

D. HIV encephalopathy

E. CD8 Encephalitis

**Additional Studies**

- RPR negative
- CD4: <18 (1%) 
- HIV Viral Load 216,000 copies/ml
- Toxo IgG negative

**CSF Studies:**

- VZV IgG/IgM negative
- JC Virus PCR negative
- CMV PCR negative
- HIV CSF viral load of 200,000
- TB PCR negative and CSF AFB cultures negative

**Reference Slides**
HIV Associated Neurocognitive Disorders (HAND)

- Neurocognitive impairment not explained by alternate cause (e.g., Parkinson's, DI)

Off ART

- HIV Associated Dementia (HAD)
  - Minor Neurocognitive Deficits (MND)
    - Impairment in cognitive functioning involving at least two ability domains producing mild interference in daily functioning.
    - Diagnosed with neuropsych testing
  - Symptomatic CSF Viral Escape
    - Evidence of CNS HIV replication in the CSF despite low or undetectable serum viral loads.
    - Treatment: intensify ART regimen

On ART

- Symptomatic CSF Viral Escape
  - Evidence of CNS HIV replication in the CSF despite low or undetectable serum viral loads.
  - Treatment: intensify ART regimen

- CD8 Encephalitis
  - Rapidly progressive encephalitis
  - Brain Biopsy: CD8 infiltration
  - LP with lymphocytic pleocytosis
  - Steroid responsive

- Cognitive impairment not explained by alternate cause (e.g., Parkinson's, OI)

Answers from Case 1 and 2

- NEISSERIA GONORRHOEAE

In both cases, the culture grew...

Gonococcal Conjunctivitis

Gonococcal conjunctivitis can affect adults!

- History may not be straightforward given inoculation of the eye may occur in many ways; concurrent GU disease not always present.
Gonococcal Conjunctivitis

- Conjunctivitis may quickly progress to corneal ulceration and panophthalmitis (both vision-limiting) within days.

Case conclusions

- Both patients were treated with CEFTRIAXONE 1G IV + AZITHROMYCIN 1G PO per CDC guidelines.
- First patient received a scleral implant, recovered well despite losing his globe.
- Second patient slowly recovered, retained ability to see light/shapes.

Answers to Case 3
Bartonella

- *B. henselae*: flea bites, cat bites/scratches
- *B. quintana*: lice infestation, homelessness
- “Typical” bartonella: cat scratch disease with lymphadenopathy, bacillary angiomatosis bacteremia, hepatic/bone, endocarditis

**Take Homes**

- Bartonella in US often associated with homelessness and/or lice, but not always the case.
- Be vigilant of atypical presentations of disease in AIDS.
- PCR-based diagnostics have become powerful tools to diagnosis challenging infections (and sometime lead to surprising results!)

**Answers to Case 4**

**Follow-up**

- Diagnosis: Syphilis Osteomyelitis
- Follow-up: Treated with BCN 2.5 MU x1 with improvement in symptoms.

<table>
<thead>
<tr>
<th>1/15 (Inpatient)</th>
<th>1/26</th>
<th>12/6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:16</td>
<td>1:5024</td>
<td>1:32</td>
</tr>
<tr>
<td>BCN 2.4MU</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Bone Syphilis

- Syphilis can infect any organ, but bony involvement is relatively rare with only approximately 40 cases reported.
- Most commonly impacts long bones of the limbs (60%), skull (57%), and ribs (14%).
- Differential radiological diagnoses include multiple myeloma, primary or metastatic cancer, amyloidosis, sarcoidosis, TB, and Paget’s disease.
- Diagnosis is difficult and only 5 cases in a 2014 literature review had detectable organisms on biopsy.


Hospital Course

- Started initially on Vancomycin and Zosyn.
- Intermittent fevers, no clinical response to broad spectrum antibiotics.
- Started on empiric MAC + TB treatment with: Rifampin, Isoniazid, Pyrazinamide, Ethambutol and Azithromycin. ART continued.
- Deep tissue cultures grew on chocolate agar incubated at 30°C and AFB blood cultures grew 4 weeks after admission.

Disseminated Mycobacterium Haemophilum with dactylitis and tenosynovitis with unmasking IRIS.

M. Haemophilum: Cause of Skin and Bone Infections in AIDS

**Clinical Manifestations:**
- Nontuberculous mycobacteria (NTM) that predominantly causes skin, bone, joint infections in the immunocompromised patients.
- Disseminated disease with IRIS in patients with AIDS

**Exposure:**
- Resides in the environment and has been isolated from biofilms in fish tanks and water systems

**Diagnosis:**
- Slow growing NTM (grows after 7 days)
- Grows at 30º C (instead of 37º C), agar with hemin.

**Selected Skin and Soft Tissue Infections from Non-Tuberculosis Mycobacteria**

**M. Tuberculosis**
- Usually reactivation.
- Fusiform swelling of the digits sparing the fingertip.

**M. Marinum**
- Nodular lesions.
- Found in salt and fresh water, aquarium cleaning, fish or shellfish injuries, nail salons.
- Grows at 30ºC.

**M. Fortuitum**
- Nodular lesions.
- Environmental, foot baths at nail salon.

<table>
<thead>
<tr>
<th>Slow Growers (culture positive&gt;7 days)</th>
<th>Rapid Growers (culture positive&lt;7 days)</th>
</tr>
</thead>
</table>

**Hospital Course (cont.)**
- Treatment changed to moxifloxacin, ethambutol, rifabutin, and azithromycin.
- Eight weeks later, spontaneous drainage of cold abscesses on wrist, elbow, and knee, without evidence of an alternative etiology. Prednisone was administered for paradoxical IRIS for 3 months, with resolution of symptoms.

**Diagnosis: HIV Associated Dementia**

**HIV Associated Dementia**

**Pathogenesis:**
- Sustained neurologic damage from untreated HIV, CD4<50.
- 20-30% patients in pre-ART area ultimately developed HAD.
- Symptoms correlate at least moderately to active viral replication in CNS (CSF VL high).

**Clinical Symptoms:** Global deficits across domains including in executive function, visuospatial reasoning, and memory.

**Imaging:** Global atrophy, can see white matter changes.

**Treatment:** Start ART
Follow up

- Started on TAF/FTC/Dolutegravir as an inpatient
- Discharged to a skilled nursing facility
- Kept forgetting he had HIV during his initial HIV primary care follow-up visits
- 8 months later moved back to his house and started teaching again!
The Foundation of HIV Prevention: What’s New and Where are We Heading?
Medical Management of HIV/AIDS and Hepatitis
December 12, 2019
Susan Buchbinder, MD
Director, Bridge HIV, SFDPH
Professor of Clinical Medicine, Epidemiology and Biostatistics, UCSF

Outline
1. In whom are new infections occurring?
2. What strategies do we have to improve HIV testing?
3. U=U: Is it enough?
5. Vaccines and monoclonal antibodies: Where are we heading?

Disclosures
I have been an investigator on studies for which Gilead Sciences has donated study drug.

The views expressed herein do not necessarily reflect the official policies of the City and County of San Francisco; nor does mention of the San Francisco Department of Public Health imply its endorsement.
ARS-1: In which population are new diagnoses increasing in the United States?

A. Women  
B. People who inject drugs  
C. Latino men who have sex with men  
D. Youth < 25 years of age
Rates of Diagnoses of HIV Infection among Adults and Adolescents by Sex and Race/Ethnicity, 2018—United States

Trends in HIV infection in MSM in the US: 2010-2016

Gay and bisexual men overall: stable
- Gay and bisexual men by age:
  - 13 to 24: stable
  - 25 to 34: up 20%
  - 35 to 44: down 24%
  - 45 to 54: down 23%
  - 55 and older: up 8%
- Gay and bisexual men by race/ethnicity:
  - Black/African American: stable
  - Hispanic/Latino: up 18%
  - Asian: up 52%
  - White: down 16%

New HIV diagnoses in women in the US: 2010-2016
- Women overall: down 21%
  - Black/African American: down 25%
  - Hispanic/Latina: down 20%
  - White: remained stable
- Women by age:
  - 13 to 24: down 32%
  - 25 to 34: down 13%
  - 35 to 44: down 27%
  - 45 to 54: down 27%
  - 55 and older: remained stable

HIV Diagnoses Among People Who Inject Drugs in the 50 States and District of Columbia, 2010-2016*
- PWID overall: down 31%
  - By race/ethnicity:
    - Black/African American: down 52%
    - Hispanic/Latino: down 30%
    - White: remained stable
* Includes infections attributed to male-to-male sexual contact and injection drug use (men who reported both risk factors).
Outbreak in PWID in Massachusetts

New HIV Diagnoses, 2006-2018

Annual Rates of Men in SF Diagnosed with HIV by Race/Ethnicity

New diagnoses in SF highlight disparities 2017
Outline

1. In whom are new infections occurring?
2. What strategies do we have to improve HIV testing?
3. U=U: Is it enough?
5. Vaccines and monoclonal antibodies: Where are we heading?

Persons Living with Diagnosed or Undiagnosed HIV Infection
HIV Care Continuum Outcomes, 2016—United States

Note: Receipt of medical care was defined as ≥1 test (CD4 or VL) in 2016. Retained in continuous medical care was defined as ≥2 tests (CD4 or VL) ≥3 months apart in 2016. Viral suppression was defined as <200 copies/mL on the most recent VL test in 2016.

eSTAMP Study on HIV Testing
MacGowan et al, JAMA Internal Medicine 2019

- 2665 MSM randomized to usual testing vs. self-testing
  - Oral and DBS testing performed
  - 12-month follow-up
  - Primary outcome: testing ≥3 times
    - Self-testers were
      - Significantly more likely to self-test (77% vs. 22%, p<0.01)
      - Identified significantly more first time HIV positives (1.9% vs. 0.8%, p<0.02)
      - Self-test reported 34 newly identified infections among social contacts to whom test kits distributed.
Undetectable = Untransmittable

U=U refers to the concept that an individual with an undetectable HIV VL is incapable of transmitting their HIV infection to sexual partners.

Reduced VL also significantly reduces risk of transmission via other routes:

- Unborn babies
- Healthcare workers who experience sharps/mucosal injuries

Undetectable VL in this context: <200 c/mL

Language Matters

Overly cautious attitudes have profound impacts. The big erasers:

- Don’t Say: I believe in U=U but use a condom just in case.
  Say: You might want to use a condom to prevent other STIs and unintended pregnancy, but condoms aren’t clinically necessary to prevent HIV.

- Don’t Say: You’re only as good as your last viral load test.
  Say: If you’re taking your medication as prescribed and getting your labs done regularly, don’t worry.

Carrie Foote, CROI 2019
Four large RCTs testing impact of test and treat

Outline
1. In whom are new infections occurring?
2. What strategies do we have to improve HIV testing?
3. U=U: Is it enough?
5. Vaccines and monoclonal antibodies: Where are we heading?

ARS-2: Compared with TDF/FTC, TAF/FTC was shown to be:
A. Better (superior) at protecting against HIV
B. Not worse (non-inferior) at protecting against HIV
C. Worse (inferior) at protecting against HIV
D. Better for transgender than cis-gender women

ARS-3: TAF/FTC PrEP was approved by the US FDA for use in:
A. Men and women
B. People who inject drugs
C. Adults ≥ 18 years of age
D. Sexual acquisition except receptive vaginal sex
TDF/FTC for PrEP available since 2012

For whom does TDF/FTC PrEP work?

- Cisgender men and women, people who inject drugs
- Transgender women
  - Small decreases in TDF with feminizing hormones, but not likely clinically significant
  - More studies underway
- Approved for all ≥ 35 kg
- Concerns for those with
  - Creatinine clearance <50 mL/min
  - Osteoporosis
Hare, CROI 2019, Abstract 104H

**DISCOVER Primary Endpoint Analysis: HIV Incidence**

22 HIV infections in 8756 PY of follow-up

- HIV Incidence: 0.34
- 15 infections: 0.16
- 7 infections: 0.10

Incidence Rate Ratio [95% CI]

- Favor FTC/TAF
- Favor FTC/DP

0.19
1.15

FTC/TAF is noninferior to FTC/DP for HIV prevention

**Bone Safety at Week 48: Bone Mineral Density Sub-study (n=383)**

- Spine: 0.94, p=0.007
- Hip: 0.16, p=0.007

Change from BL %

- FTC/TAF: 13% increase
- FTC/DP: 12% increase
- Placebo: 13% decrease

**Renal Safety Through Week 48**

- eGFR\textsubscript{\text{NL}}
- Proximal Tubular Protein to Creatinine Ratios
- RBF/Cr
- 24h Cr

- Renal discontinuations: FTC/TAF, n=2; FTC/DP, n=6
- Fanconi syndrome: FTC/TAF, n=0; FTC/DP, n=1

**FTC/TAF but not TAF alone protects against vaginal challenge in NHP**

Massul JID 2019
High risk of HIV after stopping oral PrEP

- Many anecdotal cases of infections when stop PrEP
- 18 seroconversions in people who had stopped PrEP in SF STD clinic
- 3.9/100 py in people stopping PrEP in Montreal
- HIV incidence substantially higher after stopping PrEP in LA and SF.

<table>
<thead>
<tr>
<th>Location</th>
<th>HIV incidence (infections/100 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Los Angeles, CA</td>
<td>On PrEP</td>
</tr>
<tr>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td>San Francisco, CA</td>
<td>0.1</td>
</tr>
</tbody>
</table>

- Most (80%) did not speak with a provider before discontinuing PrEP
Ipergay Results

HIV Incidence (mITT Analysis)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Follow-Up Pts-years</th>
<th>HIV Incidence per 100 Pts-years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>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>0.91 (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

Ipergay Results

Global HIV Incidence: 0.09/100 PY (95% CI: 0.01-0.33) (2 cases)

Mean Follow-up of 8.7 months and 2208 Person-Years

Rate of study discontinuation: 8.9/100 PY

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Follow-Up Pts-years</th>
<th>HIV Incidence per 100 Pts-years (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF/FTC (Daily)</td>
<td>1072.9</td>
<td>0.0 ( 0.0 – 0.3 )</td>
<td>0.132</td>
</tr>
<tr>
<td>TDF/FTC (On Demand)</td>
<td>1132.7</td>
<td>0.2 ( 0.0 – 0.6 )</td>
<td></td>
</tr>
</tbody>
</table>

143 HIV-infections averted* Molina, IAS 2019

* assuming an incidence of 6.6/100 PY as observed in the Placebo group of the ANRS Ipergay study

HIV-Infected individuals

<table>
<thead>
<tr>
<th>Cases</th>
<th>Sex, Age</th>
<th>Date Started PrEP</th>
<th>Date Enrolled in PREVENIR</th>
<th>Last Neg. HIV Test</th>
<th>Positive HIV Tests</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>MSM 52 y</td>
<td>April 2016 On demand</td>
<td>Feb 2, 2018 On demand</td>
<td>Sept 4, 2018</td>
<td>Jan 2, 2019</td>
<td>HIV serology: positive Plasma: &gt;6500 cp/mL, No RAMs to TDF/FTC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PEP stopped 10 weeks before infection and condomless sex during this period</td>
</tr>
<tr>
<td>Case 2</td>
<td>MSM 47 y</td>
<td>June 2016 Daily</td>
<td>June 20, 2017 On demand</td>
<td>Dec 6, 2018</td>
<td>Feb 18, 2019</td>
<td>HIV serology: positive Plasma: &gt;10^6 cp/mL, No RAMs to TDF/FTC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PEP stopped 7 weeks before infection and condomless sex during this period</td>
</tr>
</tbody>
</table>

Molina, IAS 2019

World Health Organization

WHAT’S THE 2+1+17?

PPEB PROPOSAL TO PREVENT HIV FOR MEN WHO HAVE SEXUAL INTERCOURSE TO OTHERS RECOMMENDATION OR TESTS

Molina, IAS 2019
**Cabotegravir Long Acting Injectable (CAB LA)**

- Cabotegravir is an analog of dolutegravir, differing by one carbon atom
- Oral t1/2: 40 hours
- CAB-LA: milled nanocrystals
- Injectable t1/2: 21-50 days
- Rifampin reduces plasma concentrations by 60%

**Summary of non-human primate challenge studies with CAB-LA**

<table>
<thead>
<tr>
<th>Challenge Model</th>
<th># of Challenges</th>
<th>Level of Protection</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-dose IV</td>
<td>1</td>
<td>7/8</td>
</tr>
<tr>
<td>Low-dose rectal</td>
<td>8</td>
<td>8/8</td>
</tr>
<tr>
<td>High-dose vaginal</td>
<td>3</td>
<td>6/8</td>
</tr>
<tr>
<td>Low-dose vaginal</td>
<td>22</td>
<td>4/4</td>
</tr>
<tr>
<td>Low-dose penile</td>
<td>12</td>
<td>5/6</td>
</tr>
</tbody>
</table>

**Two Efficacy Trials of CAB-LA for PrEP**

- **HPTN 083** for MSM/TGW globally
- **HPTN 084** for women in sub-Saharan Africa

Both have 3 steps:
1. Oral lead-in
2. Loading at 0 and 4 weeks, q 8 week injections
3. Oral to cover the PK tail for 1 year

Both trials are double-blind, double-dummy with TDF/FTC as comparator group

Both currently enrolling

Results expected 2022

**Phase 1 Cabotegravir Studies**

- Needs oral run-in phase to ensure tolerated (cannot be dialyzed off)
- Nearly 90% have an injection site reaction, but generally well-tolerated, and improves over time
- Dosing needs to be q 8 weeks for prevention, based on target PK levels
- Drug levels decline slowly – in a minority of participants, low drug levels persist up to 2 years after last injection
**Implantable devices**

Drug must be extremely potent, as total mass dose to be loaded is small
- E.g., Nexplanon 0.6mg/day

**Advantages and disadvantages of implantables vs. injectables**

**Advantages**
- Removable when needed
- More consistent and predictable drug release; lower dose per day
- Avoids long PK tail
- May remain in place for years, requiring fewer visits
- Potential for improved adherence

**Disadvantages**
- Requires specialized device and sterile technique to insert
- Requires small surgical procedure to remove unless biodegradable
- Potential for scarring
- Potential to migrate
- More challenging when need to combine agents

**Formulation PK profiles compared**

**Islatravir (MK-8591):**
A First-in-Class Nucleoside Reverse Transcriptase Translocation Inhibitor (NRTTI) With Multiple Mechanisms of Action

Translocation Inhibition
Due to the 4'-ethynyl Group

Delayed Chain Termination
Due to the 4'-ethynyl and 3'-hydroxyl Groups

Multiple mechanisms contribute to the high potency of islatravir against HIV-1 and drug-resistant variants and its high barrier to resistance.
ISL Implant Design Similar to Nexplanon®

- ISL implant based on Implanon®/Nexplanon®
  - Uses same polymer
  - Removable (not bioerodible)
- Able to use Nexplanon® applicator
- Initial trial uses prototype implant

62 mg Implant Projected to Lead to Concentrations Above Threshold for at Least 12 Months

- 62 mg implant will continue to release through 52 weeks
- ISL-TP should be above threshold (0.05 pmol/10^6 cells) for >12 months
- Projected concentration at 12 months: 0.076 pmol/10^6 cells
- Projected time at which concentration falls below 0.05 pmol/10^6 cells: 68-70 weeks (~16 months)

Dapivirine Vaginal Ring

- Female control, discrete
- Limited systemic absorption
- No apparent ARV resistance in breakthrough infections

Potential advantages:
- Female control, discrete
- Limited systemic absorption
- No apparent ARV resistance in breakthrough infections

Vaginal Rings – what does the future hold?

- Open label extension studies (HOPE, DREAM), efficacy estimated to be 54%
- Dapivirine rings currently undergoing regulatory review at European Medicines Agency
- Next generations
  - Combination ARVs
  - Longer durability (q 3 months)
  - Combination with contraception
Outline

1. In whom are new infections occurring?
2. What strategies do we have to improve HIV testing?
3. U=U: Is it enough?
5. Vaccines and monoclonal antibodies: Where are we heading?

There is a long history of using antibodies to prevent viral infections

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

Antibody-Mediated Prevention

- VRC01 administered IV q 8 weeks
  - Evaluating two doses (10mg/kg vs. 30 mg/kg) vs. placebo
  - Monthly HIV testing to evaluate threshold of protection
  - Sequence analyses of breakthrough infections will indicate whether defect is coverage vs. potency
- 2 parallel trials
  - 2700 MSM/Transgender in North/South America
  - 1900 women in Southern and East Africa
- PrEP available to all participants who want it
- Results late 2020
Breadth and potency of bNAbs

Advantage: no ARV resistance concerns
Future developments:
- Increase durability (decrease interval of administration)
- Subcutaneous administration
- Combinations

HVTN 702 Schema:
Women and Men in South Africa

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Primary vaccine regimen</th>
<th>Booster*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2700</td>
<td>AUAC-HIV (vCP2438)</td>
<td>AUAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Month 0</td>
<td>Month 1</td>
</tr>
<tr>
<td>2</td>
<td>2700</td>
<td>Placebo</td>
<td>Placebo + Placebo</td>
</tr>
<tr>
<td>Total</td>
<td>5400</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

High Level Target Product Profile:
Prophylactic vaccine offering protection against all clades of HIV-1 through an heterologous prime boost regimen

RV144 HIV Vaccine Trial in 16,000 Thai men and women

62% reduction at 1 year
31% reduction at study end

HVTN 702/GC Trial will be using gp140 for Mosaic inserts for global coverage (Gag–Pol–Env)
HVTN 705 Study Schema

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Month 0</th>
<th>Month 3</th>
<th>Month 6</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1300</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo + Placebo</td>
<td>Placebo + Placebo</td>
</tr>
</tbody>
</table>

* Total: 2600 women in sub-Saharan Africa

HPX3002/HVTN 706 Study Products & Schema

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Month 3</th>
<th>Month 6</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1900</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo + Placebo</td>
</tr>
</tbody>
</table>

Includes mosaic protein to accommodate necessary breadth for a "world-wide" vaccine. Enrollment predominantly in Clade B regions.

Why we need all prevention methods

Building on IFE: Investment Framework Enhanced

Summary

- Nationally, making no substantial progress in reducing new HIV infections; concerted prevention efforts are needed
- Home HIV self-testing can improve diagnosis rates; serve as important gateway to prevention and treatment
- Daily TDF/FTC PrEP is effective against sexual and injection exposures; TAF/TDF is non-inferior for insertive sex or receptive anal; 2-1-1 TDF/FTC is effective for MSM
- New PrEP agents are being evaluated (cabotegravir, islatravir)
- Monoclonal antibodies and vaccine efficacy studies are underway

Harmon, PLOS One 2016
Acknowledgments

Carrie Foote
Diane Havlir
Brad Hare
Raphy Landovitz
Albert Liu
Julia Marcus
John Mascola
Jean-Michel Molina

Susan Scheer
Hyman Scott
Ariane van der Straten
Pietro Vernazza
Janie Vinson
**PrEP 2019: CASES FROM THE CLINIC**

Hyman Scott, MD MPH  
Bridge HIV, San Francisco Department of Public Health  
Jonathan E. Voit, MD MPH  
Kaiser Permanente San Francisco, Department of Medicine & Infectious Diseases

**DISCLOSURES**

- We have no conflicts of interest to disclose.

---

**Audience Response #1: PrEP**

- What is your preferred 1st line medication for preexposure prophylaxis (PrEP)?
  - TDF/FTC (Truvada) daily dosing
  - TDF/FTC (Truvada) daily or on-demand dosing
  - TAF/FTC (Descovy) daily dosing
  - TAF/FTC (Descovy) daily or on-demand dosing
  - I do not prescribe PrEP

---

**CASE 1**

- 53 year-old MSM, PMH notable for CKD & bipolar disorder
  - Numerous recent STIs
  - ~300 partners in prior 6 months. As many as 8 partners/day, usually oral sex, but also bottoming-ejaculation.
  - Started daily PrEP with TDF/FTC in 2016 with worsening CrCl
  - Started “on-demand,” sex-driven PrEP dosing strategy 9/2016:
    - Uses when he plans on having condomless receptive anal sex (~3-4/month)
    - Does not use with HIV+ undetectable partners & partners on PrEP
    - Does not use with oral sex
    - Usually uses condoms with unplanned receptive anal sex with partners who are not on PrEP or not undetectable
  - HIV Ag/Ab-negative, CrCl 35 mL/min
**Audience Response #2: Case 1**

What do you recommend for this patient?

1. Stop PrEP – PrEP is contraindicated with his kidney function
2. Continue an “on-demand,” sex-driven dosing of TDF/FTC
3. Start daily dosing with TDF/FTC with very close renal monitoring
4. Start renally-dosed TDF/FTC with every other day dosing
5. Start daily TAF/FTC

---

**WHO MAY BENEFIT FROM PrEP?**

- CDC guidelines: Sexually-active MSM, heterosexual men and women & IDU “at substantial risk” of HIV acquisition
- **MORE SPECIFICALLY:**
  1. MSM or transgender women - condomless anal intercourse
  2. STIs
  3. Commercial sex workers
  4. Serodiscordant relationships – especially if detectable virus
  5. Peri-conception
  6. Persons who inject drugs
  7. Individuals asking for PrEP

---

**PrEP UPTAKE: KPNC & NATIONALLY**

- CDC estimates ~1.1 million people may benefit from PrEP
- Only ~4% of PrEP in 2017 overall & 2.9% among MSM in US Cities
**IS IT REALLY 99% EFFECTIVE?**

- Updated CDC estimates, July 2019
- MSM - ~99%
  - Adherence does NOT need to be perfect for MSM (4/week dosing)
- Heterosexual men/women - ~99%
- PWIDs - ~74-84% (limited data with TDF alone)
- Less forgiveness for women
  - Lower vaginal drug levels
  - More adherence may be needed

**PrEP CARE CASCADE**

- No infections seen in 5000 patients on PrEP at KPNC, but...
  - 0.4% infected at time of referral
    - "Late to access PrEP"
  - Incidence rate of 1.1 per 100 person-years in patients seen/referred for PrEP who did not start (95% CI 0.7-1.7)
    - "Failure to initiate PrEP"
  - Incidence rate 1.3 per 100 person-years among those who stop PrEP (95% CI 0.8-2.4)
    - "Failure to be retained in PrEP care"

**PrEP WORKS IN THE “REAL WORLD”**

Data from KP Northern California

**TAF/FTC vs. TDF/FTC (96 week DISCOVER data)**

- PrEP (TAF or TDF) works INCREDIBLY well in this population
  - TAKE HOME: TAF if CrCl 30-60
- 96 week data – side effects similar/infrequent
  - GFR with TDF vs -0.6 GFR with TAF
  - Weight gain + 0.5kg with TDF vs +1.7kg with TAF

**Overall Safety Summary**

- TAF vs TDF:
  - Lower incidences of all endpoints
  - *Note: results may differ at 72 and 96 weeks*
**CASE 2**

- 8/2016: 27-year-old MSM, 2-3 partners/week for anal sex, uses condoms “some of the time.”
  - PrEP offered and prescribed, but never picked up Rx
- 9/2019: Seen in clinic after 3rd PEP in last 3 years.
  - Treated for rectal NG in March 2019
  - Willing to take PrEP but hesitant to take daily medication because of side effect concerns

---

**Audience Response: CASE 2**

What would you preferred treatment recommendation?

1. Continue to prescribe PEP as needed
2. Start daily TDF/FTC after PEP
3. Start daily TAF/FTC after PEP
4. Start on-demand (2:1:1) TDF/FTC after PEP
5. Start on-demand (2:1:1) TAF/FTC after PEP
6. Call the PrEP/PEP Clinician Consultation Center, 855-448-7737

---

**TAF/FTC vs TDF/FTC**

**Which medication should I prescribe for daily PrEP?**

- **TDF/FTC** (Truvada)
  - Effectiveness: 99.8%
  - Side effects: Nausea, diarrhea

- **TAF/FTC** (Descovy)
  - Effectiveness: 99.5%
  - Side effects: Nausea, diarrhea

---

**Audience Response #2: Case 1**

What do you recommend for this patient?

1. Stop PrEP – PrEP is contraindicated with his kidney function
2. Continue an “on-demand,” sex-driven dosing of TDF/FTC
3. Start daily dosing with TDF/FTC with very close renal monitoring
4. Start renally-dosed TDF/FTC with every other day dosing
5. Start daily TAF/FTC
**INTERMITTENT (Sex-Driven/211) iPrEP**

- Reduction in incidence:
  - 86% in RCT & 97% in open-label study
- Open label PrEP Study (Prévenir):
  - Daily – no infections in >1000 person-years (95% CI 0.0-0.6; p<0.001)
  - On-demand – incidence 0.2 per 100 person-years (95% CI 0.0-0.6; p=0.132)

**211 PrEP: THE DETAILS**

- At KPSF, ~300 patients changed from daily to 211 after outreach, but FLUID

**211 PrEP: THE DETAILS**

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Daily PrEP</th>
<th>2-1-1 PrEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Sex</td>
<td>ALL</td>
<td>No if vagina or estrogen</td>
</tr>
<tr>
<td>Plan in Advance</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>Missed Dose Forbearance</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Cost</td>
<td>Higher ($555)</td>
<td>Lower ($)</td>
</tr>
</tbody>
</table>

**PrEP FOLLOW-UP**

- Same follow-up for on-demand & daily
- Every 3 month follow-up – Rx #90
  - HEV
  - Creatinine (every 6 months reasonable for most)
  - STIs: urine/throat/rectal NGT & syphilis (recommended)
  - More frequent STD testing, if desired
  - Hep C screening with ALT
  - Not in CDC guidelines, but picked up ~3 acute infections/year
- Annual
  - Hepatitis C antibody
POSTEXPOSURE PROPHYLAXIS (PEP) & 211 PrEP

- Start ≤ 72 hrs after an exposure
- 211 for MSM and PEP – limited data, but KPNC protocol:
  - Sex is considered protected if ≥ 4 doses in prior 7 days
  - 1) the post-sex dose was not taken or was taken less than 3 hours before sex
  - 2) the first post-sex dose was taken more than 26 hours after first dose
  - 3) the second post-sex dose was taken more than 50 hours after the first dose
- Take a dose of emtricitabine/tenofovir immediately from existing supply and continue 28 days.
- Contact clinic/ED to discuss 3rd agent (usually Integrase Inhibitors)
- No RCTs or head-to-head trials

Audience Response #3: CASE 2

What would you preferred treatment recommendation?

1. Continue to prescribe PEP as needed
2. Start daily TDF/FTC after PEP
3. Start daily TAF/FTC after PEP
4. Start on-demand (2:1:1) TDF/FTC after PEP
5. Start on-demand (2:1:1) TAF/FTC after PEP
6. Call the PrEP/PEP Clinician Consultation Center, 855-448-7737.

CASE #3

- 23 year-old Black, bisexual transgender woman
  - Receptive anal sex with male partners (-5-10/month), no recent female partners
  - Condoms ~90% of the time & usually plans sexual encounters
  - No alcohol, occasional recreational MJ
  - Rectal chlamydia 1 month prior to intake visit, more remote history of syphilis and gonorrhea
  - Rx: estrogen

Audience Response #4: CASE 3

1. Do not recommend PrEP. There are insufficient data for transwomen
2. Start daily TDF/FTC
3. Start daily TAF/FTC
4. Start on-demand PrEP with TDF/FTC
5. Start daily or on-demand PrEP with TDF/FTC depending on patient preference
**PrEP FOR TRANSGENDER WOMEN**

- Worldwide HIV prevalence 19.1%
  - OR for HIV infection 49 (95% CI 21-76) in meta-analysis
- 339 transgender women in iPrEx analysis
  - 11 HIV infections in tx arm & 10 in placebo - HR 1.1 (95% CI 0.5-2.7)
  - No new infections among transgender women taking PrEP, but drug detectable in only 13%

**PrEP CONTINUUM OF CARE FOR INSURED TRANSGENDER COHORT**

<table>
<thead>
<tr>
<th>Overall Cohort</th>
<th>Patients with =Bacterial STI</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=1339</td>
<td>N=1</td>
</tr>
<tr>
<td>Linked to TDF/ FTC (359)</td>
<td>Linked to PrEP use (49/95)</td>
</tr>
<tr>
<td>Linked to TAF/ FTC (95)</td>
<td>Linked to PrEP use (26/95)</td>
</tr>
<tr>
<td>TDF/ FTC patients with undetectable levels at week 24 (20/95) (monitored PrEP)</td>
<td>TDF/ FTC patients with undetectable levels at week 24 (21/95) (monitored PrEP)</td>
</tr>
<tr>
<td>26% ('On-demand', TDF/ FTC at a later time)</td>
<td>24% ('On-demand', TDF/ FTC at a later time)</td>
</tr>
<tr>
<td>12% (Restored PrEP/15/5)</td>
<td>12% (Restored PrEP/15/5)</td>
</tr>
</tbody>
</table>

**PrEP FOR TRANSGENDER WOMEN**

- PrEP uptake barriers – side effects, lack of transgender-inclusive PrEP promotion, medical mistrust, prioritization of hormone use
- Areas for improvement:
  - Meaningful PrEP messaging
  - Evidence based HIV prevention interventions
  - Gender discrimination, transphobia, violence
  - Concerns re: Rx-Rx interactions with PrEP & hormones
  - TDF/FTC levels may be lower in setting of hormones (10-27%), but NO impact on Estrogen levels
  - Larger well-controlled DDI study of estrogen needed

**Audience Response: CASE #3**

1. Do not recommend PrEP. There are insufficient data for transgender women
2. Start daily TDF/FTC
3. Start daily TAF/FTC
4. Start on-demand PrEP with TDF/FTC
5. Start daily or on-demand PrEP with TDF/FTC depending on patient preference
Case 4

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?

1. You don't offer PrEP because condoms have worked well for her up to this point, and you don't want to risk STIs
2. You don't offer PrEP because it doesn't work well in women
3. You offer PrEP but tell her it works less well if she has bacterial vaginosis
4. 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's 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>HIV Status</th>
<th>Overall</th>
<th>MSM</th>
<th>Hetero</th>
<th>SDC</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF/FTC</td>
<td>50%</td>
<td>60%</td>
<td>40%</td>
<td>50%</td>
</tr>
</tbody>
</table>

- PrEP works if taken regularly

Does TDF/FTC for PrEP work for cis women?

Yes, if they take it regularly

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
Fig. 2 Cumulative HIV infection probability by treatment assigned to women with vaginal Lactobacillus dominance and non-Lactobacillus bacterial dominance.

Published by AAAS

- No evidence of difference in efficacy for oral PrEP.
- Lactobacillus or non-Lactobacillus dominate didn’t impact efficacy

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?

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

2,752 HIV-uninfected females in African HIV serodiscordant couples followed for 44.8 mos in 2 HIV prevention studies between 2004-2012
- Frequent HIV and pregnancy testing
- Genetic linking of HIV infections
**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 vs. -0.79, p=0.05) and head circumference (0.24 v. 0.04) at 1 month, but NS at 1 year.

**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 M84V. He doesn't like using condoms. What do you recommend?
  - They should continue to use condoms until the partner has been fully virally suppressed for at least 6 months.
  - You prescribe TDF/FTC or TAF/FTC
  - You prescribe three drug PEP
  - Something else

**PrEP Breakthrough infections despite adherence**

<table>
<thead>
<tr>
<th>Case Report</th>
<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>M41L, V47I, V118I</td>
<td>DBS, Hair</td>
</tr>
<tr>
<td>Viss et al</td>
<td>Canada</td>
<td>24 months</td>
<td>M184V, K65R, V118I</td>
<td>DBS</td>
</tr>
<tr>
<td>Houtsmulder et al</td>
<td>US</td>
<td>6 months</td>
<td>M184V, V118I</td>
<td>DBS, Hair</td>
</tr>
<tr>
<td>Koneberg et al</td>
<td>Amsterdam</td>
<td>6 months</td>
<td>No major resistance</td>
<td>DBS</td>
</tr>
<tr>
<td>Thalen et al</td>
<td>US</td>
<td>14 months</td>
<td>M230V, L100I, V118I</td>
<td>Hair</td>
</tr>
<tr>
<td>Colby et al</td>
<td>Thailand</td>
<td>6 weeks</td>
<td>M184V</td>
<td>Hair</td>
</tr>
</tbody>
</table>

**Case 9**

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

1. Repeat the tests but continue PrEP, as you assume the 4th gen test is a false positive
2. Repeat the tests and stop PrEP, but start ART for acute HIV infection
3. Repeat the tests and stop PrEP until you can determine what the infection status is
4. Something else
Sequential Appearance of Viral Markers and Antibodies during Acute HIV Infection

How to manage ambiguous HIV Test Results

Quarterly PrEP Screening

Ambiguous or Discrepant HIV Tests
1. 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

Maintains Protection
Risk of Resistance
Facilitate Diagnosis
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)
Antiretroviral Therapy Initiation: From Guidelines to Practice: ART 101

Medical Management of AIDS & Hepatitis
December 12, 2019

Vivek Jain, M.D., M.A.S.
Associate Professor of Medicine
Division of HIV, Infectious Diseases & Global Medicine
San Francisco General Hospital, University of California, San Francisco

Goals

- Working proficiency in selecting initial ART regimens
- Review DHHS first line & alternate regimens
  - Pros and cons, considerations, choices
  - Many updates from last year (4 new drugs FDA approved in 2018)
- Will not focus on:
  - HIV drug resistance
  - ART switching in virally suppressed patients
  - ART for pediatric or pregnant patients
  - Drugs still in development (but not yet FDA approved)
  - There’s lots at this conference on all of the above, but we will focus on ART initiation
- 45 minutes... lots to cover!

Outline

- Review of Guideline regimens
- Nucleotide reverse transcriptase inhibitors (NRTI’s):
  - tenofovir, TAF, abacavir
- Integrase strand transfer inhibitors (INSTI’s):
  - dolutegravir, bictegravir, elvitegravir, raltegravir
- Protease inhibitors (PI’s):
  - darunavir, atazanavir
- Non-nucleotide reverse transcriptase inhibitors (NRTI’s):
  - rilpivirine, doravirine
- 2-drug ART regimens:
  - DTG/TDF, DTG/RPV

Disclosures

- Research grant support from National Institutes for Health (NIH), Centers for Disease Control (CDC) & President’s Emergency Plan for AIDS Relief (PEPFAR) –
  - For work ongoing in East Africa related to HIV care models
  - This disclosure is unrelated to this presentation
Outline

- Review of Guideline regimens
  - Nucleotide reverse transcriptase inhibitors (NRTI's):
    - tenofovir, TAF, abacavir
  - Integrase strand transfer inhibitors (INSTI's):
    - dolutegravir, bictegravir, elvitegravir, raltegravir
  - Protease inhibitors (PI's):
    - darunavir, atazanavir
  - Non-nucleotide reverse transcriptase inhibitors (NNRTI's):
    - rilpivirine, doravirine
  - 2-drug ART regimens:
    - DTG/3TC, DTG/RPV

DHHS Guidelines

- Available for download at:
Integrase Inhibitors
- Bictegravir
- Dolutegravir
- Elvitegravir
- Raltegravir

NRTI (nucleoside analogs)
- Tenofovir TDF
- Tenofovir TAF
- Emtricitabine FTC
- Lamivudine 3TC
- Efavirenz EFV
- Nevirapine NVP
- Didanosine DDI
- Zidovudine ZDV

Protease Inhibitors
- Darunavir DRV
- Atazanavir ATV
- Cobicistat Cobi
- Tipranavir TPV
- Saquinavir SQV
- Ritonavir RTV

NRTI (non-nucleosides)
- Abacavir ABC
- Emtricitabine FTC
- Lamivudine 3TC
- Zidovudine ZDV

NNRTI (non-nucleosides)
- Efavirenz EFV
- Nevirapine NVP

CCR5 Inhibitors
- Maraviroc MVC

Monoclonal Antibody
- Ibalizumab IBA

Outline
- Review of Guideline regimens
- Nucleotide reverse transcriptase inhibitors (NRTI's):
  - tenofovir, TAF, abacavir
- Integrase strand transfer inhibitors (INSTI's):
  - dolutegravir, bictegravir, elvitegravir, raltegravir
- Protease inhibitors (PI's):
  - darunavir, atazanavir
- Non-nucleotide reverse transcriptase inhibitors (NRTI's):
  - rilpivirine, doravirine
- 2-drug ART regimens:
  - DTG/3TC, DTG/RPV
**NRTI’s: Tenfovir-based Meds**

<table>
<thead>
<tr>
<th>TDF/FTC (Truvada)</th>
<th>TAF/FTC (Descovy)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Renal Concerns</strong></td>
<td><strong>Renal Profile</strong></td>
</tr>
<tr>
<td>Decrease in eGFR over time?</td>
<td>better?</td>
</tr>
<tr>
<td>Decrease in bone density?</td>
<td>better?</td>
</tr>
<tr>
<td>Risk of tubular toxicity/ Fanconi’s syndrome?</td>
<td>Lipid Profile</td>
</tr>
<tr>
<td>Decrease in bone density?</td>
<td>worse?</td>
</tr>
<tr>
<td>Concomitant increase risk of fracture?</td>
<td></td>
</tr>
</tbody>
</table>

**NRTI’s: TDF/FTC (Truvada)**

**TDF/FTC (Truvada): evidence supporting renal concerns?**

- Slow, small magnitude decrement in eGFR over time?
- Small risk of proximal tubular toxicity/ Fanconi’s syndrome?
- Initial case reports circa 2002-2004
- Issues: controversial topic
  - observational study vs. RCT
  - baseline eGFR
  - low body weight
  - other renal risks
  - use of r/PI
  - other nephrotoxic meds

**NRTI’s: TAF/FTC (Descovy)**

**TAF (tenofovir alafenamide)**

- Oral TAF prodrug circulates in plasma
- TAF taken into cells, processed to create tenofovir-diphosphate (TFV-DP, the active drug)

**Virologic non-inferiority of TAF to TDF when paired with cobi/EVG**

<table>
<thead>
<tr>
<th>Genotype (TAF/FTC/cobi/EVG) noninferior to Stribild (TDF/FTC/EVG) (Study 104/111):</th>
</tr>
</thead>
<tbody>
<tr>
<td>at Week 48: 90.5% VS [TAF] vs. 90.0% [TDF]</td>
</tr>
<tr>
<td>at Week 96: 87.5% VS [TAF] vs. 85.5% [TDF]</td>
</tr>
<tr>
<td>at Week 144: 83.0% VS [TAF] vs. 80.0% [TDF]</td>
</tr>
</tbody>
</table>

**Similar non-inferiority of TAF when paired with cobi/DRV**

- TAF/FTC/cobi/DRV noninferior to TDF/FTC+cobi/DRV: (AMBER Study)
  - at Week 48: 91.5% VS [TAF] vs. 88.5% [TDF]
  - at Week 96: 85.0% VS [TAF] vs. 86.0% [TDF]

**Similar AEs profile, lipid effects**

- Eron JJ et al., AMBER Study: AIDS, 2018
- Orkin, C. et al., AMBER Study: HIV Drug Therapy Glasgow, Oct. 2018
证据表明改善的肾功能？
(研究104/111数据至144周)
- 小于GFR, 尿蛋白/肌酐, RBP/肌酐, β2M/肌酐
- eGFR下降较少：
  - 中位CrCl下降:
    - TAF vs. TDF
    - 2.0 mL/min (ECF-TAF) vs. 7.5 mL/min (ECF-TDF) (p<0.001)
- 少数由于肾功能不全导致的中止事件：
  - TAF: 0
  - TDF: 12
证据表明改善的骨功能？
(研究104/111数据至144周)
- 更少的骨密度下降：
  - 臀部骨密度下降：
    - TAF vs. TDF
    - 0.7% [ECF-TAF] vs. 3.3% [ECF-TDF] (p<0.001)
  - 脊柱骨密度下降：
    - TAF vs. TDF
    - 1.0% [ECF-TAF] vs. 2.8% [ECF-TDF] (p<0.001)
- 更小的PPTH增加
- 小于的体积
- 适用于eGFR ≥ 30的患者
- 不适用于eGFR ≥ 60的患者

NRTI's: TAF/FTC (Descovy)

Smaller pill size
- TAF/FTC
- TDF/FTC

Lipid profile
- 从基线至144周的脂质变化更差在TAF vs. TDF:
  - TAF vs. TDF:
    - 总胆固醇:
      - TAF: +3 vs. TDF: +3
    - HDL:
      - TAF: +6 vs. TDF: +2
    - LDL:
      - TAF: +9 vs. TDF: +6
    - TG:
      - TAF: +21 vs. TDF: +22

Drug interactions
- Rifamycins
  - 诱导CYP3A4, P-gp,和BERTCP
  - 使TAF/FTC, OATP1B3,和OATP8B1受影响
- Not the effect of this unknown
- Do not co-administer rifamycins with TAF

TAF with cobicistat
- TAF是CYP3A4, P-gp, OATP1B3,和OATP8B1的底物
- Cobi抑制这些底物，会提高TAF水平
- 因此，Cobi与TAF配对使用会导致TAF水平升高
**TAF and TDF Summary**

<table>
<thead>
<tr>
<th>TDF/FTC (Truvada)</th>
<th>TAF/FTC (Descovy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Concerns</td>
<td>Renal Profile</td>
</tr>
<tr>
<td>Decrease in eGFR over time?</td>
<td>better?</td>
</tr>
<tr>
<td>Risk of tubular toxicity/ Fanconi’s syndrome?</td>
<td>Decrease in bone density?</td>
</tr>
<tr>
<td>Concomitant increase risk of fracture?</td>
<td>better?</td>
</tr>
</tbody>
</table>

Consider eGFR, proteinuria, osteopenia, and need for rifamycins in this decision...

And in coming years, with generic TDF available, consider cost-benefit calculations depending on patients’ insurance/coverage

**NRTI’s: ABC/3TC (Epzicom)**

<table>
<thead>
<tr>
<th>ABC/3TC (Epzicom):</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC Hypersensitivity</td>
</tr>
<tr>
<td>Cardiovascular Concerns</td>
</tr>
<tr>
<td>Basic biology</td>
</tr>
<tr>
<td>Theoretical basis for concern</td>
</tr>
<tr>
<td>HLA-B*57:01 Testing</td>
</tr>
<tr>
<td>Fully discriminative</td>
</tr>
<tr>
<td>If positive: ABC contraindicated</td>
</tr>
<tr>
<td>If negative: ABC safe</td>
</tr>
</tbody>
</table>

Guideline Language: “Increase in CV events is associated with ABC use in some, but not all, cohort studies.”

Issues: controversial topic
- observational studies vs. RCTs
- other CV risks accounted for?
- risks from other ARVs?
- duration of follow-up?
- what outcomes assessed?

**NRTIs for Patients with HBV**

- For Hepatitis B positive patients:
  - TDF/FTC:
    - 2 active agents: good choice
  - TAF/FTC:
    - 2 active agents
    - also FDA approved for HBV+ patients: good choice
  - ABC/3TC:
    - only the 3TC is active
    - if using ABC, typically combine with entecavir

**Outline**

- Review of Guideline regimens
- Nucleotide reverse transcriptase inhibitors (NRTI’s):
  - tenofovir, TAF, abacavir
- Integrase strand transfer inhibitors (INSTI’s):
  - dolutegravir, bictegravir, elvitegravir, raltegravir
- Protease inhibitors (PI’s):
  - darunavir, atazanavir
- Non-nucleotide reverse transcriptase inhibitors (NRTI’s):
  - nelfinavir, doravirine
- 2-drug ART regimens:
  - DTG/3TC, DTG/RPV
Integrase Inhibitors: Overview

- Dominant class of ART: goal is for all patients to be considered for INSTI
  - Dolutegravir
    - Part of single tablet regimen Triumeq
    - Also available separately
  - Bictegravir
    - Only available as part of single tablet Biktarvy
  - Elvitegravir (E/C/F/TAF, and E/C/F/TDF)
    - Both Genvoya and Stribild moved from 1st to 2nd line
  - Raltegravir remains on 1st line list

Integrase Inhibitors: DTG

- Dolutegravir (DTG)
  - Highly potent, highly efficacious
  - High genetic barrier to resistance
  - 50mg QD dosing, no booster
  - Available as part of Triumeq, or separately
  - Need BID if using with EFV, or with rifampin
  - Highly potent, highly efficacious
  - High genetic barrier to resistance
  - SINGLE Study: DTG + ABC/3TC vs. EFV/TDF/FTC
    - 44 week viral suppression 72% vs. 63% (superior)
  - SPRING 2 Study: DTG + (ABC/3TC or TDF/FTC) vs. RAL + (ABC/3TC or TDF/FTC)
    - 96-week viral suppression 82% vs. 78% (non-inferior)
  - FLAMINGO Study: DTG + (ABC/3TC or TDF/FTC) vs. DRV/RTV + (ABC/3TC or TDF/FTC)
    - 96-week viral suppression 71% vs. 63% (non-inferior)

Integrase Inhibitors: BIC

- Bictegravir (BIC)
  - Highly potent, highly efficacious
  - High genetic barrier to resistance
  - 25mg dose as part of single tablet Biktarvy (TAF/FTC/BIC)
  - No booster
  - Trial 1489: Biktarvy vs. Triumeq
    - 92% VS (BIC) vs. 93% (DTG) at Week 48
    - VS similar in VL<100K, VL 100K-400K and VL>400K
  - Trial 1490: Biktarvy vs. TAF/FTC + DTG
    - 89% VS (BIC) vs. 93% (DTG) at Week 48
    - 84% VS (BIC) vs. 86% (DTG) at Week 96

Notes/Caution:

- DTG alone only for eGFR>30
- DTG as Triumeq only for eGFR>50
- Inhibits OCT2 → inhibits tubular creatinine secretion, Cr will rise 0.1–0.3
- Decreased absorption when polyvalent cations given (Ca++, Mg++, Fe++, e.g.) → space DTG 2h before or 6h after these
- Caution: DTG boosts metformin levels
- Side effects → discontinuation initially thought to be <2–3% in first year
- Headache, insomnia increasingly recognized
- 15% (85/556) Amsterdam patients stopped DTG:
  - 6% (sleep), 4% (GI), 4% (malaise), 3% (psychological)
  - 3% (neurological, muscle, pain)
- Hypersensitivity/skin reactions uncommon (<1%)
Integrase Inhibitors: BIC

Cautions:
- Inhibits tubular secretion of creatinine: raises Cr by 0.1mg/dL
- Only for eGFR>90
- Not for liver disease Child-Pugh C
- Substrate of CYP3A: so any inducer of CYP3A will decrease BIC levels
- Vice versa for inhibitors of CYP3A
- Same for inducer or inhibitor of UGTs
- TAF component is a substrate of P-gp and BCRP... so inducers can reduce TAF, inhibitors can increase TAF...

- Do no co-administer with rifampin (reduces BIC and TAF)
- Boosts metformin levels
- Caution for patients with HBV when discontinuing: risk of HBV flare
- Antacids with Al/Mg/Ca: take BIC 2h before
- Fe/Ca supplements: take with BIC and food


Integrase Inhibitors: EVG & RAL

Elvitegravir (EVG)
- Well-tolerated, strong efficacy
- 150 mg QD dosing
- Requires cobimetinib (50mg QD)
- Lower genetic barrier to resistance
- Hypersensitivity rare
- 1866 patients had rash in EVG studies

Raltegravir (RAL)
- Very well-tolerated, good potency/efficacy
- 400mg BID dosing
- Can dose at 300mg QD (noninferior to 400mg BID; 8% vs 8% vs at week 48)
- No boosting required
- Lower genetic barrier to resistance
- Hypersensitivity reaction (rare, mild)
- Even rarer: DRESS syndrome

Dolutegravir and Pregnancy

- Dolutegravir in preliminary/emerging data has been associated with low rate of neural tube defects
- 2018 Guidelines: “preliminary data suggest that there is an increased risk of neural tube defects (NTDs) in infants born to people who were receiving DTG at the time of conception”
  - Negative pregnancy test result should be documented prior to initiating DTG in antiretroviral therapy (ART) naïve individuals of childbearing potential
  - DTG is not recommended for those who are pregnant and within 12 weeks post-conception
  - DTG is also not recommended for those of childbearing potential who are planning to become pregnant or who are sexually active and not using effective contraception
  - For those who are using effective contraception, use of a DTG-based regimen can be considered after assessing the risks and benefits of the drug with the patient
- It is not yet known whether other INSTIs pose a similar risk of NTDs (i.e., a class effect).
- Update from July 2019 IAS & NEJM 8/2019: Zach R et al:
  - Background rate: 0% NTD among 1529 infants analyzed (naive)
  - On DTG <5 NTDs among 1687 infants (0.3%) elevated rate, but less than seen earlier
  - Botswana: lack folate fortification. "Possibly DTG antagonism of folate?"
**INSTI’s and Weight Gain**

- There is a talk at 1pm today on this topic: highly recommend
- Weight gain being increasingly recognized with ART initiation with DTG
- Additional possibly synergistic role of TAF
- Weight gain seen in multiple registrational drug trials in US/Europe
- Also seen in ADVANCE & NAMSAL trials from Africa
- Unclear if a class effect or if certain INSTI’s worse than others
- Mechanism/metabolic pathway unclear, but does appear separate from ‘return to health’ phenomenon
- Thursday lecture devoted to this topic: will be detailed!

**Integrate Inhibitor Overview**

<table>
<thead>
<tr>
<th>Drug</th>
<th>BID</th>
<th>DQ</th>
<th>Loo 100mg</th>
<th>Loo 800mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolutegravir</td>
<td>QD</td>
<td>QD</td>
<td>100mg</td>
<td>100mg BID</td>
</tr>
<tr>
<td>Bictegravir</td>
<td>QD</td>
<td>QD</td>
<td>800mg</td>
<td>800mg BID</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>QD</td>
<td>QD</td>
<td>1200mg</td>
<td>1200mg BID</td>
</tr>
<tr>
<td>Elvitegravir</td>
<td>QD</td>
<td>QD</td>
<td>1200mg</td>
<td>1200mg BID</td>
</tr>
</tbody>
</table>

| Genetic barrier to resistance | High | High | Lower | Lower |
| Single tablet option? | Yes, Triumeq | Yes, Bikarvy | No | Yes, Genvoya or Stribild |

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Nausea, diarrhea/GI disturbance, headache, insomnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased CK, myositis, hypersensitivity, hepatotoxicity</td>
<td>Myositis, increased CK (rare)</td>
</tr>
<tr>
<td>Increased CK, myositis, hypersensitivity, hepatotoxicity, SJS/TEN</td>
<td>Hyperlipidemia</td>
</tr>
</tbody>
</table>

**Outline**

- Review of Guideline regimens
- Nucleotide reverse transcriptase inhibitors (NRTI’s):
  - tenofovir, TAF, abacavir
- Integrate strand transfer inhibitors (INSTI’s):
  - dolutegravir, bictegravir, elvitegravir, raltegravir
- Protease inhibitors (PI’s):
  - darunavir, atazanavir
- Non-nucleotide reverse transcriptase inhibitors (NRTI’s):
  - rilpivirine, doravirine
- 2-drug ART regimens:
  - DTG+3TC, DTG+RPV

**Protease Inhibitor Overview**

- **Darunavir (DRV/r)**
  - Highest potency; fewer side effects than other PI’s; well tolerated
  - More potent: DRV 800 QD (if no DRV mutations)
    - Concomitantly administer either RTV 100 QD or cobicistat 150 QD
    - 600mg BID dosing (when DRV mutations present)
  - No need for H2-blockers or PPI’s
  - Incidence of hyperbilirubinemia: no hyperbilirubinemia
  - Movements from 2017 to 2019
Trial Data Supporting D/C/F/TAF

- **Darunavir/cobi/TAF/FTC** (800/150/10/200)
  - **AMBER** Study (ART-naive adults, randomized to D/C/F/TAF (n=362) vs. DRV/cobi + FTC/TDF (n=362) to W48 (double blind phase III non-inferiority trial, 10% margin)
    - Week 48: 92% VS (STR) vs. 88% (2 tabs); non-inferior
    - Week 96: 85% VS (STR) vs. 88% (2 tabs)
  - **EMERALD** Ph. 3 switch study (in virally suppressed adults) also showed non-inferior maintenance of VS with D/C/F/TAF vs. control
    - Week 48: 2.5% viral rebound vs. 2.1%
    - Week 96: 3.1% viral rebound vs. 2.3% (late switch); VS 91% vs. 94%

**Protease Inhibitors (cont’d)**

- **Atazanavir (ATV/r)**
  - Good potency, generally well-tolerated, 300mg OD + RTV 100mg OD
  - Least effect on lipids of PIs
  - 1bilirubin: sometimes cosmetic, sometimes beyond
  - GERD: in ART-naive patients:
    - H2 blockers: give ATV 400QD 1h before or 1h after H2; give ATV/RTV/ase anytime
    - PPI: use omeprazole 20 or equivalent (maximum) 12h before ATV
  - Recommend take with food
  - Not in first line recommended list

Outline

- Review of Guideline regimens
- Nucleotide reverse transcriptase inhibitors (NRTI’s):
  - tenofovir, TAF, abacavir
- Integrase strand transfer inhibitors (INSTI’s):
  - dolutegravir, bictegravir, elvitegravir, raltegravir
- Protease inhibitors (PI’s):
  - darunavir, atazanavir
- Non-nucleotide reverse transcriptase inhibitors (NRTI’s):
  - rilpivirine, doravirine
- 2-drug ART regimens:
  - DTG/TDF, DTG/RPV

NNRTI Overview

**Rilpivirine (RPV)**

- Potency similar to EFV
- Less lipid effects
- Lower efficacy when VL>100K or CD4<200
- Requires 400 cal. meal
- H2 blocker: give 1h before or 1h after RPV
- PPI: avoid
- In second line list

**Doravirine (DOR)**

- FDA approved 200h ART-naive
- Good potency
- Has TDF in combination pill
- Platelet: No dose adjustment for renal failure or liver disease
- Delisting: only for eGFR>50
- Low rates of headache, nausea, diarrhea
- Metabolized by CYP3A
- Don’t combine with rifampin (rifabutin ok if use DOR 200 BID)
- In second line list
NNRTI Overview (cont’d)

<table>
<thead>
<tr>
<th>Efavirenz (EFV)</th>
<th>Efavirenz (EFV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potency well established</td>
<td>Potency similar to EFV</td>
</tr>
<tr>
<td>• QD</td>
<td>• BID drug</td>
</tr>
<tr>
<td>• CNS side effects: insomnia, dreams</td>
<td>• In second line list</td>
</tr>
<tr>
<td>• Lipid effects</td>
<td></td>
</tr>
<tr>
<td>• Caution with depression</td>
<td></td>
</tr>
<tr>
<td>• Rare suicidality</td>
<td></td>
</tr>
</tbody>
</table>

Etravirine (ETV)

- Potency similar to EFV
- Less lipid effects
- BID drug
- In second line list
- Not in second line list

Outline

- Review of Guideline regimens
- Nucleotide reverse transcriptase inhibitors (NRTI's):
  - tenofovir, TAF, abacavir
- Integrase strand transfer inhibitors (INSTI's):
  - dolutegravir, bictegravir, elvitegravir, raltegravir
- Protease inhibitors (PI's):
  - darunavir, atazanavir
- Non-nucleotide reverse transcriptase inhibitors (NRTI's):
  - rilpivirine, doravirine
- 2-drug ART regimens:
  - DTG/3TC, DTG/RPV

2-Drug Regimens

- Guidelines mention three 2-drug regimens in alternate section (for situations where TAF, TDF, ABC can't be used or are not optimal):
  - DTG+3TC
  - DRV/RTV + RAL BID
  - DRV/RTV + 3TC

Certain 2-Drug Regimens

- Dolutegravir + lamivudine (DTG/3TC; Dovato)
  - GEMINI-1, GEMINI-2 trials: ART-naïve, VL<500K, 48W data led to FDA approval for ART naïve patients
  - Week 48: 91% (2 drug) vs. 93% (3 drug), pooled trials analysis
  - Week 96: 86% (2 drug) vs. 90% (3 drug), pooled
  - Risks of adherence, sub-20% M184V, the "non-perfect patient"

- DRV/RTV + RAL BID

- Not in guidelines: Dolutegravir + rilpivirine (DTG/RPV; Juluca)
  - SWORD-1/SWORD-2 Trials: led to FDA approved for switch of virally suppressed patients, not FDA approved for ART-naïve patients
  - Not mentioned in guidelines for ART initiation since not FDA approved for this
Single Tablet Regimens

- Emtricitabine
- Lamivudine
- Abacavir
- Tenofovir
- Efavirenz
- Rilpivirine
- Ritonavir
- Atazanavir
- Darunavir
- Raltegravir
- Elvitegravir

NRTI
NNRTI
Protease
INSTI

Single Tablet Co-Formulations

- Emtricitabine
- Lamivudine
- Abacavir
- Tenofovir
- Thuvada
- Epzicom
- Truvada
- Epzicom
- Truvada
- Dolutegravir
- Bictegravir
- Raltegravir
- Ritonavir

NRTI
NNRTI
Protease
INSTI

Single Tablet Regimens

- Emtricitabine
- Lamivudine
- Abacavir
- Tenofovir
- Efavirenz
- Rilpivirine
- Ritonavir
- Atazanavir
- Darunavir
- Raltegravir
- Elvitegravir

NRTI
NNRTI
Protease
INSTI
Single Tablet Regimens

- NRTI
- NNRTI
- Protease
- INSTI

1. **Emtricitabine**
   - **Tenofovir**
   - **Ritonavir**

2. **Abacavir**
   - **Lamivudine**
   - **Doravirine**
   - **Efavirenz**
   - **Raltegravir**
   - **Elvitegravir**

3. **Cobicistat**
   - **Triumeq**

4. **Dolutegravir**
   - **Bictegravir**

---

5. **Rilpivirine**

---

6. **March, 2016**

7. **Dolutegravir**
   - **Cobicistat**
   - **Stribild**

8. **Bictegravir**

9. **Doravirine**

---

10. **August, 2012**

11. **Genvoya**

12. **November, 2015**

---

13. **NRTI**
14. **NNRTI**
15. **Protease**
16. **INSTI**
**U.S. DHHS Guideline Update: October, 2018**

<table>
<thead>
<tr>
<th>Initial Regimens</th>
<th>Initial Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>for Most People</em></td>
<td><em>in Certain Clinical Situations</em></td>
</tr>
<tr>
<td>BIC/TAF/FTC</td>
<td>EVG/cobi + (TDF/FTC or TAF/FTC)</td>
</tr>
<tr>
<td>DTG/ABC/3TC</td>
<td>RAL/ABC/3TC</td>
</tr>
<tr>
<td>EVG/cobi + (TDF/FTC or TAF/FTC)</td>
<td>RAL/ABC/3TC</td>
</tr>
<tr>
<td>EVG/cobi + (TDF/FTC or TAF/FTC)</td>
<td>RAL/ABC/3TC</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>(TDF/FTC or TAF/FTC)</td>
</tr>
<tr>
<td>TDF/FTC</td>
<td>(TDF/FTC or TAF/FTC)</td>
</tr>
<tr>
<td>BIC/TAF/FTC</td>
<td>(TDF/FTC or TAF/FTC)</td>
</tr>
<tr>
<td>DTG/ABC/3TC</td>
<td>(TDF/FTC or TAF/FTC)</td>
</tr>
<tr>
<td>EVG/cobi + (TDF/FTC or TAF/FTC)</td>
<td>(TDF/FTC or TAF/FTC)</td>
</tr>
<tr>
<td>RAL + (TDF/FTC or TAF/FTC)</td>
<td>(TDF/FTC or TAF/FTC)</td>
</tr>
<tr>
<td>EVG/cobi + (TDF/FTC or TAF/FTC)</td>
<td>(TDF/FTC or TAF/FTC)</td>
</tr>
<tr>
<td>DRV (cobicistat/RTV) + ABC/3TC</td>
<td>(TDF/FTC or TAF/FTC)</td>
</tr>
<tr>
<td>DRV (cobicistat/RTV) + ABC/3TC</td>
<td>(TDF/FTC or TAF/FTC)</td>
</tr>
<tr>
<td>DRV (cobicistat/RTV) + ABC/3TC</td>
<td>(TDF/FTC or TAF/FTC)</td>
</tr>
<tr>
<td>DRV (cobicistat/RTV) + ABC/3TC</td>
<td>(TDF/FTC or TAF/FTC)</td>
</tr>
<tr>
<td>DRV (cobicistat/RTV) + ABC/3TC</td>
<td>(TDF/FTC or TAF/FTC)</td>
</tr>
<tr>
<td>BPV + (TDF/FTC or TAF/FTC)</td>
<td>(TDF/FTC or TAF/FTC)</td>
</tr>
<tr>
<td>BPV + (TDF/FTC or TAF/FTC)</td>
<td>(TDF/FTC or TAF/FTC)</td>
</tr>
</tbody>
</table>

**Case 1**

- 51 year old man registering for care. VL = 41,000, CD4+ count = 682. Creatinine clearance = 55 mL/min. LDL = 68. HLAB57:01 is negative. No other medical problems. Which regimen(s) would you offer?
  - A) TAF/FTC/BIC (Biktarvy)
  - B) TAF/FTC (Descovy) + DTG (Tivicay)
  - C) ABC/3TC/DTG (Triumeq)
  - D) TDF/FTC (Truvada) + RTV/DRV
  - E) EVG(cobi)/TAF/FTC (Genvoya)
  - F) RAL + TAF/FTC (Descovy)

**Case 2**

- Same patient as Case 3, but lower eGFR.
  - 51 year old man registering for care. VL = 41,000, CD4+ count = 682. Creatinine = 1.6, creatinine clearance = 31 mL/min. LDL = 68. HLAB57:01 is negative. No other medical problems. Which regimen would you offer?
  - A) TDF/FTC (Truvada) + DTG
  - B) TAF/FTC (Descovy) + DTG
  - C) TAF/FTC/BIC (Biktarvy)
  - D) TDF/FTC + RTV/DRV
  - E) EVG(cobi)/TAF/FTC (Genvoya)
  - F) TAF/FTC (Descovy) + RAL 1200 QD
### Case 2

- 51 year old man registering for care. VL = 41,000, CD4+ count = 68. Creatinine = 1.5, and creatinine clearance = 31 mL/min. LDL = 68. HLAB57-01 is negative. No other medical problems. Which regimen would you offer?

- A) TDF/FTC (Truvada) + DTG → eGFR < 60: avoid TDF
- B) TAF/FTC (Descovy) + DTG → eGFR > 90: fine choice; monitor.
- C) TAF/FTC/BIC (Biktarvy) → eGFR > 90: fine choice; monitor.
- D) ABC/3TC/DTG (Triumeq)
  - B57 negative: eligible.
  - Some CV concerns with renal disease.
  - But Triumeq is only for eGFR > 50.
- E) TDF/FTC + RTV/DRV → eGFR < 60: avoid TDF, esp. with RTV/PI.
- F) TDF/FTC + RAL 1200 QD → Fine choice at eGFR > 30, but lower barrier to resistance, and 3 pills where single tablet is possible.

### Case 3

- 48 y.o. man, newly diagnosed last month, VL 105,000, CD4+ count = 48. Has history of hyperlipidemia (LDL = 110, Total cholesterol = 220), smokes 10 cigarettes/day, and has HBA1c = 7.3%. BUN/creatinine 14/1.2, CrCl=73 mL/min, UA: 1+ protein. Which ART is optimal?

- A) TAF/FTC (Descovy) + DTG
- B) TDF/FTC (Truvada) + DTG
- C) TAF/FTC/BIC (Biktarvy)
- D) ABC/3TC/DTG (Triumeq)
- E) TAF/FTC (Descovy) + RTV/DRV
- F) TDF/FTC/DOR (Delstrigo)

- 48 y.o. man, newly diagnosed, VL 105,000, CD4+ count = 48. Has history of hyperlipidemia (LDL = 140, Total cholesterol = 220), smokes 10 cigarettes/day, and has HBA1c = 7.3%. BUN/creatinine 14/1.2, CrCl=73 mL/min, UA: 1+ protein. Which ART is optimal?

- A) TAF/FTC (Descovy) + DTG
- B) TDF/FTC (Truvada) + DTG
- C) TAF/FTC/BIC (Biktarvy)
- D) ABC/3TC/DTG (Triumeq)
- E) TAF/FTC (Descovy) + RTV/DRV
- F) TDF/FTC/DOR (Delstrigo)
Case 4

- 34 y.o. woman, HIV VL 123,000, CD4 +610. Has chronic HBV: HBsAg+ HBsAb+ HBcAb+ HBV DNA+. HLAB57-01 negative. CrCl=90. Which regimen(s) would you offer?

  A) TAF/FTC (Descovy) + DTG → fine choice
  B) TDF/FTC (Truvada) + DTG → fine choice
  C) TAF/FTC/BIC (Biktarvy) → fine choice
  D) ABC/3TC/DTG (Triumeq) → 3TC alone: would need to add entecavir
  E) TDF/FTC (Truvada) + RTV/DRV → OK, but prefer integrase > PI
  F) ABC/3TC (Epzicom) + RAL → Combo is second line, not for HIV VL >100K (always check), would need to add entecavir with 3TC, and would prefer integrase over PI

Case 5

- 57 y.o. woman, VL=14K, CD4=390. DM2: A1c=8.0%, takes metformin at maximum 875mg TID dose + glipizide 5mg BID, CrCl=90mL/min, UA with no protein. HLAB57 negative. Which ART regimen do you favor?

  A) TDF/FTC (Truvada) + DTG → potentially ok; potentially not
     DTG boosts metformin → would need close monitoring as already on max dose (but might be ok)
     If need to reduce metformin, might have to add 2nd med, or DMI control may get worse
  B) TAF/FTC (Descovy) + DTG → same as choice A
  C) TAF/FTC/BIC (Biktarvy) → same as choice A
  D) ABC/3TC/DTG (Triumeq) → eGFR:70, no DDI→ fine choice
  E) TDF/FTC/cobi/EVG (Stribild) → eGFR:70, no DSI→ fine choice
  F) TAF/FTC (Truvada) + RAL → eGFR:70, no DSI→ fine choice

Summary / Principles

- Choosing the NRTI backbone:
  - Consider TDF vs. TAF
    - Assess creatinine clearance, proteinuria, osteopenosis, importance of pill size
    - Consider ABC vs. TDF/TAF
    - Need HLAB57-01 test. Assess question/opinion of cardiac risk issues
  - Consult with experts when all NRTI’s seem problematic
- Goal is to use INSTI in most patients unless other issues prevail
  - Consider prior history, drug intolerance, side effect, desire for single-tablet regimen, drug interactions
  - Consider DTG, BIC for most patients if possible
- Assess PI and NNRTI possibilities if needed:
  - Consider dosing (OD vs. BID), desire for single tablet regimen, psychiatric history, lipid profile, GI issues, renal status, likelihood of strong adherence/genetic barrier
  - Assess baseline VL and CD4 count
- Focus on DHHS first-line recommended regimens
Tipping the Scales: Is ART adding pounds to our patients?

Matthew D. Hickey, MD

Conflict of Interest

• I have no disclosures

Roadmap

1. Recent trends in weight gain
2. Weight gain after ART start and ART switch
3. Two RCTs of DTG +/- TAF in Sub-Saharan Africa
4. RCT data on bictegravir, dolutegravir, and TAF
5. Health consequences of weight gain and possible mechanisms

First, a case (Audience Response)

• 37 year old man with a recent diagnosis of HIV (CD4 280, VL 20,000) who is presenting to establish care.
• He also has hypertension and takes hydrochlorothiazide “most of the time”. HLA*B5701 is negative.
• Prior to seeing you, he read on the internet that HIV medications could make him gain weight and tells you that he absolutely wants to avoid weight gain.
• What do you start?

   A. DTG + TAF/FTC
   B. DTG + TDF/FTC
   C. DTG/3TC/ABC
   D. BIC/TAF/FTC
   E. DRV/c/TAF/FTC
Weight increasing at ART start

- Over time, BMI at ART start has increased at rate faster than general US population
- Prevalence of obesity:

Weight gain after ART start

- Significant weight gain after starting ART
  - Especially seen in men and non-white women
  - Some weight gain due to ‘return to health’
  - 18% treatment-emergent obesity
- Key questions:
  - How much of this weight gain is ‘return to health’?
  - Does ART cause weight gain beyond ‘return to health’?
  - Do some ART drugs cause more weight gain than others?

Unexpected finding: Weight gain with RAL vs boosted-PI

- Randomized trial to see if raltegravir had improved metabolic profile compared to protease inhibitors
- Surprisingly, weight gain worse with RAL, even when excluding baseline underweight
- Weight gain particularly significant among black race, high viral load, low CD4

Risk for severe weight gain (>10% body weight)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted Odds Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV/r vs. RAL</td>
<td>0.72</td>
<td>(0.53 to 0.99)</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>DRV/r vs. RAL</td>
<td>0.73</td>
<td>(0.53 to 0.99)</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>Black (non-Hispanic)</td>
<td>1.55</td>
<td>(1.01 to 2.36)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Baseline log10 HIV RNA</td>
<td>2.52</td>
<td>(1.90 to 3.26)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline CD4 count (100 cells/μL)</td>
<td>0.78</td>
<td>(1.18 to 1.39)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Increased weight gain with INSTI start

Greater weight gain with switch to INSTI

- Single center in southern US (n=495)
- Patients virally suppressed on EFV/TDF/FTC prior to switch
- Weight gain greatest after switch to DTG/ABC/3TC

Weight gain among treatment experienced patients switching to an INSTI

Greater weight gain with switch to INSTI

Integrase inhibitor regimens versus EFV/TDF/ FTC

- Weight gain with INSTI
- DTG/ABC/3TC versus EFV/TDF/FTC

Weight gain after switch to DTG from boosted protease inhibitor (NICE-022)

Randomized trial of patients with high cardiovascular risk on boosted PI (n=415) who were switched to:
- DTG immediate started at week 0
- DTG delayed started at week 48

Weight gain after switch from boosted PI to dolutegravir

- Start DTG
- Weight gain after switch to dolutegravir

Norwood, JAIDS. 2017

Slide credit: John Koethe, CROI 2019
Weight increases after switch to INSTI

- Among patients suppressed at time of switch to INSTI, weight stable pre-switch and increased post-switch (n=651)
- Greater weight gain among women, black people, older people.
- Weight gain greatest with switch to dolutegravir

Randomized Trials of DTG in Sub-Saharan Africa

- Two randomized trials of Dolutegravir vs standard of care (EFV/TDF/FTC) in treatment naïve patients
- ADVANCE in South Africa
- NAMSAL in Cameroon

ADVANCE Study: DTG vs EFV in South Africa

- Randomized trial in treatment naïve patients (n=1,053) comparing:
  - EFV + TDF/FTC (n=351)
  - DTG + TDF/FTC (n=351)
  - DTG + TAF/FTC (n=351)
- Over half of participants were women
- Overall, high rates of viral suppression

Greater weight gain with DTG + TAF/FTC

<table>
<thead>
<tr>
<th>Mean change in weight (kg)</th>
<th>TAF/FTC+DTG</th>
<th>TDF/FTC+DTG</th>
<th>TDF/FTC/EFV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 48</td>
<td>+6 kg</td>
<td>+3 kg</td>
<td>+1 kg</td>
</tr>
<tr>
<td>Treatment-emergent overweight, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 48</td>
<td>23%</td>
<td>14%</td>
<td>9%</td>
</tr>
<tr>
<td>Week 96</td>
<td>25%</td>
<td>13%</td>
<td>11%</td>
</tr>
<tr>
<td>Treatment-emergent obesity, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 48</td>
<td>14%</td>
<td>7%</td>
<td>0%</td>
</tr>
<tr>
<td>Week 96</td>
<td>10%</td>
<td>8%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Highly significant differences in weight change between arms, p<0.001
Clinical obesity (BMI ≥ 30 kg/m²). TAF/FTC+DTG higher than other 2 groups (p<0.01)
Not just 'return to health': weight gain differences greatest in baseline normal and overweight BMI.

<table>
<thead>
<tr>
<th></th>
<th>TAF/FTC+DTG (n=158)</th>
<th>TDF/FTC+DTG (n=156)</th>
<th>TDF/FTC/EFV (n=137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight, kg</td>
<td>+4.8 (9%)</td>
<td>+2.6 (5%)</td>
<td>+3.1 (6%)</td>
</tr>
<tr>
<td>Week 48</td>
<td>+4.5 (8%)</td>
<td>+4.0 (8%)</td>
<td>+3.2 (6%)</td>
</tr>
<tr>
<td>Normal, kg</td>
<td>+5.6 (9%)</td>
<td>+3.0 (5%)</td>
<td>+1.1 (2%)</td>
</tr>
<tr>
<td>Week 48</td>
<td>+8.3 (13%)</td>
<td>+3.9 (8%)</td>
<td>+3.3 (6%)</td>
</tr>
<tr>
<td>Overweight, kg</td>
<td>+7.0 (9%)</td>
<td>+3.6 (5%)</td>
<td>+4.6 (7%)</td>
</tr>
<tr>
<td>Week 48</td>
<td>+9.0 (12%)</td>
<td>+4.6 (6%)</td>
<td>+4.6 (7%)</td>
</tr>
<tr>
<td>Obese, kg</td>
<td>+4.4 (5%)</td>
<td>+3.2 (4%)</td>
<td>0.9 (1%)</td>
</tr>
<tr>
<td>Week 48</td>
<td>+4.6 (5%)</td>
<td>-1.5 (2%)</td>
<td>+2.6 (3%)</td>
</tr>
</tbody>
</table>

Comparison: Statistically significant differences between TAF/FTC+DTG and TDF/FTC/EFV at week 96, *p=0.025*.

Metabolic syndrome defined as any two of: elevated triglycerides, low HDL, hypertension, diabetes.

<table>
<thead>
<tr>
<th></th>
<th>TAF/FTC+DTG</th>
<th>TDF/FTC+DTG</th>
<th>TDF/FTC/EFV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline prevalence</td>
<td>16/350 (5%)</td>
<td>21/351 (6%)</td>
<td>14/351 (4%)</td>
</tr>
<tr>
<td>Normal, kg</td>
<td>20/290 (7%)</td>
<td>16/297 (5%)</td>
<td>9/189 (5%)</td>
</tr>
<tr>
<td>Week 48</td>
<td>17/189 (9%)</td>
<td>9/189 (5%)</td>
<td>6/180 (3%)</td>
</tr>
<tr>
<td>Week 96</td>
<td>10/110 (9%)</td>
<td>9/110 (8%)</td>
<td>6/110 (5%)</td>
</tr>
</tbody>
</table>


Generalized increase in body fat.

Women gained more weight than men.

Increase in metabolic syndrome with DTG+TAF.
NAMSAL Study: DTG vs EFV in Cameroon

- Randomized trial in treatment naïve patients (n=613) comparing:
  - EFV + TDF/3TC (n=310)
  - DTG + TDF/3TC (n=303)
- Nearly two thirds of participants were women
- Lower rates of viral suppression and higher baseline viral loads than ADVANCE

Substantial treatment-emergent obesity in men

<table>
<thead>
<tr>
<th>% participants</th>
<th>TDF/3TC/DTG</th>
<th>TDF/3TC/EVF</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>26%</td>
<td>19%</td>
<td>0.05</td>
</tr>
<tr>
<td>Women</td>
<td>44%</td>
<td>34%</td>
<td></td>
</tr>
</tbody>
</table>

Greater weight gain seen with DTG, again

<table>
<thead>
<tr>
<th>Week 48</th>
<th>TDF/3TC/DTG (n=293)</th>
<th>TDF/3TC/EVF400 (n=278)</th>
<th>p-value for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change from baseline:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>+5</td>
<td>+3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>+1.7</td>
<td>+1.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Summary from ADVANCE and NAMSAL

- Dolutegravir is associated with increased weight gain and obesity in both men and women
- Weight gain is greater in women and when DTG is combined with TAF/FTC
  - Is this due to weight loss associated with TDF? Or weight gain with TAF?
  - In women, weight gain does not plateau by 2 years of follow up, unknown whether weight continues to rise
  - Modest increase in metabolic syndrome with DTG+TAF/FTC
- One question: Is bictegravir associated with similar weight gain?
Pooled analysis of 8 RCTs in ART naïve patients: INSTI associated with greater increases in weight

Dolutegravir and Bictegravir associated with largest weight gain

TAF also associated with greater weight gain than TDF

Greater weight gain with INSTI+TAF
Direct study comparisons
- Greater weight gain with EVG/c/TAF/FTC than EVG/c/TDF/FTC
Greater weight gain with INSTI+TAF

Direct study comparisons

• Greater weight gain with EVG/c/TAF/FTC than
  EVG/c/TDF/FTC
• Greater weight gain with
  BIC/TAF/FTC than
  DTG/ABC/3TC

Greater weight gain with INSTI+TAF

Direct study comparisons

• Greater weight gain with
  BIC/TAF/FTC than
  DTG/ABC/3TC
• Similar weight gain in DTG vs
  BIC when combined with
  TAF/FTC

Mean weight change (kg) over 1 year

0.9kg weight gain/year among average adult aged 20-40

Patients gain weight with ART... so what?

• ADVANCE showed small increased incidence of metabolic syndrome
  in DTG+TAF/FTC compared to DTG+TDF/FTC or EFV+TDF/FTC
• Pooled analysis of 8 RCTs showed no increase in diabetes or
  hypertension; very small decreases in HDL cholesterol
• Several cohort studies with conflicting results regarding incident
dyslipidemia and diabetes with INSTI-associated weight gain

What we know and what we don’t

What we know

• Larger weight gain with INSTIs in randomized trials among ART-naive patients
• Greater weight gain when TAF combined with INSTI among ART-naive patients
• Likely weight gain from switch to INSTI or TAF, though lower quality evidence
• Risk of weight gain higher in women, black people, high viral load

What we don’t know

• Mechanism of action for INSTI and TAF associated weight gain
• Possible measures to prevent weight gain
• Reversibility of weight gain
• Long-term clinical consequences of ART-associated weight gain

Hypothesized mechanisms: INSTI

• Promotion of adipose tissue growth and insulin resistance?
  • DTG/RAL associated with increased adipocyte growth and insulin resistance¹
  • Case reports of acute-onset diabetes with INSTI switch²,³
• Better virus elimination and reduction of catabolism?
  • More rapid viral suppression with INSTI
  • Better penetration into adipocytes⁴
  • Lack of weight gain with cabotegravir for PrEP⁵

5. CROI 2019 Abstract #034.

Decisions we’re facing now in clinic

• How do we counsel patients on possibility of weight gain without scaring them away from ART?
• Should some patients be switched from TAF to TDF?
• Should we consider DTG/ABC/3TC for some patients for whom we are worried about renal/bone toxicity and weight gain?
• Is there less weight gain with two-drug therapy and should we be thinking about this for selected patients (e.g. DTG/3TC, DTG/RPV)?

Back to the case...

• 37 year old man with a recent diagnosis of HIV (CD4 280, VL 20,000) who is presenting to establish care. He has hypertension and takes hydrochlorothiazide “most of the time”. HLA*B5701 is negative
• Did your answer change?
  A. DTG + TAF/FTC
  B. DTG + TDF/FTC
  C. DTG/3TC/ABC
  D. BIC/TAF/FTC
  E. DRV/c/TAF/FTC
Answer: A-E are all reasonable options
We will be discussing further in the debate!

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A. DTG + TAF/FTC</td>
<td>B. DTG + TDF/FTC</td>
</tr>
<tr>
<td>C. DTG/3TC/ABC</td>
<td>D. BIC/TAF/FTC</td>
</tr>
<tr>
<td>E. DRV/C7TA/FTC</td>
<td></td>
</tr>
</tbody>
</table>

Thank you!
Many thanks to the conference organizers for the opportunity to speak and to everyone who helped me prepare this talk:

Diane Havlir
Annie Luetkemeyer
Carina Marquez
Vivek Jain
Ayasha Agga
Meg Newman

Matt.Hickey@ucsf.edu
STD Updates for the HIV Clinician

Susan Philip, MD MPH
Director, Disease Prevention and Control
Population Health Division
San Francisco Department of Public Health
Assistant Clinical Professor of Medicine
Division of Infectious Diseases
University of California, San Francisco

Disclosures

• The views expressed herein do not necessarily reflect the official policies of the City and County of San Francisco; nor does mention of the San Francisco Department of Public Health imply its endorsement.

Coming in 2020: Federal STI Action Plan

• **Vision:** The United States will be a place where sexually transmitted infections are prevented and where every person has high quality STI prevention, care and treatment, and lives free from stigma and discrimination.
• This vision includes all people, regardless of age, gender, disability, race, ethnicity, sexual orientation, gender identity, or socio-economic circumstance.
• **Goals:**
  • Prevent new STIs
  • Improve the health of people by reducing adverse outcomes of STIs
  • Reduce STI-related health disparities
  • Achieve integrated, coordinated efforts that address the STI epidemics across federal programs

Download the free CDC Treatment Guidelines App for iOS and Android

http://www.cdc.gov/std/tg2015/
Persons diagnosed with an STD should be given highest priority for PrEP and other HIV prevention

- Rectal GC or CT
- Primary or Secondary Syphilis
- No rectal STD or syphilis infection

1 in 15 MSM were diagnosed with HIV within 1 year.*
1 in 18 MSM were diagnosed with HIV within 1 year.**
1 in 53 MSM were diagnosed with HIV within 1 year.*


Multiple, Continued Recommendations to Screen for STDs in Patients Living with HIV

<table>
<thead>
<tr>
<th>Recommendations for HIV Prevention with Adults and Adolescents with HIV in the United States, 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Care Guidelines for the Management of Persons Infected With HIV. 2013 Update by the HIV Medicine Association of the Infectious Diseases Society of America</td>
</tr>
<tr>
<td>Centers for Disease Control and Prevention, U.S. Department of Health and Human Services</td>
</tr>
<tr>
<td>December 15, 2014</td>
</tr>
</tbody>
</table>
Primary and Secondary Syphilis — Reported Cases by Sex and Sex of Sex Partners and HIV Status, United States, 2018

Screening in HIV+ Patients: Which STDs and How Often?

For any HIV-infected patient, on entry and then at least annually — as often as every 3-6 months for those at higher risk:
- Gonorrhea
- Chlamydia
- Syphilis
- Hepatitis C serology (‘at least yearly’ in MSM)
- Hepatitis A and B serology on entry (if negative, vaccinate)
- Trichomonas using NAAT or culture annually (women only)
- HSV type specific serology can be offered at initial visit
- HPV (anal cancer): Annual digital rectal exam may be useful, some centers perform anal Pap and HRA for abnormal cytologic results

Recommended by: CDC, 2015

Rectal Gonorrhea and Chlamydia infections in MSM are often asymptomatic and so require true screening

Summary:
- Use Nucleic Acid Amplification Tests (NAATs) for symptomatic AND asymptomatic patients
- Optimal Specimens:
  - Women — vaginal swabs (may be self collected)
  - Men — first catch urine
  - Extragenital (opharyngeal, rectal) NAAT newly FDA-cleared May 2019 (Hologic Aptima Combo 2, Cepheid Xpert CT/NG)
Can we screen a single anatomic site (i.e. urine) and assume concordance at the pharynx and rectum? No, will miss majority of cases.

Gonorrhea and Chlamydia Screening Outcomes in HIV Clinic Patients

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>NNS Genital</th>
<th>NNS Rectal</th>
<th>NNS Pharyngeal</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSM</td>
<td>≤25</td>
<td>20</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Women</td>
<td>≤25</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>≥25</td>
<td>210</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Separate analysis in Birmingham found 1.0% positivity for CT, 0.1% for NG when 84% of HIV+ women in care were screened.
- Findings call into question CDC recommendation for universal annual screening in all women.

STD Screening in HIV Primary Care: Opportunities to Improve

Gonorrhea and Chlamydia Screening Outcomes in HIV Clinic Patients

Extra-genital screening in Women?

- 4402 women screened at Baltimore STD clinics
- 57 (2%) had isolated extragenital CT
- 50 (1%) had isolated extragenital GC
- This accounted for 14% of the 412 total CT and 30% of the 165 total GC
- Self-reported anal sex not predictive of rectal CT infection in women!
- Potential benefits of screening women at extra-gen sites:
  - Prevent sequelae of cervical infxn (either in pt or her partner’s partner)?
  - Diminish incidence of GC and CT at population level?
  - Prevent HIV acquisition and transmission

Bottom line:
- Women get rectal infections too! Test for extra-genital STDs if symptomatic
- No current recommendations for targeted extra-genital screening in asx women

References:
- Marcus et al. STD Oct 2011; 38: 922-4
- Slide Courtesy: Park MS, MD
- Mattson CID 2017
- Tuddenham STI 2019
- Dionne Odom STD 2018
- Dombrowski 2015; Trebach 2014; Gatrix 2015; Lau 2019
Addressing Barriers to Screening, a few ideas:

- Specimen self-collection for NG and CT
- Standing Orders
- Having written STI screening policies associated with higher likelihood of patients being screened for syphilis (94% vs. 43%, P<0.001)

Gonorrhea is becoming less susceptible to treatment worldwide, no confirmed treatment failures with first line treatment in the US

**Gonorrhea Screening and Treatment is one of CDC's key strategies to reducing risk of resistant Neisseria gonorrhoeae**

Recommended: Ceftriaxone 250mg IM x 1 and Azithromycin 1 Gram PO x 1

Alternatives:
- Cefixime 400mg PO x 1 and Azithromycin 1g PO x 1
- Gemifloxacin 320mg PO x 1 AND Azithromycin 2g PO x 1
- Gentamicin 240mg IM x 1 AND Azithromycin 2g PO x 1

Antibiotic Resistance Threats in the United States, CDC 2013

**Rectal Chlamydia Treatment**

- Meta-analysis pooled efficacy 82.9% for azithromycin 1g PO x 1, 99.6% for doxycycline 100mg PO bid x 7 days but all observational
- Australian, European guidelines have moved to doxycycline. U.S. CDC Guidelines remain azithromycin 1g PO x 1
- RCT data coming soon
- Double blind, placebo controlled RCT, Fenway and University of Washington (expected Fall 2020)
- Australian RCT began 2016, recruitment completed June 2019
- Some experts already routinely use doxycycline 100mg bid x 7 days – discussed at CDC guidelines meeting.
**Mycoplasma Genitalium**

- Can cause PID, infertility, chronic urethritis, prostatitis, epididymitis
- Doxycycline x 7 days has poor cure rates
- Efficacy of azithromycin 1g declining, high rates of resistance in some settings
- Moxifloxacin 400 mg PO daily x 7-14 days as second line
- FDA approved test for M. genitalium now available: vaginal, endocervical, urine, urethral
- Routine screening not recommended.

**Doxy vs. Azithro for M. gent**

- Doxycycline x 7 days has poor cure rates
- Efficacy of azithromycin 1g declining, high rates of resistance in some settings
- Moxifloxacin 400 mg PO daily x 7-14 days as second line

**Management of Trichomoniasis with HIV co-infection**

- HIV-infected women should be screened for Trichomonas vaginalis including at entry to care and annually
- Culture or NAAT preferred over wet mount
- HIV-infected, pregnant women should be screened for TV at first prenatal visit; again 3 months later if positive
- HIV-infected women diagnosed with TV should receive metronidazole 500mg BID for 7 days (not 2g x 1) to improve cure rates (RR 0.46; 95%CI 0.21-0.98)

**Shifting Gears to Syphilis: Natural History**

- Incubation Period 2-6 weeks
- Early primary illness: chancre
- Early latent illness: 0-2 years
- Late latent illness: >2 years
- Tertiary syphilis: 2nd stage of disease
- Neurosyphilis can occur at any stage
Primary, Secondary & Early Latent:
- Benzathine penicillin G 2.4 million units IM in a single dose

Late Latent and Unknown Duration:
- Benzathine Penicillin G 7.2 million units total, given as 3 doses of 2.4 million units each at 1 week intervals

Neurosyphilis or Ocular Syphilis:
- Aqueous Crystalline Penicillin G 18-24 million units IV daily administered as 3-4 million IV q 4 hr for 10-14 d

Alternatives in non-pregnant adults include doxycycline, ceftriaxone; ONLY penicillin is acceptable in pregnancy.

Preventing Congenital Syphilis: Clinical-Public Health Partnerships
- Cases associated with women experiencing homelessness, methamphetamine use, injection drug use
- Screen all pregnant women at start of prenatal care, AND (in CA) at start of 3rd trimester and, if high risk, again at delivery: 3 total screens.
- Public health prioritizes female partners of male syphilis cases – please prepare patients and encourage them to work with us to ensure partners are treated
- Remember that penicillin is the only acceptable treatment for pregnant women with syphilis – must desensitize if true serious allergy
- Must adhere to strict 7-day interval for weekly benzathine penicillin in pregnant patients with late latent syphilis. If delayed, must restart series.

Genital Herpes
- While HSV-2 is the more common cause, HSV-1 has increased
- Many cases are asymptomatic or atypical

<table>
<thead>
<tr>
<th>Categorization</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Genital Herpes – No prior HSV-1 or HSV-2</td>
<td>Can have severe widespread genital ulcers, dysuria, urinary retention, aseptic meningitis Can also be asymptomatic!</td>
</tr>
<tr>
<td>Non-primary first episode genital herpes History of either HSV-1 or HSV-2; newly infected with other type</td>
<td>Fewer lesions, less systemic symptoms Can also be asymptomatic!</td>
</tr>
<tr>
<td>Recurrent genital herpes</td>
<td>Less severe, usually decrease frequency, intensity, duration over time Can also be asymptomatic!</td>
</tr>
</tbody>
</table>

Genital Herpes - Diagnosis
- If lesions – test here first!
- PCR is test of choice.
- Serology is useful in specific instances
  - Must be type specific (Glycoprotein G) and use IgG, not IgM (IgM can be present in recurrences, so presence ≠ primary or first episode infection)
  - Patient with history of genital ulcers, but none currently
  - Patient’s partner(s) with genital herpes
- General screening of adolescents and adults outside those parameters (including in pregnancy) is NOT recommended
Genital herpes – Suppressive Therapy

- Long term safety and efficacy documented
- Reduces recurrences by 70-80%
- Reduces transmission to an uninfected partner by 50%

**Regimens**
- Acyclovir 400 mg twice per day
- Valacyclovir 500 mg once per day
- Famciclovir 250 mg twice per day

Licensed HPV Vaccines in the United States

**Bivalent (2vHPV): GSK Cervarix®**
- Types 16, 18
- Prevents cervical cancer; anal cancer
- FDA approved for females and males 10-26
- 3-dose series; $365

**Quadrivalent (4vHPV): Merck Gardasil®**
- Types 6, 11, 16, 18
- Prevents warts, cervical cancer, anal cancer
- FDA-approved for females and males 9-26
- 3-dose series; $375

**Nonavalent (9vHPV): Merck Gardasil9®**
- Types 6, 11, 16, 18, 31, 33, 45, 52, 58
- FDA approved for females and males 9-45
- $227/dose

---

Prior ACIP HPV Vaccine Recommendations

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Age</td>
</tr>
<tr>
<td>Females</td>
<td>&lt;15</td>
</tr>
<tr>
<td></td>
<td>15-26</td>
</tr>
<tr>
<td>Males</td>
<td>&lt;15</td>
</tr>
<tr>
<td></td>
<td>15-26</td>
</tr>
<tr>
<td></td>
<td>22-26</td>
</tr>
<tr>
<td>All with immune compromise (inc. HIV), Transgender, and MSM</td>
<td>22-26</td>
</tr>
</tbody>
</table>

Irrespective of history of abnormal Pap, HPV, genital warts

---

Current ACIP HPV Vaccine Recommendations

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Age</td>
</tr>
<tr>
<td>ALL</td>
<td>9-14 (target 11-12)</td>
</tr>
<tr>
<td></td>
<td>15-26</td>
</tr>
<tr>
<td>ALL</td>
<td>27-45</td>
</tr>
</tbody>
</table>

Irrespective of history of abnormal Pap, HPV, genital warts
ACIP HPV Vaccine Recommendations for Common Clinical Scenarios

• HPV vaccination can provide protection against infection with HPV vaccine types not already acquired. Therefore, vaccination is recommended through the recommended age for females regardless of whether they have an abnormal Pap test result, and for females or males regardless of known HPV infection, HPV-associated precancer lesions, or anogenital warts.

• If vaccination providers do not know or do not have available the HPV vaccine product previously administered, or are in settings transitioning to 9vHPV, any HPV vaccine product may be used to continue and complete the series for females; 4vHPV or 9vHPV may be used to continue or complete the series for males.

• No indication to restart series with 9vHPV if a patient has completed 4vHPV or 2vHPV previously.

What’s ahead in STD Treatment and Prevention?

What about PEP or PrEP for STDs?

Randomized Controlled Trial of Doxy PEP

<table>
<thead>
<tr>
<th>Study Population</th>
<th>HIV-negative MSM enrolled in open-label extension of the IPERGAY study of on-demand HIV PEP (n=333)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Doxycycline 200 mg approx. 24 h after sex, up to 72 h (≤ 6 pills/week)</td>
</tr>
<tr>
<td>Study design</td>
<td>Randomized 2:1 to Doxy vs. no PEP</td>
</tr>
<tr>
<td>Follow-up</td>
<td>02 months x 10 months</td>
</tr>
<tr>
<td>Overall reduction in STI</td>
<td>67% (0.33-0.85, p=0.008)</td>
</tr>
<tr>
<td>Reduction in syphilis</td>
<td>72% (0.07-0.98, p=0.047)</td>
</tr>
</tbody>
</table>


Impact on anti-microbial resistance among STDs and non-STD pathogens (staph aureus, GI flora, microbome) unknown

Not yet ready for prime time

DOXYPEP: Proposed Study Design

Aim 1: STI Reduction & Safety/Tolerability

- STI: GC, CT, syphilis
- Risk reduction and adherence counseling, condoms & lubricant
- Ongoing App-based assessment of PEP use (intervention arm) & sexual activity (both arms)

Co-Prin: A. Luetkemeyer (UCSF), C. Celum (UW)
Summary

• Prompt screening and correct treatment of STDs in HIV positive patients is important for their health and to help reduce community transmission.

• We have lots of room to improve screening in HIV clinics, and some promising models to expand upon.

• The CDC STD Treatment Guidelines App is a must-have; look for revised guidelines in 2020.

• Potentially practice changing trials include the ongoing rectal CT treatment trials and doxycycline PEP for syphilis and chlamydia.

Thank you!

Acknowledgements:
• Christine Mattson
• Annie Luetkemeyer
• Stephanie Cohen
• Ina Park.

2015 CDC STD Treatment Guidelines:

Susan.Phipps@sfdph.org
www.sfcityclinic.org

National Network of STD Clinical Prevention Training Centers – a great resource!
• CDC supported
• Clinician classroom and practicum courses
• Online CME
• Expert clinical consultation

National STD Curriculum (free CE/CME):
www.std.uw.edu

https://www.nnptc.org/
HCV in 2019
A Case-based Update

Annie Luetkemeyer, MD
HIV, ID and Global Medicine, ZSFG, UCSF

Disclosures

I have received research grant support to UCSF related to HCV from the following:
- AbbVie
- Gilead
- Merck
- Proteus
- ACTG (NIH)

Additional Resources

- Drug interactions
  http://www.hep-druginteractions.org
- Free downloadable app
- HCV Consultation Services “Warmline”
  www.nccc.ucsf.edu or 844-437-4636
- Patient education
  http://www.hcvadvocate.org/

• New Simplified HCV Treatment for Treatment-naive Patients Without Cirrhosis
• Initial Treatment of HCV Infection: Shortened Glecaprevir/Pibrentasvir (G/P) regimen for use in compensated cirrhosis
• HCV Testing and Linkage to Care: Universal screening for adults
• Management of Acute HCV Infection
• Retreatment of Persons in Whom Prior Therapy Failed: Update on SOF/VEL/Vox and G/P failures
• HCV in Children: New treatment regimens for children aged 3 to 11 years
• Kidney Transplant Patients: Updated treatment recommendations
• Liver Transplantation: New information about transplantation of organs from HCV-infected donors

HCV Guidelines http://www.hcvguidelines.org
Case #1

- 25 year old man, HIV uninfected, takes TDF/FTC as intermittent PrEP
- Has been reluctant to get his HCV treated as he hates pills and feels fine. Only takes PrEP when he thinks he needs it as 2:1:1

“I just need this to be really easy or else it isn’t going to work”

ARS: Which of the following is true?

1) Undetectable HCV RNA 12 weeks after therapy means HCV is now latent in the liver and therefore not infectious (but could still reactivate)
2) HCV antibody will protect them from future HCV infection
3) HCV cure is associated with reduction in stroke, heart attack and kidney disease
4) HCV cure will reduce the risk of liver cancer, but won’t impact cirrhosis if already present.

Which of the following is true?

1) Undetectable HCV RNA 12 weeks after therapy means HCV is now latent in the liver and therefore not infectious (but could still reactivate)
2) HCV antibody will protect them from future HCV infection
3) HCV cure is associated with reduction in stroke, heart attack and kidney disease
4) HCV cure will reduce the risk of liver cancer, but won’t impact cirrhosis if already present.
WHO IS ELIGIBLE FOR SIMPLIFIED TREATMENT

Patients with chronic hepatitis C who do not have cirrhosis and have not previously received hepatitis C treatment

WHO IS NOT ELIGIBLE

Patients who have any of the following characteristics:
- Prior hepatitis C treatment
- Cirrhosis
- Prior liver transplant
- HIV or HBsAg positive
- End-stage renal disease (e.g., eGFR < 30 mL/min/1.73 m²)
- Currently pregnant

For straightforward HIV patients, a simplified approach is also possible

Simplified Algorithm: Pretreatment

<table>
<thead>
<tr>
<th>Laboratory testing (parentheses are my additions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within 6 months of treatment</td>
</tr>
<tr>
<td>CBC</td>
</tr>
<tr>
<td>LFTs</td>
</tr>
<tr>
<td>Renal: eGFR</td>
</tr>
<tr>
<td>HIV RNA if HIV</td>
</tr>
<tr>
<td>Anytime prior to antiviral therapy</td>
</tr>
<tr>
<td>HCV RNA (HCV GT): still required by many insurers</td>
</tr>
<tr>
<td>(HAV Ab)</td>
</tr>
<tr>
<td>HIV testing</td>
</tr>
</tbody>
</table>

Exclude cirrhosis

- If any test suggests cirrhosis, treat as cirrhosis.
- Do NOT need all tests: Platelets and FIB-4 or APRI is sufficient

Medications

Reconcile & review interactions, including OTC medications

Liverpool HCV drug interactions & HCV guidelines

Simplified treatment options

**Glecaprevir/Pibrentasvir (G/P)**
- “Mavyret”
- HCV PI + N55a inhibitor
- Pangenotypic (GT 1-6)
- 3 pills/once daily 8 weeks

**Sofosbuvir/Velpastasvir (SOF/VEL)**
- “Epclusa”
- HCV Polymerase + NS5 Inhibitor
- 1 pill daily
- 12 weeks

**SYMPTOMS:** Headache, Nausea, Fatigue
### Simplified Algorithm: Monitoring during & after treatment

<table>
<thead>
<tr>
<th>Laboratory monitoring</th>
<th><strong>NONE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence counselling &amp; Symptom Assessment</td>
<td>As needed</td>
</tr>
<tr>
<td>Disease specific guidance</td>
<td></td>
</tr>
<tr>
<td>• Diabetics on treatment: may be at risk for hypoglycemia</td>
<td></td>
</tr>
<tr>
<td>• Monitor INR if on warfarin</td>
<td></td>
</tr>
</tbody>
</table>

### Assessment for Cure (SVR12)

- HCV RNA 12 weeks after completing therapy
- LFTs at time of SVR12 to ensure transaminase normalization

### Post-cure follow-up

- Test for reinfection at least annually if ongoing HCV risk
- If persistent transaminits despite cure, evaluate for non-HCV related causes
- No liver-related follow up for non-cirrhotic patients

### Back to the case

- **Pretreatment assessment**
  - Platelets 215,000
  - eGFR 85, AST 35, ALT 35
  - FIB-4 0.68 (< 3.25 non-cirrhotic)
  - HAV immune, Hep B S ag (-)
  - Meds: Truvada only, no over the counter
  - He chooses SOF/VEL as daily pills feels easiest to him, takes 12 weeks of medications, and is cured.

  **“OK, that actually WAS easy! Can you treat my partner?”**

### Case #2

At your request, he brings in a partner who is also HCV (+)

- 30 year old, HIV(+), well controlled on BIC/TAF/FTC x 2 years
- HCV Genotype 1a, non-cirrhotic, treatment naïve
- No other medications or comorbidities
Case #2

- He chooses G/P as shorter treatment is his priority and has an undetectable HCV RNA 12 weeks after treatment completion = CURE!

**TAKE HOME:**
- For straightforward HIV/HCV patients with well-controlled HIV and lacking comorbidities, simplified therapy should be an option as well
- We tend to monitor HIV (+) persons with labs regularly but not clear that laboratory testing necessary while on HCV treatment specifically is needed
- Stay tuned for results from ACTG “MINMON” study which examines this minimal monitoring approach in HIV/HCV co-infection.

Case #3

52 year old woman, HIV well controlled on Dolutegravir + Rilpivirine

**Known cirrhosis and mild renal insufficiency (eGFR 40)**
- **NRTI sparing regimen:**
  - Cirrhosis: abacavir requires dose reduction
  - Renal impairment: avoiding tenofovir
  - HCV Genotype 1b, treatment naïve
  - Cirrhosis by FIB-4 (3.8) and imaging, Child-Pugh A
- No history of hepatic decompensation
  - No ascites, variceal bleed, hepatic encephalopathy

“I want the shortest treatment possible, please!”
ARS: What would you give her?

1) G/P x 8 weeks
2) SOF/VEL x 8 weeks
3) SOF VEL x 12 weeks
4) SOF/VEL x 12 weeks with low dose RBV
5) Refer her for transplant evaluation before treatment

Genotype 1b, compensated cirrhosis, mild renal insufficiency, wants shortest possible treatment

---

ARS: What would you give her?

1) G/P x 8 weeks- possibly
2) SOF/VEL x 8 weeks
3) SOF VEL x 12 weeks
4) SOF/VEL x 12 weeks with low dose RBV
5) Refer her for transplant evaluation before treatment

Genotype 1b, compensated cirrhosis, mild renal insufficiency, wants shortest possible treatment

---

Not pangenotypic:
- Elbasvir/Grazoprevir &
- Sofosbuvir/Ledipasvir

Pangenotypic:
- Sofobuvir/velpatasvir &
- Glecaprevir/Pibrentasivir
**HIV/HCV-coinfected patients**, a treatment duration of 12 weeks is recommended.

<table>
<thead>
<tr>
<th>REGIME/MODEL</th>
<th>DURATION</th>
<th>RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily fixed-dose combination of daclatasvir (60 mg)/grazoprevir (100 mg)</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily fixed-dose combination of sofosbuvir (300 mg)/velpatasvir (100 mg)</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily fixed-dose combination of glecaprevir (300 mg)/plenaviren (120 mg)</td>
<td>8 weeks</td>
<td>I, B</td>
</tr>
</tbody>
</table>

*For HIV/HCV-coinfected patients, a treatment duration of 12 weeks is recommended.*

**G/P: 8 weeks in compensated cirrhosis?**

- EXPEDITION-8: Open Label G/P, excluded HIV coinfect, SVR 97-98%.
- 1B recommendation and good option
- GT3: avoids resistance testing recommended with SOF/VEL in cirrhosis

**Can we use 8 weeks in HIV+ cirrhotics?**

- G/P has generally been equivalent in HIV(+) vs HIV (-)
- Controlled data in HIV(+) cirrhotics unlikely
- My take home: 8 weeks a consideration for HIV(+) if 12 weeks not feasible

**HCV treatment in Renal Failure**

**Case #3**

- 35 year old man, HIV (+)
- Recent relapse with IDU, now coming in to reengage in care and to start buprenorphine
- Labs
  - AST 340, ALT 400
  - Last LFTS 3 months ago were normal, HCV Ab (-) one year ago
- HCV Ab (-), HCV RNA 1.6 million IU/mL
- HAV Ab (-), HbsAb (+)
ARS: What do you recommend for this patient with Acute HCV?

1) Treat now
2) Wait 1 month and treat if HCV RNA hasn’t declined by 2 log
3) Wait 3 months and treat if HCV RNA still (+)
4) Treat when abstinent for > 3 months

Acute HCV treatment

• IDSA/AASLD guidelines now recommend immediate treatment- don’t wait for spontaneous resolution
• Benefits
  • Decreases risk for lost to follow up
  • Reduces forward transmission
• If patient prefers to wait, consider HCV RNA at 1 month. Failure to drop by 2 log suggest unlikely to spontaneously clear
• If HCV becomes undetectable without treatment, repeat HCV in several months to confirm clearance
Acute HCV: What to treat

<table>
<thead>
<tr>
<th>Recommended Regimens for Patients With Acute HCV Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RECOMMENDED</strong></td>
</tr>
<tr>
<td>RECOMMENDED</td>
</tr>
<tr>
<td>OUT [DG]</td>
</tr>
<tr>
<td>Curing in high efficacy and safety, the same regimen that are recommended for chronic HCV infection are recommended for acute infection</td>
</tr>
</tbody>
</table>

- What about shorter course of therapy?
  - 8 weeks of SOF/VEL (Naggie 2017, Rockstroh 2017)
  - 6 weeks of G/P (Martineau 2019)

- Generally high SVR rates, but failures at very high HCV RNA & limited data in HIV
  - Is there really an advantage to 6-8 weeks vs 8-12 weeks?
  - 4 weeks of G/P for acute HCV? Stay tuned...
  - Actively enrolling in San Francisco

HCV Testing updates

- **Universal HCV testing** for all adults at least once (HCV guidelines & draft USPTF)
- Test all pregnant women for HCV
  - Prevalence as high as 20% in some settings

Unmet Needs

- Pregnant women
  - Still no FDA approved treatment in pregnancy
  - Risk of maternal-child transmission ~ 5%, higher in HIV(+) women (up to 10-20%)  
  - Limited PK data for SOF/LDV in pregnancy (NCT02683005)
- Those who can’t complete 8-12 weeks of oral medications
  - Oral therapy <8 weeks in chronic HCV infection unlikely
  - Long acting HCV injectable...
- HCV preventative vaccine in active PWID

Retreatment of Persons in Whom Prior Therapy Failed: Update on SOF/VEL/VOX and G/P failures

HCV in Children: New treatment regimens for children aged 3 to 11 years

Liver Transplantation: New information about transplantation of organs from HCV-infected donors

Kidney Transplant Patients: Updated treatment recommendations

HCV Guidelines [http://www.hcvguidelines.org]
Improving our grade

- Screen and vaccinate your patients for HAV & HBV
- Screen for HCV at least once and then regularly if ongoing risk and at time of pregnancy
- Don’t delay HCV treatment when identified, including those with acute HCV
- Ask about MSM and IDU partnerships when treating your patients
- Easy well tolerated regimens available, even for the hardest to treat

Thank you!
Nonalcoholic fatty liver disease: what the clinician needs to know

Danielle Brandman, MD, MAS
Program director, Transplant hepatology fellowship
Director, UCSF Fatty Liver Clin.
Associate Professor of Clinical Medicine
University of California San Francisco

Research/clinical trials: Gilead, Allergan

Causes of Fatty Liver

Metabolic Syndrome
- Abdominal Obesity
- IGT/Diabetes
- Dyslipidemia
- Hypertension

Nutritional Syndromes
- JI Bypass
- TPN
- Rapid weight loss

Drugs and Toxins
- Alcohol
- Corticosteroids
- Tamoxifen
- Amiodarone
- Industrial solvents

Inherited Metabolic Diseases
- Lipodystrophy
- Abetalipoproteinemia
- Wilson Disease

Prevalence of Self-Reported Obesity Among U.S. Adults by State and Territory

*Sample sizes varied by state and territory, with the standard error ranging from 3% to 11%.

**Causes of Fatty Liver**

- **Metabolic Syndrome**
  - Abdominal Obesity
  - IGT/Diabetes
  - Dyslipidemia
  - Hypertension

- **Nutritional Syndromes**
  - JI Bypass
  - TPN
  - Rapid weight loss

- **Drugs and Toxins**
  - Alcohol
  - Corticosteroids
  - Tamoxifen
  - Amiodarone
  - Industrial solvents

- **Inherited Metabolic Diseases**
  - Lipodystrophy
  - Abetalipoproteinemia
  - Wilson Disease

**Epidemiology**

- Prevalence of NAFLD: ___ US population
- Prevalence of NASH: ___% population

- Prevalence of NAFLD: 16-29% US population
- Prevalence of NASH: 2-7% population

- 2/3 of obese adults
- 84-96% bariatric surgery population
- Up to 76% of diabetics
- Prevalence of NASH: 2-7% population
- 10-30% of NAFLD
- 20% of obese adults

---

High prevalence of NAFLD in HIV

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Country</th>
<th>Number of subjects</th>
<th>Statistical assessment</th>
<th>Prevalence of NAFLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hadigan, C. (2007)</td>
<td>USA</td>
<td>33</td>
<td>MR spectroscopy</td>
<td>42%</td>
</tr>
<tr>
<td>Moreno-Torres, A. (2007)</td>
<td>Spain</td>
<td>29</td>
<td>MR spectroscopy</td>
<td>58%</td>
</tr>
<tr>
<td>Mohammed, SS (2007)</td>
<td>Canada</td>
<td>26</td>
<td>Liver biopsy</td>
<td>45%</td>
</tr>
<tr>
<td>Guaraldi, G. (2008)</td>
<td>Italy</td>
<td>225</td>
<td>CT</td>
<td>37%</td>
</tr>
<tr>
<td>Crum-Cianflone, P. (2009)</td>
<td>USA</td>
<td>216</td>
<td>Ultrasound</td>
<td>31%</td>
</tr>
<tr>
<td>Ingiliz, P. (2009)</td>
<td>France</td>
<td>30</td>
<td>Liver biopsy</td>
<td>60%</td>
</tr>
<tr>
<td>Nishijima, T. (2014)</td>
<td>Japan</td>
<td>435</td>
<td>Ultrasound</td>
<td>31%</td>
</tr>
<tr>
<td>Price, JC (2014)</td>
<td>USA</td>
<td>46</td>
<td>CT</td>
<td>13%</td>
</tr>
<tr>
<td>Macias, J. (2014)</td>
<td>Spain</td>
<td>50</td>
<td>CAP**</td>
<td>40%</td>
</tr>
<tr>
<td>Lui, G. (2016)</td>
<td>Japan</td>
<td>80</td>
<td>MR spectroscopy</td>
<td>29%</td>
</tr>
<tr>
<td>Lombardi, R. (2016)</td>
<td>Greece</td>
<td>125</td>
<td>Ultrasound</td>
<td>55%</td>
</tr>
<tr>
<td>Price, JC (2017)</td>
<td>USA</td>
<td>122</td>
<td>MR spectroscopy</td>
<td>28%</td>
</tr>
</tbody>
</table>

*Includes HIV+ HCV or HBV; **CAP= controlled attenuation parameter, obtained with Fibroscan

Courtesy of Dr. Jennifer Price

Factors associated with NAFLD in HIV+

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean Difference (MD) or Odds Ratio (OR)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>MD 2.9 (2.4 to 3.7)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>MD 8.0 (5.5 to 10.6)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>OR 1.6 (1.1 to 2.4)</td>
<td>p=0.02</td>
</tr>
<tr>
<td>Hypertension</td>
<td>OR 1.8 (1.3 to 2.4)</td>
<td>p=0.001</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>MD 62 (24 to 99)</td>
<td>p=0.001</td>
</tr>
<tr>
<td>HDL</td>
<td>MD -4.2 (-6.8 to -1.6)</td>
<td>p=0.002</td>
</tr>
<tr>
<td>Duration of HAART</td>
<td>MD -15 (-33 to 3.5)</td>
<td>p=0.11</td>
</tr>
<tr>
<td>Cumulative ddi exposure</td>
<td>OR 1.4 (1.1 to 2.0)</td>
<td>p=0.02</td>
</tr>
<tr>
<td>CD4 count</td>
<td>MD 55 (12 to 98)</td>
<td>p=0.01</td>
</tr>
</tbody>
</table>

Case

- 54yo woman was found to have fatty liver on ultrasound done for abdominal pain
54yo woman was found to have fatty liver on ultrasound done for abdominal pain. The pain has since resolved, but he wonders how worried he should be about fatty liver.

Her weight has fluctuated within the past few years, during which time her BMI has ranged from 30-33.

PMH: prediabetes (HbA1c 5.9), dyslipidemia (HDL 36, TGs 180), HTN.

Meds: atorvastatin, lisinopril.

Family history: Parents with diabetes.

Labs: AST 38, ALT 71, albumin 4.1, INR 1.0, platelets 200.

Upon review of prior lab results, she has largely had AST 20s-40s and ALT 40s-80s since 2015.
**What further work-up is needed?**

A. Liver biopsy
B. Counsel her on lifestyle modification to try to lose weight and repeat liver tests again in 6 months
C. Evaluate for other causes of chronic liver disease
D. Transient elastography (Fibroscan)

---

**Symptoms:**
- None: 20 - 77%
- Right upper quadrant pain: 25 - 48%
- Fatigue: 50 - 75% (Obstructive sleep apnea in 40%)

**Signs:**
- Overweight/Obese: 85 - 95%
- Acanthosis nigricans: 10 - 15%
- Hepatomegaly: 25 - 50%

**Laboratory:**
- ALT, AST - modest elevation
- "Normal enzymes"
  - Normal ALT <19-25 for women, <30-35 for men

**NAFLD: A clinically silent disease**

**Diagnostic criteria**
- Hepatic steatosis on imaging or liver biopsy
- No "significant" alcohol intake
- Absence of other causes of liver disease
- No medications known to cause hepatic steatosis

---

**What further work-up is needed?**

A. Liver biopsy
B. Counsel her on lifestyle modification to try to lose weight and repeat liver tests again in 6 months
C. Evaluate for other causes of chronic liver disease
D. Transient elastography (Fibroscan)
**Diagnostic criteria**
- Hepatic steatosis on imaging or liver biopsy
- No "significant" alcohol intake
- Absence of other causes of liver disease
- No medications known to cause hepatic steatosis

**NAFLD is a diagnosis of exclusion**

**Evaluation of Suspected NAFLD**
- Liver tests
- Abdominal ultrasound
- Other serologic evaluation:
  - HBsAg, sAb, cAb
  - HCV Ab
  - AMA, IgM (for PBC)
  - ASMA, ANA, IgG
  - A1AT phenotype
  - Iron, Tsat, ferritin
  - Ceruloplasmin age < 45
  - HAV Ab (for vaccination status)
How can you distinguish between NAFL and NASH?

A. Fibroscan  
B. MR elastography  
C. Liver biopsy

Noninvasive assessment of liver fibrosis

- FIB-4
- NAFLD fibrosis score

Indications for Liver Biopsy

- Suspicious for NASH
  - Significant liver enzyme elevation
  - Hepatomegaly
  - Diabetes
- Suspicious for advanced fibrosis or cirrhosis
  - Thrombocytopenia
  - Imaging (e.g., splenomegaly)
  - Noninvasive assessment: FIB-4, Fibroscan
  - Diabetes
  - Older age
- Unable to rule out other diseases

Diagnosis and staging of NAFL vs NASH

- Liver biopsy is the only method to reliably distinguish between NAFL and NASH
- Noninvasive assessment of fibrosis
  - Fibroscan
  - Clinical prediction rules (e.g., FIB-4, NAFLD fibrosis score)

Chalassani, Hepatology 2012.
**Fibrosis progression**

**NASH vs NAFL**

- **NASH**: 7 years per 1 stage
  - ~28 years 0 → cirrhosis

- **NAFL**: 14 years per 1 stage
  - ~56 years 0 → cirrhosis

**Noninvasive staging of NAFLD**

<table>
<thead>
<tr>
<th></th>
<th>AUROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any fibrosis</td>
<td>0.74-0.78</td>
</tr>
<tr>
<td>≥ F2</td>
<td>0.79-0.84</td>
</tr>
<tr>
<td>F3-4</td>
<td>0.83-0.88</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>0.86-0.93</td>
</tr>
<tr>
<td>MR elastography</td>
<td>0.83</td>
</tr>
<tr>
<td>0</td>
<td>0.91</td>
</tr>
<tr>
<td>0.83-0.89</td>
<td>0.89</td>
</tr>
<tr>
<td>0.97</td>
<td>NAFLD fibrosis score</td>
</tr>
<tr>
<td>0.82</td>
<td>0.72-0.82</td>
</tr>
<tr>
<td>0.73-0.86</td>
<td>0.77-0.92</td>
</tr>
<tr>
<td>FIB-4</td>
<td>0.8</td>
</tr>
<tr>
<td>0.72-0.83</td>
<td>0.78-0.86</td>
</tr>
</tbody>
</table>
| 0.78-0.88      | Siddiqui, ... Brandman et al. Clin Gastro Hep, 2018.
|                | Boursier, J Hepatol 2016.
|                | Imajo, Gastroenterology 2016.
|                | Hsu, Clin Gastro Hep, 2018. |

**Algorithm to “triage” NAFLD**
Fibrosis stage is the strongest predictor of outcomes in NASH

Case (cont’d)

- The patient was reluctant to undergo liver biopsy and opted instead for Fibroscan
- Liver stiffness measurement: 13kPa (IQR 0.9)
- CAP score: 330 (IQR 13)
- Interpretation: Cirrhosis (F4), though LSM could be overestimated due to the presence of severe steatosis (CAP>300)
### Case (cont’d)
- The patient was reluctant to undergo liver biopsy and opted instead for Fibroscan
  - Liver stiffness measurement: 13kPa (IQR 0.9)
  - CAP score: 330 (IQR 13)
  - Interpretation: Cirrhosis (F4), though LSM could be overestimated due to the presence of severe steatosis (CAP>300)
  - NFS -0.4 (indeterminate), FIB-4 1.24 (90% NPV for advanced fibrosis)

### Case (cont’d)
- Because of the concern for cirrhosis, you again recommend liver biopsy for more definitive diagnosis and staging

### Case (cont’d)
- Because of the concern for cirrhosis, you again recommend liver biopsy for more definitive diagnosis and staging
- The patient is now amenable to liver biopsy

### Case (cont’d)
- Impression: steatohepatitis
  - >20 portal tracts present, no fragmentation
  - Severe steatosis (>66%)
  - Ballooned hepatocytes
  - Moderate lobular inflammation
  - Fibrosis: stage 3, with bridging fibrosis and areas of centrizonal fibrosis
What do you tell the patient about her disease?

What is the most common cause of death in NAFLD?

A. Cardiovascular disease
B. Malignancy
C. Liver disease
D. Kidney disease

What is the most common cause of death in NAFLD?

A. Cardiovascular disease
B. Malignancy
C. Liver disease
D. Kidney disease

Increased risk of incident CV in NAFLD

[Graph showing Kaplan-Meier survival estimates]
The patient is interested to know what can be done to treat disease and prevent or reverse fibrosis.
**What treatment options are available to her currently?**

A. Bariatric surgery  
B. Vitamin E  
C. Ursodiol  
D. Lifestyle modification for weight loss  
E. B & D

**Diet & Exercise**

- Combination is best
- Avoid fructose-sweetened beverages, added sugars
- Loss of >7 - 10% weight to improve NASH+/fibrosis
- Exercise alone reduces liver fat
  - Aerobic >150-250 minutes per week
  - Resistance training 45 minutes/day x 3 days/week

*Harrison. Hepatology, 2009.*  
*Promrat, Hepatology, 2010*  
*Vilar-Gomez, Gastro, 2015*  
*Chalasani, Hepatology 2012.*

**NAFLD treatment: Weight Loss**

**Weight loss thresholds and impact on NAFLD**
### Treatment of NASH: Pharmacotherapy

- Currently available
  - Vitamin E, pioglitazone (PIVENS trial; NEJM 2011)
- Potentially available in the future
  - Obeticholic acid
  - Elafibranor
  - Cenicriviroc
  - Many others in phase 2 trials

### NAFLD treatment trials in HIV+

- Tesamorelin
  - Synthetic growth hormone-releasing hormone, targets visceral fat
  - 50 HIV+ patients randomized to tesamorelin 2 mg (n=28) or placebo (n=22) SC daily x 6 months
  - Modest but significant reduction in liver fat in tesamorelin group vs placebo
- Aramchol
  - Fatty acid-bile acid conjugate
  - Reduction in liver fat in phase 2 trial in primary NAFLD
  - 50 HIV+ patients with lipodystrophy and NAFLD
  - Failed to meet primary endpoint of improvement in liver fat at 12 weeks


### NAFLD pathways/targets for treatment

### Treatment of Metabolic Syndrome in NAFLD

- Statins
  - Safe for use in NAFLD
  - Potential benefits of NAFLD/liver enzyme improvement and reduced risk of liver death or HCC
  - Not proven in randomized controlled trials
- Metformin
  - Safe for use in NAFLD
  - Some studies show improvement in liver biopsy and liver enzymes
  - Not proven in randomized controlled trials
  - Possible anti-neoplastic effects
NAFLD is common, and most patients with metabolic syndrome comorbidities will have NAFLD, with ~16 million in the US having NASH.

NAFLD is an umbrella term that includes NAFL and NASH
- NASH has risk of progression to cirrhosis
- Biopsy is needed to characterize NAFLD

Management hinges on weight loss, exercise, avoiding added carbohydrates, metabolic syndrome control
- Vitamin E only for biopsy-proven NASH
- Many drugs in the pipeline for NASH and fibrosis

Summary

- NAFLD is common, and most patients with metabolic syndrome comorbidities will have NAFLD, with ~16 million in the US having NASH.
- NAFLD is an umbrella term that includes NAFL and NASH.
  - NASH has risk of progression to cirrhosis.
  - Biopsy is needed to characterize NAFLD.
- Management hinges on weight loss, exercise, avoiding added carbohydrates, metabolic syndrome control.
  - Vitamin E only for biopsy-proven NASH.
  - Many drugs in the pipeline for NASH and fibrosis.
- HIV psoriasis responds beautifully to ARV’s.
- pt is a non-adherent and RESPONDS as soon as his immune system encounters the ARV’s
IS THIS A DIRECT EFFECT on HIS T CELLS?
ARV’s controlling downstream inflammation

• No relevant disclosures

Concept of the HIV reservoir and downstream inflammation

• MEMORY T CELLS: Live for at least 72 years—Chomont Nat Med 2009 and Siliciano J Virol 2009
• They hide in the gut, lymphoid tissue, genitourinary system, bone marrow and brain
• Occasionally they leave the sanctuary or the RESERVOIR
HIV reservoirs, latency, and reactivation: prospects for eradication.
Dahl V, Josefsson L, Palmer S. Antiviral Res 2010
Low level viremia

- If pts start ARV's at LOW CD4 counts, the reservoir has a chance to build up.
- Even though viral loads are UNDETECTABLE there is viral replication from the RESERVOIR causing viremia and inflammation.
- Antiretrovirals only control what is in the PERIPHERAL blood stream and not the reservoir.
- ARV's are controlling only downstream inflammation and not the RESERVOIR.

And What is so BAD about low level viremia?

- ACUTE and CHRONIC INFLAMMATION
- TURNS ON OTHER VIRUSES
- CAUSES PREMATURE AGING

Acute Inflammation

- Most people take 12-16 weeks to respond to ARV's re: psoriasis
- In the interim, can use acitretin 25 qd
- Topicals can be used after ARV's stabilize the pt much easier to handle the psoriasis and don't really need much more than the occasional topical
- We have never had to go to biologics for HIV related psoriasis can theorize on many to the possible side effects.
Eosionophilic folliculitis

- Pruritic urticarial papules on the face/neck scalp and chest
- CD4 under 50 OR when starting ARV’s
- Not a drug reaction
- DO NOT STOP ARV’s
- Takes 12-16 wks until ARV’s kick in to control the inflammation
- In the meantime-use intraconazole for acute inflammation

We have known for decades that if you had a history of eczema AND you started ARV’s under CD4 200, you will always have blips of eczema even if you are fully reconstituted.

This is the Pruritic Papular Eruption of HIV
- Often a presenting sign of HIV in the tropics
- Thought to be exaggerated bug bite reaction
- Responds to ARV’s in the first 12-16 wks but RECURS every 4 months
- Signifies Chronic inflammation in persons starting ARVS’s with CD4’s under 500

HIV INFLAMMATION TURNING ON OTHER VIRUSES
- Herpes simplex virus
- Human papilloma virus
Verrucous HSV

- Usually ACV resistant
- Emerging as a problem worldwide
- Suppressive doses of ACV used in recurrent HSV infection in HIV may be selecting out resistant strains
- Treat with topical or injectable cidofovir

Human Papilloma Virus

- Still a burden on cutaneous skin and genital skin
- Local destructive techniques to include liquid nitrogen and podophyllin under occlusion
- Cidofovir injections
- Biopsy for SCC

And now some examples of Premature Aging

- Myocardial infarcts
- Kidney dysfunction
- Dementia
- Squamous cell cancer
- Kaposi sarcoma

Recurrence Rates of SCC

- Higher recurrence rates of SCC in HIV infected vs uninfected -17% vs 3%
- Ave years of known infection= 11 years
- Virally suppressed and CD4 counts ave 350

Chren, Hausauer
PREMATURE AGING?
Kaposis sarcoma

- CD4 counts 500-800, virally undetectable for years, CD4 nadir never less than 300
- Compared to HIV infected subjects without KS:
  More CD57+ cells, CD28- cells and waning pools of naïve T cells suggesting immunosenescence (Unemori, AIDS March 2013)

The Good News

- Drugs that infiltrate the reservoir are on the horizon—will eventuate in the CURE of HIV
- Starting antiretrovirals early (high CD4 counts) shrinks the reservoir—less chance for downstream inflammation
- START HIV MEDS AT THE EARLIEST TIME POSSIBLE!!!!
- Pts can never go off antiretrovirals (ARV’s)—need constant control of inflammation

Syphilis

- Many morphologies on the skin
- Lots of syphilis—not picked up and spreading, reinfection
- Biopsy if in doubt, empiric treatment
- Monitor for reinfection or failed treatment—at 1 month, 3 months, 6 months, 12 months, 18 months post treatment

- Check HIV status—not all persons with KS are HIV infected
- Seeing HIV negative gay men in large metropolitan area with HIV negative KS
- If HIV infected, look for systemic symptoms: hemoptysis, melena, lymphedema—start chemotherapy and monitor
- If HIV infected BUT no systemic symptoms—start ARV’s and wait for resolution at least 9-18 months
- HIV negative gay men with KS—give us a call—injecting local chemo, starting CCR5 blockers, injecting local PD-1 inhibitors
• Restarts ARV’s-gets KS IRIS with lymphedema –start chemo and continue ARV’s

New Approaches

• Trying different chemos
• Starting pomolodimide
• Systemic PD-1 inhibitor
• Controlling lymphedema
• Contact us-SF Dept of Public Health/NIH AIDS Malignancy Division-KS Centers of Excellence are being built for better diagnosis, optimal treatment regimens and opening access to clinical trials
415-9998295; toby.maurer@ucsf.edu; toby.maurer@sfdph.org
HIV Pharmacology

Parya Saberi, PharmD, MAS, AAHIVP
Associate Professor, UCSF Center for AIDS Prevention Studies
The Medical Management of HIV and Hepatitis
December 2019

Objectives

1. List ARV medications & examine their mechanisms of action.
2. Review pharmacology basics.
3. Examine dose, adverse effects, drug interactions, & special considerations of ARVs in recommended regimens.
4. Review ART regimens & tailoring.

Disclosure

• I have nothing to disclose

FDA-approved ARVs

Nucleoside Reverse Transcriptase Inhibitors
- Alifenvir (ABC): Zidovudine (ZDV; Retrovir)
- Emtricitabine (FTC): Emtriva
- Lamivudine (3TC): Epivir
- Tenofovir (TDF): Viread
- Zidovudine (ZDV; Retrovir)

Non-nucleoside Reverse Transcriptase Inhibitors
- Dapivirine (DDI): Stavudine (DV): Stocrin
- Delavirdine (DEA): Stocrin
- Nevirapine (NVP & NVP XR): Viramune
- Rilpivirine (RPV): Edurant

Integrase Inhibitors
- Raltegravir (RAL): Isentress
- Dolutegravir (DTG): Tivicay
- Elvitegravir (EVG): Vitekta
- Raltegravir (RAL): Isentress

Fusion Inhibitors
- Enfuvirtide (EMT): Fuzeon

Protease Inhibitors
- Atazanavir (ATV): Reyataz
- Darunavir (DRV): Prezista
- Fosamprenavir (Fos-APV): Lexiva
- Ritonavir (RTV): Norvir
- Tipranavir (TPV): Aptivus

Pharmacokinetic Enhancers
- Cobicistat (CQR): Tybost

Post-Attachment Inhibitors
- Bocavirus (BKA): Imaginon

CCR5 Co-receptor Antagonists
- Maraviro (MVC): Selzentry
**Fixed Dose Combinations**

<table>
<thead>
<tr>
<th>Combination ARVS</th>
<th>Single Pill Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC/3TC (Epzicom)</td>
<td>BIC/TAF/FTC (Biktarvy)</td>
</tr>
<tr>
<td>ABC/ZDV/3TC (Trizivir)</td>
<td>CAB/RPV (Cabenuva)</td>
</tr>
<tr>
<td>ATV/c (Evozatu)</td>
<td>DTG/ABC/3TC (Triumeq)</td>
</tr>
<tr>
<td>DRV/c (Prezocib)</td>
<td>DTG/3TC (Dovato)</td>
</tr>
<tr>
<td>LPV/r (Kaletra)</td>
<td>DTG/RPV (Julucy)</td>
</tr>
<tr>
<td>TAF/FTC (Descovy)</td>
<td>DOR/TDF/3TC (Delstrigo)</td>
</tr>
<tr>
<td>TDF/FTC (Truvada)</td>
<td>DRV/c/TAF/FTC (Symtuza)</td>
</tr>
<tr>
<td>TDF/3TC (Cimduo)</td>
<td>EFV/TDF/FTC (Atripla)</td>
</tr>
<tr>
<td>ZDV/3TC (Combivir)</td>
<td>EVG/c/TDF/FTC (Stribild)</td>
</tr>
<tr>
<td></td>
<td>EVG/c/TAF/FTC (Genvoya)</td>
</tr>
<tr>
<td></td>
<td>RPV/TDF/FTC (Complera)</td>
</tr>
<tr>
<td></td>
<td>RPV/TAF/FTC (Odefsey)</td>
</tr>
</tbody>
</table>

**HIV Life-cycle**

- **Fusion Inhibitors**
- **CCR5 Co-receptor Inhibitors**
- **Reverse Transcriptase Inhibitors**
- **Integrase Inhibitors**
- **Protease Inhibitors**

**Recommended Initial Regimens for Most People with HIV**

(regimens with durable virologic efficacy, favorable tolerability & toxicity profiles, & ease of use)

- DTG
- RAL
- BIC
- TDF/FTC or TAF/FTC
- ABC/3TC

1. TDF/FTC not recommended if CrCl <60 mL/min & TAF/FTC not recommended if CrCl <30
2. If HLA-B*5701 is negative
3. Part of the “Recommended Initial Regimen” when used with TAF/FTC

**Recommended Initial Regimens in Certain Clinical Situations**

(Effective & tolerable regimens, but some disadvantages vs. regimens listed previously, or less supporting data from RCTs. However, may be preferred in certain clinical situations.)

- Efavirenz (EFV)
- Dolutegravir (DTG)
- Ritonavir-boosted/Drug (DRV/r)
- Darunavir (DRV)
- Atazanavir (ATV)
- Ritonavir (RAL)
- Tenofovir (TDF)
- Emtricitabine (FTC)

TDF/FTC or TAF/FTC
- ABC/3TC
- 3TC

1. TDF/FTC not recommended if CrCl <70 & TAF/FTC not recommended if CrCl <30
2. If HLA-B*5701 is negative
3. If pre-treatment HIV RNA <200,000 copies/mL & CD4 >200 cells/mm³
4. If HIV RNA <100,000 copies/mL

**Additional Resources**

- [http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf](http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf)
Lightening Fast Pharmacology Review

Pharmacology Review

- **PK**
  - What your body does to the drug
  - Study & characterization of time course of drug
    Absorption, Distribution, Metabolism, & Excretion
- **PD**
  - What the drug does to your body
  - Subjective (anxiety level) or objective (BP, pupil size)

EXCRETION

Transporters

- **P-glycoprotein (P-gp)**: efflux enzyme that “pushes” drugs out of GI blood stream back into GI lumen
  - P-gp inhibitor: RTV, COBI
  - P-gp inducer: SJW, DFI, rifampin
- **Organic Anion Transporters (OAT)** & **Organic Cation Transporters (OCT)**: involved in drug secretion or reabsorption; in kidneys, brain, liver, skeletal muscle, heart, small intestine, prostate, ...
  - OAT inhibitor: COBI, RTV
  - OCT inhibitor: RTV, DTG
- **Multidrug & Toxin Extrusion (MATE) Transporter**: role in renal & biliary excretion of organic cations; involved in tubular secretion of Cr; in liver, kidneys, ...
  - MATE inhibitor: RTV, COBI, DTG
- **Breast Cancer Resistance Protein (BCRP)**: role in drug disposition & tissue protection; in small intestine, liver, kidneys, & blood-brain barrier
  - BCRP inhibitor: RTV, COBI
**METABOLISM**

**Cytochrome P450 Enzymes**

- Essential for metabolism of 2/3 of meds cleared by metabolism
  - >50 enzymes; however, 6 metabolize 90% of drugs: CYP1A2, CYP2C9, CYP2C19, CYP2D6, **CYP3A4**, & CYP3A5
- Primary cause of majority of drug-drug & drug-food interactions
- **CYP450 Inducers**: ↑CYP450 enzyme activity by ↑enzyme synthesis (e.g., EFV, rifampin)
- **CYP450 Inhibitors**: Block metabolic activity of CYP450 enzymes (e.g., PIs)

**Question #1: How quickly does CYP450 induction occur?**

1. 1-2 hours
2. 1-2 days
3. 1-2 weeks
4. 1-2 months

**Uridine Diphospho-Glucuronosyltransferase (UGT)**

- Responsible for glucuronidation, a major part of metabolism (conjugation)
  - UGT 1A1 Substrate: RAL, DTG
  - UGT 1A1 Inhibitor: ATV
  - UGT 1A1 Inducer: RTV, rifampin
CYP450 Inducers

- Onset gradual (**1-2 weeks**)
- Onset depends on half-life (t_{1/2}) of inducer & synthesis of new enzymes
- Offset depends on inducer elimination & decay of enzyme stores

**Question #2:** How quickly does CYP450 inhibition occur?

1. 1-2 hours
2. 1-2 days
3. 1-2 weeks
4. 1-2 months

---

CYP450 Inhibitors

- Onset is rapid (**after 1-2 doses**)
- Extent of inhibition depends on dose & binding ability of inhibitor
- Offset depends on elimination of inhibitor & half-life of the inhibitor at enzyme site
- All PIs are net inhibitors of CYP3A4
  - **Boosting:** use of low-dose CYP450 inhibitor to ↑ ARV exposure

---

Boosting

- Taking advantage of a drug-drug interaction
- Low-dose CYP450 inhibitors (e.g., RTV or COBI) lead to:
  - ↑ AUC, ↑ Cmin & ↑ Cmax
  - ↓ risk of drug resistance
  - Can use lower doses of PI
  - May eliminate food restriction
  - ↑ plasma half-life (t_{1/2})
  - ↓ dosing frequency
**Drawbacks of Boosting**

- ↑ potential of other drug-drug interactions
- ↑ risk of metabolic AEs

**Important to note that**

- Boosting with RTV or COBI is recommended for PI- & EVG-based regimens

---

**Question #3: Which of the following is (are) true re: RTV & COBI?**

1. Both inhibit P-gp & BCRP transporters
2. Both inhibit MATE & OAT transporters
3. Both result in increased Scr & TG
4. Both inhibit or induce CYP450 enzymes
5. Options 1, 2, & 3
6. Uhhh... What?
RTV vs COBI: PK

Interchangeable as CYP3A inhibitors

Absorption
- Both inhibit intestinal transporters P-gp & BCRP:
  - ↑ absorption of TDF, TAF, ATV, DRV
  - ↑ AUC of TDF by 25-37% when w/ boosted ARV regimen
  - TAF dose= 25mg w/ unboosted regimens; 10mg w/ boosted regimens

Excretion
- Both inhibit OAT & MATE:
  - ↑ Scr due to inhibition of Cr secretion vs. impairment of renal function
  - COBI results in higher Scr vs. RTV; may be due to COBI accumulating in tubular cells & having higher concentrations to inhibit MATE

<table>
<thead>
<tr>
<th>RTV</th>
<th>COBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Both inhibit intestinal transporters P-gp &amp; BCRP: ↑ absorption of TDF, TAF, ATV, DRV</td>
</tr>
<tr>
<td>Excretion</td>
<td>Both inhibit OAT &amp; MATE:</td>
</tr>
</tbody>
</table>
  - ↑ Scr due to inhibition of Cr secretion vs. impairment of renal function  
  - COBI results in higher Scr vs. RTV; may be due to COBI accumulating in tubular cells & having higher concentrations to inhibit MATE |

RTV vs COBI: DDIs

Summary of differences in predicted interaction profiles:

<table>
<thead>
<tr>
<th>Meds that are...</th>
<th>RTV</th>
<th>COBI</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only glucuronidated</td>
<td>↓</td>
<td>not affected</td>
<td>Bupropion or Methadone</td>
</tr>
<tr>
<td>Glucuronidated &amp;/or metabolized by inducible CYPs &gt; CYP3A</td>
<td>↓</td>
<td>moderately ↑</td>
<td>Sertraline</td>
</tr>
<tr>
<td>CYP substrate</td>
<td>↓ or ↑</td>
<td>only ↑</td>
<td>Duloxetine</td>
</tr>
</tbody>
</table>

• Inducible CYPs: CYP1A2, CYP2B6, CYP2C9, & CYP2C19
• ELV: inducer of CYP2C9 (ELV/c overall effect: ↓ warfarin)

Protease Inhibitors

Darunavir

- No DRV-specific mutations: 800mg DRV+100mg RTV QD or COBI 150mg QD
- ≥1 DRV-specific mutations: 600mg DRV+100mg RTV BID
- Precaution: sulfa moiety
  - fos-amprenavir, darunavir, & tipranavir
  - Seems safe to administer DRV in those allergic to TMP-SMX as long as allergy not life-threatening

<table>
<thead>
<tr>
<th>Darunavir, DRV</th>
<th>AM</th>
<th>PM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Take 1 tablet (800mg) orally once daily with ritonavir with food</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ritonavir, RTV</th>
<th>AM</th>
<th>PM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Take 1 tablet (100mg) orally once daily</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Summary: Protease Inhibitors

- Many drug-drug interactions with booster mainly due to CYP450 inhibition
- PI class is associated with GI, metabolic, & CV adverse effects
- DRV is the PI with greater tolerability, highest genetic barrier to resistance, & lowest pill burden

Integrase Inhibitors

Question #4: Which INSTIs are available as once-daily?

1. Elvitegravir/c
2. Dolutegravir
3. Bictegravir
4. Raltegravir
5. Only 1, 2, & 3
6. All of the above
**Raltegravir**

- Little effect on lipids & glucose
- AE: rash & HSR, ↑CK, myositis, rhabdomyolysis
- Few drug-drug interactions
  - Eliminated by UGT1A1
  - w/ rifampin, ↑ dose to 800mg bid
- RAL HD: 1200mg (2x600mg tabs) QD
  - Do not use with ETR

**Elvitegravir/c**

- EVG: Inducer of CYP2C9; metabolized by CYP3A
- COBI
  - COBI inhibitor of CYP3A, P-gp, OAT
  - Inhibits tubular secretion of Cr
  - ↑ Scr & ↓ CrCl w/o ↓ GFR
- Check CrCl, U. glucose, U. protein, & phos before & during tx
- EVG/COBI/TDF/FTC: D/C if CrCl <50 mL/min
- EVG/COBI/TAF/FTC: Don’t start if CrCl <30 mL/min
- Closely monitor ↑ in Scr of >0.4 mg/dL from baseline
- Common AEs: diarrhea, nausea, headache

**Dolutegravir**

- Inhibits tubular secretion of Cr (inhibits renal OCT & MATE)
  - Mean ↑ Scr within 1st 4wks of treatment; 0.15 mg/dL increase
  - DTG ↑ concentrations of drugs eliminated via OCT or MATE (e.g., metformin)
- Common AEs: weight gain, insomnia, headache, rash
- Metabolized by UGT1A1 & CYP3A (10-15%)
- Only use w/ ETR if w/ ATV/r, DRV/r, or LPV/r
- Based on DHHS, DTG should not be prescribed for those:
  - pregnant & within 12 weeks post-conception;
  - of childbearing potential & planning to become pregnant;
  - of childbearing potential, sexually active, & not using effective contraception
- Class effect? chemical structure of BIC similar to DTG (BIC not recommended in pregnancy b/c of insufficient data)
- EVG/c not recommended in pregnancy b/c low EVG recommendations during 2nd & 3rd trimesters

--{
<table>
<thead>
<tr>
<th>Adult Population</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>INSTI-naive</td>
<td>50 mg QD</td>
</tr>
<tr>
<td>When used w/ potent UGT1A/CYP3A inducers (e.g., EFV or rifampin)</td>
<td>50 mg BID</td>
</tr>
<tr>
<td>INSTI-exp w/ certain INSTI resistance or suspected INSTI resistance</td>
<td>50 mg BID</td>
</tr>
</tbody>
</table>

**DTG & Neural Tube Defect**

- Based on DHHS, DTG should not be prescribed for those:
  - pregnant & within 12 weeks post-conception;
  - of childbearing potential & planning to become pregnant;
  - of childbearing potential, sexually active, & not using effective contraception
- Class effect? chemical structure of BIC similar to DTG (BIC not recommended in pregnancy b/c of insufficient data)
- EVG/c not recommended in pregnancy b/c low EVG recommendations during 2nd & 3rd trimesters

--{
<table>
<thead>
<tr>
<th>PtnNbr: 1460</th>
<th>0.29% (0.15, 0.40)</th>
<th>0.29% (0.15, 0.40)</th>
<th>0.30% (0.16, 0.42)</th>
<th>0.29% (0.15, 0.40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>6.36% (5.94, 6.79)</td>
<td>6.36% (5.94, 6.79)</td>
<td>6.36% (5.94, 6.79)</td>
<td>6.36% (5.94, 6.79)</td>
</tr>
<tr>
<td>Prevalence Difference (95% CI)</td>
<td>ref</td>
<td>0.29% (0.15, 0.40)</td>
<td>0.29% (0.15, 0.40)</td>
<td>0.29% (0.15, 0.40)</td>
</tr>
</tbody>
</table>

Zaaij et al NEJM 2019, IAS 2019
Bictegravir

- Newest unboosted INSTI
- Only in FDC with TAF/FTC
- Not recommended if CrCl< 30 mL/min
- Contraindicated: Rifampin
- Most common AEs: N/D & HA

**Bictegravir, BIC (in Biktarvy)**

<table>
<thead>
<tr>
<th>AM</th>
<th>PM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Take 1 tablets (50mg) orally daily with or without food</td>
<td></td>
</tr>
</tbody>
</table>

**INSTI & Weight Gain**

- Pooled analyses of 8 Gilead trials
- ↑ weight in 3 classes at 96-week
  - InSTI: 3.24 kg
  - NNRTI: 1.93 kg
  - PI: 1.72 kg
- BIC & DTG demonstrated similar weight gain, both greater than EVG/c at 96-week
  - BIC: 4.24 kg
  - DTG: 4.07 kg
  - EVG/c: 2.72 kg
- Mechanism: INSTIs exert direct impact on adipose tissue adipogenesis, fibrosis, & insulin resistance
- Risk factors: CD4<200, HIV VL>100K, black race, female sex, age<50
- Other ARVs associated with weight gain: RPV and TAF

**Question #5:** Which cations can be taken together with DTG if taking them with food?

1. Calcium & Magnesium
2. Calcium & Iron
3. Magnesium & Iron
4. Magnesium & Aluminum
**Question #6:** Which of the following is correct?

1. RAL is NOT recommended to be co-administered or staggered w/ Al or Mg-antacids
2. There is no dose adjustment necessary when RAL is co-administered with Ca carbonate antacids
3. Separate EVG & antacids containing Ca, Mg, or Al by at least 2 hours
4. Administer DTG 2 hours before or 6 hours after Mg, Al, Ca, or Fe
5. All of the above are correct
6. Huh???

<table>
<thead>
<tr>
<th>INSTI-Cation Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAL</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Ca</td>
</tr>
<tr>
<td>Mg</td>
</tr>
<tr>
<td>Al</td>
</tr>
<tr>
<td>Fe</td>
</tr>
</tbody>
</table>

**Summary:** Integrase Inhibitors

- Generally well-tolerated
- BIC, DTG, & RAL: ARV preferred regimens
- EVG/c: many DDIs due to CYP3A inhibition
- Unexpected adverse effects:
  - Weight gain
- Unexpected interactions:
  - DTG + ETR
  - INSTI + polyvalent cations
- BIC, DTG, & EVG/c ↓ CrCl without affecting GFR
  - Monitor Scr

**Non-Nucleoside Reverse Transcriptase Inhibitors**
**Doravirine**
- Newer NNRTI
- In FDC with TDF/3TC (Delstrigo) or by itself (Pifeltro)
- Dose:
  - 1 tab (100mg) QD w/ or w/o food
  - W/ rifabutin: 1 tab BID
- Contraindicated w/ strong CYP3A inducers
- Common AEs: N/D, dizziness, HA, fatigue, GI pain, weight gain, & abnormal dreams

<table>
<thead>
<tr>
<th>Doravirine, DOR</th>
<th>Take 1 tablets (100mg) orally daily with or without food</th>
<th>AM</th>
<th>PM</th>
</tr>
</thead>
</table>

**Nucleos(t)ide Reverse Transcriptase Inhibitors**

**Lamivudine**
- Treatment of HIV & HBV

<table>
<thead>
<tr>
<th>Lamivudine, 3TC</th>
<th>Take 1 tablet (150mg) orally twice daily with or without food</th>
<th>AM</th>
<th>PM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine, 3TC</td>
<td>Take 1 tablet (300mg) orally once daily with or without food</td>
<td>AM</td>
<td>PM</td>
</tr>
</tbody>
</table>

**Emtricitabine**
- Fluorinated analog of 3TC
- Treatment of HIV & HBV

<table>
<thead>
<tr>
<th>Emtricitabine, FTC</th>
<th>Take 1 capsule (200mg) orally once daily with or without food</th>
<th>AM</th>
<th>PM</th>
</tr>
</thead>
</table>

**Abacavir**
- Does not need to be renally dosed
- Hypersensitivity reaction (HSR)
  - ~8% of patients; usually in 6 weeks of initiation
  - ≥2 of: 1-fever, 2-rash, 3-GI (N/V/D, pain), 4-constitutional (fatigue, achiness), 5-respiratory (dyspnea, cough, pharyngitis)
  - May lead to anaphylaxis, organ failure, & death
  - D/C & never rechallenge: ABC allergy in medical record
- Standard of care: HLA-B*5701 prior to ABC use

<table>
<thead>
<tr>
<th>Abacavir, ABC</th>
<th>Take 1 tablet (300mg) orally twice daily with or without food or Take 2 tablets (600mg) orally once daily</th>
<th>AM</th>
<th>PM</th>
</tr>
</thead>
</table>

P. Saberi, PharmD, MAS
Renal insufficiency
- Risk factors: advanced HIV disease, on boosted ARV regimen, nephrotoxic drugs, HTN, DM, age, & pre-existing renal impairment
- Monitor renal function
- ↑ monitoring frequency if proteinuria, ↓ GFR, DM, or HTN

Decrease BMD
- DEXA screening for postmenopausal women & men ≥50 years
- Switch ART for those with low BMD or osteoporosis taking TDF

Treatment of HBV

<table>
<thead>
<tr>
<th>Tenofovir Disoproxil Fumarate</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Renal insufficiency</td>
</tr>
<tr>
<td>– Risk factors: advanced HIV disease, on boosted ARV regimen, nephrotoxic drugs, HTN, DM, age, &amp; pre-existing renal impairment</td>
</tr>
<tr>
<td>– Monitor renal function</td>
</tr>
<tr>
<td>– ↑ monitoring frequency if proteinuria, ↓ GFR, DM, or HTN</td>
</tr>
<tr>
<td>• Decrease BMD</td>
</tr>
<tr>
<td>– DEXA screening for postmenopausal women &amp; men ≥50 years</td>
</tr>
<tr>
<td>– Switch ART for those with low BMD or osteoporosis taking TDF</td>
</tr>
<tr>
<td>• Treatment of HBV</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tenofovir Alafenamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>• TDF &amp; TAF require conversion to active drug tenofovir (TFV) diphosphate</td>
</tr>
<tr>
<td>• As effective as TDF in virologic suppression but less kidneys &amp; bone AEs</td>
</tr>
<tr>
<td>• Treatment of HBV</td>
</tr>
<tr>
<td>• Increases in LDL &amp; TG compared to TDF</td>
</tr>
<tr>
<td>• Check phos, CrCl, U. glucose, U. protein before &amp; during tx</td>
</tr>
<tr>
<td>• Do not use if CrCl&lt;30 mL/min</td>
</tr>
</tbody>
</table>

**TAF, LDL, & Weight Gain**

After switch, mean ↑ TC=7.9%, LDL=11.1%, HDL=7.1%, & TG=23.8%

**Changes in Lipids After a Direct Switch from TDF to TAF. CRDI. 2019. #652.**

**Venter WDF, et al. Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV. NEJM. 2019.**

**Mallon P, et al. Changes in Lipids After a Direct Switch from TDF to TAF. CRDI. 2019. #652.**

**No difference in renal and bone toxicity of TDF versus TAF when using unboosted ARV regimen.**

**TDF & TAF**

<table>
<thead>
<tr>
<th>TDF</th>
<th>Dose</th>
<th>TAF</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF (Viread)</td>
<td>300mg</td>
<td>TAF (Vemlidy)</td>
<td>25mg</td>
</tr>
<tr>
<td>TDF/FTC (Truvada)</td>
<td>300mg</td>
<td>TAF/FTC (Descovy)</td>
<td>25mg</td>
</tr>
<tr>
<td>TDF/FTC/RPV (Complera)</td>
<td>300mg</td>
<td>TAF/FTC/RPV (Odefsey)</td>
<td>25mg</td>
</tr>
<tr>
<td>TDF/FTC/ELV/c (Stribild)</td>
<td>300mg</td>
<td>TAF/FTC/ELV/c (Genvoya)</td>
<td>10mg</td>
</tr>
</tbody>
</table>

**TDF**
- 18 years of data
- Favorable lipid effects
- ↓CrCl & BMD, but unknown clinical renal & bone outcomes (esp. in unboosted regimens)
- Lower cost when TDF generic is available

**TAF**
- 4 years of data
- More favorable renal & bone outcomes
  - Important in those with or at high risk for renal or bone complications but may not have added benefits for others
  - ↑weight, LDL, & TG

**When could you use TAF over TDF?**
- Those with or at high risk for:
  - osteoporosis/osteopenia
  - renal disease
- If using boosted PIs, TAF may be advantageous

**When could you use TDF over TAF?**
- Possibly if patient has CVD, hyperlipidemia, or worried about weight gain
- If not using boosted PIs; little benefit of TAF over TDF
- Those on rifabutin, rifampin, or rifapentine (↑TAF levels)
- TDF generic will cost much less than TAF
**Tailoring ART Regimens: Pre-ART**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Preferred Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-B*5701 +</td>
<td>Do not use ABC</td>
</tr>
<tr>
<td>CD4 count &lt; 200</td>
<td>Avoid RPV, DRV/r + RAL</td>
</tr>
<tr>
<td>VL &gt; 100,000</td>
<td>Avoid RPV, ABC/3TC + ATV/c or ATV/r, ABC/3TC + RAL, ABC/3TC + EFV, DRV/r + RAL</td>
</tr>
<tr>
<td>Uncertain adherence or resistance test</td>
<td>Use DRV/r or DRV/c + TAF/FTC or TDF/FTC</td>
</tr>
<tr>
<td>unavailable</td>
<td>DTG + TAF/FTC or TDF/FTC, BIC may also be an option (avoid ABC or NNRTIs)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Consider not initiating DTG</td>
</tr>
</tbody>
</table>

**Tailoring ART Regimens: ART-Specific**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Preferred Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 pill QD regimen</td>
<td>BIC/TAF/FTC, DTG/ABC/3TC, DTG/RPV, DOR/TDF/3TC, DRV/c/TAF/FTC, EFV/TDF/FTC,</td>
</tr>
<tr>
<td></td>
<td>EVG/c/TDF/FTC, EVG/c/TAF/FTC, RPV/TDF/FTC, RPV/TAF/FTC</td>
</tr>
<tr>
<td>No food requirements</td>
<td>DOR, BIC, RAL- or DTG-based regimens</td>
</tr>
<tr>
<td>Acid-lowering therapy</td>
<td>Avoid/caution with RPV or ATV</td>
</tr>
<tr>
<td>CYP3A4 metabolized meds</td>
<td>Avoid/caution with PI/r, PI/c, EVG/c, EFV, DOR</td>
</tr>
<tr>
<td>Cations</td>
<td>Refer to INSTI dosing table</td>
</tr>
</tbody>
</table>

**Tailoring ART Regimens: Co-morbidities**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Preferred Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporosis/osteopenia</td>
<td>Avoid TDF (use TAF or ABC)</td>
</tr>
<tr>
<td>CKD (eGFR &lt; 60)</td>
<td>Avoid TDF (use TAF or ABC)</td>
</tr>
<tr>
<td>CKD (eGFR &lt; 30)</td>
<td>Avoid TAF</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Avoid PI/r, PI/c, EFV, EVG/c; Consider TDF over TAF or ABC; BIC, DOR, DTG, RAL,</td>
</tr>
<tr>
<td></td>
<td>RAL and RPV have fewer lipid effects</td>
</tr>
<tr>
<td>High cardiac risk</td>
<td>Consider avoiding ABC- &amp; LPV/r-based regimens; Consider BIC-, DOR-, DTG-, RAL-</td>
</tr>
<tr>
<td></td>
<td>or RPV-based regimens</td>
</tr>
<tr>
<td>Psychiatric illness</td>
<td>Avoid EFV- &amp; RPV-based regimens</td>
</tr>
</tbody>
</table>

**Tailoring ART Regimens: Co-infections**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Preferred Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB Tx w/ rifampin-based regimen</td>
<td>Data w/ EFV, RAL (800 mg BID) or DTG (50 mg BID); PI/c or PI/r, BIC, EVG, DOR,</td>
</tr>
<tr>
<td></td>
<td>RPV, or TAF not recommended with rifampin</td>
</tr>
<tr>
<td>HBV</td>
<td>TDF/FTC or TAF/FTC</td>
</tr>
<tr>
<td>HCV Therapy Anticipated</td>
<td>BIC, RAL, or DTG: fewer DDIs</td>
</tr>
</tbody>
</table>
Case
You would like to start ART for your 55 y/o White female patient. She would like a once-daily regimen (1-2 pills once-daily). She has normal liver & kidney function, no ARV drug resistance, & has never taken ARVs before.

Labs:  
VL=178,000 copies/mL  
CD4+= 458 cells/mm^3  
HLA-B*5701+  
Allergies: sulfa (mild rash)

Meds:  
ethinyl estradiol/norethindrone  
TUMS (calcium carbonate)

Recommended Initial Regimens for Most People with HIV
(regimens with durable virologic efficacy, favorable tolerability & toxicity profiles, & ease of use)

ABC/3TC

Recommended Initial Regimens in Certain Clinical Situations
(Effective & tolerable regimens, but some disadvantages vs. regimens listed previously, or less supporting data from RCTs. However, may be preferred in certain clinical situations.)

ABC/3TC

3TC

Oral contraceptive
Recommended Initial Regimens in Certain Clinical Situations

(Effective & tolerable regimens, but some disadvantages vs. regimens listed previously, or less supporting data from RCTs. However, may be preferred in certain clinical situations.)

- ABC/3TC
- RAL
- DRV/c
- DRV/r
- DTG

- TDF/FTC or TAF/FTC
- ABC/3TC
- 3TC

Treatment Options

- BIC/TAF/FTC (Biktarvy)
- DOR/TDF/3TC (Delstrigo)
- DTG/3TC (Dovato)
  Or
- BIC + TDF/FTC
- DTG + TDF/FTC or TAF/FTC
- DOR + TAF/FTC

New ARVs

Drug Information Resources

- Drug resistance
  - HIV Drug Resistance Testing Database: hivdb.stanford.edu/
- Drug-drug interactions
  - Package inserts
  - Toronto General HIV Clinic: www.hivclinic.ca
  - University of Liverpool: www.hiv-druginteractions.org/
  - Pubmed
  - HIV InSite: hivinsite.ucsf.edu/InSite
  - NATAP: natap.org
- Dosage modifications
  - NCCC chart: ncc.ucsf.edu
  - Micromedex
  - Package inserts
The Clinician Consultation Center is a free telephone advice service for clinicians by clinicians. Receive expert clinical advice on HIV, PrEP, PEP, hepatitis C, substance use and perinatal HIV.

See nccc.ucsf.edu for more information.

HIV
- testing,
- ARV regimens,
- resistance,
- and comorbidities

HCV
- testing,
- monitoring,
- treatment

Substance use evaluation and management

Pregnant women with HIV or at-risk for HIV & their infants

Pre-exposure prophylaxis for persons at risk of contracting HIV

Occupational + non-occupational exposure management

Thank you!

- Meg Newman, MD, FACP
- Diane V. Havlir, MD
- Annie Luetkemeyer, MD

University of California
San Francisco
Reproductive Health for People Living with HIV in the US

Deborah Cohan, MD, MPH
Professor
UCSF Dept of Obstetrics and Gynecology
HIVE
National Perinatal HIV Hotline

I have no financial conflicts of interest to disclose.

Overview

- Reproductive health resources
- Pregnancy care
  - ARV selection and management
  - Acute infection
- Postpartum care
  - Breastfeeding
- Additional slides about:
  - Preconception care
  - PrEP/PEP during pregnancy and breastfeeding
  - Intrapartum care
  - Postpartum adherence/retention in care
  - Infant feeding
  - Contraception
  - Cervical cancer prevention and screening

Natl Perinatal HIV Hotline & Clinicians Network
1-888-448-8765 (24/7)
Repro ID_HIV listserv
marliese.warren@ucsf.edu
We hold true that in order for people to be free and equal they must be able to exercise complete autonomy over their bodies.

Consider adding to your job description

- Provision of non-judgmental reproductive & sexual healthcare.
- Addressing structural violence (i.e. the way the “systems” in which we work discriminate and perpetuate injustice).

Epidemiology of structural racism

- Black women represent 37% of WLHIV in SF
  - 6% of SF females
  - Mortality rate: 43 deaths per 100,000

Reproductive & sexual health = primary care

- If we integrate preconception, family planning and sexual wellness into primary care model
  - HIV-exposed pregnancies will be planned and well-timed
  - Timely access to safe abortion
  - No HIV transmission to sexual partners or infants
  - Health of all HIV-affected parents and infants will be optimized.
Every interaction is an opportunity to...

- Check in about sex
- Assess disclosure to partners (and honoring obstacles)
- Discuss HIV status and testing of partners
- Assess adherence and remind about TasP
- Educate about PEP and PrEP
- Discuss reproductive health desires
  – Want to have a child at some point?
  – Want to avoid having a child?

It may take time and we many not feel fully equipped to deal with the answers...

And ...

- Helping them find path to living a healthy, integrated life
- Satisfying for us to connect deeply and authentically

HIVE: a hub of positive sexual and reproductive health
www.HIVEonline.org

www.HIVEonline.org
Reproductive Desires & Intentions

- Reproductive desires
  - Do you want to have children in the future?
  - If no and “at risk” of pregnancy/impregnating → ask about contraceptive use

- Reproductive intentions
  - If so, what would be your ideal timeline?
  - Discuss partner HIV status, conception options, birth spacing (at least 12-18 months between delivery and subsequent conception)
  - surrogacy, foster care, adoption, alternative family building options

Engaging HIV+ Women in Reproductive Topics

- Reproductive desires
  - Do you want to have children in the future?

- Reproductive intentions
  - If so, what would be your ideal timeline?
  - Discuss partner HIV status, conception options, birth spacing (at least 12-18 months between delivery and subsequent conception)
  - surrogacy, foster care, adoption, alternative family building options
Pregnancy for those who identify as trans or gender non-binary

- Video with Juno Obedin-Maliver
  - [https://www.hiveonline.org/juno-obedin-maliver-on-reproductive-health-for-transmen/](https://www.hiveonline.org/juno-obedin-maliver-on-reproductive-health-for-transmen/)

---

LGBTQ+ Health: Case Report

Providing Patient-Centered Perinatal Care for Transgender Men and Gender-Diverse Individuals: A Collaborative Multidisciplinary Team Approach

Mona Haid, MD, MPH
Neil Zelman, MD, MPH
Shawna Wilke, MD, FACC
Dwight Cohen, MD, MS, and Juno Obedin-Maliver, MD, MPH

BACKGROUND: Little is documented about the experiences of pregnancies for transgender and gender-diverse individuals. There is scant clinical guidance for providing preconception, prenatal, intrapartum, and postpartum care to transgender and gender-diverse people who are pregnant.

CASE: Our team provided prenatal care to a 19-year-old transgender man, which prompted collaborative enhancements in the care delivery model. Lessons learned from this patient experience are shared in the perinatal care setting.

CONCLUSION: Transgender and gender-diverse interventions were adopted to ensure comprehensive care and includes care in and around pregnancy. Basic practices to mitigate stigma and promote gender-affirming care include: cultural humility and sensitivity, and use of appropriative name and pronouns in patient interactions and medical documentation. Various factors are important to consider regarding testosterone therapy for transgender individuals desiring pregnancy.

[https://www.hiveonline.org/transgender-care-presidents](https://www.hiveonline.org/transgender-care-presidents)

---

Sally is on Dolutegravir

- Sally is 18 yo on TDF/ABC/DTG for a year.
- Living in an encampment under freeway
- Has been diagnosed with bipolar in past
- Uses methamphetamine few times/week
- Reports 100% ARV adherence
- Consistent viral suppression
- She tells street outreach medical team she thinks she is pregnant.

---

I'M PREGNANT!
More about Sally

• Sally says her period is irregular but thinks it was ~ 2-3 months ago.
• Comes to clinic: + pregnancy test
• Sally is thrilled and expresses desire to continue pregnancy.
• N.B. no assumptions about reactions to and plans for pregnancy, including visit-to-visit

What’s your next step?

1. Schedule an appointment with OB within next 7 days.
2. Switch to TDF/FTC + RAL.
3. Continue Sally on TDF/ABC/DTG because it has worked for her.
4. Obtain same-day ultrasound and discuss switching DTG based on that.

Neural Tube Defects

- Neural tube defects develop within 4 weeks after conception (6 weeks post-LMP/gestational age)
- Botswana 119,033 deliveries; 0.08% NTD
  - 1683 deliveries with mom on DTG at conception: 0.3% NTD (n=5)
  - 14,792 deliveries with mom on non-DTG ARV: 0.1% NTD (n=15)
  - 7959 deliveries with mom on EFV: 0.04% (n=3)
- 2 defects in Botswana possibly “post-neurulation” (i.e. between neural tube closure and the end of the 1st trimester)
- No cases of NTD among women with 1st tri DTG in Antiretroviral Preg Registry (n=307)

Gestational age and DTG risk

- Botto, NEJM 1999

Zash NEJM Aug 2019; Zash NEJM Sept 2018; apregistry.com Jan 2019
When Sally was my patient:

- Same day ultrasound: 6 weeks pregnant
- Discussed Botswana data
- Discussed options:
  - Stay on DTG (NTD ≤4 wks of conception or ≤6 wks from LMP)
  - DTG → RAL vs. ATV/r
  - RPV regimen, though pK in 2nd and 3rd trimester

Sally shares...

- Botswana feels irrelevant to her
- ABC/3TC/DTG FDC is a source of stability and the “one thing she is doing right” in her life right now.
- She stayed on DTG
- We obtained Level 2 fetal sono, integrated genetic screening to assess for NTD, reported to Antiretroviral Preg Registry (100% reporters)
- I don’t try too hard to convince woman to stop DTG even if <12 weeks if otherwise working for her.
- Tivicay, Juluca, Triumeq, Dovato

Folate receptor as etiology of DTG toxicity?

- DTG = noncompetitive antagonist at folate receptor (FOLR1) in human placenta cells
- No downstream disruption of folate metabolism
- Zebrafish
  - share 70% genetic code with humans
  - DTG toxic with very early embryonic exposure
  - Folic acid ↓ DTG toxicity
- Supplemental folic acid for pregnant humans taking DTG?

ART in Pregnancy
Art in Pregnancy (aka prescribe what they will take)

<table>
<thead>
<tr>
<th></th>
<th>NRTI/NtRTI</th>
<th>NNRTI</th>
<th>PI</th>
<th>EI/II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred</td>
<td>ABC/3TC</td>
<td>TDF/F(3)TC</td>
<td>ATV/ r</td>
<td>RAL (BID) DTG &gt; 12w</td>
</tr>
<tr>
<td>Alternative</td>
<td>ZDV/3TC</td>
<td>EFV RPV</td>
<td>LPV/ r</td>
<td>(600/150 BID in 2nd/3rd)</td>
</tr>
<tr>
<td>Not recommended</td>
<td>ETR NVP</td>
<td>DRV/COBI ATV/COBI DTG &lt; 12w EVG/COBI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insufficient data</td>
<td>TAF DOR</td>
<td>BIC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Avoid COBI (+ EVG or DRV or ATV) in pregnancy?**

- IMPAACT 1026; intensive pK, n=30
- Pregnancy vs. postpartum
- COBI ↓ 44% in 2nd tri, ↓59% in 3rd
- EVG AUC ↓ 24% in 2nd tri, ↓44% in 3rd
- pK WNL in preconception and 1st tri
  - Switch preconception? Switch later in pregnancy?
  - Consider TDM: Dr. Brooke Best @ UCSD
  - COBI/ATV no pregnancy studies, likely ↓ pK
  - Genvoya, Strivil, Prezobix, Symtuza, Evotaz

Momper AIDS 2018
Rilpivirine pK = likely ok

- Levels variable among pregnant women
- Total RPV AUC ~ 30 to 40% ↓ during pregnancy vs. postpartum
- Unbound (pharmacologically active) less affected by pregnancy
- ~10% women trough < EC90 (level needed to inhibit 90% replication)
- Therefore, 90% women with OK trough

FDA Oct 2018; Elite JACS 2018; Osyemi Inf Dis Ther 2018; Schalkwijk CID 2017

Let women make informed choices.

Antiretroviral Pregnancy Registry

- Assesses birth defects based on 1st vs. 2nd vs. 3rd trimester exposure
- 1-800-258-4263
- www.apregistry.com
- Now on-line patient enrollment
- 100% reporter: retrospective enrollment ok
- Report WLHIV or women taking PEP or PrEP during pregnancy
- Interim reports every 6 months

Other aspects of prenatal care

- OI prophylaxis:
  - Azithro for MAC;
  - TMP-SMX ok (incl. 3rd tri); may disrupt folate-assoc organogenesis
- Monthly viral load, including @ term
  - UBC (n=318): VL <50 at 34wk → Viremic @ delivery
  - 6% viral rebound; 2% VL >1000 copies
  - 50% with rebound within 1 day before delivery

Boucoiran ObGyn 2017
Other aspects of prenatal care

- Prenatal vitamins (counsel re: timing)
  - e.g. DTG 2hr before, 6 hr after PNV
- TDaP @ 28wks, flu vac; other inactivated vac prn (HAV, HBV, etc)
- Contraception plan
- Discussion of infant feeding options
- Nutrition/food security, exercise, safety, housing, substance use, mental health

Levison CID 2014

Acute HIV during pregnancy

- High risk of perinatal (and sexual, lactational) transmission **U=U**
- Start ART ASAP (expedited confirmatory testing)
- Goal = rapid viral decay (frequent serial VL "stat")
  - n=50; ART initiation >20wks
  - Median time 1-log decay: INSTI =8 d vs. non-INSTI = 35 d
- DTG vs. RAL
  - Both PREFERRED after 12wks
  - Adherence=critical; once daily DTG vs. BID RAL
  - Higher barrier to resistance DTG
  - Avoid 3TC/ABC co-formulation vs. risk AHR while await HLA?
- Consider DOT (inpatient or outpatient)
  - 3rd trimester DOT = cost-effective

Role of cesarean for 3rd tri viremia?

- Older data suggested elective cesarean at 38 weeks (no labor, no ROM) ↓ risk of intrapartum transmission
- Official rec: offer if VL @ term > 1000 copies
  - Not protective if woman on combo ART and/or infant received more than AZT PEP

ART timing → VL decay → transmission **U=U**

<table>
<thead>
<tr>
<th>Region</th>
<th>%</th>
<th>VL @ delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK/Ireland</td>
<td>0.1%</td>
<td>&lt;50 copies</td>
</tr>
<tr>
<td>France</td>
<td>No cases</td>
<td>preconception or 1st tri start and &lt;50 copies @ delivery</td>
</tr>
<tr>
<td></td>
<td>0.5%</td>
<td>14-27wk start and &lt;50 copies @ delivery</td>
</tr>
<tr>
<td></td>
<td>OR 23.2</td>
<td>&gt; 500 copies @ ~30wks</td>
</tr>
<tr>
<td>So. Africa</td>
<td>OR 0.92</td>
<td>per week of ART</td>
</tr>
</tbody>
</table>

- Start as early as can tolerate...
- Aggressive optimization/adherence interventions if slow decay (<1 log by 4 weeks) or viremic in 3rd trimester

Townsend AIDS 2008; Hoffman AIDS 2010; Tubiana CID 2010; Tubiana CRoi 2011
If a woman is viremic in 3rd tri, don’t rely on cesarean

- Doesn’t address in-utero transmission prior to delivery (i.e. missed opportunity)
- Doesn’t help if labor or ROM before cesarean
- No benefit if infant receives more than AZT
  - HPTN 040, women with no ARVs pre-delivery
  - RCT infant AZT vs. AZT/3 dose NVP vs. AZT/3TC/NFV
  - Cesarean before ROM/labor: OR 0.6 (0.3–1.3)
- Risks of cesarean for woman (infn, anemia, postop recovery) and baby (tachypnea, microbiome); delayed skin-to-skin/bonding

Postpartum Care

- ART adherence support
  - May lose motivation to take ART
- Cabergoline lactation suppression (1mg x1, rpt prn)
- Infant feeding: formula, banked human milk
  - https://www.hmbana.org
- Harm reduction approach if considering breastfeeding
- Contraception
- Infant PEP
  - 8 wks AZT if consistent maternal viral suppression
  - If maternal viremia in 3rd trimester and/or delivery → call National Perinatal HIV Hotline

Harm-reduction approach to breastfeeding

**Guidance for Counseling and Managing Women Living with HIV in the United States Who Desire to Breastfeed**

Panel’s Recommendations

- Breastfeeding is not recommended for women living with HIV in the United States (All)
- Women who have questions about breastfeeding or who desire to breastfeed should receive patient-centered, evidence-based counseling on infant feeding options (All)
- When women with HIV choose to breastfeed despite intensive counseling, they should be counseled to use harm-reduction measures to minimize the risk of HIV transmission to their infants (All)

Confusing for WLHIV to navigate mixed messages about breastfeeding
ARVs and Breastfeeding?

- Antiretroviral use during breastfeeding
  - Maternal plasma (and breast milk) viral load
  - Transfer to some ARVs via breast milk = infant PrEP/PEP
  - Infant PEP
- Some of the many unknowns
  - Role of cell-associated vs. cell-free HIV in transmission
  - Which ARVs are most protective
  - Penetration into breast milk compartment
  - Optimal infant PEP regimen if breastfed
  - How often to monitor maternal viral load (most suggest monthly) and test infant
  - Importance of exclusive breastfeeding if on ARVs with viral suppression (is mixed feeding a problem if formula safe?)

Discussing breastfeeding

- An open-ended conversation, not a provider-led mandate about formula
  - “In the US, we recommend that women with HIV not breastfeed. “Please tell me your feelings and thoughts about this.”
  - Validate her desire to breastfeed
  - Seek to understand her motivation

Discussing breastfeeding

- I will support you, regardless of what you decide.
- My role is making sure you understand the risks so that you can make an informed decision you feel good about.
- What is most important is that we have honest communication and that you don’t avoid telling me something out of fear.
- The official recommendation is for women with HIV in the US to avoid breastfeeding.
- There are other options:
  - Milk bank covered by Medi-Cal
  - Flash heating (time-consuming; no long-term data)
  - Wet nurse

Human Milk Banking Association of America

https://www.hmbana.org/about
Discussing breastfeeding

• We know that BF has a host of health benefits for the baby, especially in regions of the world where water quality is bad and formula isn’t a safe option.
• I understand the pressure to BF and the messages about the importance of choosing milk over formula.
• BF can be a beautiful way to bond with your baby. I honor the loss and emotional difficulty of giving up BF.
• There are other ways to bond with your baby, including doing skin-to-skin while bottle feeding.

Discussing breastfeeding

• ART 🔄 (doesn’t eliminate) HIV transmission.
• Monthly viral loads throughout breastfeeding.
• Much we don’t know including:
  – most effective ARV regimens
  – most effective infant PEP regimen
  – long-term impact of ARV exposure through milk
  – optimal amount of HIV testing to do for your baby
  – role of exclusive breastfeeding where formula safe

Discussing breastfeeding

• I share the story of the 1 woman in Uganda in PROMOTE trial who transmitted via BF despite having VL <400 copies within a month of transmission
  – LPV doesn’t penetrate into breast milk compartment?
  – She had low level viremia below level of detection for that assay?
  – She became viremic at some point after the <400 result?
Discussing breastfeeding

• The official recommendation used to be for women with HIV to not get pregnant. Now we know how to prevent HIV transmission during pregnancy and we don’t discourage WLHIV from getting pregnant.
• At some point, we will figure out how to prevent HIV transmission during breastfeeding. We are almost there, but not quite.

Take It Home...

• Reproductive and sexual healthcare is primary care
• Women who desire pregnancy or are “at-risk” of pregnancy
  – DTG not recommended (1st tri issues)
    • Though may be OK if adequate folic acid
  – COBI not recommended (2nd/3rd tri issues)
  – RPV ok but maybe not ideal (unless ideal for her)

Take It Home...

• Women who get pregnant while on ART
  – DTG: continue if >12-14wks gestational age
    • Switch vs. continue if <12-14wks depending on her circumstances
  – Prenatal vits, extra folic acid may be future recommendation
  – COBI: switch vs. continue with frequent VL, TDM
  – RPV: probably ok to continue with frequent VL, consider TDM
• Women started on DTG in pregnancy: discuss importance of future preconception care for subsequent pregnancies

Take It Home

• Aggressive optimization of ART, adherence for viral suppression by 3rd trimester
• Elective cesarean as last resort intervention
• Harm reduction approach to infant feeding
• Informed free choice about ARV selection and all aspects of reproductive and sexual wellness
Resources

- HIVE
  - www.HIVEonline.org
- National Perinatal HIV Hotline/Clinicians’ Network
  - www.nccc.ucsf.edu
- Repro ID HIV listserv
  - Marliese.Warren@ucsf.edu
- 2018 Perinatal ARV Guidelines (Dec 20, 2018)
  - www.aidsinfo.nih.gov

“She must decide about her own body – so that she can decide about her life and her future. Without question.”
#SheDecides

Additional relevant slides

- Preconception care
- PrEP/PEP during pregnancy and breastfeeding
- Intrapartum care
- Postpartum adherence/retention in care
- Infant feeding
- Contraception
- Cervical cancer prevention and screening
WE WANT TO GET PREGNANT!

Who influences reproductive desires of WLHIV?

- U Miami, n=49 WLHIV
- KAP survey re: fertility planning, reproductive desires, and safer conception practices
- younger and less education influenced by partners’ desires
- older and more education influenced by physician endorsement of childbearing

Desires among MSM with HIV?

- n=84, UK
- 77.6% no discussion with a doctor about becoming a parent
- 68.2% felt not sufficiently informed

www.GaysWithKids.com

Jones et al. PLOS One, Sept 2016

Fertility desires among PLHIV

<table>
<thead>
<tr>
<th>US reproductive-aged women</th>
<th>35%</th>
</tr>
</thead>
<tbody>
<tr>
<td>WLHIV</td>
<td>US, HCSUS Rochester British Columbia (Baltimore) Eurosupport V</td>
</tr>
<tr>
<td>MLHIV (MSW)</td>
<td>US, HCSUS Eurosupport V</td>
</tr>
</tbody>
</table>

Predictors: age <30y, childless (meta-analysis 20 studies)

Goals of HIV-informed preconception care

- Prevent unintended pregnancy
- Prevent HIV transmission to partner
  - Viral suppression, PEP, PrEP
- Optimize maternal & paternal health
  - Vaccination, OI prophylaxis, smoking cessation, etc
- Improve maternal and fetal outcomes
- Prevent perinatal HIV transmission

ACOG Practice Bulletin No 117, December, 2010

Take advantage of the desire to get pregnant/conceive as an opportunity to optimize health and encourage other forward-thinking behavior.

Preconception management

- Antiretroviral therapy
  - Not on ART? → start before attempting conception, esp if serodifferent
  - What to start?? (more on this in a moment)
- Folate (400mcg) or prenatal vitamins
- OI prophylaxis
  - TMP-SMX and NTD risk
    - 4-10mg folate (vs. defer conception until CD4>200 x 3 mos)
    - Azithro (vs. defer conception until CD4>100 x 3 mos)

Preconception ARV Summary

- Informed-free choice
- Dolutegravir
  - Supplemental folic acid: standard dose in PNV?
  - Consider switching preconception, restarting in 2nd tri
- COBI
  - Significant pK issues in 2nd/3rd trimester
  - Consider switching preconception
- Rilpivirine
  - Less significant pK issues in 2nd/3rd trimester
Preconception management

• Screen/treat STIs
• Vaccinate prn
• Optimize nutrition, exercise
• Address trauma
• Address tobacco, drug, alcohol use
• Comprehensive med review (including OTC, herbs, etc)
• Engaging the partner
  – HIV and STI testing
  – PEP, PrEP education, prescription prn
  – Linkage to care
  – Smoking cessation, drug treatment
• Testing children

Ideal birth spacing = 18+ months

• 18+ months between delivery and subsequent conception
• Birth spacing <18 months associated with:
  – preterm birth
  – neonatal morbidity
  – low birth weight
• In US (2006-10), ~33% pregnancies began <18 months after previous live birth
• Reassuring data on shorter interval after miscarriage and stillbirth → attempt conception “when ready”

HIV PROVIDERS DISCUSSING REPRODUCTIVE DESIRES WITH PATIENTS

PRO-Men Survey

• Online anonymous REDCap survey
• Healthcare providers doing primary care for PLHIV in SF Bay Area
• n=72
• 87.5% MD/DO, 12.5% NP
• 59% public, 35% private, 13% VA
When do providers ask male patients about reproductive issues?

How often do providers ask?

SAFER CONCEPTION

- Videos:
  - HIV+ Men: Having a Healthy Sex Life and Healthy Family
  - Adherence
  - Disclosure
- Clinical algorithms: integrating reproductive health into primary HIV care
- Educational brochures: safer conception, contraception
- PRO MEN... on the go...

www.HIVEonline.org
No documented cases of male ⇨ female sexual transmission if on ART and undetectable viral load
only one case of male ⇨ male sex transmission

TDF safety in pregnancy when reasonable minds differ?
- JAIDS meta-analysis (17 studies; WHO funded)
  - PTB <37w RR 0.9 (0.81-0.99); <34w RR 1.08 (0.72-1.62)
  - Stillbirth RR 0.6 (0.43-0.84)
  - Neonatal mortality RR 0.74 (1.70-1.79) driven by PROMISE
  - 1 study clinically irrelevant: Δ length and HC z-scores
  - No Δ maternal AE, SGA, LBW, anomalies, infant AE, infant mortality
  - “The latest WHO guidelines continue to recommend TDF + FTC (or 3TC) + EFV as first-line ART for adults, including pregnant women.”
- BMJ Open meta-analysis (10 studies)
  - Stillbirth/neonatal mortality RR 4.40 (1.75-11.01)
  - PTB (≤37w) RR 2.30 (1.06 to 4.97)
  - Driven by PROMISE (used LPV/r; lower than expected PTB in non-TDF arm)
  - “The adverse effect on stillbirths and neonatal mortality is likely an overestimate... fully informed pregnant women living with HIV are likely to choose regimens that do not include tenofovir or FTC.”
- “After fully considering the results of the PROMISE study, both the Perinatal (GL) Panel and the BHIVA do not support these recommendations.” Nachega JAIDS 2017; Siemieniuk BMJ Open 2017

- The Swiss
  - MLHV on ARV; HIV-RNA <50 copies/ml x >3 mos
  - HIV-RNA in semen undetectable at baseline
  - TDF 36 hrs and 12 hours before sex
  - n=46 pregnancy per attempt
    - 26% (1) → 66% (5) → 75% (12)
    - No seroconversions or adverse events
- The Americans (SF and NY)
  - Retrospective cohort of “at-risk” women (2010-15)
  - n=27 (5 preconception)
  - No seroconversions or adverse events


TDF safety in pregnancy when reasonable minds differ?
- JAIDS meta-analysis (17 studies; WHO funded)
  - PTB <37w RR 0.9 (0.81-0.99); <34w RR 1.08 (0.72-1.62)
  - Stillbirth RR 0.6 (0.43-0.84)
  - Neonatal mortality RR 0.74 (1.70-1.79) driven by PROMISE
  - 1 study clinically irrelevant: Δ length and HC z-scores
  - No Δ maternal AE, SGA, LBW, anomalies, infant AE, infant mortality
  - “The latest WHO guidelines continue to recommend TDF + FTC (or 3TC) + EFV as first-line ART for adults, including pregnant women.”
- BMJ Open meta-analysis (10 studies)
  - Stillbirth/neonatal mortality RR 4.40 (1.75-11.01)
  - PTB (≤37w) RR 2.30 (1.06 to 4.97)
  - Driven by PROMISE (used LPV/r; lower than expected PTB in non-TDF arm)
  - “The adverse effect on stillbirths and neonatal mortality is likely an overestimate... fully informed pregnant women living with HIV are likely to choose regimens that do not include tenofovir or FTC.”
- “After fully considering the results of the PROMISE study, both the Perinatal (GL) Panel and the BHIVA do not support these recommendations.” Nachega JAIDS 2017; Siemieniuk BMJ Open 2017

- The Swiss
  - MLHV on ARV; HIV-RNA <50 copies/ml x >3 mos
  - HIV-RNA in semen undetectable at baseline
  - TDF 36 hrs and 12 hours before sex
  - n=46 pregnancy per attempt
    - 26% (1) → 66% (5) → 75% (12)
    - No seroconversions or adverse events
- The Americans (SF and NY)
  - Retrospective cohort of “at-risk” women (2010-15)
  - n=27 (5 preconception)
  - No seroconversions or adverse events

Assisted Reproduction and HIV

- Sperm washing with IVF or IUI = safe
- No cases of transmission with current techniques
- Expensive (esp IVF)
- Limited availability
  - Geographic
  - Practices choosing to not provide care
- There is no ethical reason to withhold fertility services at clinics with the necessary resources to provide care to HIV-infected individuals and couples who are willing to use recommended risk-reducing therapies. Clinics without sufficient resources to offer care should assist in referral to providers equipped to manage such patients. (ASRM 2015)

PrEP during Pregnancy and Breastfeeding

- Appears safe (some controversy as above)
  - Breastmilk <<<< plasma concentration
- During pregnancy and breastfeeding
  - Paul: monthly viral loads
  - Caitlin: HIV Ag/Ab testing qtri and during BF at minimum
    - Viral loads depending on condom use, his viral load

Ovulation predictor kits

Numerous methods to eliminate HIV transmission risk while trying to conceive.

Nachega AIDS 2017; Brown Hepatology 2016; Wang CID 2015; Ehrhardt CID 2015; Fowler PROMISE 2014; Palombi 2016; Mugo 2014
INTRAPARTUM CARE

Intrapartum Care

- If recent viral load < 1000 copies
  - No IV AZT (consider if <1000 only very recent)
  - Trial of labor ok
  - HPTN 040: No IV AZT 1.1 (0.6–2.0)
- Continue oral ARVs even if NPO
- Avoid fetal scalp electrode
- Consider avoiding AROM
  - chorioamnionitis
  - Duration of ROM not risk factor for transmission if viral suppression, on combination ART

POSTPARTUM CARE, CONTINUED

Postpartum loss to follow-up and poor ARV adherence = global health crisis!

- Meta-analysis: 51 studies, 20,153 pregnant WLHIV (14 studies in US)
- Adequate adherence (≥80% ARV)
  - Antepartum: 75.7% (71.5%–79.7%)
  - Postpartum: 53.0% (32.8%–72.7%)
- Barriers to adherence:
  - Physical, economic, emotion stress
  - Depression (especially postpartum)
  - Alcohol, drug use
  - ARV dosing frequency or pill burden

Nachega AIDS 2012
Post-partum challenges: HIVE Patient Death Review

2004-2016
- Perinatal transmissions in SF = ZERO!
- Maternal deaths of HIVE clients = NINE!
  - 4 died within 2 years of delivery
  - 8 had significant lifetime trauma and/or IPV
  - 8 had postpartum depression
  - 6 homeless or marginally housed
  - 7 died of HIV-related causes
  - 4 experienced custody loss of their children
  - 4 virally suppressed at delivery

www.HIVEOnline.org

Loss to follow-up among postpartum WLHIV in Mississippi
- Retrospective, n=274, n=297 deliveries.
- Median age 25, 89% were black.
- 37% with 2+ HIV provider visits within 1st postpartum year.
- Postpartum follow-up associated with presenting before the 3rd tri (OR 2.1)

HIV Care Postpartum Retention

- Women engaged in HIV care within 90 days postpartum more likely to remain engaged
  - 1 yr pp, AOR 11.4 (7.7-16.7)
  - 2 yr pp, AOR 6.2 (4.0-9.5)
- Factors associated with no HIV care postpartum
  - HIV diagnosis < 2 years before delivery, 0.6 (0.3-0.9)
  - Inadequate prenatal care, 0.4 (0.2-0.7)
Care Retention among Women Diagnosed with HIV during Pregnancy

- Retrospective (2008-10), NY State HIV Surveillance Registry, n=254
- 87% HIV care before delivery
- 75% viral suppression @ delivery -> 50% viremic in 1st year PP

- Factors associated with no HIV care
  - IDU, RR 5.5 (3-10)
  - Late prenatal care, RR 9.7 (2.45)

- Factors associated with maternal loss to follow up
  - Diagnosis in 3rd trimester, RR 2.2 (1.4-3.5)
  - Cesarean delivery, RR 1.7 (1.1-2.9)
  - White race, RR 1.9 (1.1-3.4)
  - Unsuppressed VL, RR 1.9 (1.3-2.9) (bivariate only)


Structured Guidance for Postpartum Retention in HIV care

- Medical safety net
- Depression screening
- Substance use assessment
- Assess factors associated with need for intensive follow up
- Infant feeding preferences
- Reproductive desires
- Insurance plan transitions

Adapted from CDC's Elimination of Perinatal HIV Transmission Stakeholders Group
Courtesy of Gwen Lazenby

Elimination of Mother-to-Child Transmission Risk Assessment Tool (ERAT)

- Co-location: patient goes to one clinic
  - prenatal provider comes to HIV clinic
  - HIV provider comes to prenatal clinic
- Separate clinics: patient goes to both clinics on same or different campuses
- One clinic/clinician during pregnancy
  - Prenatal provider does the primary HIV care during pregnancy -> refers back to primary HIV provider postpartum
  - Primary HIV provider does the prenatal care
- Can often continue HIV care postpartum (woman +/- infant)
- And then after delivery...
  - Infant may be seen at different clinic/campus from mom’s care
  - Sometimes 2 sites (Peds primary care + HIV-nurse out management)
- How can we help women navigate our disconnected healthcare system?

Common models of prenatal-HIV care
Interventions to increase Postpartum Retention

- **Routine**
  - Schedule appointments prior to delivery
  - Dispense adequate ARVs for mom and baby before hospital discharge

- **Enhanced**
  - Case management
  - Patient navigators

- **Intensive**
  - Home and community visits
  - Community agency involvement

Adapted from CDC EMCT Care Workgroup

Improving Postpartum Retention in Care for WLHIV

- Care coordination and case management
  - “deliberate organization of patient care activities to facilitate the appropriate delivery of healthcare services”
  - Integrated maternal postpartum/infant care: viral suppression @ 1yr postpartum in South Africa
  - Philadelphia, n=898 live births (2005-13), WLHIV with perinatal case management: viral suppression before delivery (aOR 1.90) vs in HIV care @ 1 yr PP (aOR 1.59), but no difference in viral suppression @ 1yr PP

Momplaisir AIDS 2018; Myer CROI 2017; Anderson AIDS Behavior 2017

Improving Postpartum Retention in Care for WLHIV

- **Peer support**
  - Many programs in Africa have shown postpartum benefits
  - mothers2mothers (m2m) peer support program: www.m2m.org
  - CenteringPregnancy group visit model = promising model in US

- **Technology**
  - Text/phone call reminders associated with visit attendance @ 6-10 weeks postpartum
  - US-based “text4baby” associated with self-reported EIDH use postpartum (OR 0.2)

What do WLHIV say they want

- Mixed methods study, 1-on-1 interviews and focus groups
- 18 WLHIV in Alabama
- Asked about barriers and facilitators of postpartum HIV care adherence.
- African-American (83.3%), single (66.7%), income <$1000/month (55.6%)
  - Barriers to retention in HIV care:
    - access to and cost of transportation
    - work & childcare schedules
  - Facilitators to HIV care adherence:
    - wanting to stay healthy for their own well-being
    - wanting to stay healthy to care of their children
    - family support
    - appointment reminders

Brief Summary

- Women living with HIV are at increased risk of loss to HIV care postpartum
  - Woman at increased risk are those
    - Newly diagnosed with HIV
    - Not taking or non-adherent to ARVs
    - Receiving inadequate or presenting late to prenatal care
  - Systems for improving retention are necessary
    - Culturally and locally-appropriate
    - Creative
    - Woman and family-centered
    - Begin before postpartum

Other possible interventions not yet studied in postpartum period and/or with WLHIV

- Conditional cash transfers
  - ↑ retention in prenatal care, no change in adherence/viral load (Congo)
- Directly observed therapy
  - Cost-effective for pregnant WLHIV with viremia (US)
  - WLHIV in Puerto Rico reported DOT acceptable
- Mindfulness training
  - upcoming RCT among adults with HIV (NE US)
  - Phone-based mindfulness-based stress reduction (MBSR), health coaching
- Trauma-informed therapy

Addressing postpartum depression: Brexanolone

- Not specifically studied among WLHIV
- FDA approved November 2018
- IV over 60 hours; 30 day follow-up
- RCT 1:1:1: 90 mcg/kg vs. 60 mcg/kg vs. placebo
  - n=246, <6 mos postpartum
- Hamilton Rating Scale for Depression
  - Significant and durable improvement over 60h, 30d
INFANT FEEDING, CONTINUED

Premastication of infant food

- Several cases of HIV transmission via premastication (prechewing or prewarming in the mother’s mouth) of infant food.
- Unknown (but likely tiny or non-existent) risk of HIV transmission with premastication of food if woman with viral suppression.

Breastfeeding in Perinatal HIV Guidelines

- Avoidance of breastfeeding has been and continues to be a standard, strong recommendation for women living with HIV in the United States, because maternal ART dramatically reduces but does not eliminate breastmilk transmission, and safe infant feeding alternatives are readily available. There are also other concerns, including the potential for drug toxicity in the neonate or, should HIV transmission occur, the risk that the infant will develop ARV drug resistance due to subtherapeutic drug levels in breastmilk.

However...

- “Clinicians should be aware that women may face social, familial, and personal pressures to consider breastfeeding despite this recommendation...
- this may be particularly problematic for women from cultures where breastfeeding is important, as they may fear that formula feeding would reveal their HIV status.
- It is therefore important to address these possible barriers to formula feeding during the antenatal period”
Without ARV prophylaxis—risk highest in first 4-6 weeks of life
- 0.7%/month during months 1-5
- 0.6%/month during months 6-11
- 0.3%/month during months 12-17

Breastfeeding and HIV International Transmission Study meta-analysis:
- After 1 month of age, risk 8.9 transmission per 100 P-Y

Risk is higher with acute HIV infection
- ~14% in chronic infection
- ~25-30% in acute infection

Other factors:
- High maternal plasma (and breast milk) viral load
- Low maternal CD4+ cell count
- Breast infections (mastitis, abscess)
- Mixed breast-bottle (in settings where formula NOT AFSS)

Breastfeeding and HIV Transmission

Miotti JAMA 1999; Coutsoudis CID 2004

“Achieving the highest standard of sexual & reproductive health & rights is based on the fundamental human rights of all individuals to:

- Have their bodily integrity, privacy, and personal autonomy respected
- Freely define their own sexuality
- Decide whether and when to be sexually active
- Choose their sexual partners
- Have safe and pleasurable sexual experiences
- Decide whether, when, and whom to marry
- Decide whether, when, and by what means to have a child or children, and how many children to have.”

Access over their lifetimes to the information, resources, services, and support necessary to achieve all the above, free from discrimination, coercion, exploitation, and violence.”

How effective are ARVs at preventing breast milk transmission?

- Kesho Bora RCT: triple ARV in pregnancy through weaning vs. AZT in pregnancy + SD-NVP in labor
  - 1 week postpartum AZT/3TC to women who got SD-NVP
  - Infants SD-NVP at birth and 1 week AZT
  - HIV transmission @ 12 months: 5.4 vs. 9.5%
- PROMOTE Pregnant Women & Infant Trial: RCT
  - AZT/3TC + LPV vs. EFV in pregnancy-1 yr BF
  - N=389; 2 cases infant HIV (1 in-utero, 1 BF) both in LPV arm
  - 1 case BF transmission: woman with VL <400 within month of transmission

Kesho Bora. Lancet 2011; Cohan AIDS 2015
Breastmilk-ARV pharmacokinetics

- Breastmilk:maternal plasma ratio (BM:MP)
  - NRTI: 0.89-1.21 (14 studies, 1159 paired samples)
  - NNRTI: 0.71-0.94 (17 studies, 965 paired samples)
  - PI: 0.17-0.21 (8 studies, 477 paired samples)
- Estimated infant BF levels compared to Peds treatment doses
  - 3TC: 8.4% (95% CI 1.9-15.0)
  - NVP: 12.5% (95% CI 2.6-22.3)
  - EFV: 1.1% (95% CI 0-3.6)

Waitt, J Antimicrob Chemother 2015

Contraceptive Failure (1st year)

- Sterilization
- Implantation
- LNG IUS
- CopperT
- DMPSA
- Ring
- Patch
- OCP
- Diaphragm
- Condoms
- Withdrawal

Efficacy driven by frequency of method

- Permanent: sterilization
- Every 10 years: Copper T IUD
- Every 5 years: Mirena IUD
- Every 3 years: Nexplanon or Skyla IUD
- Every 3 Months: DMPA
- Monthly: vaginal ring
- Weekly: patch
- Daily: pill, natural family planning (NFP)
- Episodic: barrier methods, NFP

Adapted from J. Trussell Glob. Libr. Women's Med 2011

CONTRACEPTION
Hormonal Contraception & ART

<table>
<thead>
<tr>
<th></th>
<th>Combo hormones/POP</th>
<th>Implant</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LNG AUC ↓58-83%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPA AUC ↓64%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>?/AUC ↓25-48%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NE/AUC ↓14-34%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

★ Pregnancy and implants: 12-15% EFV vs. 0% non-E芙 (n=570, n=57)

Perry AIDS 2014; Scarsi CID 2016

Timing of postpartum contraception

- Implant, DMPA, progesterone-only pills: anytime
- IUD: within 10 minutes of placental delivery (vaginal or cesarean) or after ~4-6 weeks
- Estrogen-containing method (COC pills, patch, ring): wait at least 3 weeks b/c hypercoagulability
  - wait 6 weeks if BMI 30+, smoker, 35+y0, cesarean, PPH, immobility, PreEclampsia

Cytologic methods

- Cytology alone
  - Conventional Pap
  - Liquid-based cytology
- Cytology/HPV co-testing
- NOT recommended in setting of HIV
  - Primary HPV testing
LIQUID BASED CYTOLOGY (LBC)

Conventional vs. Liquid-based cytology
(I am not endorsing ThinPrep.)

Cytology reliable (enough)
- HIV Epidemiology Research (HER) Study
- 189 with HIV vs. 95 without HIV
- 2x/year x 6 year follow-up (1993-99): conventional pap, colposcopy, biopsy
- Any CIN: 14.3% vs. 1.2% (p<.01)
- Discordant pap/biopsy
  - Any HPV: aOR 3.1 (1.0-9.8)
  - CD4 < 500: aOR 6.5 (1.5-29.2)
- 19 HIV+ with normal pap and CIN
  - 18 abnormal pap within 1 yr of discordant results

Anderson CID 2006

Conventional vs. Liquid-based cytology
- France, 2008-12, changed to LBC in Sept 2009
  - 277 conventional (n=216); 268 LBC (n=210); all HIV+ patients
  - Unblinded to method, blinded to 1st read
  - Agreement between 2 readers
    - Conventional: 79 abnl, 10 unsatis; 78% (kappa 0.69)
    - LBC: 123 abnl, 2 unsatis; 84% (kappa 0.82)
- Baltimore, 2000-01, changed to LBC (n=358 HIV+)
  - 209 conventional; 490 LBC
    - LSIL+: 24% conventional, 23% LBC
    - ASC-US: 15% conventional, 9% LBC
  - LSIL +/- biopsy: 29% conventional, 65% LBC

Heard Cytopathology 2015; Swierczynski Acta Cytol 2004
AGE-BASED SCREENING ALGORITHMS

Cervical CA screening < 30 yo

<table>
<thead>
<tr>
<th></th>
<th>CYTOLOGY/HPV co-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>@ HIV dx</td>
</tr>
<tr>
<td>Method</td>
<td>CYTOLOGY (conventional or liquid-based)</td>
</tr>
<tr>
<td></td>
<td>HPV co-testing NOT recommended</td>
</tr>
<tr>
<td>Initial</td>
<td>Q12 months</td>
</tr>
<tr>
<td></td>
<td>?Q6 mos x 2 in 1st yr (CIII)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>3 normal, consecutive (\rightarrow) Q3 yr</td>
</tr>
<tr>
<td>Stop</td>
<td>Stop if hysterectomy for benign dz</td>
</tr>
<tr>
<td></td>
<td>Continue if hysterectomy and hx of CIN 2/3, adenoCA-in-situ, cervical CA</td>
</tr>
</tbody>
</table>

Cervical CA screening 30+ yo

<table>
<thead>
<tr>
<th>CYTOLOGY ALONE</th>
<th>CYTOLOGY/HPV co-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>@ HIV dx</td>
</tr>
<tr>
<td>Method</td>
<td>CYTOLOGY (conventional or LBC)</td>
</tr>
<tr>
<td></td>
<td>(if ASC-US on LBC, ± reflex HPV)</td>
</tr>
<tr>
<td>Initial f/u</td>
<td>Q12 months</td>
</tr>
<tr>
<td></td>
<td>?Q6 mos x 2 in 1st yr (CIII)</td>
</tr>
<tr>
<td></td>
<td>If ASC-US/HPV (\rightarrow) pap in 6-12m or co-test in 12m</td>
</tr>
<tr>
<td>Follow-up</td>
<td>3 normal, consecutive (\rightarrow) Q3yr</td>
</tr>
<tr>
<td></td>
<td>ASC-US or repeat (\rightarrow) colpo</td>
</tr>
<tr>
<td>Stop</td>
<td>No age cut-off (vs. 65 yr old among for HIV-neg)</td>
</tr>
<tr>
<td></td>
<td>Stop if hysterectomy for benign dz</td>
</tr>
<tr>
<td></td>
<td>Continue if hysterectomy (CIN 2/3, adenoCIS, cervical CA)</td>
</tr>
</tbody>
</table>
Differences based on HIV

- Initiation: no screening < 21yo (HIV-) vs. w/in 1 yr sex debut if <21yo (HIV+)
- Frequency:
  - <30 yr old: q3 yrs (HIV-) vs. annual x 3 (HIV+)
  - 30+ yr old:
    - cytology q3 yrs (HIV-) vs. annual x 3 (HIV+)
    - cytology/HPV co-testing q6ys (HIV-) vs. q3ys (HIV+)
- Stopping: 65 yo (HIV-) vs. no age-limit
- Management of abnormal results:
  - <25yo ASC-US/HPV
    - cytology 12/24m (HIV-) vs. colpo (HIV+)
  - ASC-US/unknown HPV
    - cytology 12m (HIV-) vs. 6/12m (HIV+)
    - <25yo LSIL
      - cytology 12/24m (HIV-) vs. colpo (HIV+)

Less intensive screening if CD4>500?

- Kaiser nested case-control
- 1996-2014, incident CIN2, CIN3, or cervical cancer
- 5:1 match, 20,146 cases, 100,780 controls (n=115 HIV+)
  - CIN 2+ (n=20,146)
    - HIV: OR 2.0
      - CD4 < 200: OR 5.7
      - CD4 200-499: OR 3.0
      - No difference CD4 500+ vs. HIV-uninfected (OR 0.8)
  - CIN 3+ (n=11,275)
    - HIV: OR 2.3
      - CD4 < 200: OR 4.5
      - CD4 200-499: OR 3.6
      - No difference CD4 500+ vs. HIV-uninfected (OR 0.8)

Silverberg CROI 2016

Indications for colposcopy among women living with HIV

- ASC-US with + reflex HPV
  - If HPV unavailable: cytology at 6 & 12 months
  - If ASC-US+ on follow-up → colposcopy
- LSIL
- ASC-H
- AGC
- HSIL

Silverberg CROI 2016
TREATMENT FOR CERVICAL DYSPLASIA

Treatment

- CIN 2 or 3
  - Satisfactory colpo, negative endocervical curettage (ECC)
    - Ablation (cryotherapy, laser)
    - Excision (LEEP, laser, cold-knife cone)
  - Unsatisfactory colpo, + ECC
    - Excision (some only offer cone to get clean margin)

- Recurrent CIN 2/3 → excision
- Hysterectomy: consider if recurrent/persistent CIN 3

PREVENTION OF HPV
HPV vaccines

• 3 FDA-approved HPV vaccines
  – Bivalent: HPV 16, 18
  – Quadrivalent: HPV 6, 11, 16, 18
  – 9-valent: HPV-6, 11, 16, 18, 31, 33, 45, 52, 58
  • Vax with 9-valent if prior bi/quad vax?
• Age cut-off for PLHIV? Oct 2018: FDA approved through 45 yo

• Among those with HIV:
  – Safe
  – Immunogenic
  – ♪ titer: HIV-infection (vs. not); detectable VL: clinical significance?
  – Seroconversion ♪ CD4 < 200

• New recommendations up to 45yo relevant for WLHIV?

Kojic CID 2014; Money Vaccine 2016; Kahn CID 2013; Weinberg JD 2012
Anal disease and HIV in 2019

Medical Management of AIDS
December 13, 2019

Joel Palefsky
Department of Medicine
University of California, San Francisco

Outline
- Scope of the problem
- What's new in primary prevention
- What's new in secondary prevention- status of screening approaches

Disclosures
- Merck and Co- research and travel support
- Vir Biotechnologies- consultant, stock options
- Janssen- invited speaker
- Vacitech- consultant
- Virion Therapeutics- consultant, stock options
- Antiva Biosciences- research grant support and travel support

Cervical cancer
Incidence per 100,000

Cervical cancer

People living with HIV/AIDS are living into older ages
- In 2015 it was estimated that over half of people living with HIV/AIDS (PLWHA) in the U.S. were over the age of 50 years
- The 2011 CDC HIV Surveillance report estimates that over 311,000 PLWHA were over 50 years old in 2012

PLWHA may be aging prematurely

- Several illnesses associated with advanced age are now common among HIV-infected individuals receiving ART
- Cardiovascular disease (CVD), liver disease, renal disease, diabetes
- Neurocognitive decline and a number of cancers

The future of HPV-related cancer in HIV-infected men and women

<table>
<thead>
<tr>
<th>Increased incidence of cancer</th>
<th>Decreased incidence of cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing age</td>
<td>Possibly</td>
</tr>
<tr>
<td>Accelerated biological aging</td>
<td>Possibly</td>
</tr>
<tr>
<td>Lower current CD4 count</td>
<td>Likely</td>
</tr>
<tr>
<td>Earlier initiation of ART</td>
<td>Possibly</td>
</tr>
<tr>
<td>Testing for and removal of HPV</td>
<td>Definitely (concurrent)</td>
</tr>
<tr>
<td>HPV vaccination</td>
<td>Likely in the future</td>
</tr>
</tbody>
</table>


Incidence/100,000 (85% CI)

- HIV-infected
  - MSM: 131 (109-157)
  - MSW: 46 (25-77)
  - Women: 30 (17-50)

Silverberg M et al. CID 2012; 54:1026-34

Recent trends in anal cancer incidence
AIDS and cancer registry match study

Colon Lopez V. et al J Clin Oncol 2018; 36:68-75
Future indicators: prevalence of AIN among MSM
Population-based data

<table>
<thead>
<tr>
<th></th>
<th>Prevalence, %</th>
<th>HIV-negative participants</th>
<th>HIV-positive participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>22</td>
<td>30</td>
<td>35</td>
</tr>
<tr>
<td>HIV-negative</td>
<td>17</td>
<td>30</td>
<td>32</td>
</tr>
<tr>
<td>HIV-positive</td>
<td>37</td>
<td>40</td>
<td>43</td>
</tr>
</tbody>
</table>

High prevalence of anal HSIL in HIV+ women

- AMC-084- 27% of HIV+ women

The nonavalent HPV vaccine

New ACIP recommendations for HPV vaccine

- For males and females: two injections at least 6 months apart if starting at age 14 or less
- May begin at 9, target 11-12, up to 26 years
- Three injections at 0,1-2 and 6 months if:
  - 15 or older
  - HIV-positive or otherwise immunosuppressed
  - Up to age 45 after discussion with provider
- One dose under investigation!
HPV vaccination among HIV+ MSM >27 years
ACTG 5298

- No efficacy against anal HSIL or HPV


AMC-072
HPV vaccination among HIV+ MSM 18-26 years

- 34% had HSIL at screening
- 23/47/47/63% of participants were naïve at baseline to HPV 6/11/16/18, respectively
- There were no cases of incident qHPV-associated anal HSIL among naïve men

J. Palefsky, personal communication

Secondary prevention
Screening for anal cancer

Anal cytology screening for ASIL

Screen
- Normal
- ASCUS
- LSIL
- HSIL

Repeat in 12 months (HIV+)
Repeat in 2-3 years (HIV-)

Anoscopy with biopsy
- No lesion seen
- LSIL
- HSIL
- Treat or follow
- Treat

High resolution anoscopy (HRA)

HRA is an office-based procedure examining the anus, anal canal and perianus using a colposcope or operating microscope with 5% acetic acid and Lugol’s solution.

Who should be screened?

- All HIV-positive men regardless of sexual orientation
- All HIV-negative MSM
- Women with high-grade cervical or vulvar lesions or cancer
- All HIV+ women
- All men and women with perianal condyloma
- Solid organ transplant recipients
- Over 25 years if immunosuppressed, inc. HIV
- Over 40 years if immunocompetent

Digital anorectal exam (DARE!)

Challenges of anal cancer screening

- Limited sensitivity of anal cytology
- May be better in HIV+, others?
- Other diagnostic approaches
  - HPV testing
    - Better sensitivity than cytology
    - Lower specificity and PPV
HPV testing for anal screening

<table>
<thead>
<tr>
<th>Cytology</th>
<th>HPV result comparison</th>
<th>Absolute risk (%)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal ASC-US</td>
<td>16+ vs. 16-</td>
<td>10.7 vs. 6.6</td>
<td>6.9 (1.3 to 37.5)</td>
</tr>
<tr>
<td>LSIL</td>
<td>16+ vs. 16-</td>
<td>25.2 vs. 9.8</td>
<td>3.3 (1.8 to 5.9)</td>
</tr>
<tr>
<td>LSIL</td>
<td>16- vs. 16+</td>
<td>30.4 vs. 11.8</td>
<td>2.8 (1.6 to 4.9)</td>
</tr>
</tbody>
</table>

Treatment of HSIL
- Prevention of anal cancer
- Relief of symptoms

Choice of treatment
- Location internal or external
- Size of the lesion or volume of disease
- Type of lesion: LSIL or HSIL
- Patient preference and tolerance

Treatment of anal HSIL
- Challenging due to multifocal nature, size of lesions
- Multiple procedures often needed
- High recurrence rate and incidence of new lesions
- Therapy is primarily ablative
  - infra-red coagulation/hyfrecation
  - 85% trichloroacetic acid
**Screening for anal cancer**

**Yes or no?**

**IDSA**
Oct 5, 2019

Joel Palefsky
Department of Medicine
University of California, San Francisco

---

**Does screening for anal cancer and its precursors meet current screening standards?**

- Dobrow MJ et al. CMAJ 2018 April 9;190:E422-9.

---

**IRC and electrocautery ablation in HIV+ MSM**

* No statistically significant differences


<table>
<thead>
<tr>
<th></th>
<th>Infra-red coagulation</th>
<th>Electrocautery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>68</td>
<td>132</td>
</tr>
<tr>
<td>Number of lesions treated</td>
<td>165</td>
<td>375</td>
</tr>
<tr>
<td>% lesions gone after 1 treatment</td>
<td>72%</td>
<td>75%</td>
</tr>
<tr>
<td>% with metachronous lesions</td>
<td>59%</td>
<td>49%</td>
</tr>
</tbody>
</table>

---

**AMC 076: RCT of IRC**

- 121 participants
- CR for IRC and control arms was 63% and 27%, respectively, for a risk difference of 37% (95% CI: 18-53%, p<0.001)
- Any response (CR or PR) was 75% and 43%, respectively for a risk difference of 32% (95% CI: 13-49%, p<0.001)

• Incidence of anal cancer is high in well-defined at-risk populations
• Treatment of cervical HSIL is proven to reduce the incidence of cervical cancer
• Treating anal HSIL will therefore reduce the incidence of anal cancer and so we should be screening for anal HSIL

#10 “...overall benefit of the screening program outweighs its potential harms”

• Anal and cervical HSIL are very similar—treatment should work: Here’s why not:
  • In many at-risk people lesions are large and multifocal
  • Clinicians may miss lesions
  • Clinicians may inadequately treat lesions
  • New lesions often arise—anal whack-a-mole!

Here’s why not

• Primary aim: To determine whether treating anal high-grade squamous intraepithelial lesions (HSIL) is effective in reducing the incidence of anal cancer in HIV-infected men and women

ANCHOR study

NCI UM1CA121947 and OAR
Screen >17,385
Enroll 5,085
Retain for 5 or more years

ANCHOR study as of 11/25/19
- Screened: 8926
- Enrolled: 3587
- Call 415-353-7443
- 844-HIV-BUTT
- www-anchorstudy.org

Until ANCHOR results are available:
- Refer eligible patients to ANCHOR
- For patients ineligible or not interested in ANCHOR: screen with cytology or HPV and refer for HRA

Elimination of cervical cancer as a public health problem is a flagship project of WHO.

In May 2018, the Director-General of the World Health Organization announced a global call to action towards the elimination of cervical cancer, underscoring renewed political will to make elimination a reality, and called for all stakeholders to unite behind this common goal.
Summary

- Anal cancer is increasing in general population, remains high in HIV+ population
  - In the long run we can probably eliminate anal cancer
- The HPV vaccine is highly efficacious and is an Important tool to prevent anal cancer
  - Vaccinate age 26 and under!
  - After age 26= individual decision

Summary

- Anal HSIL can be sought and treated in an effort to reduce the risk of anal cancer
  - Treatment can be challenging and efficacy not yet demonstrated

......we’re getting there!
Introduction to ARV Drug Resistance
New Clinicians’ Workshop
Medical Management of HIV and Hepatitis
December 2019
Susa Coffey, MD
Division of HIV, ID and Global Medicine

Disclosures
I have no disclosures

ARS Question
Which resistance test do you order for ART-naive patients?

1. Standard genotype (RT and PR)
2. Standard phenotype (RT and PR)
3. Genotype + phenotype (RT and PR)
4. Integrase phenotype
5. RT/PR/IN genotype

Introduction
What this is:
▪ For new clinicians (not experts)
▪ Focus on
  ▪ Currently-used ARVs
  ▪ Common resistance scenarios
  ▪ Genotype tests
  ▪ Approaches to interpreting R test results (with strategies for each class)
▪ Proviral DNA genotype: a few words
Background: Mechanisms of HIV Drug Resistance

- High rate of HIV replication: $10^9$ virions per day
- Many mutations and quasi species
  - Reverse transcriptase (RT): error-prone, no copyediting
- In setting of drug pressure with viral replication, selection of resistant viruses
  - Inadequate adherence to ART
  - Wrong ARVs (potency), wrong doses (drug levels), drug-drug interactions, absorption issues, etc.
  - (Corollary: in absence of drug pressure, possible "disappearance" of mutations [minority populations])

Bottom Line: Assume that once there, always there (archived resistance)

Mechanisms of HIV Drug Resistance

- Mutations may decrease susceptibility to ARVs, and cause or contribute to virologic failure
  - (a few mutations may increase susceptibility)
- Some mutations may impair viral fitness
- Some single mutations severely impact certain ARVs (e.g., M184I/V)
- In some cases, several mutations are needed to cause significant resistance, esp. with NRTIs and PIs (e.g., TAMs)
- Cross-resistance within an ARV class is common

When to do Resistance Test: DHHS Recommendations

- Before ART -- at first visit (as close to the time of infection as possible)
  - Resistance mutations more likely to be detected earlier in the course of HIV infection
  - Genotype (GT): RT, PR; IN if concern for transmitted INSTI resistance
- Virologic failure -- do while on failing ARVs or shortly after ARVs are stopped (w/in 4 weeks)
  - GT for 1st or 2nd ART, add phenotype (PT) if "known or suspected complex drug resistance pattern"
  - IN GT if virologic failure on INSTI
- Suboptimal virologic response on ART
- Pregnancy

Case: Transmitted Drug Resistance

- 31 yo man with new diagnosis of HIV, chronicity unknown (no previous HIV test)
- CD4: 525, HIV RNA: 93,000 c/mL
- GT: RT - M41L, K103N; PR - L63P

Genotypic analysis of samples from newly diagnosed patients in CDC National HIV Surveillance System (N = 12,668)


Genotype Test

- Standard GT examines RT and PR
- For IN, must order special test
- With GT, often possible to predict/anticipate resistance depending on the specific mutations, but is not a direct measure of resistance

Phenotype Test

- Measures inhibition of viral replication by individual ARVs in vitro
- IC\(_{50}\) = concentration of drug required to inhibit viral replication by 50%
- Compares patient virus IC\(_{50}\) to that of a reference strain, -> fold-change in IC\(_{50}\) relative to the reference strain
  
  $$ FC = \frac{IC_{50}_{\text{patient}}}{IC_{50}_{\text{reference}}} $$
**Limitations of GT and PT**

- Conventional tests reliably detect mutant virus that comprises about 20% of the circulating viral quasispecies
- May miss minority populations
- HIV RNA must be >500-1,000 c/mL
- Do not assess interaction of ARVs

**NRTI Resistance**

- A number of key mutations for 3TC/FTC, TDF/TAF, ABC; + numerous others
- Some *single* mutations severely impact viral replication, but in other cases *several* mutations usually required for high-level resistance
  - (more = worse)

**NRTI Strategy:**
- Know key mutations (*M184V, K65R, TAMs*)
- Look up others

**NRTI Resistance: M184I/V**

- Selected by 3TC, FTC (sometimes ABC), cause resistance to 3TC, FTC
- Very common -- 3TC/FTC have low genetic barrier to resistance
- Cross resistance: decreases susceptibility to ABC, ddI (especially if TAMs)
- *Increases* susceptibility to TDF/TAF, AZT, d4T
  - Partially restores activity if TAMs present
- Decreases viral fitness
### NRTI Resistance: K65R

- Selected by TDF/TAF, ABC, ddI
- Causes resistance to TDF/TAF, all other NRTIs except AZT
- Increases susceptibility to AZT
- Decreases viral fitness

### NRTI Resistance: TAMs (thymidine-associated mutations)

- Selected by AZT, d4T
- Decrease susceptibility to AZT, d4T, TDF/TAF, ABC; to all NRTIs if numerous
- Cross resistance: increases with increasing number of TAMs
  - (more = worse)
- 2 pathways:
  - M41L, L210W, T215Y (more resistance; incl. more impact on TDF)
  - D67N, K70R, T215F, K219Q/E

### NRTI Resistance: L74V/I

- Selected by ABC and ddI
  - (L74V sometimes selected by TDF)
- Resistance to ABC and ddI
- Increases susceptibility to TDF/TAF, AZT

### Case 1: PrEP Failure

- 31 yo MSM on PrEP (TDF/FTC, Truvada), presents to clinic after absence of 6 months, reports spotty adherence to his PrEP, but continues to take.
- HIV Ab+, HIV RNA 65,000 c/mL
- HIV genotype: RT - K65R, M184V; PR - WT, IN - WT

### NRTI Strategy:

- Know key mutations (M184V, K65R, TAMs)
- Look up others
Case 2: Audience Response
Which ART regimen would be most likely to be effective?
1. Rilpivirine (RPV)/TAF/FTC (Odefsey)
2. Dolutegravir (DTG)/ABC/3TC (Triumeq)
3. Bictegravir (BIC)/TAF/FTC (Biktarvy)
4. Darunavir (DRV)/cobi/TAF/FTC (Symtuza) + DTG (Tivicay)

RT - K65R, M184V
PR - WT
IN - WT

Bottom Line: need 3 active ARVs, if possible (especially if ARVs have low genetic barrier to resistance).

NNRTI Resistance
- Several single mutations confer high-level resistance to certain NNRTIs; numerous others contribute to resistance
- Low genetic barrier to resistance (except etravirine, doravirine)
- Cross resistance is common

NNRTI Strategy:
• Know 3-4 key mutations (K103N, Y181///, E138K [V106])
• Look up others
• Be aware of mutation scoring system for etravirine (ETR)
• Be cautious about doravirine (DOR) – little is known

NNRTI Resistance: Important Mutations
- **K103N**
  - Commonly selected by EFV
  - Emerges early in VF (low genetic barrier to resistance)
  - Commonly transmitted
  - Resistance to EFV, NVP
  - By itself, does not decrease susceptibility to ETR, RPV, DOR
- **Y181I/V/C/F/G/S**
  - Selected by NNRTIs
  - Cross resistance to all NNRTIs (except DOR?)
- **E138K**
  - Selected by rilpivirine (RPV)
  - Usually occurs with M184I or M184V; this enhances resistance to RPV
  - Resistance to RPV, cross resistance to EFV, ETR, 7DOR
- **V106I/TV**
  - Frequently seen after DOR failure, with other mutations

Doravirine
- In vitro, active against common NNRTI resistance mutations (incl K103N, E138K, Y181C, G190A)
- In vivo, emergent resistance:
  - Treatment-naïve trials: V106I, Y188L, H22Y, P225H, F227C
  - ALSO NNRTI resistance mutations – eg, M184V, K65R, M41L
  - Switch study (DRIVE-SHIFT): none
- NO clinical data in salvage settings
Case 2: NNRTI Resistance

- 53 yo man with VF years ago on EFV + ABC/3TC (Epzicom), now on dolutegravir + TAF/3TC (Descovy); VL <40 c/mL x 1 year. He complains of significant weight gain and wants to change ARVs.
- Previous GT (after stopping EFV + ABC/3TC):

| Virus      | Resistance
genotype |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>RT</td>
<td>Yes</td>
</tr>
<tr>
<td>PR</td>
<td>No</td>
</tr>
<tr>
<td>NNRTI</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Could we use rilpivirine (or doravirine) + 2 NRTIs as his next ART regimen?**

- K103N alone should not affect RPV, DOR, or ETR

**Issues:**
- Accuracy of GT?
- Mutations may fade from view with time and removal of selective drug pressure
- GT captures strains that comprise >5-20% of the circulating viruses
- Once there, always there: “archived” mutations

**Bottom Line:** caution in interpreting GTs – consider what may be hidden from view

Case 3: 1st ART Failure

- 35 yo woman on RPV/TAF/FTC (Odefsey). HIV RNA suppressed x 2 years, then increases to >5,000 c/mL in setting of several months of OTC PPI use.
- Genotype:
  - PR: no mutations

Case 3: Audience Response

Could you use etravirine (ETR) or doravirine (DOR) in her next regimen?

1. Yes – should have full activity
2. No – not effective after rilpivirine failure
3. I need more information

**NNRTI Strategy:**
- Know several key mutations (K103N, Y181\\/\, E138K, V106\)
- Look up others
- Mutation scoring system for ETR
- Caution re DOR – little is known

RT: K101E, E138K, Y181C, M184I
PR: none
**Etravirine Resistance**

### Mutation Weight Factor

<table>
<thead>
<tr>
<th>Genotypic score</th>
<th>% Responders (DUET trial)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>74.4%</td>
</tr>
<tr>
<td>2.5-3.5</td>
<td>62%</td>
</tr>
<tr>
<td>≥4</td>
<td>38%</td>
</tr>
</tbody>
</table>


**Bottom line:** ETR may not be effective if ETR score >2

---

**INSTI Resistance**

- Raltegravir (RAL) and elvitegravir (EVG) have low-ish barriers to resistance
  - Several possible mutation pathways
  - Different effects on dolutegravir, bictegravir
- Dolutegravir (DTG), bictegravir (BIC) (and cabotegravir (CAB)) primary resistance is rare, not well understood
- Order integrase genotype (not phenotype) = special order
  - Important for predicting sensitivity to DTG, BIC, CAB

---

**Integrase Inhibitor Resistance**

### INSTI Strategy:

- Assume cross-resistance between RAL and EVG
- Recognize Q148/// (most damaging to DTG, BIC, CAB)
- Look up all others
  - (Be very cautious about BIC – little is known)
  - (Concerns re emergent CAB resistance in clinical trials)

---

**Integrase Inhibitor Resistance**

<table>
<thead>
<tr>
<th>Pathway/mutations</th>
<th>Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raltegravir G148H/K/R, G140S/A N155H, E82Q Y143R/H/C</td>
<td>RAL, EVG (for DTG, Q148 + at least one other)</td>
</tr>
<tr>
<td>Elvitegravir E92Q Q148H/K/R, G140S/A T66I</td>
<td>RAL, EVG, low level DTG, BIC</td>
</tr>
<tr>
<td></td>
<td>All INIs (for DTG, Q148 + at least one other)</td>
</tr>
<tr>
<td></td>
<td>EVG</td>
</tr>
<tr>
<td></td>
<td>RAL, EVG</td>
</tr>
</tbody>
</table>

---

Kulkarni R et al, CROI 2013, Abs. 587.
**Integrase Inhibitor Resistance**

**Dolutegravir (DTG)**
- Rare reports of emergent mutations if used in 3-drug regimen for initial therapy
- Various mutations if used as monotherapy
  - Q148H/K/R + others, N155H + others, R263K

**Bictegravir (BIC)**
- No reported emergent mutations if used in 3-drug regimen for initial therapy
- No data for use in salvage therapy

**Cabotegravir (CAB)**
- Few data; resistance mutations incl. Q148R, G140R occurred in Phase 2 and 3 studies

---

**Case 4: INSTI Resistance**

**Will dolutegravir be potent in his salvage regimen?**

1. Yes, these elvitegravir mutations do not affect DTG
2. No, full cross resistance is likely
3. Possibly, if we increase the dose of DTG to 50 mg BID

**IN: G140S, Q148R**

**INSTI Strategy:**
- Assume cross-resistance between RAL and EVG
- Recognize Q148R (most damaging to DTG)
- Look up all others
- Caution re BIC – little is known

---

**Dolutegravir Resistance**

**Viking 3 Study:**
- Virologic response lowest in patients with Q148 + 2 secondary mutations

**Bottom Line:**
- If Q148 + 0 or 1 other mutation, DTG may be effective (with other active ARVs)
- Use BID dosing

---

**Case 4: INSTI Resistance**

- 50 yo man, on ATV/r/TDF/FTC for years, switched to EVG/cobi/TAF/FTC to simplify his ART
- VL remained <40 c/mL x 9 months, then increased to 7,200 c/mL
- GT (incl. integrase) done:
Bictegravir: *in vitro* activity against resistant virus

**PI Resistance**

- **Primary/Major mutations**
  - Emerge first, decrease antiviral effect
- **Secondary/Minor mutations**
  - Emerge later, increase fitness of strains with primary mutations or further decrease antiviral effect
- Specific primary and secondary PI mutations, depending upon PI
- **Accumulation of mutations usually required for high-level resistance**
- Cross resistance is complex

**PI Strategy:**
- Be aware of (but don’t memorize) list of DRV resistance-associated mutations (RAMs)
- Look up all others

**DRV Resistance-Associated Mutations (DRV-RAMs)**

- 11 mutations associated with resistance to DRV:
  - V11I, V32I, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V, L89V
- Once-daily dosing possible if no DRV-RAMS (ODIN study)
- Twice-daily dosing recommended if ≥1 DRV-RAM
- DRV response diminished with ≥2 DRV-RAMS

Cahn et al, AIDS. 2011;25:929-39
Case 5: PI (and other) Resistance

• 48 yo man, reports that he has been on “everything” in the past (except INSTIs), sometimes with poor adherence.

Historic genotype(s):
• PR – L10I, L33F, M36I/M, M46L, I54V, L63S, I64V, V82A

PI Strategy:
• Be aware of DRV RAMs
• Look up all others

Case 5: PI resistance

• Assess PI resistance:
  • Check for DRV resistance-mutations
    - V11I, V32I, L33F, I47V, I50V, I54V/L, T74P, L76V, I84V, L89V
  • One DRV-RAM: L33F -> DRV/r likely to be effective but should be given BID
  • Look up all other mutations

Case 5: Multiclass Resistance, use strategies

• 48 yo man, reports that he has been on “everything” in the past (except INSTIs), sometimes with poor adherence.

Historic genotype(s):
• RT – M41L, D67N, L210W, T215Y, V106I, Y181V
• PR – L10I, L33F, M36I/M, M46L, I54V, L63S, I64V, V82A

Approaching this: be methodical, apply strategies
• NRTI
• NNRTI
• PI
• (IN)

Case 5: Multiclass Resistance (2)

Assess NRTI resistance:
• 4 mutations (all TAMs) - affect TDF/TAF, ABC
• Anything missing?
  • No M184 V/I – why???

Historic genotype(s):
• RT – M41L, D67N, L210W, T215Y, V106I, Y181V
• PR – L10I, L33F, M36I/M, M46L, I54V, L63S, I64V, V82A

NRTI Strategy:
• Know key mutations (M184V, K65R, TAMs)
• Look up others
Case 5: Multiclass Resistance (3)

- **Assess NNRTI resistance:**
  - 2 NNRTI mutations (incl. Y181)
  - ETR score:
    - 4.5
  - DOR: little known (caution: V106I)

- **Historic genotype(s):**
  - PR: L10I, L33F, M36I/M, M46L, I54V, L63S, I64V, V82A

- **NNRTI Strategy:**
  - Know several key mutations (K103N, Y181///, E138K [V106])
  - Look up others
  - Mutation scoring system for ETR
  - Caution re. DOR – little is known

<table>
<thead>
<tr>
<th>ETR Mutation Weight Factor</th>
<th>Mutation</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>V90I</td>
<td>1.0</td>
</tr>
<tr>
<td>0.8</td>
<td>A98G</td>
<td>0.8</td>
</tr>
<tr>
<td>0.7</td>
<td>K101E/H</td>
<td>0.7</td>
</tr>
<tr>
<td>1.3</td>
<td>V106I</td>
<td>1.3</td>
</tr>
<tr>
<td>1.0</td>
<td>E138A</td>
<td>1.0</td>
</tr>
<tr>
<td>1.0</td>
<td>V179F</td>
<td>1.0</td>
</tr>
<tr>
<td>1.0</td>
<td>G190S</td>
<td>1.0</td>
</tr>
<tr>
<td>2.5</td>
<td>L100I</td>
<td>2.5</td>
</tr>
<tr>
<td>1.5</td>
<td>K101P</td>
<td>1.5</td>
</tr>
<tr>
<td>1.0</td>
<td>Y181C</td>
<td>1.0</td>
</tr>
<tr>
<td>3.0</td>
<td>Y181I</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Case 5: Multiclass Resistance (4)

- **Assess PI resistance:**
  - 8 PI mutations (1 DRV mutation)

- **Historic genotype(s):**
  - PR: L10I, L33F, M36I/M, M46L, I54V, L63S, I64V, V82A

- **PI Strategy:**
  - Be aware of list of DRV RAMs
  - Look up all others

Case 5, continued

**Summary:**

- **3-class resistance:**
  - NRTI: 4 mutations (TAMs): M41L, D67N, 210W, T215Y
    - Cross resistance to TDF, ABC
    - No M184V/I but we will assume it is there
  - 3TC/FTC resistance
  - NNRTI: 2 mutations: V106I, Y181V
    - Likely resistance to ETR, DOR
  - PI: 8 mutations (1 DRV RAM)
  - Integrase inhibitors: never exposed
  - What ARVs should we use in the next regimen?
What ARVs should we use in the next regimen?

- Integrase inhibitor?
- Darunavir/r?
- NNRTI?
- NRTIs?
- CCR5 antagonist?

Proviral DNA Genotype

Background:

- Standard resistance test requires plasma HIV RNA of >500-1,000 c/mL.
- Many patients currently on ART with VL <40 may have resistance from previous regimens but have no available resistance tests to guide ART changes (e.g., simplification).
- Can we do resistance testing on archived HIV?

Proviral DNA Genotype

- Amplifies cell-associated HIV-1 proviral DNA from infected cells (PBMCs)
  - Whole blood samples
- Analyzes HIV-1 polymerase region by new generation sequencing technology

Proviral DNA Genotyping – How Accurate?
Proviral DNA Genotyping – How Accurate?

GS.1824: switch to E/c/TAF in persons with M184V/I (only)
N=37

Bottom Line:
• Can be helpful if shows resistance mutations.
• May miss some or all existing resistance mutations: caution re negative results.
• No clinical data.

Resources:
- Stanford HIV Drug Resistance Database
  - http://hivdb.stanford.edu
- IAS-USA HIV Drug Resistance Mutations Figures and User Notes
  - https://www.iasusa.org
- Clinician Consultation Center
  - (800) 933-3413
  - Monday – Friday, 9 a.m. – 8 p.m. EST (Free)
The Clinician Consultation Center is a free telephone advice service for clinicians by clinicians. Receive expert clinical advice on HIV, PrEP, PEP, hepatitis C, substance use and perinatal HIV.

See nccc.ucsf.edu for more information.

- HIV/AIDS Warmline 800-955-6513
- Hepatitis Warmline 844-425-9100
- Substance Use Warmline 800-200-3455

For HIV/AIDs, ARVs, resistance, and co-morbidities.

- Perinatal HIV Hotline 888-698-0875
- PrEPline 855-HIV-PEP
- PEPline 888-464-4012

For pregnant women with HIV at risk for HIV & their infants; management of patients at risk of contracting HIV; occupational & non-occupational exposure management.
Opportunistic Infections and Immune Reconstitution Inflammatory Syndrome
5 Things You Need To Know

Carina Marquez, MD, MPH
Assistant Professor
University of California, San Francisco
Division of HIV, ID, and Global Medicine
Zuckerberg San Francisco General Hospital

Disclosures
• I have no disclosures to report

Key Fact #1: CD4 count correlates with risk of specific OIs in untreated HIV disease

CD4 count correlates with risk of specific OI’s in untreated HIV disease

CD4 Count Category

>500 400 300 200 100 50 0

TB, PCP, PML, Histoplasmosis, Cryptococcosis, Toxoplasmosis, Primary CNS lymphoma, NHL, Kaposis Sarcoma, oropharyngeal candidiasis

CD4 Count

Adapted from Bartlett JG, Galant JE, Pham PA. Medical Management of HIV. 2012
Case #1

44 y/o M with HIV (CD4 94, not on ARVs or prophylaxis) presents with 1 month of progressive SOB, non-productive cough, fevers, night sweats, and weight loss.

• Exam: Afebrile, 90% RA. Diffuse crackles, thrush, bilaterally and mild wheezing.

• Labs: WBC 8.3. LDH 386, BDG>500.

• ABG: 7.44/35/59 on RA

Case #1: continued

ARS: Which is the following is NOT true

A. He should be started on empiric treatment for community acquired pneumonia, TMP/SMX, and prednisone

B. If this patient has a septra allergy you should consider septra desensitization.

C. Pneumocystis carinii causes pneumonia in rats.

D. The specificity of beta d-glucan with PCP is 92%

When to suspect PCP

• Subacute presentation of cough: often present with dry cough, DOE

• CD4 <200
  • >90% of cases occur with CD4<200

• CXR and chest imaging:
  • Diffuse bilateral symmetric infiltrates, seen in 60% of cases
  • HRCT for ground glass (Sensitivity ~100%, specificity 89%)
  • Pneumothorax common, 35% in cystic PCP
  • Lymphadenopathy, cavitations and effusion are NOT common

• Early presentation
  • Hypoxemia with normal CXR (possible in early disease)
  • Desaturation with exertion
PCP: Laboratory Diagnostics

- **No culture system for P. jiroveci**
- **Sensitivity of stained respiratory secretions**
  - Induced sputum: 80-90%
  - BAL: 95-100%
- **Elevated LDH**
  - Sensitivity 83%, specificity 25-85%
- **Beta D Glucan**
  - (1-3) β-D-glucan is a component of the cell wall of most fungi (including P. jiroveci)
  - Sensitivity 92%, specificity 65% for PCP using a cutoff of 80 pg/ml
- **Other fungal causes of positive BDG:** candidiasis, histoplasmosis, cryptococcus
  - Most useful if negative

PCP Treatment

- **TMP-SMX is first-line therapy**
  - **Dosing:**
    - TMP/SMX: 15-20 mg/kg/day divided qd-
    - Usual dose of TMP/SMX for prophylaxis to severe disease aid may switch to PO after clinical improvement
    - Patients who get PCP despite TMP-SMX prophylaxis still require standard dosing
    - Desensitization protocols available for patients with allergy
  - **Steroids within 72 hours in severe disease:** RA PaO2 <70 mm Hg or A-a gradient>35 mm Hg
    - Prednisone 40 mg bid x 5d then
    - Prednisone 40 mg qd x 3d then
    - Prednisone 20 mg qd x 11d
  - **Duration of therapy:** 21 days then start secondary prophylaxis
    - **Adverse effects are common in HIV+ patients**
      - Rash, fever, leukopenia, thrombocytopenia, astenemia, hepatitis, hyperkalemia
      - Try to "treat through" common (non-life threatening) reactions if possible

Alternative Rx for Failure or Toxality

- **Moderate to severe disease (PaO2<70, A-a grad >35):**
  - **Pentamidine (IV)** 4 mg/kg IV daily
    - Historically preferred as the 2nd line agent for severe disease (A-a gradient > 45) because of more efficacy data
    - Serious side effects (irreversible renal and pancreatic islet cell toxicity, orthostatic hypotension, profound hypoglycemia, cytopenias).
  - **Clindamycin (IV):** 600mg Q6h or 900mg Q8h. PO: 450mg Q8h + Primaquine (30mg PO daily, check G6PD)
  - **Mild disease (PaO2 >70, A-a grad<35):**
    - Clindamycin (450 mg q6hr or 600mg q8hr) + primaquine 30mg (base) PO daily
    - Atovaquone 750mg PO BID with food
    - Dapsone 100mg PO daily + TMP 15mg/kg/day PO [3 divided doses]

Back to Case 1

- Started on empiric CTX/doxy + TMP-SMX/prednisone.
- Could not get induced sputum.
- **BAL:**
  - AFB smear and cx neg
  - Bacterial: oral flora
  - **PCP positive**
- After BAL returned: CTX/doxy stopped, TMP-SMX/prednisone continued.
Case #2

37 y/o man with HIV (CD4 28) presents with fever, AMS, and seizure.

ARS: What do you recommend?

A. Brain biopsy
B. Start empiric therapy for toxoplasmosis
C. Start RIPE to treat empirically for TB

Selected Ddx of Space Occupying Lesions in HIV

**Short Differential**

- Toxoplasma gondii
- Primary CNS lymphoma

**Long Differential**

<table>
<thead>
<tr>
<th>Bacterial</th>
<th>Fungal</th>
<th>Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyogenic abscess</td>
<td>Cryptococcoma</td>
<td>Primary CNS lymphoma</td>
</tr>
<tr>
<td>Nocardia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhodococcus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuberculoma/NTM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Parasitic**

- Toxoplasma gondii
- Chagas disease/chagoma

**CNS Toxoplasmosis: Epi and Clinical**

- Occurs at CD4<100, but highest risk if CD<50
- Almost exclusively due to reactivation of latent infection
- Transmission occurs by ingesting oocysts excreted in cat feces (in cat litter or soil) or by ingesting undercooked meat (pork and lamb) or raw shellfish containing tissue cysts
- Subacute presentation over several weeks: HA, fever, behavioral changes, confusion, hemiparesis, seizures, ataxia, CN palsies, diffuse encephalitis.

**CNS Toxoplasmosis: Imaging**

- Lesions are most commonly located in the parietal or frontal lobes and at the corticomedullary junction, basal ganglia, thalamus, and pituitary gland
- Lesions can be single or multiple:
  - Classic finding is ≥2 ring-enhancing lesions with surrounding edema
  - But up to 27%–43% of patients have a single lesion
- In rare cases patients can have diffuse encephalitis with no focal lesions

Source: CID 2002

Source: CID 2002

Source: CID 2002
CNS Toxoplasmosis: Laboratory Diagnosis

- Serum toxo IgG: if negative then virtually excludes infection because <3%–6% of patients with TE have negative IgG
- CSF studies:
  - Chemistry may be normal or show mild increase in protein, lymphocytic pleocytosis, low glucose
  - Toxo CSF PCR: sensitivity only 50% although specificity 96–100%. A negative test does not rule out disease.
  - It is very difficult to distinguish between Toxo and primary CNS lymphoma based on clinical findings alone

CNS Toxoplasmosis: Treatment

- Usually treat empirically based on positive serum IgG
  - Should see radiographic improvement within 2 weeks – if not then consider alternative diagnosis, pursue biopsy to rule out other causes
- First choice regimen: Pyrimethamine plus sulfadiazine plus leucovorin x 6 weeks
  - Then secondary ppx: pyrimethamine plus sulfadiazine plus clindamycin
  - Pyrimethamine: rash, nausea, and bone marrow suppression (can reverse by increasing leucovorin dose)
  - Sulfadiazine: rash, fever, leukopenia, hepatitis, nausea, vomiting, diarrhea, and crystalluria (encourage hydration)
- Alternative regimen (for toxicity or clinical failure)
  - Pyrimethamine free: TMP/SMX alone or Atovaquone+/-sulfadiazine
  - Pyrimethamine plus cldindamycin
  - Other possible regimens listed in CDC guidelines, especially if need IV options
  - Avoid steroids (if possible) if treating empirically because this will treat lymphoma as well

Primary CNS Lymphoma

- Occurs usually at CD4<50, subacute presentation
- Imaging:
  - Lesions can be single or multifocal, or often single
  - Usually enhance homogenously, but can also be rim-enhancing
  - Characteristic finding is to be next to CSF (eg periventricular, meningeal, subependymal)
- CSF findings:
  - Mild elevated protein and pleocytosis
  - EBV PCR: sensitivity >80%, specificity 94–100%

Case #3

- CC: 51 y/o M /w shortness of breath
- HPI:
  - Dyspnea & reduced exercise tolerance x 1 mo
  - Sweats, fevers, 10 lb weight loss x 1-2 mo

36 yo M with AIDS v/p ART (CD4 10, VL 314K) who presented for altered mental status, found to have CNS lymphoma.

CSF: EBV DNA +, Toxo IgG neg
Serum: Toxo IgG neg
Cryptococcal Meningitis

- Most cases occur when CD4<100

- Clinical:
  - Presents as subacute meningitis or meningoencephalitis
  - Can also see encephalopathic signs/sx due to elevated ICP

- Diagnosis:
  - Serum and CSF CrAg are almost always positive
  - CSF studies: lymphocytic pleocytosis or no cells, mildly elevated protein, glucose normal to low, elevated OP
  - Low CSF WBC portends a poorer prognosis

- Induction (14 days):
  - Amphotericin 0.7 mg/kg/d or liposomal amphotericin 3-4 mg/kg/d plus
  - Fluconazole (5-FC) 100mg/kg/d in 4 divided doses

- Consolidation therapy (8 weeks):
  - Fluconazole 400mg PO daily

- Chronic maintenance therapy:
  - Fluconazole 200mg PO daily
  - Consider stopping when CD4>200 and VL suppressed for 6 mo

Cryptococcal Meningitis: Treatment

Cryptococcal Meningitis: Management of Elevated ICP

- Elevated ICP is the leading cause of death from CM in the first 2 wks after diagnosis

- Management strategy:
  - Measure OP at diagnosis (normal is <20 cm H2O)
  - If OP is elevated, daily LPs to remove volume (~20-30cc) that at least decreases OP 50%
  - Aim for at least 1-2 days of stable pressures
  - If symptoms persist or can’t do daily LPs, then consider EVD/lumbar drain
  - VP shunt can be done in the setting of anti-fungals if other measures fail
Key Take Home: Patients with Cryptococcal Meningitis may not have a headache....

47 yo M with CD4 10, VL 1 million p/w fever x months. No headache and normal neuro exam.

Serum CrAg 1:16860
CSF CrAg 1:8000, culture. Cryptococcal neoformans
Dx: Cryptococcoma with cryptococcal meningitis

Case #3 continued

ARS: when do you start antiretroviral therapy?

A. Within 2 weeks
B. 5 weeks from start of anti-fungal therapy
C. 8 weeks from start of anti-fungal therapy

Starting ARVs during an Acute OI

**Advantages**
- Sometimes ARVs are the best treatment for the OI
- PML, cryptosporidiosis, KS, microsporidiosis
- Prevention of a second OI
- Restore pathogen-specific immunity (more rapid clearance of OI)
- Slow HIV progression

**Disadvantages**
- Risk of IRIS (especially if occurs in CNS)

ART Timing in Cryptococcal Meningitis

<table>
<thead>
<tr>
<th>COAT Study, 2013 (trial halted)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cryptococcal Optimal ART Timing (COAT) Study AID</strong></td>
</tr>
<tr>
<td>Study Design (UG+S.Af.)</td>
</tr>
<tr>
<td>CSF sterile (n=88)</td>
</tr>
<tr>
<td>Median CD4+ count (9-69)</td>
</tr>
<tr>
<td>Death CSF WBC &lt; 5 cells/mm³</td>
</tr>
<tr>
<td>HR 2.21 (0.95-5.34)</td>
</tr>
<tr>
<td>COX AIDS</td>
</tr>
</tbody>
</table>
Summary Cryptococcal Meningitis

- DHHS 2019 Guidelines: delay ART 2-10 weeks.
  - Usually delay after 4-5 weeks.
- Patients with <5 CSF WBC have a higher risk of mortality and have more to gain with delayed ART.

When NOT to immediately start ART in the setting of an OI: the Zuckerberg San Francisco General Hospital Experience

- CMV retinitis: We wait 14 days. Limited data.
- Inflammatory CNS lesion: For those who have evidence of brain edema, mass effect, or neurologic deficit we recommend waiting at least 14 days of OI antimicrobial therapy. Data limited.
- Cryptococcal Meningitis
- TB meningitis

Key Fact #2: OIs can be prevented with ART and primary and secondary prophylaxis

Primary Prophylaxis of OIs: The Basics

<table>
<thead>
<tr>
<th>OI</th>
<th>Indications for Primary ppx</th>
<th>Regimen of Choice</th>
<th>Alternative Regimens</th>
<th>When to stop ppx</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCP</td>
<td>CD4&lt;200 or CD4&lt;12% or HIV RNA &gt;100,000 or AIDS defining illness</td>
<td>TMP-SMX 1 DS daily or SS</td>
<td>TMP-SMX 1 DS daily or 1 SS x 3 12.5 mg 3x per week, pyrimethamine + leucovorin</td>
<td>CD4&gt;200 for &gt;3 mos, HIV RNA &lt;40</td>
</tr>
<tr>
<td>Toxoplasma gondii</td>
<td>14 day positive AIDS defining illness</td>
<td>TMP-SMX 1 DS daily</td>
<td>TMP-SMX 1 DS daily or 1 SS x 3 12.5 mg 3x per week, pyrimethamine + leucovorin</td>
<td>CD4&gt;200 for &gt;3 mos, HIV RNA &lt;40</td>
</tr>
<tr>
<td>MAC</td>
<td>CD4&lt;50 and no active MAC</td>
<td>600 mg q4wk</td>
<td>600 mg q4wk, rifabutin</td>
<td>CD4&gt;100 for &gt;3 mos, HIV RNA &lt;40</td>
</tr>
</tbody>
</table>

Primary prophylaxis for MAC no longer recommended for adults who immediately initiate ART.
Why is primary prophylaxis against MAC no longer recommended?

- Prior guidelines recommended starting MAC primary prophylaxis with weekly azithromycin if CD4<50.
- Recommendations based on studies from the pre-ART area
- DHHS OI guidelines 2019 no longer recommend MAC primary prophylaxis
- Benefit not proven in the setting of ART and ART reduces the risk of MAC
- High dose azithromycin has side-effects
- Patients with CD4<50 may have undiagnosed MAC - worry about azithromycin 'monotherapy'
- Are there cases where I do start MAC prophylaxis?
  - Rare, usually when ART deferred for cryptococcal meningitis

One month of Isoniazid and Rifampin Effective in People Living with HIV

- Randomized open-label trial comparing 1 month of daily isoniazid plus rifampin (1HP) to 9 months of isoniazid (9-H) (N=3,000) 1
- Primary outcome: diagnosis of tuberculosis or death from tuberculosis or unknown cause.
  - Effective: 1 month of isoniazid found to be non-inferior
  - Safe: No difference in serious adverse events
  - Improved Adherence: Treatment completion higher in the 1-month group.
- DHHS has not updated its guidelines to include this regimen yet.
- Limitations currently are drug drug interactions, await further data on interactions between dolutegravir and rifapentine.

LTBI/HIV Treatment Options

<table>
<thead>
<tr>
<th>LTBI Regimen</th>
<th>Common DDI with ART</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid x 9 mo +B6</td>
<td></td>
<td>Therapy long</td>
</tr>
<tr>
<td>Rifampin x 4 mo</td>
<td></td>
<td>Check for DDI</td>
</tr>
<tr>
<td>Rifabutin x 4 mo</td>
<td></td>
<td>Check for DDI</td>
</tr>
<tr>
<td>Isoniazid + Rifampin weekly x 3 mo</td>
<td>Only effective or categorize based regimens (1H combination with either abacavir/lamivudine [ABC/3TC] or tenofovir disoproxil fumarate/emtricitabine [TDF/FTC])</td>
<td>Check for DDI, Cannot use with ART</td>
</tr>
</tbody>
</table>


Key Fact #3. Ockham’s Razor does not apply to OIs and AIDS

1. Surveillance NEJM 2019
Case #5

40 yo M, with HIV (last CD4 420 and undetectable VL, one and half years ago, loss to follow-up) presents to urgent care with cachexia, fever, diarrhea (10x a day), and abdominal pain

- PMH:
  - HIV diagnosed 2 years ago, CD4 380 VL 80K.
  - Started on truvada and dolutegravir, suppressed for 6 months, but then lost to follow up

- SH: immigrated from Mexico 20 years ago, marginally housed

- Labs: Hgb 7, CD4 48 (6%), VL 200K, nl LFTs and Cr 1.0

Syndromic Differential Can Help Predict Pathogens in Patients with a CD4<50

- Short DDx: AIDS + Fever + Wasting + LAD
  - Disseminated MAC
  - Tuberculosis
  - Disseminated Fungal (Crypt, Hink, Cocc)
  - Malignancy

- Short DDx: AIDS + Pulmonary Nodules
  - Tuberculosis
  - Kaposi’s Sarcoma
  - Fungal (Cryptococcus, Coccidioidomycosis)
  - Lymphoma

- Short DDx: AIDS+ Chronic Diarrhea
  - Parasites (cryptosporidium, microsporidium)
  - Bacterial (salmonella, shigella), mycobacterial (MAC colitis, TB ileitis)
  - Viral: CMV colitis, Kaposi’s Sarcoma (HHV8)
  - Fungal: histoplasmosis
  - Other: HIV enteropathy

Imaging

Abdominal CT

Bulky mesenteric, retroperitoneal, and paraaortic lymphadenopathy. Non-dilated fluid-filled loops of small bowel and cals suggestive of ileus.

Chest CT

Numerous pulmonary nodules US and RML - largest 1.8cm.

Case 4 (cont.)

- Stool cultures and O&P - giardia ag pos, entamoeba histolytica, cryptosporidium.
- Serum CrAG-negative
- Urine histo Ag-negative
Colonoscopy

Cytopathic changes consistent with CMV

Nucleomegaly and Smudgy chromatin

Colonoscopy

Granulomatous inflammation with AFB

Lung Biopsy- Kaposi’s Sarcoma

Stains for HHV-8

H&E- spindle cells
**Case 4-Final Diagnosis**

1. Disseminated KS: Tongue, skin, colon, and lungs
2. CMV esophagitis and colitis
3. Disseminated MAC – MAC on LN and colon biopsies; blood cultures grew MAC

**When to suspect Mycobacterium Avium Complex**

**Clinical:**
- Fever, weight loss, wasting, +/- diarrhea, +/- abdominal pain

**Laboratory:**
- CD4<50
- Elevated AlkPhos
- Often with anemia or pancytopenia due to bone marrow infiltration

**Diagnostics:**
- AFB Blood Cultures (important to draw prior to given azithromycin)
  - Sensitivity 91% for 1 AFB blood cultures
  - Sensitivity 98% for 2 AFB blood cultures
- CT abdomen often reveals hepatosplenomegally and intrabdominal lymphadenopathy
- May need tissue biopsy

**MAC Treatment: At Least 2 Drugs**

- **Drug 1**
  - Consider a 3rd drug when:
    - High burden of disease
    - Not on ARTs
    - Mortality benefit with 3 drugs vs. 2 drugs, but pre-HAART era

- **Drug 2**
  - Ethambutol
  - Rifabutin
  - Moxifloxacin
  - Levofoxacin
  - Ciprofloxacin
  - Amikacin
  - Streptomycin

- **Drug 3**
  - Clarithro (more data)
  - Or Azithro (better tolerated, less drug interactions)*

- **Drug 4**
  - Ethambutol
  - Rifabutin
  - Moxifloxacin
  - Levofoxacin
  - Ciprofloxacin
  - Amikacin
  - Streptomycin

**CMV and AIDS**

- Usually occurs when CD4<50
- Screening eye exams in patients with CD4<50 recommended
- CMV in AIDS manifests as (in order of frequency):
  - Retinitis (before HAART), 30-40% developed this
  - GI: esophagitis (<5-10%), colitis (5-10%)
  - Neuro: encephalitis, polyradiculomyelopathy
  - Pneumonitis: very rare, usually bystander in BAL and not cause of pulmonary disease

*Dunne CID 2000
**Benson CID 2003

**Diagnostics**
- CMV PCR not helpful, except for in setting of CNS involvement
- Need tissue (aside from ocular disease)
Key Fact #4: There is an increased risk of IRIS with CD4<50-100

Case #5 continued

5 weeks after starting ARVs, the patient was readmitted with new fever to 39.4, CT showed mild increase in size of mediastinal/intra-abdominal nodes.

CD4 went from 46 -> 85, and VL 200 K→ 110

What’s on your ddx?

DDx: Worsening of OI After Starting ARVs

• Immune reconstitution inflammatory syndrome (IRIS)
• Adverse med effect
• Treatment failure (noncompliance, resistance, poor absorption of meds)
• New OI, malignancy, autoimmune process

ARS: Chose the statement that is FALSE

A. NSAIDS can be used to treat mild IRIS
B. Mortality of cryptococcus IRIS is over 20%
C. This patient could have KS IRIS
D. PCP IRIS is common
What is Immune Reconstitution Inflammatory Syndrome (IRIS)?

• Broadly defined as a syndrome of an exaggerated immune response to antigens AFTER starting ARVs

• Usually occurs with infections but can also be malignancy (KS-IRIS).

• Little is known about pathogenesis

2 Types of Immune Reconstitution Inflammatory Syndrome (IRIS)

<table>
<thead>
<tr>
<th>Patient NOT on treatment for OIs</th>
<th>Start ART</th>
<th>Unmasking IRIS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Unmasking: Exaggerated immune response to visible pathogens that were subclinical and not being treated

<table>
<thead>
<tr>
<th>Patient ON treatment for Oil</th>
<th>Start ART</th>
<th>Paradoxical IRIS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Paradoxical: Exaggerated immune response to persistent antigens of an OI that is being treated

Classic IRIS Presentations

<table>
<thead>
<tr>
<th>MAC</th>
<th>Localized Disease (e.g., lymphadenitis, abscesses)</th>
<th>Bacteremia absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mtb</td>
<td>Recurrence of meningitis frequently associated with increased ICP</td>
<td>Cryptococcomas</td>
</tr>
<tr>
<td>TB</td>
<td>Fever, lymphadenitis, cold abscesses, worsening pulmonary disease</td>
<td></td>
</tr>
<tr>
<td>CMV</td>
<td>Immune recovery uveitis; can be sight threatening</td>
<td></td>
</tr>
<tr>
<td>KS</td>
<td>Rapid progression of KS lesion</td>
<td></td>
</tr>
</tbody>
</table>

• PCP-IRIS has been documented, but rare

Example of Paradoxical TB-IRIS

29 yr M with CD4 310, VL 380K with TB ileitis

<table>
<thead>
<tr>
<th>4 weeks after ART start</th>
<th>6 weeks after TB treatment start</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FNA: AFB smear + necrotizing, granulomatous inflammation
IRIS Incidence and Outcome

- Overall incidence of IRIS is ~15-30%
- Risk if starting ARVs at a low CD4 (<50) or high VL (>100K)
- ~5% mortality in IRIS:
  - 3% with TB-IRIS
  - 20% with Cryptococcal Meningitis (CCM)-IRIS, risk highest if CSF WBC<5
- Risk of IRIS may be increased with dolutegravir/INSTI

IRIS: Treatment

- **Step 1:** Optimize or initiate treatment of the OI
- **Step 2:** Supportive and symptom-directed therapy (most cases are self-limiting). Most cases resolve in several weeks.
- **Step 3:** Consider anti-inflammatory therapies
  - NSAIDs for less severe symptoms
  - Corticosteroids most commonly used for moderate to severe disease. Often start prednisone 1mg/kg and taper based on clinical response (dose for TB IRIS).
  - Steroids decrease hospitalization and mortality in TB IRIS
- Make sure there is no evidence of Kaposi Sarcoma, steroids are contraindicated in this case
- **Don’t Stop ART!**

Case #4: Follow-Up

- The patient was started on NSAIDS and symptoms resolved. We avoided steroids because patient had known Kaposi’s Sarcoma.
- Likely paradoxical IRIS
- AFB blood cultures negative
- Two months later, imaging showed improvement in abdominal LAD, and pulmonary lesions.

Key References

- HIV Insite and Ward 86 Management Recommendations: [http://hivinsite.ucsf.edu](http://hivinsite.ucsf.edu)
- AIDS Education and Training Centers’ National Resource Center: [www.aidsetc.org](http://www.aidsetc.org)
I.D. Corner
Vaccine Update – for people with HIV

Lisa Winston, MD
University of California, San Francisco / Zuckerberg San Francisco General

Nothing to disclose....

Topic areas
- Measles
- Hepatitis B
- Meningococcus
- Varicella Zoster
- Human Papilloma Virus
- Pneumococcus

Measles outbreaks

Number of Measles Cases Reported by Year
2001-2019* as of December 1, 2019

- 2019: 1261 cases confirmed in 31 states
- More than 75% of cases linked to outbreaks in NY
- Greatest number of cases reported in the U.S. since 1992 and since measles was declared eliminated in U.S. in 2000
- Most unvaccinated
Thinking about measles vaccine

- One dose: 93% effective
- Two doses: 97% effective
- Presumptive evidence of immunity:
  - Written documentation of adequate vaccination
  - Laboratory evidence of immunity (measles IgG)
  - Previous laboratory confirmation of measles
  - Birth before 1991
- PLWH: MMR can be given so long as CD4 count > 200 cells/µL

Practical approach:
1) Focus on international travelers and known/potentially unvaccinated
2) If there are local cases, check with Public Health

Which vaccine is contraindicated in all PLWH?
A. Japanese encephalitis virus
B. Varicella vaccine for chickenpox (Varivax)
C. Yellow fever vaccine
D. Oral typhoid vaccine (Ty21a)
E. Adjuvanted subunit herpes zoster vaccine (Shingrix)

Hepatitis B vaccine

- Indicated for all PLWH
- In most settings, PLWH have increased risk of exposure to HBV
  - Increased risk of chronic infection after HBV infection
  - Increased risk of reactivation of HBV after development of protective (surface) antibodies
- Protective response to traditional HBV vaccines decreased in PLWH — reported ranges 34% - 89%

New hepatitis B vaccine for adults

HEPLISAV-B
- Recombinant, adjuvanted vaccine
- Contains recombinant hepatitis B surface antigen plus novel adjuvant Cpg 1018 — oligodeoxynucleotide that enhances B cell and T cell responses
- Given as two doses, one month apart
  - Hope for better completion of series
  - Approved for 18 years and older
  - Higher rates of seroprotection (90-95%) compared with Engerix-B
  - No clinical trials specifically evaluating PLWH
New hepatitis B vaccine for adults

Consider HEPLISAV-B with
- Diabetes
- Renal disease
- Immunosuppression
- Obesity
- Older age
- Smokers
- Non-responders

Meningococcal Vaccines - MenACWY

- Two tetravalent protein conjugate vaccines covering strains A, C, Y, W-135
- Menactra: 9 months – 55 years; Menveo – 2 months – 55 years
- Advantages compared to polysaccharide vaccine which is no longer in use
  - Longer lasting antibody titers
  - Good antibody response to revaccination
- Serogroup B not covered by tetravalent vaccines [B, C, and Y circulate in U.S.]

MenACWY vaccine and PLWH

- Since 2016, MenACWY recommended for all people with HIV age 2 months and above
  - 5 – 24 fold increased risk invasive meningococcal disease
  - 2 dose primary series, doses given 8-12 weeks apart
  - Booster dose every 5 years
  - If Menactra will be used, give PCV-13 first and wait at least 4 weeks before MenACWY
    - Possible immune interference with response to PCV-13

Who else should get MenACWY vaccine?

- Clusters in New York City and Southern California among men who have sex with men – vaccine may be recommended before travel
- San Francisco Department of Public Health recommends MenACWY locally for MSM and transgender persons who have sex with men
MenACWY vaccine and PLWH

- Relative risk of disease is striking but absolute increased risk is small (rare disease)
- Vaccine response worse than in those without HIV, even with two doses
- Responses wane relatively quickly
- Risk of disease increases with lower CD4 count – but less likely to respond to vaccine
- Vaccine is safe and well tolerated

Epidemiology meningococcal disease United States

- Incidence of all serogroups has declined
- Decline occurred prior to routine MenACWY vaccine and has continued
- Historically, most cases are sporadic
- Serogroup B now causes an increased proportion of cases in adolescents and young adults

Two meningococcal serogroup B vaccines available in US

- Both approved ages 10-25 years
- MenB-FHbp (Trumenba) approved Oct 2014
  - 2 or 3-dose series (high risk – 3 doses preferred)
  - Contains two recombinant factor H binding protein antigens
  - One from each subfamily A and B
- MenB-4C (Bexsero) approved Jan 2015
  - 2-dose series
  - Contains four components
  - Cover most but not all serogroup B strains
- Not interchangeable
- Not routine for PLWH
Zoster in PLWH

- Pre-ART, risk > 15-fold higher in PLWH
- Risk greater at lower CD4 counts
- Post-ART, risk about 3-fold higher in PLWH
- Risk may be increased in the 6-month period after started ART, potentially related to IRIS


Shingrix study in PLWH

- Phase 1/2a
- 3 cohorts:
  - 94 persons receiving ART, CD4 ≥ 200 cells/mm³
  - 14 persons receiving ART, CD4 50 – 199 cells/mm³
  - 15 persons ART naïve, CD4 ≥ 500 cells/mm³
- 3 doses given at 0, 2, 6 months
- Vaccine immunogenic and no serious adverse events

1 Infect Dis 2015;211(8):1279-87
Zoster Vaccine Recombinant (Shingrix)

- FDA approved 10/20/17
- Contains recombinant glycoprotein E plus a novel adjuvant (AS01B)
- Given as two doses, 2 to 6 months apart
- Recommended as a routine vaccine for ages 50 and older
- Still give if history of zoster
- Revaccinate those who received Zostavax – has been studied after 5 years, wait at least 2 months
- No need to screen for history of chickenpox or do laboratory testing

HPV in PLWH

- Cervical intraepithelial neoplasia rate 4-5x higher in women and girls with HIV
- Persistent infection with HPV is more likely
- Based on data from 1990s to early 2000s
- In MSM with HIV compared to MSM without HIV, HPV prevalence in anal canal higher, prevalence high risk types higher, and anal intraepithelial neoplasia more likely
- Anal cancer incidence estimated to be at least 2X higher
- HPV is a risk factor for anal intraepithelial neoplasia in women
- Low CD4 count risk factor for intraepithelial neoplasia
- Studies on effect of ART inconsistent

Human Papillomavirus (HPV) Vaccines

- Genital HPV most common sexually transmitted infection in the U.S.
- Nine-valent HPV vaccine (Gardasil)
  - Quadrivalent vaccine phased out in 2016
- Bivalent vaccine (Cervarix) no longer marketed in U.S.
- All HPV vaccines protect against types 16 & 18 - associated with 66% cervical cancer
- HPV 16 most commonly linked to anal cancer
- Types 6 & 11 associated with 80% genital warts

https://www.cdc.gov/vaccines/vpd/shingles/hcp/shingrix/recommendations.html
https://www.cdc.gov/mmwr/volumes/67/wr/mm6703a5.htm

Zoster Vaccine Recombinant (Shingrix)

- Indicated with chronic medical conditions and low dose immunosuppressive therapy, e.g. < 20 mg prednisone
- No current recommendations for other immunocompromise – pending OI guidelines recommend administration to PLWH >50 years with 2-dose schedule
- Shortage due to high demand
- Side effects: adverse events (AEs) are common
  - Most people (78%) have some pain at injection site
  - Systemic AEs include myalgia, fatigue, headache, and fever
  - 1 in 6 people have AEs that interfere with daily activities
  - Somewhat fewer AEs in those 70 and older

https://www.cdc.gov/vaccines/vpd/shingles/hcp/shingrix/recommendations.html
https://www.cdc.gov/mmwr/volumes/67/wr/mm6703a5.htm
Nine-valent HPV vaccine

- Protects against 6, 11, 16, 18 plus 31, 33, 45, 52, 58 (high risk types for cervical cancer)
  - ~ 97% reduction in cervical, vaginal, vulvar pre-cancers due to types 31, 33, 45, 52, 58 compared with quadrivalent vaccine
  - 5 additional types account for about 20% of cervical cancers

HPV Vaccines Recommendations for Use

- Routine vaccination beginning at age 11-12
- Females: vaccinate through age 26
- Routine vaccination for all males to age 26 - new recommendation in 2019
- Previously to age 21 with exceptions for MSM and PLWH
- Okay to continue series with a different vaccine
- No need to revaccinate with 9-valent vaccine if series previously completed

2019: vaccination for women and men ages 27-45 years based on shared clinical decision making

HPV vaccine: two dose series

- October 2016: ACIP and CDC recommended two-dose HPV series if started before age 15
- 9 – 14 years olds should receive two doses at least 6 months apart
- If started at 15+ years, three doses still needed

HPV Vaccines

- Excellent efficacy in studies (nearly 100%) in preventing infection with HPV types included in vaccine, if not previously infected
- Prevent cervical and anal intraepithelial neoplasia
- Greatest benefit before onset of sexual activity / infection with HPV
- No protection against types with which already infected at time of vaccination
- Some partial cross protection against non-vaccine serotypes
HPV Vaccine: External Genital Lesions

- 4065 healthy men and boys ages 16 – 26
- Randomized, double-blind, placebo controlled study
- 36 external genital lesions in vaccine group, 89 in placebo group (intent to treat efficacy 60%)
- In seronegative group with all doses received, vaccine was 90% effective against genital lesions due to HPV types 6, 11, 16, 18 (mostly 6 and 11)

HPV Vaccines - questions

- Relatively expensive
- Not clear what long-term effect will be on risk of cancer (but promising!)
- No recommendation to change cervical cancer screening based on vaccination status

HPV Vaccines - uptake

- In 2017, 68.6% of girls and 62.6% of boys ages 13 – 17 had received one of more doses of HPV vaccine
  - Lower than coverage with Tdap and MenACWY
  - MMWR 2018;67:909-17

HPV infections due to vaccine types have been dropping even with imperfect uptake, and there is evidence of herd immunity

- Data are not conclusive regarding effectiveness of pneumococcal vaccination in PLWH, but most studies suggest benefit

Pneumococcal disease in PLWH

- PLWH have ~ 35-fold increased risk of invasive pneumococcal disease compared with age-matched controls
  - Based on data from year 2000
  - About half the increased relative risk in 1995
  - Decline attributed to ART
  - Heffernan et al, J Infect Dis 2005

- Data are not conclusive regarding effectiveness of pneumococcal vaccination in PLWH, but most studies suggest benefit
Pneumococcal Vaccines

- Two vaccines are widely used in the U.S.
- Pneumococcal polysaccharide vaccine
  - PPSV-23 (Pneumovax); 23 valent
  - In use since 1983
- Pneumococcal protein conjugate vaccine
  - PCV-13 (Prevnar); 13 valent
  - Recommended for selected adults in U.S. (including PLWH) in 2012
  - Was recommended for everyone 65 and older in 2014
  - In adults, only one-time dose indicated

Pneumococcal 13-Valent Conjugate Vaccine for Adults

- Clinical trial in the Netherlands: 84,496 adults > 65 randomized to PCV13 vs. placebo — (CAPiTA trial)
  - 46% fewer first cases of vaccine type pneumococcal community acquired pneumonia (CAP) - primary outcome
  - 75% fewer first cases vaccine type invasive pneumococcal disease
  - No difference CAP from any cause

Single dose PCV-13 and repeat PPSV-23 five years after first dose (age < 65)

<table>
<thead>
<tr>
<th>Condition</th>
<th>PCV-13 single dose</th>
<th>PPSV-23 single dose</th>
<th>PPSV-23 repeat 5 years after 1st dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickle cell disease</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Aspergillosis</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HIV</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Renal failure</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Leukemia</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hodgkin disease</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Generalized malignancy</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Solid organ transplant</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Other immunosuppression</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

PPSV-23 in adults 65 and older

- Single dose recommended for all
  - Regardless of any prior doses
  - At least 5 years after most recent prior dose
New recommendations for PCV-13

Advisory Committee Immunization Practices (ACIP) meeting June 2019:

“Shared decision making” for adults 65 and older without
immunocompromising conditions

Invasive, vaccine-type pneumococcal disease in adults –
only indirect effects seen:
- 9-fold overall decrease 2000 – 2014 (PCV-7 kids)
- 3-fold decrease 2010 – 2014 (PCV-13 kids)
- No further decrease IPD since 2014
- No further decrease in pneumococcal pneumonia

IPD: invasive pneumococcal disease

Population-Level Impact on IPD

Population-Level Impact on Non-Invasive and Invasive Pneumonia

Key Points:
- No changes in IPD incidence since 2014
- Non-PCV13 serotypes now make up the majority of the disease burden
- For 65 and older (no immunocompromise): wait at least one year before PPSV-23
- Wait at least 8 weeks for persons with immunocompromise
- If PCV-13 and PPSV-23 both planned and PPSV-23 has already been administered
- Wait at least one year before PCV-13
Expanding HIV Testing,
Prevention and Treatment in Jail

Are we equipped to traverse “the last mile”?

A Asa Clemensi-Allen, MD, MAS

About Me

• UCSF
  • Internal Medicine Residency
  • Fellowship in Infectious Diseases
  • Master of Advanced Sciences, Clinical Research

• Director of HIV & Integrated Services,
  • Jail Health Services, San Francisco Department of Public Health

• Assistant Clinical Professor (Volunteer), Div HIV, ID and Global Medicine
  • Ward 86 Positive Health Onsite-program for Unstably-housed Populations (POP UP) program

Disclosures

• No Potential Conflicts of Interest to Disclosure

Clinical Case #1

33 trans-, latinx female, diagnosed with HIV in February, 2018 but remains disconnected from care

• Diagnosis
  • HIV testing performed per request of patient within 4 days of intake of first episode of incarceration
  • Initial CD4 402/HIV VL 80k
  • Initiated ART within 7 days of diagnosis

• Post-Release Follow-Up
  • No outpatient visit since diagnosis
  • Ongoing unstable housing and substance use disorder (amphetamine)
Clinical Case #1
33 trans-, latinx female, diagnosed with HIV in February, 2018 but remains disconnected from care
• Connection to Care
  • 2 incarcerations in the last year were only time she had been on ART
  • Left substance use treatment program following release from jail
• Motivated to connect to care and remain on ART

Clinical Case #2
38 African American male, born and raised in the Bayview neighborhood with new diagnosis of HIV
• Initially refused testing at intake, but accepted after referral from HIV Testing Services
  • Previously tested negative for HIV 8 months ago while in jail
  • Diagnosed and treated for Gonococcal urethritis and late-latent syphilis
  • Untreated HCV
• HIV risk
  • Amphetamine and heroin use (no IVDU) x3 years which started after divorce
  • Sex with women only, but often in the setting of substance use
  • Became homeless in the context of divorce and substance use

Clinical Case #1
33 trans-, latinx female, diagnosed with HIV in February, 2018 but remains disconnected from care
• What services or strategies are available to HIV optimize outcomes for this patient?
Promoting Linkage to Testing and Care

Discussion Outline

- What are the individual and structural barriers to engagement in HIV testing, prevention and care?
- What is the current state of HIV testing and treatment in Jails
- What are the strategies to enhance
  - Reach of HIV Testing
  - Linkage to Prevention Services
  - Retention in Care Among People Living with HIV

Jails v Prisons

- Prison
  - Long-term incarceration for people convicted of a crime
  - Overseen by state and federal governments

- Jails
  - Short-term incarceration for people awaiting charges or convictions
  - run by city, counties

HIV Prevalence In Correctional Settings

- 1.5% - HIV seroprevalence among incarcerated individuals (Beckwith et al. 2010 MMWR)
  - Approximately 3 times greater than among the general U.S. population
  - Approximately 150,000 people living with HIV in jail or prison

- 14-16% - people living with HIV pass through jail (Spaulding et al. 2009 PLOS)
At-Risk for HIV, Disengagement from Care

- Substance Use Disorder
- Homelessness/Unstable Housing
- Racial/Ethnic Minority
- Psychiatric Disease

Westergaard et al 2013 Curr Opin Infect Dis; Prins et al 2015 Psych Serv

Structural Barriers during Incarceration

- Incarceration patterns prevent linkage to appropriate services (Spaulding et al 2010 AJPH)
  - 50% - with less than 7-days stay
  - 25% - <2 days, 75% < 15 days
  - 60% - with one incarceration (general population from 2001 – 2018)
  - 17% - with 2 incarcerations
  - 11% - 3-4 incarcerations

- Stigma and mistrust of institutions prevent (Westergaard et al 2013 Curr Opin Infect Dis)
  - Disclosure of HIV-risk behaviors
  - Disclosure of HIV diagnosis

Suboptimal Care Engagement

- 40% - were engaged in HIV care prior to incarceration
- 36% - Have one visit post-release
- 21% - Achieve virologic suppression post-release
- 36% - of those undergoing HIV testing had not received prior testing

Nijawan et al 2015 AJPH
Gaps in HIV Testing in U.S. Jails

80% of jails nationally confirm to best practice HIV testing policies
- 100% provide testing services
- 85% have opt-out testing

Solomon et al 2014 Health Aff

Interventions to Address Current Gaps

1. Increase HIV, STD and HCV Screening
   - Opt-out testing is feasible and Acceptable to increase HIV testing in jail
     - Offered at the time of entry in order to maximize likelihood of acceptance of testing and timely linkage to appropriate medical care
   - Pilot studies demonstrated increase in testing 6-7x in jail settings (Devkota et al 2018 AJPH)
     - Identify previously undiagnosed people living with HIV
     - Identify previously diagnosed who are out of care
     - Enhance connection to low barrier, harm reduction services for those who are HIV negative, but at increased risk
   - Can increase testing for STDs and other communicable diseases (West
<table>
<thead>
<tr>
<th>2. Addressing Unmet Needs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Connection to supportive housing within the general population is associated with</td>
</tr>
<tr>
<td>• Lower risk for HIV acquisition (Lee et al. 2019 AIDS Behav)</td>
</tr>
<tr>
<td>• Improvements in virologic suppression (Zhong et al. 2018 CROI)</td>
</tr>
<tr>
<td>• Connection to Medical-Assisted Therapy for substance abuse</td>
</tr>
<tr>
<td>• Naltrexone for alcohol use disorder improves virologic suppression (Springer et al. JAIDS 2018)</td>
</tr>
<tr>
<td>• Buprenorphine for opiate use disorder improves virologic suppression (Springer et al. 2012 PLOS)</td>
</tr>
<tr>
<td>• Connection to medical services for Hepatitis C treatment</td>
</tr>
<tr>
<td>• Initiation of treatment in jail is feasible (Akiyama et al. 2018 BMC Infect Dis)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Pre-Exposure Prophylaxis in Jails</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Feasible setting for implementation, but</td>
</tr>
<tr>
<td>• Major obstacles remain</td>
</tr>
<tr>
<td>• Patient education (Davis et al. 2018 Adherence Conference)</td>
</tr>
<tr>
<td>• Cost and institutional constraints</td>
</tr>
<tr>
<td>• Implementation of risk assessment tools for clinicians (Brinkley-Rubinstein et al. 2015 Curr HIV/AIDS Rep)</td>
</tr>
<tr>
<td>• Development and implementation of standardized procedures (ibid)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. Case Management and Navigation Services</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Peer-led (Cunningham et al. 2018 JAMA Int Med)</td>
</tr>
<tr>
<td>• Can improve virologic suppression and engagement in care</td>
</tr>
<tr>
<td>• Particularly effective among people experiencing homelessness</td>
</tr>
<tr>
<td>• Financial Incentives to enhance connection to services (Stitzer et al. 2017 Addict Sci Clin Pract)</td>
</tr>
<tr>
<td>• Demonstrated to improve connection to navigators among people who inject drugs</td>
</tr>
<tr>
<td>• Improves connection to methadone treatment (Sorensen et al. 2007)</td>
</tr>
<tr>
<td>• No difference in substance use between in group receiving financial incentives</td>
</tr>
<tr>
<td>• Strengths-based case management (e.g. Motivational Interviewing)</td>
</tr>
<tr>
<td>• Effective in improving retention in care when initiated prior to release (Gordon et al. 2018 AIDS Behav)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. Transition to Low-barrier, Community-based Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Low-barrier, drop-in appointments (e.g. without a scheduled clinic visit) are a major barrier to attending clinic visits (Dombrowski et al. AIDS Care 2017; Nehsa et al. BMJ Infect Dis 2017)</td>
</tr>
<tr>
<td>• Evidence demonstrates feasibility for people living with HIV in people who are homeless or unstably housed (Dombrowski et al. 2018 AIDS Care, Kertesz et al. 2013 AJPH)</td>
</tr>
</tbody>
</table>
6. Approaches to Patient Engagement

Minimal evidence to date, but widely accepted in clinical practice

- **Relationship-Centered Care** [Beach et al. 2012 JGIM]
  - Focus on goals and priorities of patient’s in order to promote trusting doctor-patient relationship

- **Trauma-Informed** [Bowen et al. 2016 AJPH]
  - Organizational change process centered on principles intended to promote healing and reduce the risk of retraumatization for vulnerable individuals
  - Composed of 6 key components: Safety, Trustworthiness and Transparency, Collaboration and Peer-Support, Empowerment, Choice, Intersectionality
  - May be limited in jail (institutional trauma)

Clinical Case #1 – Follow-up

33 trans-, latinx female, diagnosed with HIV in February, 2018 but remains disconnected from care

- Which interventions would you prioritize to improve connection to HIV care?
  A. Case Management
  B. Navigation Services plus Financial Incentives
  C. Navigation Services
  D. Text Messaging
  E. All of the above

Clinical Case #1 – Follow-up

33 trans-, latinx female, diagnosed with HIV in February, 2018 but remains disconnected from care

- Intensive case management to address multiple unmet needs
  - Connected patient to transitional housing through a substance use treatment program

- Navigation
  - Patient was accompanied to initial appointments with a navigator and a peer from her treatment program

Clinical Case #2 – Follow-up

38 African American male, born and raised in the Bayview neighborhood with new diagnosis of HIV

- Which of following are NOT demonstrable limitations of methods to enhance navigation services?
  A. Financial incentives are associated with increase substance use
  B. Financial incentives improve connection to navigators, but no impact on virologic suppression for people living with HIV
  C. Peer-support navigation models are important features of Trauma-Informed Care models
  D. Both A & C
Clinical Case #2 – Follow-up

38 African American male, born and raised in the Bayview neighborhood with new diagnosis of HIV

- Financial Incentives
  - Attended follow-up drop-in visit at HIVIS office
- Case management
  - Ensured medication acquisition and adherence
- Peer support
  - Supported her in substance use treatment and medical care

Is there a roadmap to get there?

Pre-Incarceration
Disengagement from Care
Opportunities for testing and linkage to treatment and prevention services
Engagement in Care and Prevention Services

Implications for Ending the HIV Epidemic

- Additional funding for program implementation and research may become available for people who are criminally-justice involved
- HIV & Integrate Services team at Jail Health Services has submitted a request to fund a multi-component, evidence-based intervention to improve retention in care and connection to HIV prevention services
  - Flexible, on-demand navigation services to HIV treatment and prevention services
  - Enhanced with financial incentives, trauma-informed care and
  - Coupled with low-barrier, community-based clinical care

Goals for Program Development and Evaluation

- Using Implementation Sciences framework to guide Community-Based Participatory Research agenda
  - Define HIV incidence in people with recent criminal justice involvement
  - What proportion of new HIV infections can be avoided with connection to HIV prevention services while in jail?
- Quantify the contribution of people with CJI to local HIV transmission
  - What will be the community-level impact of HIV treatment in jail on HIV transmission?
- Evaluate patient preferences for HIV treatment and prevention services for CJI patients
  - Can we refine interventions by soliciting patient preferences for HIV treatment and prevention services?
- Augment coordination data-sharing between DPH departments to provide real-time metrics of program performance
Conclusions

• Jail remains an institutional contact for people with elevated risk for HIV acquisition and disengagement from HIV care
  • Well-positioned to institute HIV testing, prevention and treatment outcomes

• Substantial individual-level and structural barriers
  • Major gaps in optimal seek, test, treat and retain strategies

• Multiple interventions are available to implement in these institutions to close these gaps

• “Ending the HIV Epidemic” initiative provides a roadmap for implementing and evaluating program development to target this key population

Acknowledgements

• Dr Meg Newman, Diane Havlir and Annie Leutkermeyer

• Fellowship Mentors
  • Monica Gandhi
  • Elvin Geng
  • Katerina Christopoulos

• Compassionate, dedicated service providers extending the reach of life-saving prevention and treatment services

Questions/Comments

• Thank You!
Lipids, Statins and HIV: Topics in Clinical Management

Medical Management of AIDS & Hepatitis
December 14, 2019

Vivek Jain, M.D., M.A.S.
Associate Professor of Medicine
Division of HIV, Infectious Diseases & Global Medicine
San Francisco General Hospital
University of California, San Francisco

Disclosures
• Research grant support from National Institutes of Health (NIH), Centers for Disease Control (CDC) & President’s Emergency Plan for AIDS Relief (PEPFAR) –
  – For work ongoing in East Africa related to HIV care models
  – This disclosure is unrelated to this presentation

Outline
• Who should be on statins? Recent guidance
• Practical use of statins in patients with HIV
  – specific drug interactions with ARV’s
• What can statins achieve?
  – Lipid lowering, CV risk mitigation, malignancy reduction
• What downside risks do statins pose?
  – Diabetes?, myopathy?, cognitive changes?
• If statins don’t achieve their goals, or can’t be used, what can ARV switching do to improve lipids?
• Ezetimibe and the PCSK9 inhibitors

Outline
• Who should be on statins? Recent guidance
• Practical use of statins in patients with HIV
  – specific drug interactions with ARV’s
• What can statins achieve?
  – Lipid lowering, CV risk mitigation, malignancy reduction
• What downside risks do statins pose?
  – Diabetes?, myopathy?, cognitive changes?
• If statins don’t achieve their goals, or can’t be used, what can ARV switching do to improve lipids?
• Ezetimibe and the PCSK9 inhibitors
Older System: LDL-based goals

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL (mg/dL)</th>
<th>Non-HDL (mg/dL)</th>
<th>LDL to Consider Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary target</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very High</td>
<td>&lt; 70</td>
<td>&lt; 100</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>High</td>
<td>&lt; 100</td>
<td>&lt; 130</td>
<td>≥ 100</td>
</tr>
<tr>
<td>CHD or CHD Risk Equiv.</td>
<td>&lt; 130</td>
<td>&lt; 160</td>
<td>≥ 130</td>
</tr>
<tr>
<td>(10-year risk &gt; 20%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate High &gt; 2 Risk Factors (10-year risk 10-20%)</td>
<td>&lt; 130</td>
<td>&lt; 160</td>
<td>≥ 160</td>
</tr>
<tr>
<td>Moderate ≥ 2 Risk Factors (10-year risk &lt; 20%)</td>
<td>&lt; 160</td>
<td>&lt; 190</td>
<td>≥ 190</td>
</tr>
<tr>
<td>Low</td>
<td>&lt; 190</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Risk Category LDL (mg/dL) Primary target Non-HDL (mg/dL) Secondary target LDL to Consider Drug Therapy

- Very High: LDL < 70, Non-HDL < 100, Drug Therapy for > 100
- High: LDL < 100, Non-HDL < 130, Drug Therapy for ≥ 100
- CHD or CHD Risk Equiv: LDL < 130, Non-HDL < 160, Drug Therapy for ≥ 130
- Moderate High > 2 Risk Factors (10-year risk > 20%): LDL < 130, Non-HDL < 160, Drug Therapy for ≥ 160
- Moderate ≥ 2 Risk Factors (10-year risk 10-20%): LDL < 160, Non-HDL < 190, Drug Therapy for ≥ 190
- Low: LDL < 190, Non-HDL, Drug Therapy for

2013 Guidelines Changes

- AHA/ACC guidelines Nov. 2013:
  - assess risk of "hard" CV events
  - used a new "global risk prediction score"
  - recommend statins when 10-year risk is >7.5%
  - consider statins when 10-year risk is 5 - 7.5%

- Controversies:
  - do new guidelines mean there are many patients on statins who do not need to be?
  - do new guidelines mean many low risk patients not on statins should be initiated?
  - Huge resource questions involving millions of patients

2018 Guideline Changes

- Key Changes to new 2018 guidelines:
  - Amplifies patient-clinician discussion
    - Patient specific risks and benefits of statin
  - Emphasis on early lifestyle modifications
    - Diet: high vegetable, fruit, lean protein, whole grains, limit sweets & processed fats
    - Exercise: 40 minutes, vigorous, 3-4 times per week
  - Understand high/moderate/low intensity statins
  - Use new updated risk calculator ("risk plus")
    - Still based on pooled population based risk equations; "launch point" for shared decision making

Controversy over new guidelines

- New calculator can overestimate risk and therefore recommend statins for too many people
- No statin RCT used a "global risk prediction score" as an entry criterion
- Smoking and HTN are major drivers of risk...but could end up being addressed by a statin rather than by habit reduction
- Can have odd individual situations where statin unexpectedly is or isn't recommended
- Heavily influenced by age: 42% of men and 28% of women age 60-69 have risk>20%, and many age 65+ with no risk factors will meet risk criteria...however, no statin trials ever enrolled persons of these ages with zero risk factors
- However, new risk calculator became widely recognized
- Goal was to use it as a starting point to foster individualized discussions

Grundy SM et al, 2018AHA/ACC Guideline on the Management of Blood Cholesterol
Overview of New 2018 Guidelines

Consider many factors simultaneously:
- Focus on ASCVD risk, as well as certain numeric LDL targets
- Differentiate who needs statin for ASCVD (secondary prevention) vs. who needs it for primary prevention
- Differentiate high-intensity statin from moderate intensity statin
- Screen for LDL>190 and diabetes
- Calculate patient 10-year risk: is it >7.5%?
- Consider whether the patient has any "risk enhancers"
- Consider obtaining a coronary artery calcium score

Also include in discussion:
- Smoking cessation
- Diet
- HTN control
- Exercise

Strength of Recommendations in Guidelines

New Cholesterol Guidelines: Primary Prevention

Step by Step: Does patient have LDL>190, DM, or age>75?
2018 Cholesterol Guidelines: Secondary Prevention

2018 Cholesterol Guidelines

- Initiate statin to achieve goals
- Consider ezetimibe if not at goal
- Consider PCSK-9 inhibitor if not at goal
- Consider coronary artery calcium score in patients >40 with uncertain risk status: if ≥100 Agatson units = ASCVD risk ≥7.5% = start statin
Updated Web-based Calculator

“Risk Plus Calculator”
http://tools.acc.org/ASCVD-Risk-Estimator-Plus

Read out 10-year and life-time risk:

And how this risk can be optimized/lowered with therapies:

http://tools.acc.org/ASCVD-Risk-Estimator-Plus

Outline

• Who should be on statins? Recent guidance
• Practical use of statins in patients with HIV
  – specific drug interactions with ARV’s
• What can statins achieve?
  – Lipid lowering, CV risk mitigation, malignancy reduction
• What downside risks do statins pose?
  – Myopathy, diabetes?, cognitive changes?
• If statins don’t achieve their goals, or can’t be used,
  what can ARV switching do to improve lipids?
• Ezetimibe and the PCSK9 inhibitors

Statin Choices: a review

Most statins metabolized by CYP3A4 system
(pravastatin & pitavastatin are not)

When using INSTIs with cobic: follow PI rules

Inhibitors: reduce CYP3A4

Atorvastatin
Loxatin
Pravastatin
Simvastatin
Fluvastatin
Less potent statin use at lower doses
Fluvastatin: can use at 4mg dose

When using PI’s: use at 10-20mg

NTRIs:

Fluvastatin: can reduce statin levels
Fluvastatin: can increase statin levels

NNRTIs:

Efavirenz: can reduce statin levels
Efavirenz: can increase statin levels

Etravirine: can reduce atorvastatin, increase fluvastatin, no change on pravastatin

ART* can reduce statin levels

Example: Cobicistat is a PI that is a booster for INSTIs

http://tools.acc.org/ASCVD-Risk-Estimator-Plus

Statin Choices: a review

Most statins metabolized by CYP3A4 system
(pravastatin & pitavastatin are not)

When using INSTIs with cobic: follow PI rules

Inhibitors: reduce CYP3A4

Atorvastatin
Loxatin
Pravastatin
Simvastatin
Fluvastatin
Less potent statin use at lower doses
Fluvastatin: can use at 4mg dose

When using PI’s: use at 10-20mg

NTRIs:

Fluvastatin: can reduce statin levels
Fluvastatin: can increase statin levels

NNRTIs:

Efavirenz: can reduce statin levels
Efavirenz: can increase statin levels

Etravirine: can reduce atorvastatin, increase fluvastatin, no change on pravastatin

ART* can reduce statin levels

Example: Cobicistat is a PI that is a booster for INSTIs

http://tools.acc.org/ASCVD-Risk-Estimator-Plus

Statin Choices: a review

Most statins metabolized by CYP3A4 system
(pravastatin & pitavastatin are not)

When using INSTIs with cobic: follow PI rules

Inhibitors: reduce CYP3A4

Atorvastatin
Loxatin
Pravastatin
Simvastatin
Fluvastatin
Less potent statin use at lower doses
Fluvastatin: can use at 4mg dose

When using PI’s: use at 10-20mg

NTRIs:

Fluvastatin: can reduce statin levels
Fluvastatin: can increase statin levels

NNRTIs:

Efavirenz: can reduce statin levels
Efavirenz: can increase statin levels

Etravirine: can reduce atorvastatin, increase fluvastatin, no change on pravastatin

ART* can reduce statin levels

Example: Cobicistat is a PI that is a booster for INSTIs

http://tools.acc.org/ASCVD-Risk-Estimator-Plus

Statin Choices: a review

Most statins metabolized by CYP3A4 system
(pravastatin & pitavastatin are not)

When using INSTIs with cobic: follow PI rules

Inhibitors: reduce CYP3A4

Atorvastatin
Loxatin
Pravastatin
Simvastatin
Fluvastatin
Less potent statin use at lower doses
Fluvastatin: can use at 4mg dose

When using PI’s: use at 10-20mg

NTRIs:

Fluvastatin: can reduce statin levels
Fluvastatin: can increase statin levels

NNRTIs:

Efavirenz: can reduce statin levels
Efavirenz: can increase statin levels

Etravirine: can reduce atorvastatin, increase fluvastatin, no change on pravastatin

ART* can reduce statin levels

Example: Cobicistat is a PI that is a booster for INSTIs

http://tools.acc.org/ASCVD-Risk-Estimator-Plus
Outline

- Who should be on statins? Recent guidance
- Practical use of statins in patients with HIV
  - specific drug interactions with ARV’s
- What can statins achieve?
  - Lipid lowering, CV risk mitigation, malignancy reduction
- What downside risks do statins pose?
  - Myopathy, diabetes?, cognitive changes?
- If statins don’t achieve their goals, or can’t be used, what can ARV switching do to improve lipids?
- Ezetimibe and the PCSK9 inhibitors

Statin potency in HIV+ patients: Excellent, same as in HIV-negative

- Retrospective study: 700 HIV+ patients, 2 large US clinics initiating statin
  - Both atorvastatin and rosuvastatin did better than pravastatin in reducing total cholesterol, LDL, TGs and non-HDL cholesterol
  - Less accumulated data with rosuvastatin limits its use

Table 1. Changes in Plasma Lipid Concentrations After 12 Months of Statin Therapy Compared With Baseline by Individual Statin or Adjunct Ancillary

<table>
<thead>
<tr>
<th>Statin</th>
<th>Total Cholesterol</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Statin</td>
<td>175±46</td>
<td>123±23</td>
<td>47±11</td>
<td>159±67</td>
</tr>
<tr>
<td>Atorvastatin 40mg</td>
<td>138±30</td>
<td>84±17</td>
<td>49±10</td>
<td>122±35</td>
</tr>
<tr>
<td>Rosuvastatin 40mg</td>
<td>138±30</td>
<td>84±17</td>
<td>49±10</td>
<td>122±35</td>
</tr>
<tr>
<td>Pravastatin 40mg</td>
<td>138±30</td>
<td>84±17</td>
<td>49±10</td>
<td>122±35</td>
</tr>
</tbody>
</table>

Intrepid Study (cont’d)

- Outcomes:
  - pitavastatin 4mg lowered LDL more at 12 weeks than pravastatin 40mg
  - effect durable at 52 weeks
  - Good safety; low discontinuation rate

- Study is important b/c first RCT of 2 statins in HIV
- And: pitava is used in REPRIEVE trial...

Pitavastatin vs. Pravastatin

- INTREPID Study: First double blind RCT of 2 statins in HIV+ population; first trial of pitavastatin

**INTREPID RCT Design**:

- Age 18-70
- ART<6mo.; 15% CD4<200
- 4-week diet stabilization, then LDL 130-220, TG≤400
- No DRV, familial hypercholesterolemia, CAD, DM, high fasting glucose

**Randomized to**: pitavastatin 4mg QD vs. pravastatin 40mg PO QD

**Who Enrolled (pitava/prava arms):**

- 253/253 incl; 56% male, 80% white
- CD4: 648±283; mean HIV duration: 12.6±3.5y
- ART: 74% on NNRTI, 26% on PI
- Framingham 10 year risk 6.6%; 26.6% on PI

**Primary outcomes**: % change in LDL at Week 12

**Intrepid Study (cont’d)**

- Pitavastatin vs. Pravastatin

<table>
<thead>
<tr>
<th>Time</th>
<th>Lipid</th>
<th>Pitavastatin</th>
<th>Pravastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 Weeks</td>
<td>LDL</td>
<td>-31.1%</td>
<td>-20.9%</td>
</tr>
<tr>
<td></td>
<td>Tot. Chol.</td>
<td>-20.4%</td>
<td>-13.8%</td>
</tr>
<tr>
<td></td>
<td>Triglycerides</td>
<td>-3.2%</td>
<td>-3.6%</td>
</tr>
<tr>
<td>52 Weeks</td>
<td>LDL</td>
<td>-29.7%</td>
<td>-20.5%</td>
</tr>
<tr>
<td></td>
<td>Tot. Chol.</td>
<td>-19.1%</td>
<td>-13.7%</td>
</tr>
<tr>
<td></td>
<td>Triglycerides</td>
<td>-2.8%</td>
<td>-8.3%</td>
</tr>
</tbody>
</table>

- Critiques of study:
  - (a) choice of pravastatin comparator (weak statin)
  - (b) short 12 week outcome
  - (c) no long term cardiovascular event outcomes
  - (d) diabetes and CAD exclusions (many statin patients have these diseases)
  - (e) very few patients on INSTI’s
  - (f) many patients on EFV (may have dropped prava levels more than pitava levels)
### Outline

- Who should be on statins? Recent guidance
- Practical use of statins in patients with HIV
  - specific drug interactions with ARV’s
- What can statins achieve?
  - Lipid lowering, CV risk mitigation, malignancy reduction
- What downside risks do statins pose?
  - Myopathy, diabetes?, cognitive changes?
- If statins don’t achieve their goals, or can’t be used, what can ARV switching do to improve lipids?
- Ezetimibe and the PCSK9 inhibitors

### Reducing CV Events and Death

- Statins prevent mortality by reducing LDL and by lowering inflammation
- Systemic inflammation persists in HIV infection despite successful virologic suppression
- Treatment with statin of normal LDL patients with high CRP levels reduced cardiac events
- Do statins lower mortality in HIV patients?

### Statins Reduce Mortality in HIV+

- Large meta-analysis: 7 studies, 35,708 participants
- Varied settings, varied statins

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discountor et al. 2013</td>
<td>25864</td>
<td>2.08 (2.04, 2.12)</td>
</tr>
<tr>
<td>Arndt et al. 2015</td>
<td>1438</td>
<td>1.03 (0.96, 1.09)</td>
</tr>
<tr>
<td>Nøkleby et al. 2015</td>
<td>800</td>
<td>1.20 (1.11, 1.30)</td>
</tr>
<tr>
<td>Lang et al. 2016</td>
<td>1716</td>
<td>1.01 (1.00, 1.02)</td>
</tr>
<tr>
<td>Monari et al. 2017</td>
<td>1604</td>
<td>0.93 (0.84, 1.02)</td>
</tr>
<tr>
<td>Overton et al. 2015</td>
<td>3601</td>
<td>0.81 (0.76, 0.86)</td>
</tr>
<tr>
<td>Ramasesan et al. 2015</td>
<td>1728</td>
<td>0.78 (0.74, 0.82)</td>
</tr>
<tr>
<td>Repas overall (low-informative prior)</td>
<td>8.87 (3.86, 18.96)</td>
<td></td>
</tr>
<tr>
<td>Predictive interval</td>
<td>0.21 (0.11, 0.37)</td>
<td></td>
</tr>
</tbody>
</table>

Statins reduced hazard of death by 33%

Many methodologic issues remain; certain studies didn’t report which statin was used; others didn’t distinguish cardiac deaths from other deaths… RCT needed

Grinspoon et al., Am. Heart J., 2019

### REPRIEVE Study: ACTG 5332

- First RCT to randomize HIV-positve patients to statin vs. placebo
- Adults age 40-75, no prior history of CV disease, on ART ≥ 6 mo.
  - Randomize to pitavastatin 4mg vs. placebo
- Largest clinical trial ever in the HIV field; 120 sites/11 countries
  - Goal size 7,500; fully enrolled. Mean age 59, Females 32%, mean duration of HIV: 13 years
  - Will follow patients for up to 8 years
- Primary outcome: “MACE” (major adverse cardiovascular events)
- Secondary outcomes: components of MACE, all cause mortality, LDL, immune function, non-CV events, safety

Grinspoon et al., Am. Heart J., 2019
Statins and Malignancy in HIV+ Persons

Statins may have several anticancer properties:

- Arrest cell cycle progression
- Induce apoptosis
- Reduce inflammation-mediated immune dysregulation
  - dysregulation can impact cancer surveillance mechanisms
  - dysregulation can allow for infection-related malignancies

Growing literature on anti-cancer effects in general population... what about in HIV+ persons?

Outline

- Who should be on statins? Recent guidance
- Practical use of statins in patients with HIV
  - specific drug interactions with ARV's
- What can statins achieve?
  - Lipid lowering, CV risk mitigation, malignancy reduction
- What downside risks do statins pose?
  - Myopathy, diabetes?, cognitive changes?
- If statins don't achieve their goals, or can't be used, what can ARV switching do to improve lipids?
- Ezetimibe and the PCSK9 inhibitors

3 Studies Show Lower Cancer Rates in HIV+

1. Kaiser CA cohort: statin use associated with 44% lower hazard of Non-Hodgkin's Lymphoma (NHL) vs. patients on non-statin lipid therapy
   n=339 NHL+ → 8% were on statin
   n=293 NHL- → 13% were on statin
   Hazard Ratio: 0.53 (95% CI: 0.31-0.95)
   45% reduction in hazard of NHL
   Chao et al., AIDS, 2011

2. ACTG "ALLRT" cohort: statin vs. non statin use compared across a variety of outcomes. Associated with 37% lower hazard of overall, adjusted for HIV/ART status and co-morbidities.
   Hazard Ratio: 0.63 (95% CI: 0.49-0.94)
   37% reduction in hazard of cancer overall
   Overton et al., Clin. Infect. Dis., 2013

3. Milan cohort: 6,937 patients, initiated ART 1995-2012; 14% initiated statin. 44% lower hazard of Cancer (AIDS-defining and non-AIDS-defining combined).
   Hazard Ratio: 0.59 (95% CI: 0.36-0.98)
   44% reduction in hazard of cancer overall
   Dal Maso et al., JCO, 2015
Mechanism for increasing diabetes risk?

- Largely unknown
- Reduction in GLUT-4, glucose transporter → phenotype of reduced insulin sensitivity?
- Reduction in pancreatic B-cell insulin secretion due to inhibition of glucose-stimulated cytoplasmic calcium channels?

Statins and diabetes (general population)

JUPITER Trial, NEJM 2008:
Men>50, women>60, LDL<130, CRP>2.0
Randomized to rosvuastatin or placebo
Reduced all levels of cholesterol, reduced death, MI, stroke

Raised concern about incident diabetes... what were the data?

<table>
<thead>
<tr>
<th>Statin</th>
<th>LDL (mg/dL)</th>
<th>CRP (mg/L)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin</td>
<td>110 (67)</td>
<td>2.0 (1.2)</td>
<td>0.05</td>
</tr>
<tr>
<td>Placebo</td>
<td>125 (72)</td>
<td>2.0 (1.2)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Mills et al., QJM, 2011

Statins and diabetes: HIV+ population

- HOPS Cohort (HIV Outpatient Study)
  - n=4,692 (2002-2012), no prior statin or DM, median F/U 4 years
  - Comparison of incident diabetes in statin users vs. non-statin users, adjusted for propensity scores
  - n=590 (12.6%) received statins
  - n=355 developed new, incident DM during F/U
  - HR 1.14 per year of statin exposure (95%CI, 1.02-1.27)

Acknowledging limitations of meta-analyses, indicated a ~9% increased odds of incident diabetes
Summary of diabetes risk

- Likely a small 5-10% elevation in risk for diabetes with statin use
  - unclear if specific to particular statins
  - possible that risk is slightly higher in HIV+ patients
- When using statin, monitor HBA1c% regularly, along with clinical symptoms of diabetes

Outline

- Who should be on statins? Recent guidance
- Practical use of statins in patients with HIV
  - specific drug interactions with ARV’s
- What can statins achieve?
  - Lipid lowering, CV risk mitigation, malignancy reduction
- What downside risks do statins pose?
  - Diabetes?, myopathy?, cognitive changes?
- If statins don’t achieve their goals, or can’t be used, what can ARV switching do to improve lipids?
- Ezetimibe and the PCSK9 inhibitors

Statin diabetes, myopathy, & cognitive changes

- Statins and Myopathy:
  - hard to study
  - conflicting data
  - most “cases” are with CK elevations
  - myopathy without CK elevation wouldn’t get tallied in RCTs
  - data on myopathy without CK elevation scarce
  - hard to separate statin myopathy from myriad other causes of musculoskeletal pains
  - Ganga et al., Am Heart J., 2014
  - Cohen et al., J Clin Lipidol., 2012

- Statins and Cognitive Changes:
  - 2012 FDA safety warning for statins: “Memory loss and confusion have been reported with statin use. These reported events were generally not serious and went away once the drug was no longer being taken”
  - review of post-marketing adverse events:
    - did not reveal an association between the adverse event and the specific statin, the age of the individual, the statin dose, or concomitant medication use
    - http://www.fda.gov/drugs/drugsafety/ucm293101.htm

Outline

- Who should be on statins? Recent guidance
- Practical use of statins in patients with HIV
  - specific drug interactions with ARV’s
- What can statins achieve?
  - Lipid lowering, CV risk mitigation, malignancy reduction
- What downside risks do statins pose?
  - Diabetes?, myopathy?, cognitive changes?
- If statins don’t achieve their goals, or can’t be used, what can ARV switching do to improve lipids?
- Ezetimibe and the PCSK9 inhibitors
Points on ART Optimization

- INSTIs have least lipid effects of all classes
- TDF lowers lipids; ABC and TAF raise lipids
- With change from NNRTI or PI → INSTI, and simultaneous TDF → TAF: overall effect?
- Difficult question: staying on TDF for lipid reasons?
- 2-drug regimens (e.g. DTG/RPV or DTG/3TC): we will need to examine lipid profiles

 INSTI class: less lipid derangement vs. PI and NNRTI in ART initiators

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment</th>
<th>Baseline</th>
<th>Change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC (mg/dL)</td>
<td>TDF</td>
<td>186</td>
<td>160</td>
</tr>
<tr>
<td></td>
<td>RPV</td>
<td>163</td>
<td>159</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>TDF</td>
<td>97</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>RPV</td>
<td>95</td>
<td>92</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>TDF</td>
<td>54</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>RPV</td>
<td>54</td>
<td>52</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>TDF</td>
<td>486</td>
<td>466</td>
</tr>
<tr>
<td></td>
<td>RPV</td>
<td>472</td>
<td>447</td>
</tr>
<tr>
<td>TC/HDLC ratio</td>
<td>TDF</td>
<td>5.9</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td>RPV</td>
<td>5.9</td>
<td>5.1</td>
</tr>
</tbody>
</table>

Green boxes (INSTI) show smaller rise in lipids than red boxes (NNRTI or PI)

NEAT 022: PI → DTG Switch

- NEAT022: 2 NRTI + PI → 2 NRTI + DTG
  - ~8-9 point drop in TC and LDL
  - NRTIs: ~65% TDF/FTC, ~33% ABC/3TC (no TAF)

STRIIVING Study: ART → DTG switch

- Switch from any ART to Triumeq (dolutegravir):
  - STRIVIEVING study:
    - small worsening in lipids overall:
      - total cholesterol up by 1.8% (early switch group)
      - and up by 2.5% (late switch group)
    - however, 26% already on INSTI
      - (so maybe lipid-improving effects wouldn't be as large?)
    - and 34% of patients switched from TDF/FTC to ABC/3TC
      - (so loss of TDF lipid-improving effects were lost?)
Switching to EVG and DTG

**EVG**
- Switch from NNRTI (mostly EFV) to Strivil (elvitegravir):
  - STRATEGY-NRRTI study:
    - little impact on lipids
    - may have been because of balance of benefit of NNRTI⇒INSTI, at the same time as disbenefit of adding cobicistat
  - Pozniak et al., Lancet Infect Dis., 2014

**SPIRAL study: PI⇒RAL switch**
- Substantial improvements in TG, TC, LDL, & HDL with switch from PI to RAL

**SPIRIT Study: PI⇒RPV switch**
- Palella et al., AIDS, 2014

Outline
- Who should be on statins? Recent guidance
- Practical use of statins in patients with HIV
  - specific drug interactions with ARV’s
- What can statins achieve?
  - Lipid lowering, CV risk mitigation, malignancy reduction
- What downside risks do statins pose?
  - Diabetes?, myopathy?, cognitive changes?
- If statins don’t achieve their goals, or can’t be used, what can ARV switching do to improve lipids?
- Ezetimibe and the PCSK9 inhibitors
Ezetimibe

- Cholesterol absorption inhibitor: inhibits dietary and biliary uptake of cholesterol
- Reliably lowers LDL, beyond what statin achieves... but does it lower CV outcomes?

**IMPROVE-IT Trial:**
- Patients with acute coronary syndrome (i.e., secondary prevention) randomized to statin + ezetimibe vs. statin alone
- Composite outcome of CV death, MI, admission for unstable angina, revascularization 29d later, CVA
- Outcomes lower with ezetimibe:
  - Hazard ratio (HR) 0.94, 95% CI 0.89-0.99
  - 7-year event rate 31.7 vs. 34.2 percent

**Questions:**
- Is ezetimibe indicated for primary prevention?
- Max out statin dose first? Or add EZ to statin for synergistic/additive effects, and avoid max statin dose?

---

PCSK9 Inhibitors: New class of anti-lipid drugs

- **Target populations:**
  - Persons on statin and ezetimibe but not at goal LDL
  - Persons with heterozygous familial hypercholesterolemia (~1/500)
  - Persons with statin intolerance

- **FDA approved medications:**
  - Evolocumab: Repatha (Amgen)
    - 140mg S.O. q2weeks or 420mg S.O. qMonth
  - Alirocumab: Praluent (Regeneron)
    - 75mg S.O. q2weeks, can increase to 150mg in 4-8 weeks

---

PCSK9 Inhibitors: New class of anti-lipid drugs

- **PCSK9 Inhibitors:**
  - Binds to PCSK9, allows LDL-R to stay on surface
  - LDL-C plasma levels are decreased

**Anti-PCSK9 mAb:**
- Placebo trials only
  - LDL reduction: -58.8% (95% CI -63.0% to -56.5%)

**PCSK9 Inhibitors:**
- 24 studies, 10,159 patients (mix of PCSK9 vs. placebo and PCSK9 vs. ezetimibe)
- LDL reduction: -47.5% (95% CI -65.0% to -25.4%)

**Substantial LDL Reductions**

- 90% vs 45%

**PCSK9 Inhibitors:**
- Navarese et al., Ann Intern Med 2015

---

Navarese et al., Ann Intern Med 2015
**PCSK9 Long-term Follow-up Results**

**Evolocumab**
- **FOURIER Trial**
  - n=30,564 patients; already on maximal-intensity statin; RCT of evolocumab vs. placebo
  - Median 2.2 years of follow-up
  - Primary endpoint: composite of CV death, MI, hospitalization for unstable angina
    - 98% lower risk of death (HR 0.52 vs. placebo, 95% CI 0.48–0.57)
    - Lower risk of non-fatal MI (HR 0.6, 95% CI 0.50–0.74)
    - Lower risk of non-fatal stroke (HR 0.76, 95% CI 0.60–0.96)
    - Lower risk of CV death (HR 0.34, 95% CI 0.24–0.48)
  - Reduced CV events but no reduction in mortality

**Alirocumab**
- **ODYSSEY-OUTCOMES Trial**
  - n=2,922 patients; acute coronary syndrome in past year; on high-intensity or dose-maximized statin, and with LDL >70, non-HDL >100, or apolipoprotein B >50; RCT of alirocumab SQ vs. placebo injection qweeks
  - Primary endpoint: composite of CHD death, non-fatal MI, non-fatal stroke, or hospitalization from unstable angina
    - Median 2.8 years follow-up
      - 98% lower risk of death (HR 0.50 vs. placebo, 95% CI 0.46–0.54)
      - Lower risk of non-fatal MI (HR 0.66, 95% CI 0.52–0.83)
      - Lower risk of non-fatal stroke (HR 0.82, 95% CI 0.65–1.00)
      - All-cause mortality (HR 0.77, 95% CI 0.60–0.97)
  - Reduced CV events and reduced mortality

---

**What about PCSK9 in HIV+ Patients?**

**PCSK9 Inhibition in HIV+ Patients: RCT**
- PCSK9 in HIV Evaluation Study: A Phase 3, Double-Blind, Randomized, Placebo-Controlled Study to Assess the Efficacy and Safety of PCSK9 Inhibition in HIV-Infected Subjects at UCSF
  - Alirocumab or placebo (n=200)
    - Alirocumab or placebo injected subcutaneously every 2 weeks for a duration of 52 weeks
  - Outcomes: endothelial function (flow-mediated vasodilation [FMD] of the brachial artery), vascular inflammation (FDG-PET/CT scanning), and coronary plaque (CT angiography)
  - Funded by Pfizer/Sanofi/Regeneron, PI: Priscilla Hsue MD, UCSF

---

**What about PCSK9 in HIV+ Patients?**

Reduction in LDL-C in HIV+ patients treated with Evolocumab (n=6)
- PCSK9 inhibitors show similarly potent lipid-lowering effects in HIV+ patients

Reduction in Lp(a) in HIV+ patients treated with Evolocumab (n=6)
**PCSK9: Summary**

- Dramatic LDL lowering
- Studies w/2-3 year follow up (FOURIER [evolocumab] and ODYSSEY OUTCOMES [alirocumab]) showed:
  - CV event reduction (but smaller than expected)
  - Mortality reduction in alirocumab only
- In HIV-positive patients: longer term data needed
- Think of PCSK9 inhibitors for patients who:
  - Are already on statins and ezetimibe but not at goal
  - Can’t tolerate statins

---

**Inflammation in SATURN Study (HIV+ patients)**

- In the SATURN Study, HIV+ patients on ART, suppressed, with normal LDL and elevated CRP:
  - decreased LDL (as expected)
  - did not statistically significantly decrease IL-6, CRP, d-dimers, and other biomarkers of inflammation and hypercoagulation
  - did decrease Lp-PLA2 levels, even accounting for LDL reduction, indicating possible anti-inflammatory effect

_Eckard et al., J Infect Dis, 2014_

---

**Summary / Conclusions**

| Practical use of statins in HIV+ patients | • Atorvastatin, pravastatin
  • Caution darunavir—pravastatin
  • Caution EFV/statins |
| Who should be on statins? Updates on 2018 guidelines | • Evolving. Use risk calculator
  • Have individualized conversations |
| What can statins achieve? | • Lipid lowering
  • Prevention of CV morbidity/mortality?
  • Reduce malignancies |
| What downside risks do statins pose? | • Diabetes
  • Higher DM risk: monitor HbA1c
  • Monitor for cognitive changes |
| If statins don’t achieve their goals, or can’t be used, what can ARV switching do to improve lipids? | • Switching PIs/NNRTIs to INSTI’s
  • Consider whether TAF is raising lipids |
| New PCSK9 inhibitor class of drugs | • Powerful meds
  • Watch for emerging data in HIV... |

---

**Thank You!**

- Happy to take any questions!
- Thank you to Dr. Priscilla Hsue, SF General Hospital, Division of Cardiology
- For further questions: Please email me at vivek.jain@ucsf.edu
Curing HIV with Gene Therapy
Moving from science fiction to reality

Steven Deeks, MD
Professor of Medicine
Division of HIV, Infectious Diseases, and Global Medicine
Zuckerberg San Francisco General
University of California, San Francisco

Why do we need a cure in an era of effective ART?

- Individual perspective
  - Treatment toxicity
  - Polypharmacy
  - Stigma/discrimination
- Public health perspective
  - 38 million currently living with HIV
    - ~50% on effective ART
    - 2 million new infections every year
    - Life-long treatment challenging for many now driving the epidemic
  - Total spent on HIV/AIDS: ~$50 billion per year
    - Shifting financing landscape

Disclosures

- Research support: Gilead, Merck, ViiV
- Consulting: AbbVie, Eli Lilly
- Scientific advisory board: BryoLogyx, Enochian Biosciences

The ideal curative intervention will be readily scalable, safe, effective in those populations that are not currently doing well on ART (for any reason) and protective against re-infection
**Viable pathways toward a durable remission or cure**

- **Early ART**: Not curative, PTC rare, unpredictable
- **Shock and kill**: Reservoir reduction; not curative
- **Block and lock**: Reservoir reduction; not curative
- **Immunotherapy**: Most viable options require complex combinations (LRA/vaccine/bNAb/adjuvants)
- **Gene and cell-based therapy**

Should this work, multiple pathways are evolving that make in vivo gene editing scalable and effective (“one shot cures”).

**Gene editing for an HIV Cure: Proof of Concept**

“*It’s great that I finally have someone added to my family. It’s been too long.*

Timothy Brown, *Science* March 2019

**Gene and Cell Therapy**

<table>
<thead>
<tr>
<th>Name</th>
<th>Type</th>
<th>Status</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic Fibrosis</td>
<td>CRISPR</td>
<td>In progress</td>
<td>2023</td>
</tr>
<tr>
<td>Sickle Cell Disease</td>
<td>CAR-T cells</td>
<td>FDA approval pending</td>
<td>2022</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>RNA interference</td>
<td>FDA approval pending</td>
<td>2021</td>
</tr>
<tr>
<td>Thalassemia</td>
<td>Gene editing</td>
<td>FDA approval pending</td>
<td>2020</td>
</tr>
</tbody>
</table>

Ex vivo cures achieved by gene modification of stem cells

β-thalassemia: Blunted production of β-globulin, leading to abnormal hemoglobin

CD34+ stem cells are harvested from the bone marrow or from the mobilized peripheral blood and subjected to gene transfer with an integrating lentiviral vector encoding the β-globin complementary DNA.

- Autologous HSCs gene-modified with lentiviral vector expressing an anti-sickling β-globin gene
- Partial engraftment: approximately 50% of β-like-globin chains
- All disease-related complications resolved
Gene editing clinical trials

<table>
<thead>
<tr>
<th>Phase</th>
<th>Status</th>
<th>Gene Therapy</th>
<th>Antiviral Genes</th>
<th>CCR5</th>
<th>HIV Provirus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>Released</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Phase 2</td>
<td>Underway</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Planned</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

**Gene Therapy and an HIV Cure**

Deleting, repairing and/or inserting genes

*Delete* CCR5

*Copy and Paste* CAR-T

**Antiviral genes**

HIV Cure: *Ex vivo* approaches

Paula Canon
HIV-infected man with leukemia who received gene-modified (CRISPR) allogenic stem cell transplant

Safety acceptable (n=1), although gene therapy-associated cancers take several years to develop
No immunogenicity
No off-target effects detected with whole-genome sequencing
Chinese regulatory environment allowed translation from discovery of CRISPR-Cas9 to phase I clinical trial in two years (NCT03164135).

Sangamo Trial
ZF editing of CCR5

902 Trial
• Single dose
• Nine enrolled in San Francisco

1101 Trial
• Cyclophosphamide to "make space"
• Single dose
• Treatment interruption six weeks later
• 5 individuals enrolled at multiple centers

902 Trial: Despite the observation that only ~5% of have evidence of CCR5 disruption, we found that a single administration of SB-528-T was associated with durable decline in reservoir

Participant 01-060: Long-term post-treatment control
CD4 nadir 12 cells/mm³

• Advanced AIDS prior to ART
• Cyclophosphamide conditioning; single infusion of SB-528-T
• ~8% of cells have bi-allelic disruption of CCR5
• Durable post-ART control
NIH UO1: RCT of ex vivo CCR5-deletion
Cleveland, Cincinnati, San Francisco

- **Intervention:** Ex vivo disruption of CCR5 in T cells
- **Study Design:** Randomized clinical trial of autologous cells either gene-modified (n=20) or not gene-modified (n=10)
  - Cyclophosphamide conditioning
- **Population:** Treated HIV disease (chronic)
- **Outcomes:** Safety, immune function, reservoir reduction
- **Status:** Actively enrolling

**HIV Cure: In vivo approaches**

One-shot cure approaches

Gene delivery of long-acting antiviral (bANb) or direct *in vivo* gene editing (HIV, CCR5) might eventually lead to durable cure for treated and even untreated people.

Aspirational, but theoretically possible

Gates and NIH join forces on HIV and sickle cell diseases

Sickle cell disease and HIV have similar disease distribution with the major burden being in Africa.

Gene therapy works in sickle cell disease and potentially promising for HIV.

The goal is to avoid development of expensive, complex strategies that require stem cell transplantation.
Can we “repair” the immune system so it will more effectively target HIV?

CAR-T cells are now curing many leukemias and lymphomas

June, NEJM 2018

CAR-T cells: Modified cells persist for decades, based on our experience with first generation of CAR-T cells in 1990s

**Intervention**: Multi-specific autologous LVgp120 duoCAR-T cells

**Study Design**: Open-label dose-escalating
- Cohort 1: No CTX; single dose of 3 x 10^5 cells/kg followed by ATI
- Cohort 2: Non-ablative CTX conditioning; single dose of 3 x 10^5 cells/kg followed by ATI
- Cohort 3: Non-ablative CTX conditioning; single dose of 1 x 10^6 cells/kg followed by ATI
- Cohort 4: Non-ablative CTX conditioning; two doses of 1 x 10^6 cells/kg (day 0 and 14 of ATI)

**Population**: Treated HIV disease

**Outcomes**: Safety, reservoir reduction

**Status**: IND submission pending
Conclusions

• A truly transformative cure will need to be administered to everyone regardless of treatment status, be fully effective, and prevent re-infection
  – Aspirational but a viable pathway exits
• Most cure strategies involve combinations that reduce reservoir while enhance host-control mechanisms ("reduce and control")
  – Field may shift toward true curative interventions, particularly those involving gene therapies
Screening, Vaping, and The 12 Steps of Christmas
Addiction Medicine Update

Katherine Grieco DO FASAM
Medical Director, HAVEN
Health & Wellness Program for Healthcare Professionals, Connecticut
December 2019

Outline
- SAMHSA National Survey on Drug Use, 2018
- Data Update Stimulants
- USPSTF Screening Recommendations
- National Academies of Science, Engineering, & Medicine
- Recovery Community
- CBD Oil
- Vaping

The National Survey on Drug Use and Health: 2018
Elinore F. McCance-Katz, MD, PhD
Assistant Secretary for Mental Health and Substance Use
Substance Abuse and Mental Health Services Administration
U.S. Department of Health and Human Services
Illicit Drug Use: Marijuana Most Used Drug

PAST YEAR, 2018 NSDUH, 12+

Opioids’ Grip Lessening: Prescription Pain Reliever Misuse

PAST YEAR, 2018 NSDUH, 12+

Rx = prescription.
Opioid misuse is defined as heroin use or prescription pain reliever misuse.

+ Difference between this estimate and the 2017 estimate is statistically significant at the .05 level.

Treatment Gains: Number of Individuals Receiving Pharmacotherapy for Opioid Use Disorder (MAT)

Total Number receiving MAT (all types)

Significant Increase in Marijuana Use among Adults 26+

Past Month Use

Past Year Daily or Almost Daily Use

+ Difference between this estimate and the 2016 estimate is statistically significant at the .05 level.
Marijuana Use Disorder

PAST YEAR, 2015-2018 NSDUH, 12+

Difference between this estimate and the 2018 estimate is statistically significant at the .05 level.

Methamphetamine Use: Significant Increase in Adults > 26 y.o.

PAST YEAR, 2015-2018 NSDUH, 12+

Difference between this estimate and the 2018 estimate is statistically significant at the .05 level.

Cocaine & Psychostimulants OD on the rise – MMWR 5/19

2017: opioids were involved in
– 72.7% cocaine-involved overdoses
– 50.4% psychostimulant-involved overdoses

Cocaine: 2012-2017 - increases in cocaine-involved OD deaths driven primarily by synthetic opioids

Psychostimulant: 2010-2017-psychostimulant involved deaths occurred largely independent of opioids
– increased co-involvement of synthetic opioids in recent years.


Age-adjusted rates of drug overdose deaths involving cocaine with and without synthetic opioids other than methadone (synthetic opioids) and any opioids — United States, 2003–2017

Age-adjusted rates of drug overdose deaths involving psychostimulants with abuse potential (psychostimulants) with and without synthetic opioids other than methadone (synthetic opioids) and any opioids—United States, 2003–2017


Methamphetamine
- Methylenedioxy-methamphetamine (MDMA)
- Dextroamphetamine
- Levoamphetamine
- Methylphenidate
- Caffeine

USPSTF Screening

- Screen for illicit drug use (including non-medical use of prescription drugs) in adults age 18 years or older.
  - Screening should be implemented when services for accurate diagnosis, effective treatment, and appropriate care can be offered or referred.
- Draft Recommendation Statement
  - Final recommendation yet to be determined.
- Category B
  - The USPSTF recommends the service. There is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial.

Source: DEA


Meth. We’re On It.
USPSTF Screening

- Change from 2008 – insufficient evidence to support screening
  - Currently: No studies provide direct evidence on the benefits and harms of screening.
  - USPSTF found adequate evidence that available screening tools can detect illicit drug use.

2017, an estimated 11.5% of Americans age 18 years or older reported current illicit drug use.


Rec to screen is challenging

- No recs on which screening tools to use – “Just do it”
- How often to screen? Little guidance
- At least once, then based on risk behaviors like accidents, injuries, depression/change in behavior/mood
- More for pts who are asymptomatic; those in the throes of addiction may be easier to identify
- Know your state laws
- Report pregnant pts
- Report licensed healthcare professionals

NIH Screening & Assessment Tools Chart

<table>
<thead>
<tr>
<th>Substance Use</th>
<th>Alcohol</th>
<th>Drug</th>
<th>Self</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening tool</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brief counseling for tobacco, nicotine, and other drugs</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Measure, Assessment, Identification, and Follow-up</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Measure, counseling, identification, and follow-up</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Measure, counseling, identification, and follow-up</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Measure, counseling, identification, and follow-up</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Measure, counseling, identification, and follow-up</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Measure, counseling, identification, and follow-up</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

TAPS
Tobacco, Alcohol, Prescription medication, and other Substance use Tool

In the PAST 12 MONTHS, how often have you used tobacco or any other nicotine delivery product (i.e., e-cigarette, vaping or chewing tobacco)?

- Never
- Less Than Monthly
- Monthly
- Weekly
- Daily or almost daily

7% complete
Medications for Opioid Use Disorder Saves Lives

- 7 outcomes
- Opioid use disorder is a treatable chronic brain disease.
- FDA-approved meds to treat OUD are effective & save lives.
- Long-term retention on meds for OUD is associated with improved outcomes.
- A lack of availability of behavioral interventions is not sufficient justification to withhold meds to treat OUD.
- Life-saving aspects of these meds have been established even in the absence of accompanying behavioral interventions.
- BUT can't ignore mental health

National Academies of Science, Engineering, & Medicine Report

Most people who could benefit from medication-based treatment for OUD do not receive it
- access is inequitable across subgroups of the population.
- Withholding or failing to have available all classes of FDA-approved meds for the tx of OUD in any care or criminal justice setting is denying appropriate medical tx.
- Confronting the major barriers to the use of meds to treat OUD is critical to addressing the opioid crisis.
The Recovery Community

- Recovery activities: what are they?
  - Sobriety vs Recovery
  - "Such knowledge is an ethical and professional imperative [for providers]."
- Awareness vs Endorsing
- Endorsed by ASAM, AAAP
  - "In most cases of addiction, the integration of psychosocial rehabilitation & evidence-based pharmacological therapy provides the best results."
- It's NOT fluff
- Consider your patient population

William Haning, MD DFASAM; Editorial Comment: The other community recovery groups. The ASAM Magazine, 8/5/19

Which statement is FALSE?

A) If a person has opioid use disorder, but no history of alcoholism, AA is an appropriate meeting to attend.
B) AA meetings are available in airports.
C) It’s recommended to begin the 12 Steps of Recovery after at least 90 days of sobriety.
D) There are several alternative recovery mtgs available for those who do not subscribe to the AA/NA model.

Self Help Groups

- AA model – AA, NA, CMA, GA, etc
  - Addiction to drugs/alcohol and process addictions
  - Oldest recovery model
  - FREE
- AA, NA – fluid criteria for attendance
- Promotes Recovery Activities
  - ‘Outside’ of professional help
  - Creates fellowship based on recovery
  - Instills HOPE

12-Step Recovery

- Step 1: admit powerless over alcohol
- Step 2: accept that a higher power, in whatever form, will restore your sanity
- Step 3: make a decision to turn your will and life over to a higher power
- Step 4: take a moral inventory of yourself
- Step 5: admit to a higher power, another human, and yourself the nature of your wrongdoings
- Step 6: accept that a higher power will remove your shortcomings
  - Learn to manage weaknesses, faults
12-Step Recovery

- **Step 7**: Humbly request the higher power to remove your shortcomings.
- **Step 8**: List people you hurt during your addiction and be willing to make amends.
- **Step 9**: Make amends to those people unless it would harm them.
- **Step 10**: Continue to take a personal inventory, and when you’re wrong, admit it.
- **Step 11**: Use prayer and meditation to connect with higher power.
- **Step 12**: Carry the message of AA to other alcoholics and continue to practice the principles of the 12 steps in your daily life.

Self Help Groups: AA, NA

- Different types of AA mtgs
  - Speaker, Step, Beginners
  - Big Book - 1939, written by AA founders (Bill Wilson, Dr. Bob)
- Finding a sponsor
- Working through the steps
  - Can take months or years
  - Can revisit any step at any time
- Identifying a ‘Home’ group
  - 90 in 90 – 90 mtgs in 90 days
  - Marathon Meetings – holidays (Christmas)
- Locations: all over USA
  - Cruise ships
  - Airports: “Friends of Bill W”
- DOC

Efficacy??

- Remains controversial
- Study results very divergent.
  - 2006 Cochrane Review: unclear effectiveness, needs further study
  - 2008 Review of literature: Rates of abstinence are about twice as high among those who attend AA
- Prior AA attendance is predictive of subsequent abstinence
- Barriers to an ideal study design
  - Anonymity
  - Admitting to relapse
  - Alcohol vs other drugs
  - Definition of efficacy/success
- Anecdotally – support seems real

AA Mtgs: San Francisco Area

<table>
<thead>
<tr>
<th>Title</th>
<th>Meeting</th>
<th>Location</th>
<th>Address</th>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 00am Speaker’s Message</td>
<td>Central Office Center</td>
<td>5525 Fill Ave</td>
<td>Invert Forest</td>
<td></td>
</tr>
<tr>
<td>11 00am Group Discussion</td>
<td>Meeting Place</td>
<td>1507 20th St</td>
<td>Invasion</td>
<td></td>
</tr>
<tr>
<td>11 00am Local Group</td>
<td>St. Francis Lutheran Church</td>
<td>1902 Church St</td>
<td>Carney</td>
<td></td>
</tr>
<tr>
<td>11 00am Women’s Meeting</td>
<td>Mission</td>
<td>566 Lincoln Ave</td>
<td>San Rafael</td>
<td></td>
</tr>
<tr>
<td>11 00am Sunday Night 3rd Step Group</td>
<td>St. Paul’s Church</td>
<td>6455 Church St</td>
<td>Nice Vale</td>
<td></td>
</tr>
<tr>
<td>11 00am 12 Step Meeting</td>
<td>Dry Dock</td>
<td>2114 Greenwell St</td>
<td>Marla</td>
<td></td>
</tr>
<tr>
<td>11 00am Speaker Discussion</td>
<td>First Rose</td>
<td>4120 36th St</td>
<td>Seacliff</td>
<td></td>
</tr>
<tr>
<td>11 00am Intensive - AA Core of Aa Book Study</td>
<td>City Hall</td>
<td>405 Litar St</td>
<td>Sausalito</td>
<td></td>
</tr>
<tr>
<td>11 00am 90/90 After</td>
<td>Delight Park Church</td>
<td>61 Delight St</td>
<td>Mission</td>
<td></td>
</tr>
<tr>
<td>11 00am Sobriety</td>
<td>Mission</td>
<td>5860 Lincoln Ave</td>
<td>San Rafael</td>
<td></td>
</tr>
<tr>
<td>11 00am Washington Square</td>
<td>Washington Square</td>
<td>5854 Panora St</td>
<td>North Beach</td>
<td></td>
</tr>
</tbody>
</table>
**Self Help Groups**

- **SMART Recovery: Self Management And Recovery Training**
  - Online meetings
  - [www.smartrecovery.org](http://www.smartrecovery.org)

- **Refuge Recovery: Buddhist principles**
  - [refugerecovery.org](http://refugerecovery.org)
  - [recoverydharma.org](http://recoverydharma.org)

- **Secular Organizations for Sobriety (SOS)**
  - [www.sossobriety.org](http://www.sossobriety.org)

- **Celebrate Recovery: Christ centered; CA prison system**
  - [www.crecovery.com](http://www.crecovery.com)
  - [codependency.com](http://codependency.com)

- **Women For Sobriety**
  - *relating over-reliance on substances to the loss of identity many women feel with competing roles in society…guilt, low self-esteem*
  - [womenforsobriety.org](http://womenforsobriety.org)

**Exercise Activities**

- **Yoga 12-step**
  - [y12sr.com](http://y12sr.com)

- **CrossFit Redemption**

- **Wild Recovery – NA**
  - Based in the Bay Area
  - Destination hikes followed by NA mtgs
  - [wildrecovery.org](http://wildrecovery.org)

---

**Castro Country Club**

**GaL - AA**

- **Gays and Lesbians AA**
  - Serves LGBT+ members of AA

- **Roundups**
  - 12-step mtgs, workshops, activities
  - Provincetown, Houston, Toronto and others

---

**Yoga 12-step**

- [y12sr.com](http://y12sr.com)

- **CrossFit Redemption**

- **Wild Recovery – NA**
  - Based in the Bay Area
  - Destination hikes followed by NA mtgs
  - [wildrecovery.org](http://wildrecovery.org)
Proceed with caution…

Moderation Management
- Harm reduction model for alcohol use
- Effort to intervene early for “problem drinkers” to avoid progression to full alcohol use disorder
- Freedom for the individual to choose controlled drinking vs abstinence
- NOT for severe alcohol use disorder
- NOT for safety sensitive occupations
- www.moderation.org

12-Step Facilitation Therapy
- Evidence-based
- Not a 12-step support group
- Not a manual
- Facilitated by a therapist
- Includes at least 12 mtgs – individual and group
- Goals
  - Acceptance, surrender, active involvement in 12 step mtgs/activities


CBD Oil
- Shown to have anxiolytic, antidepressant, antipsychotic, antiseizure properties mostly in animal models
- May help prevent relapse
- Curb cravings in opioid addiction
- Tincture, balm, capsules, gummies

*Hurd, Y et al. Cannabidiol for the Reduction of Cue-Induced Craving and Anxiety in Drug-Abstinent Individuals With Heroin Use Disorder: A Double-Blind Randomized Placebo-Controlled Trial Published Online:21 May 2019

Which statement is TRUE?

- A) CBD oil is made only from hemp and contains no THC.
- B) CBD oil is made only from hemp and contains THC.
- C) CBD oil is made from marijuana but contains no THC.
- D) CBD oil is made from cannabis and may contain THC.

THC: tetrahydrocannabinol; psychoactive component of marijuana
Cannabidiol Oil

- Cannabis:
  - Hemp - almost void of THC (less than 0.3%) – federally legal
  - Marijuana – has THC – federally illegal
- CBD oil is extracted from either, most from hemp
  - Isolate – pure compound
  - Full-spectrum product – various active plant compounds including THC
- Not FDA regulated – products often mislabeled (2 studies)
  - Only 30% labeled correctly; 70% mislabeled amounts of THC
- Exception: CBD for epilepsy (2 forms)
- Cross contamination during extraction process
- Concern CBD oil products may have THC present at unknown levels
- Implications for UDS – depends on level of detection


CBD Oil

- Low affinity for cannabinoid receptors, may interact with opioid and glycine receptors (serotonin)
- Liver damage?
  - Very high doses caused severe liver damage in mice
  - Much higher than the standard dose of CBD oil for humans ~20mg/kg
- Drug interactions: cytochrome p450


Vaping

- Electronic cigarettes: also called e-cigs, vapes, e-hookahs, vape pens, tank systems, electronic nicotine delivery systems (ENDS).
- Heats a liquid to produce an aerosol that users inhale into their lungs.
- Liquid can contain
  - nicotine, tetrahydrocannabinol (THC) and cannabinoid (CBD) oils, and other substances and additives.

EVALI

- E-cigarette, or Vaping, product use Associated Lung Injury
- As of November 13, 2019
  - 2,290 cases reported to CDC from 49 states (all except Alaska), the District of Columbia, and 2 U.S. territories.
  - 47 deaths in 25 states and the District of Columbia: California (4)
  - Median age of deceased patients 53 years
    - ranged from 17 to 75 years
All EVALI patients have reported a history of using e-cigarette/vaping products.

THC is present in most of samples tested by FDA to date – most pts report a history of using THC in some form.

Latest findings suggest products containing THC, particularly from illicit/informal sources, are linked to most of the cases.

Diagnosis of exclusion

Vitamin E acetate: ‘chemical of concern’

- Vitamins, topical skin creams- doesn’t cause harm
- Inhalation – may interfere with normal lung function.
- Additive in vaping products, similar to THC oil
  – Odorless, colorless
  – Illicit cannabis vaping products – stretches the amount in cartridges
- thickening ingredient – like honey or grease
- Boiling point of 363 degrees F, vs water 212 degrees

29 BAL samples sent to CDC 8/19 – 10/19
- All 29 tested + vitamin E
- 2 pts died
- From 10 different states
- Other potential culprits not detected
  - Plant oils, petroleum

At this time, no cause identified of lung injuries
- Common denominator: all patients report use of e-cig/vape
- No one compound or ingredient has emerged as the cause to date
- Many different substances/product sources under investigation
Reporting to CDC

- Send BAL specimens to CDC
- CDC offers aerosol emissions testing of case-related vape products
- CDC updates every Thursday
  - Outbreak of Lung Injury Associated with the Use of E-Cigarette, or Vaping, Products
  - https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html
Interim Guidance

History
- Scope of sxs – most started with resp; some had GI sxs; several s/off
- Ask about THC use! And other nicotine use

Physical Exam
- O2 sats majority less than 95%
- Tachycardia/tachypnea
- Auscultation was unremarkable

Laboratory
- Laboratory testing should be guided by clinical findings.
  - respiratory virus panel, including influenza testing
  - guidelines for evaluation of community-acquired PNA
  - Infectious diseases to consider include Strep pneumoniae, Legionella pneumophila, Mycoplasma pneumoniae, endemic mycoses, and OIs

Urine toxicology
- Check for THC – also consider cocaine

Bronchoscopy – BALs? Lung biopsy?

Imaging
- Chest X-ray
- Consider chest CT for severe or worsening disease, complications, other illnesses; or if CXR results do not correlate w/clinical findings.
- EVALI findings include pulmonary infiltrates on CXR and opacities on CT scan

EVALI Treatment
- Consider corticosteroids –except for fungal PNA – may worsen
- Treatment for influenza, CAP, PCP, etc
STOP vaping
If not, then avoid all THC products

Thank you for your attention, and for your commitment to treating those patients with substance use disorders.
Objectives

1. Describe antiretroviral options for use with an M184V mutation
2. Create an ART regimen compatible with anticoagulation medications
3. Discuss use of BIC/TAF/FTC with Doravirine
4. Discuss treatment of toxoplasmosis in 2019

Roadmap

- ART with M184V
- Anticoagulants and ART
- Doravirine as Salvage
- A Modern Toxo Tale
Case 1

53M with HIV comes in for regularly scheduled follow-up
- Last CD4 683 cells/mm³, HIV RNA <40 copies/mL
- On TAF/FTC/RPV + DTG since 2016

HIV History
- Diagnosed 12/2002, started 3TC/AZT + NFV, complicated by nausea/vomiting
- 4/2003 HIV RNA 16K copies/mL, genotype with M184V mutation
- Switched to new regimen and HIV RNA has been undetectable since then

He has been hesitant to simplify his ART

ARS: What would you do with his ART in light of the M184V?

A. Continue current regimen (TAF/FTC/RPV + DTG)
B. Simplify to TAF/FTC/RPV alone
C. Switch to TAF/FTC + DTG
D. Switch to BIC/TAF/FTC
E. Switch to TAF/FTC/c/DRV
F. Switch to ABC/3TC/DTG
What would you do with his ART in light of the M184V?

A. Continue current regimen (TAF/FTC/RPV + DTG)
B. Simplify to TAF/FTC/RPV alone
C. Switch to TAF/FTC + DTG
D. Switch to BIC/TAF/FTC
E. Switch to TAF/FTC/c/DRV
F. Switch to ABC/3TC/DTG

What is the data for use of these ARVs with an M184V?

Option C: Switch to TAF/FTC + DTG

• Background
  • DAWNING (IAS 2017): In 627 patients worldwide failing NNRTI therapy but with ≥1 active NRTI, DTG was superior to r/LPV as salvage
  • DAWNING sub-analysis (CROI 2019): Looked at different NRTI mutations and the impact of those mutations in the DTG and r/LPV
  • Patients were NOT virologically suppressed before starting the study but did have genotypes available

DAWNING Sub-Analysis: Virologic outcomes

DAWNING Sub-Analysis: Results

• DTG maintained virologic suppression at 48w when paired with 2 NRTIs regardless of pre-existing RAM to one of the NRTIs, including use of XTC with a M184V
• Virologic failure (VF) lower in DTG arm (11) than r/LPV arm (30)
  • RAMs emerged in 2 in DTG and 3 in PI arm
  • DTG failures: INSTI-R (G118R, R263K)
  • r/LPV failures: No PI-R
  • Reaffirming that DTG does fail with INSTI resistance, but b/PIs generally do not
Option D: Switch to BIC/TAF/FTC

- **Background**
  - BIC/TAF/FTC (Biktarvy) has been found to be non-inferior in:
    - Treatment-naive individuals (Studies 1489, 1490)\(^1,2\)
    - As switch in virologically suppressed individuals (Studies 1844, 1878)\(^3,4\)
    - Women (1961)\(^5\)
  - But what about its use in people with underlying resistance?

Switch to BIC/TAF/FTC in Patients with Historical Resistance

- **Study GS-4030**: Placebo-controlled RCT of 565 virologically suppressed patients on TAF/FTC + DTG or TDF/FTC + DTG
  - Randomized to cont. DTG regimen or switch to BIC/TAF/FTC
  - Genotypic data from historical + proviral DNA
  - Excluded INSTI-R

- **Baseline drug resistance in 222 (39%) of the study:**
  - NRTI-R (24%), NNRTI-R (24%), PI-R (8%)

- **48 Week Results**
  - Overall, 93 vs 91% virologic suppression overall
  - 99% with any drug resistance maintained suppression
  - 98% with M184 (81) maintained suppression
  - No treatment-emergent resistance

Historical Resistance in Switch Studies 1844 + 1878

- **OLE of 572 patients aimed to evaluate virologic outcomes based on analysis of pre-existing resistance**
  - Baseline resistance from historical and proviral genotypes (543, 95%)
    - NRTI-R: 10% (M184 in 10%)
    - NNRTI-R: 21%
    - PI-R: 8%
    - INSTI-R: 1.9%

- **48 Week Results**
  - Overall, 98% of B/F/TAF-treated participants were suppressed
  - 96% (52/54) with archived M184V/I were suppressed
  - 100% (13/13) with INSTI-R were suppressed

Option E: Switch to TAF/FTC/c/DRV

- **Background**
  - TAF/FTC/c/DRV (Symtuza) was FDA approved July 2018

- **EMERALD Study**
  - Randomized controlled trial switch study of 1,141 virologically suppressed to TAF/FTC/c/DRV vs continued TDF/FTC + b/DRV (non-inferior)
    - 58% had ≥5 prior ARV regimens
    - 15% with previous virologic failure but not to DRV
    - Resistance allowed, but not to DRV (4% with M184 but on proviral DNA)
ART with M184V: Take-home points

1. DAWNING subanalysis affirms the practice of using DTG with <2 active NRTIs, but ≥ 1 active NRTI (to avoid DTG monotherapy)
2. If already suppressed with baseline M184, can likely switch to BIC/TAF/FTC and stay virologically suppressed
3. TAF/FTC/c/DRV is a good option for the heavily treatment experienced with M184 and other baseline RAMs (but not to DRV)

Roadmap

- ART with M184V
- Anticoagulants and ART
  - Doravirine as Salvage
  - A Modern Toxo Tale

Case 2

- 61M with HIV presents to urgent care with RLE swelling
- Last CD4 348 cells/mm³, HIV RNA <40 copies/mL
- Diagnosed with acute unprovoked DVT, needs anticoagulation
- On ABC/3TC/r/DRV since 2016
ARS: Which regimen will you use if he is unable to switch his ART regimen?
A. Warfarin
B. Apixaban
C. Dabigatran
D. Rivaroxaban

ARS: Which regimen will you use if the patient cannot switch ART and cannot adhere to INR monitoring?
A. Warfarin
B. Apixaban
C. Dabigatran
D. Rivaroxaban

Background
- Direct-acting oral anticoagulant medication (DOAC) use is increasing
- Commonly used DOACs - apixaban, rivaroxaban, and dabigatran – are eliminated either via CYP450 enzymes, P-glycoprotein, or both
- Warfarin is metabolized by CYP2C9

ART & Anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>DOAC</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Apixaban</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td>NRTI</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>NNRTI</td>
<td>Caution</td>
<td>Caution</td>
</tr>
<tr>
<td>PI</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>INSTI</td>
<td>✗</td>
<td>✓</td>
</tr>
</tbody>
</table>
### ART & Anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>DOAC</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>Apixaban</td>
<td>Red</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban</td>
<td>Yellow</td>
</tr>
<tr>
<td></td>
<td>Dabigatran</td>
<td>Green</td>
</tr>
<tr>
<td>NNRTI</td>
<td>Apixaban</td>
<td>Red</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban</td>
<td>Yellow</td>
</tr>
<tr>
<td></td>
<td>Dabigatran</td>
<td>Green</td>
</tr>
<tr>
<td>INSTI</td>
<td>Apixaban</td>
<td>Red</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban</td>
<td>Yellow</td>
</tr>
<tr>
<td></td>
<td>Dabigatran</td>
<td>Green</td>
</tr>
</tbody>
</table>

### NNRTIs & Anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>DOAC</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>Apixaban</td>
<td>Red</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban</td>
<td>Yellow</td>
</tr>
<tr>
<td></td>
<td>Dabigatran</td>
<td>Green</td>
</tr>
</tbody>
</table>

- CYP450 enzyme induction by NNRTIs may DECREASE levels of the DOAC
- NNRTIs can alter warfarin levels

### Protease Inhibitors & Anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>DOAC</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>Apixaban</td>
<td>Red</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban</td>
<td>Yellow</td>
</tr>
<tr>
<td></td>
<td>Dabigatran</td>
<td>Green</td>
</tr>
</tbody>
</table>

- PIs can alter warfarin levels
- CYP450 inhibition by PIs or boosters may INCREASE levels of the DOAC
- Adult and Adolescent ARV Guidelines recommend avoiding DOACs + PIs

### But what if you HAVE to use a PI and a DOAC?

- Rivaroxaban
  - Co-administration not been studied
- Apixaban
  - 50% dose reduction is recommended with close monitoring for bleeding
  - No adverse outcomes in PWH on half-dose apixaban while on ritonavir- or cobicistat-boosted regimens
- Dabigatran
  - Dabigatran administered 2 hours before ritonavir 100mg resulted in dabigatran AUC decrease by 29%, so take PI together with dabigatran if needed
  - Cobicistat 150mg with dabigatran increased dabigatran AUC by > 2-fold

---

1. Liverpool HIV Drug Interactions
2. National HIV Curriculum
3. Nisly SA, Int J STD AIDS, 2019
4. AIDSinfo.gov
Take-Home Points

- In general, NRTIs and INSTIs (except EVG) ok with DOACs and warfarin
- NNRTIs and PIs can alter warfarin levels
- NNRTIs can decrease DOAC levels – use caution
- PIs can increase DOAC levels – avoid
  - If have to use apixaban, use half-dose
  - Do not use cobicistat with dabigatran
- If using ritonavir with dabigatran, take PI and dabigatran at the same time

Roadmap

- ART with M184V
- Anticoagulants and ART
- Doravirine as Salvage
- A Modern Toxo Tale

Case 3

- 65M with HIV and multiple medical problems comes in for follow-up
- Last CD4 388 cells/mm³, HIV RNA undetectable
- On BIC/TAF/FTC + Doravirine

Is this the best regimen for him?
Case 3: Prior Genotype Results

- RT: M41L, K103N, Y181C, M184V, T215Y, H221Y
- PI: None
- INSTI: none

M41L, T215Y (TAMs) – resistance to ABC and TDF/TAF
M184V – resistance to ABC, 3TC, and FTC
K103N – resistance to EFV and NVP
Y181C – resistance to EFV, NVP, ETR, and DOR
H221Y – some resistance to all NNRTIs

Background

- Doravirine = NNRTI FDA approved in 8/2018
- Available in 100mg dose
  - Delstrigo (TDF/3TC/DOR) daily
  - Pifeltro (DOR) daily
- No food requirements
- OK with PPIs
- Few drug-drug interactions

Doravirine Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRIVE-AHEAD1</td>
<td>ART start DOR/TDF/3TC non-inferior to TDF/FTC/EFV</td>
</tr>
<tr>
<td>DRIVE-FORWARD2</td>
<td>ART start DOR + 2NRTI non-inferior to rDRV + 2NRTI</td>
</tr>
<tr>
<td>DRIVE-SHIFT3</td>
<td>ART switch DOR/TDF/3TC non-inferior at 24w and 48w vs baseline ART at 24w</td>
</tr>
</tbody>
</table>

DOR as Salvage: Questions

1. What mutations arise with Doravirine use?
2. With what NNRTI mutations can we use Doravirine?
3. What is Doravirine’s role in salvage therapy?
4. What data exists for use of BIC/TAF/FTC + Doravirine?
Emergent Resistance in ART Naïve Studies with Doravirine

<table>
<thead>
<tr>
<th>Field Change by Virus</th>
<th>NNRTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>1.0</td>
</tr>
<tr>
<td>NTR (Y181C)</td>
<td>1.0</td>
</tr>
<tr>
<td>H221</td>
<td>2.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Resistance in DRIVE-SHIFT Switch Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Baseline mutations</td>
</tr>
<tr>
<td>• Virologic suppression maintained in 24 patients with baseline NNRTI resistance (K103N, Y181C, G190A)</td>
</tr>
<tr>
<td>• Viral failure</td>
</tr>
<tr>
<td>• PDVF occurred in 6 people in immediate switch, 1 in delayed switch, and 1 in baseline ART</td>
</tr>
<tr>
<td>• Treatment-emergent resistance</td>
</tr>
<tr>
<td>• No resistance in DOR group, one person in baseline ART had a M184</td>
</tr>
<tr>
<td>• No resistance in those with early discontinuation</td>
</tr>
</tbody>
</table>

DOR as Salvage: Answers

1. **What mutations arise with Doravirine use?**
   - V106, P225, F227, H221

2. **With what NNRTI mutations can we use Doravirine?**
   - Can use with a K103, Y181, G190
   - Beware E138, and do not use with other NNRTI mutations

3. **What is Doravirine’s role in salvage therapy?**
   - Can use in a TRIO-like regimen, with 3 Ds = DTG/d/DRV/DOR

4. **What data exists for use of Biktarvy + Doravirine?**
   - None

Roadmap

- ART with M184V
- Anticoagulants and ART
- Doravirine as Salvage
- A Modern Toxo Tale
Case 4
A Modern Toxo Tale

Background

• *Toxoplasma gondii* is a protozoan parasite that is acquired congenitally, through consumption of cysts in undercooked meats, and exposure to cat feces.

• In immunocompromised hosts, it can reactivate and cause encephalitis, but can also disseminate to eyes, heart, lungs, etc.

• Today, it is rarely seen due to ART and effective prophylaxis, but toxoplasmosis made the news in 2015 due to cost of pyrimethamine.

A young man from East Africa presents with...

Avidly ring-enhancing intramedullary spinal cord lesion at T12 with adjacent abnormal cord signal and cord expansion.
A young man from East Africa is admitted with...

10/2018
Urinary retention and low back pain,
new dx HIV (CD4 11/3%)

10/2018
Pyrimethamine + Leucovorin
Sulfadiazine

11/2018
Spinal cord lesion vastly improved,
but experiences medication side effects

11/2018
Pyrimethamine + Leucovorin
Sulfadiazine
Clindamycin BIC/TAF/FTC

Toxoplasmosis Treatment

Prefered Regimen (ZV):
- Pyrimethamine 100 mg PO once, followed by dose based on body weight:
  - Body weight < 40 kg: pyrimethamine 50 mg PO daily + sulfadiazine 1000 mg PO qid + leucovorin 10-25 mg PO daily (can increase to 30 mg daily or BID)
  - Body weight ≥ 40 kg: pyrimethamine 75 mg PO daily + sulfadiazine 1000 mg PO qid + leucovorin 15-25 mg PO daily (can increase to 50 mg daily or BID)

Alternative Therapy:
- (Pyrimethamine + leucovorin) + clindamycin 600 mg IV or PO qd, (AIDS preferred alternative for patients intolerant of sulfadiazine or who don't tolerate pyrimethamine)
- Trimethoprim 5 mg/kg and sulfamethoxazole 25 mg/kg orally PO (BID) or IV (Q12H) + pyrimethamine +/- sulfadiazine
- Acyclovir 10 mg/kg BID + pyrimethamine + sulfadiazine
- Acyclovir 15 mg/kg BID + pyrimethamine + sulfadiazine
- Acyclovir 20 mg/kg BID + pyrimethamine + sulfadiazine
Toxoplasmosis Treatment cont.

- If pyrimethamine is unavailable or there is a delay in obtaining it, TMP-SMX should be used in place of pyrimethamine-sulfadiazine (B1).
- For patients with a history of sulfa allergy, sulfa desensitization should be attempted (B1).
- Atovaquone should be administered until therapeutic doses of TMP-SMX are achieved (CIII).

**Total Duration for Treating Acute Infection:**
- At least 24 weeks (B2): Longer duration if clinical or radiologic disease is extensive or response is incomplete at 12 weeks
- After completion of the acute therapy, all patients should be continued on chronic maintenance therapy

---

**Chronic maintenance therapy**

**Chronic Maintenance Therapy for Temporally-Proximal Toxoplasmosis**

**Preferred Regimen:**
- Pyrimethamine 25-30 mg PO daily + sulfadiazine 2000-2400 mg PO daily (it's a divided dose) + trimethoprim 16.25 mg PO daily (B1)

**Alternative Regimen:**
- Clindamycin 900 mg PO q8h + pyrimethamine 25-30 mg PO daily (B1) + trimethoprim 16.25 mg PO daily (B1) + sulfadiazine 2000-2400 mg PO daily (it's a divided dose) (B2)

**Discontinuing Chronic Maintenance Therapy:**
- Successfully completed oral therapy, remain asymptomatic of signs and symptoms of T. gondii, and CD4 count >100 cells/mm^3 for at least 6 months in response to ART (B1)

**Criteria for Restarting Secondary Toxoplasmosis/Chronic Maintenance Therapy**
- CD4 count <100 cells/mm^3 (B1)
Internal development of numerous ring and punctate enhancing lesions in bilateral cerebral hemispheres, right greater than left basal ganglia, bilateral cerebellar hemispheres.

10/2018 Urinary retention and low back pain, new deMyH (CD4 11/3%)

A young man from East Africa returns with...

11/2018 Spinal cord lesion vastly improved, but experiences medication side effects

11/2018 Discharged to SNF

11/2018 New headaches and vision loss, abnormalities on brain MRI

12/2018 Discharged to self care after DOT and symptomatic improvement

6/2019 New headaches and vision loss, abnormalities on brain MRI

6/2019 Discharged to self care after DOT and symptomatic improvement

A young man from East Africa returns with...

7/2019 Presents to clinic

Toxoplasmosis Primary Prophylaxis

- For PWH with CD4 < 100 cells/mm² & Toxoplasma seropositivity (IgG)

Regimens for Toxoplasmosis Encephalitis Primary Prophylaxis

Preferred Regimen:
- Trimethoprim-sulfamethoxazole, 1 D5 PO daily (BID)

Alternative Regimens:
- Trimethoprim-sulfamethoxazole 1.15 cap 2x/day (BID) or
- Eprosamide (350 mg PO or intravenous) 2x/day (BID) or
- Atovaquone (750 mg PO) 2x/day (BID) or
- Sulfadiazine (1 g PO) 2x/day (BID)

Image from National HIV Curriculum.
Take-Home Points

- Toxoplasmosis is a rare but treatable infection with a high likelihood of dissemination and recurrence.
- Treatment includes induction (at least 6 weeks), followed by chronic maintenance (or secondary prophylaxis) until immune reconstitution.
- Many options exist for toxoplasmosis treatment and prophylaxis, even in the setting of high pyrimethamine costs.

Case Recap

- Case 1: In a patient with a history of M184 only who is already virologically suppressed, ART simplification options reviewed include TAF/FTC or TDF/FTC + DTG, BIC/TAF/FTC, or TAF/FTC/c/DRV.
- Case 2: Beware DOACs with NNRTIs, and avoid DOACs with PIs.
- Case 3: There is no data regarding use of BIC/TAF/FTC + Doravirine.
- Case 4: Toxoplasmosis is rare, but if treatment or prophylaxis is needed, alternative options to pyrimethamine exist.

Supplementary Materials

DAWNING: Baseline Characteristics

- Resistance
  - 80% received <2 fully active NRTIs
  - 90% with NRTI-R
  - 82% with a M184V (+/- other RAMs)
  - 30% with a K65R
  - 24% with ≥ 1 TAM
- Baseline NRTI regimen, post randomization
  - AZT + 3TC (41%)
  - TDF + XTC (42%)
  - TDF + AZT (12%)
  - ABC + 3TC (2%)
DAWNING Sub-Analysis: Results

Virologic outcomes

- AZT/3TC: 25.9%
- AZT/3TC: 12.5%
- WT: 30.0%
- WT: 15.0%
- AZT + other NRTI: 6.0%
- AZT + other NRTI: 3.0%

Source: Brown, CROI 2019 #144
Objectives

- Select and interpret diagnostic tests for latent tuberculosis infection (LTBI) in HIV-infected patients
- Design an LTBI treatment plan that accounts for ART drug interactions
- Identify appropriate methods to screen for LTBI vs. diagnose active TB
- Describe when to start ART in TB and major rifamycin-ART interactions
- Manage TB immune reconstitution inflammatory syndrome (IRIS)

Tuberculosis: A major global health problem

- 2018:
  - 10.0 million cases/year
  - 1.5 million deaths/year
- #1 cause of death among PLHIV

Disclosure

I have no relevant financial relationships with any companies related to the content of this course.
Epidemiology of TB in the United States


Epidemiology of TB in California


- California reports 20% of TB cases in the US each year
- >2000 cases annually
- LTBI cases estimated at 2.4 million
- 1 in 17 Californians
- 1 in 5 foreign-born Californians

Audience response

How many people have you started on latent TB treatment in the past year?
A. None.
B. <5
C. 5-10
D. Who has time to count!?

Case 1

A 41 year-old man from San Francisco presents to your clinic for evaluation. Two weeks ago, he was diagnosed with HIV.

- Initial labs show:
  - CD4 120, HIV RNA 75,000
  - Interferon gamma release assay (IGRA): Indeterminate
- He denies any history of TB infection and does not know of any contacts with TB
- He has experienced homelessness and has had brief periods of incarceration in the past
Audience Response

What is the correct interpretation of this indeterminate IGRA result and what is your next step?

A. TB infected; rule out active TB and treat him
B. TB exposed, uninfected; do nothing
C. TB infection cannot be determined; re-test when CD4 is higher
D. TB exposed OR BCG vaccinated; obtain a PPD “tie-breaker”
E. TB infection cannot be determined; obtain a PPD “tie-breaker”

Screening for LTBI in HIV

- WHO?
  - All HIV patients, regardless of risk factors
- WHY?
  - Increased risk of progression to active disease
  - Poor outcomes with active disease
  - Screening tests exist
  - Effective treatments exist

- WHEN?
  - At HIV diagnosis or entry into care
  - In those with negative LTBI test & CD4<200 → repeat after ART started & CD4>200
  - If likely ongoing/repeat exposure to active TB: Screen annually
  - Recent contact with a known TB case

Testing for LTBI

Option 1: Tuberculin Skin Test
- Vast experience, abundant data
- Cheaper
- Requires 2 visits
- False positives possible with BCG
- Can remain positive after LTBI, active TB

Option 2: Interferon Gamma Release Assay
- Requires 1 visit
- Interpretation not subjective
- More specific than TST
- Unaffected by BCG
- Requires 2 visits
- Technical errors
- Must be processed in 8-30hrs
- False positives with some other mycobacteria
- Limited data in children, recent TB exposure, CD4<200
- Can remain positive after LTBI, active TB

Neither distinguishes between latent and active disease
Negative does NOT rule out active disease

Diagnostic Approach | Strengths | Limitations
--- | --- | ---
TST | Vast experience, abundant data, Cheaper | Requires 2 visits
  
IGRAs | Requires 1 visit, Interpretation not subjective, More specific than TST, Unaffected by BCG | Technical errors, Must be processed in 8-30hrs, False positives with some other mycobacteria, Limited data in children, recent TB exposure, CD4<200, Can remain positive after LTBI, active TB

*BCG status should NOT affect PPD interpretation
QuantiFERON-TB Gold-Plus

- 4th generation IGRA FDA approved 6/2017
- Advances/Advantages1
  - Adds CD8+ T cell antigens
  - Option for single tube blood collection
  - Non-inferior sensitivity

- PLHIV2
  - Overall sensitivity not affected by HIV status
  - Lower sensitivity with severe immunosuppression


QuantiFERON-TB: Interpretation

<table>
<thead>
<tr>
<th>Nil (IU/ml)</th>
<th>TB minus Nil (IU/ml)</th>
<th>Mitogen minus Nil (IU/ml)</th>
<th>QFT-Plus Result</th>
<th>Report/Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤8.0</td>
<td>Any</td>
<td>Any</td>
<td>Nil</td>
<td>Negative</td>
</tr>
<tr>
<td>&gt;8.0</td>
<td>Any</td>
<td>Any</td>
<td>Nil</td>
<td>Negative</td>
</tr>
<tr>
<td>0.35 and ≤25% Nil</td>
<td>≥0.35</td>
<td>Any</td>
<td>Nil</td>
<td>Negative</td>
</tr>
<tr>
<td>&gt;0.35 OR ≥0.5</td>
<td>≥0.35 and &gt;25% Nil</td>
<td>Any</td>
<td>Nil</td>
<td>Negative</td>
</tr>
</tbody>
</table>

...but wouldn't a tie-breaker help?

“...the predictive value of this approach is not clear, and its adoption would be more expensive and more difficult to implement. The routine use of both TST and IGRAs to screen for LTBI is not recommended in the United States”2


Notes:
- Low risk pt. concern for false positive
- Borderline positive: concern for false positive
Case 1 (continued)
41M from SF with new HIV (CD4 120, VL UD) and indeterminate IGRA

- You start him on Descovy (TAF/FTC) and Dolutegravir
- 3 month labs demonstrate:
  - CD4 is 230, VL undetectable
  - Repeat QuantiFERON positive
- He is asymptomatic
- CXR is within normal limits

You decide to treat him for LTBI.

Current Guidelines for TB Preventive Therapy

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Adult Dosage</th>
<th>Durations, Months</th>
<th>Evidence Rating in HIV-Positive Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid* daily</td>
<td>300 mg/day</td>
<td>9</td>
<td>A I</td>
</tr>
<tr>
<td>Isoniazid* daily</td>
<td>300 mg/day</td>
<td>6</td>
<td>C I</td>
</tr>
<tr>
<td>Rifampin daily</td>
<td>600 mg/day</td>
<td>4</td>
<td>B I</td>
</tr>
<tr>
<td>Rifapentine + Isoniazid† weekly</td>
<td>Maximum: 800 mg/900 mg (+/- DOT)</td>
<td>3</td>
<td>A II</td>
</tr>
</tbody>
</table>

*Give pyridoxine 10-50 mg/day with isoniazid to prevent neuropathy in HIV-positive pts.
†Rifapentine and isoniazid recommended only with Efavirenz and Raltegravir + ABC/3TC or TDF/FTC.

DHHS OI Guidelines, 2019; Borisov, MMWR, 2018.

LTBI Treatment Options

- Preferred
  - SH: INH x 9 months (with B6)
- Alternative
  - 3HP: INH + Rifapentine weekly (with B6) †
  - 4R: Rifampin x 4 months
  - 6H: INH x 6 months (with B6)*
  - ZRP: Rifampin + Pyrazinamide x 2 months
- **High risk of hepatotoxicity**†

†Rifapentine and isoniazid recommended only with Efavirenz and Raltegravir + ABC/3TC or TDF/FTC.

Audience Response
41M from SF with new HIV (CD4 230, VL UD) on TAF/FTC/DTG with positive IGRA

Which one of the following regimens do you select to treat LTBI in this patient?

A. Isoniazid, pyrazinamide, rifampin, ethambutol, and pyridoxine for 2 months
B. Isoniazid and pyridoxine daily for 9 months
C. Isoniazid and pyridoxine daily for 6 months
D. Isoniazid and pyridoxine plus rifapentine weekly for 3 months
What is an “acceptable drug-drug” interaction with rifapentine?
Rifapentine and Antiretrovirals

- **Efavirenz (n=87)**
  - No PIs
  - 1HP qD
  - EFV >1mg/L: 98%>95% (0-4 weeks)
  - VL undetectable: 93%>95% (0-8 weeks)
  - Raltegravir (n=16)
    - No P vs. P-900 qweek vs. P-600 qD
    - P-900 week increased raltegravir AUC 89%
    - P-600 qD decreased trough, not Cmax or AUC
    - No intolerance observed
  - Dolutegravir?

Previous study.

DOLPHIN Trial:
**DOLutegravir + P(rifapentine)-H(isoniazid) INvestigation**

- HIV+ adults suppressed on EFV-based ART
- Switched to DTG+ TDF/FTC x 8 weeks then started on 3HP
- HP decreased DTG bioavailability by 29%.
- 59/60 with trough levels >DTG IC90
- Viral suppression maintained, no adverse events

→ Dolutegravir may be given with 3HP

DOLPHIN Study (n=60)

- HIV+ adults suppressed on EFV-based ART
- Switched to DTG+ TDF/FTC x 8 weeks then started on 3HP
- HP decreased DTG bioavailability by 29%.
- 59/60 with trough levels >DTG IC90
- Viral suppression maintained, no adverse events

→ Dolutegravir may be given with 3HP
but dose BID?
Sarah Puryear, 11/25/2019
One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis

**BRIEF-TB**: Multinational, randomized, open-label, phase III trial
- Intervention: Rifapentine 600mg + Isoniazid 300 mg QD x 28 days
- Control: Isoniazid 300mg daily x 9 months
- Population: HIV infected, ≥13 years old, without active TB
- Median CD4 470 (IQR 346-635), 50% on ART
- Findings: 24 TB cases in 1HP, 29 cases in 9H → Noninferior
- Completion rates: 97% in 1HP, 90% in 9H
- Author Conclusion: 1HP safe and effective in preventing TB disease compared to 9H at 156 week follow up

Swindells, NEJM, 2019

---

But which regimen should I use?

**My generalized approach**

1. **Is your patient on ART?**
   - No: Are you going to start now?
   - Yes:
     - Is it RAL or EFV based w/o TAF?
       - No: Choose by frequency, SE, med interactions for THIS pt. (this is rare)
       - Yes: Proceed to other side

Check for medication interactions and contraindicated co-morbidities before initiating any regimen! *Data for 4R in HIV+ patients is inferior to data for 3HP. If using RAL with 4R, increase RAL dose*
But which regimen should I use?

My generalized approach

Is your patient on ART?

Yes:

Is it RAL or EFV based w/o TAF?

No:

Are you going to start now?

No:

Can/should you change their regimen? Do you want to?

Yes:

3HP or 4R* (Or 9H)

No:

Choose by frequency, SE, med. interactions for THIS pt. (this is now).

Yes: Proceed to other side

But which regimen should I use?

My generalized approach

Is your patient on ART?

Yes:

Is it RAL or EFV based w/o TAF?

No:

Are you going to start now?

No:

Can/should you change their regimen? Do you want to?

Yes:

3HP or 4R* (Or 9H)

No:

Choose by frequency, SE, med. interactions for THIS pt. (this is now).

Yes: Proceed to other side

Check for medication interactions and contraindicated co-morbidities before initiating any regimen!

*Data for 4R in HIV+ patients is inferior to data for 3HP. If using RAL with 4R, increase RAL dose

Indications to Treat HIV-positive patients for LTBI

1. New positive LTBI test and negative workup for active TB
2. Close contact with active TB and negative workup for active TB

→ BCG history should not affect the decision to treat in HIV positive individuals for LTBI

Exceptions to Treating LTBI: Pregnancy

Isotiazid Preventive Therapy in HIV-Infected Pregnant and Postpartum Women

Gupta, NEJM, 2019

- Population: 956 HIV+ women (all but 1 on ART)
- Exposure: IPT during pregnancy vs. IPT 12 weeks post-partum
- Primary Outcome: Maternal adverse events + Tx discontinuation
  - Occurred in 15.1% immediate group vs 15.2% deferred group
  - Adverse pregnancy outcome: 24% immediate, 17% deferred (p=0.01)
- In high prevalence TB setting, safer to defer IPT until 12 weeks postpartum in WLHIV on ART (unless recent TB exposure)
LTBI Treatment monitoring

- Baseline LFTs in all HIV-positive individuals on ART
- Repeat LFTs if:
  - Abnormal LFTs at baseline
  - Underlying liver disease (HBV, HCV, EtOH, cirrhosis)
  - Regular EtOH
  - Concomitant hepatotoxic medications
- Elevated LFTs—when to stop?
  - Symptomatic + >3x ULN
  - Asymptomatic + >5x ULN

LTBI Treatment and ART reduce risk of TB disease and death in PLHIV

Case 2

- 27 year old woman from El Salvador is admitted with cough, fevers, and an 18 pound weight loss over the past month
- Chest x-ray shows a diffuse infiltrate
- HIV test is positive: CD4 30 cells/mm³, viral load pending
- AFB smear of sputum is negative
- PJP negative
- Pregnancy test is negative

Diagnosis of active TB

- Clinical suspicion is a must!
  - Pulmonary symptoms: Prolonged cough, hemoptysis, chest pain
  - Systemic symptoms: fevers, chills, night sweats, appetite loss, weight-loss, fatigability
- Testing options
  - Chest X-ray
  - Sputum microscopy (AFB smear)
  - MTB Culture
  - Xpert MTB/RIF assay
TB Diagnosis: Chest X-ray
- Obtain a chest x-ray if positive IGRA/TST, TB exposure, or TB sx
- CXR can be normal in HIV positive individuals with active TB

<table>
<thead>
<tr>
<th>CD4 Cell Count (cells/μL)</th>
<th>% Normal CXR</th>
<th>% Normal CXR</th>
<th>% Normal CXR</th>
<th>% Normal CXR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-50</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>51-100</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>101-150</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>151-200</td>
<td>15%</td>
<td>15%</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td>201-250</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>251-300</td>
<td>25%</td>
<td>25%</td>
<td>25%</td>
<td>25%</td>
</tr>
<tr>
<td>301-350</td>
<td>30%</td>
<td>30%</td>
<td>30%</td>
<td>30%</td>
</tr>
<tr>
<td>351-400</td>
<td>35%</td>
<td>35%</td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td>401-450</td>
<td>40%</td>
<td>40%</td>
<td>40%</td>
<td>40%</td>
</tr>
<tr>
<td>451-500</td>
<td>45%</td>
<td>45%</td>
<td>45%</td>
<td>45%</td>
</tr>
<tr>
<td>&gt;500</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
</tr>
</tbody>
</table>

873 HIV/PTB cases
21% normal CXR with CD4<50

Cain, NEJM, 2010; Chamie, IJTLD, 2010

TB Diagnosis: Smear microscopy
- Overall sensitivity of sputum microscopy ~50%
- Lower in HIV+

TB Diagnosis: Culture
- More sensitive and specific than smear
- Methods
  - Traditional Culture
    - SLOW
  - Rapid culture: BACTEC, MGIT
    - 7-12 days
    - Problematic for non-sputum

TB Diagnosis: Xpert
- More sensitive than smear
- Useful in children and EPTB samples
- Screens for Rif resistance

Boehme, NEJM, 2010
Xpert MTB/RIF Performance in HIV +

- High sensitivity
  - Overall 79% sensitive
    - 97% sensitive in smear + / culture +
    - 61% sensitive in smear - / culture +
  - Improves with repeated samples
- High specificity
  - Overall 98% specific
  - In US cohorts 99.2% specific

1Steingart, Cochrane Database Syst Rev, 2014; 2Luetkemeyer, CID, 2016

Xpert Ultra

- Two different amplification targets/new design
- Designed to overcome lower sensitivity in smear negative pulmonary TB
- PTB diagnostic accuracy study: 8 countries
  - Increased sensitivity (17%) in smear negative PTB
  - Decreased specificity (98 to 96%)
  - Greater loss in specificity if history of prior TB
  - No difference in detection of Rif-resistance
  - No decrease in sensitivity if HIV+

1Dorman, Lancet ID, 2018

Case 2 (cont.)
27F from El Salvador with new dx HIV (CD4 30, VL pend) presents with pulmonary infiltrates, fever, cough, wt loss x 1 month

- The GeneXpert returns positive
- No Rif resistance detected
- You start the patient on RIPE therapy

Audience Response
27F from El Salvador with new dx HIV (CD4 30, VL pend) presents with with pulmonary TB now on RIPE

When should antiretroviral therapy be started?

A. In 2 months, when she starts consolidation phase
B. Within 2 weeks of TB therapy start
C. After she completes TB therapy
D. Within 8 weeks of TB therapy start
## ART Timing: DHHS Guidelines

- ART recommended in all PLHIV with TB (AI)
- CD4 < 50 cells/mm³, initiate ART ASAP within 2 weeks of TB treatment start (AI)
- CD4 = 50 cells/mm³, initiate ART within 8 weeks (AI)

**EXCEPTION:** TB meningitis → early ART associated with increased AE, exercise caution

## Antiretrovirals and anti-TB therapy: It’s complicated!

- Pill burden: 4 drugs for TB + HIV Meds
- Overlapping toxicities: Common side effects
- Coordination of the programs: TB care and HIV care are not always linked
- First line TB regimens should contain a rifamycin (rifampin, rifabutin)
  - Rifampin potent inducer of metabolizing enzymes and transporters
  - Rifabutin metabolism inhibited by PIs

**Excellent review article:**
Drug-drug interactions: NRTIs and Rifamycins

- **TDF/FTC & ABC/3TC**
  - Can use with rifampin, rifabutin, and rifapentine without dose adjustment

- **TAF**
  - BID TAF + rifampin vs. qD TAF alone
  - Plasma TAF AUC reduced 15% when given with RIF
  - Trough levels of tenofovir (metabolite) similar

  Cerrone, J Antimicrob Chemother 2019
  - TAF qD + Rifampin (n=21) in HIV-negative individuals
    - Plasma TAF AUC reduced 55%
    - Intracellular tenofovir levels reduced 36%
    - HOWEVER, IC levels 4.2 times higher than TDF alone

  Cerrone, J Antimicrob Chemother 2019

Do NOT use TAF with Rifamycins..yet

HOT OFF THE PRESS

Drug-drug interactions: Rifamycins and INSTIs

- **Dolutegravir**: RIF reduces plasma levels of DTG
  - Overcome by BID dosing

  Dooley et al, CID, 2019. “INSPIRING” Study
  - Open-label, randomized non-comparative phase IIIb
  - N=113 ART-naïve patients with TB/HIV coinfection
  - DTG BID + 2 NRTIs vs. EFV qD + 2 NRTIs & Rif based TB therapy
  - Week 48: Suppression 75% in DTG, 82% in EFV (DTG driven by LTIFU)
  - Supports the BID DTG recommendation

- **Bictegravir**
  - BIC/FTC/TAF qD vs. BIC/FTC/TAF BID + rifampin (n=52)
    - AUC BIC reduced 61% and trough reduced 80% even with BID
  - Co-administration not recommended

  Dooley et al, CID, 2019. “INSPIRING” Study
  - ANRS 12300 Reflate TB2: RAL vs EFV as initial therapy for people with HIV and active TB

  - Exposure: RAL 400mg BID +3TC/TDF vs. EFV 600mg qD+3TC/TDF
  - Non-inferiority margin: -12%

  De Castro, IAS 2019, MOAB0101

  RAL-EFV Treatment Difference (95% CI)

  - At Wk 48, RAL did not meet criteria for noninferior virologic efficacy vs EFV

Rifamycins and ART

<table>
<thead>
<tr>
<th>Rifamycins and ART</th>
<th>Rifampin</th>
<th>Rifabutin</th>
<th>Rifapentine</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF/FTC &amp; ABC/3TC</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>TAF</td>
<td>✗</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNRTIs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elavirenz</td>
<td>✓</td>
<td></td>
<td>(increase RFB)</td>
</tr>
<tr>
<td>Etravirine</td>
<td>✗</td>
<td></td>
<td>(potentially)</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>✗</td>
<td></td>
<td>(potentially)</td>
</tr>
<tr>
<td>PIr</td>
<td>✗</td>
<td>Dose 150mg QD</td>
<td>✗</td>
</tr>
<tr>
<td>PIcobi</td>
<td>✗</td>
<td>Dose 150mg QO</td>
<td>✗</td>
</tr>
<tr>
<td>INSTI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raltegravir</td>
<td>800mg BID</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Elvitegravir</td>
<td>✗</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>50mg BID</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Bictegravir</td>
<td>✗</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>
do y'all still agree with this? or are keeping patients of taf who are starting tb therapy?
Sarah Puryear, 11/25/2019
Case 2
27F from El Salvador with new dx HIV (CD4 30, VL pend) and pulmonary TB, recently started on RIPE and ART

- Your patient has now been on TB therapy for 20 days and on ART for 10 days
- She has recurrent fevers and notes worsening dyspnea and cough
- You obtain a repeat CXR, which now shows progression of pulmonary infiltrates
- You suspect Immune Reconstitution Inflammatory Syndrome (IRIS)

Audience Response
27F from El Salvador with new dx HIV (CD4 30, VL pend) and pulmonary TB, recently started on RIPE and ART with concern for IRIS

What is the best way to manage her symptoms?
A. Start a course of prednisone
B. Hold ART
C. Start NSAIDS
D. Watchful waiting; continue ART and TB therapy

Paradoxical TB IRIS

Timing:
- Typically 1-4 weeks after ART; most w/in 3 months

Epidemiology:
- Incidence estimated at 15.7% (case fatality of ~<3%)\(^1\)
- Rarely severe or fatal

Predictors:
- CD4<50 at ART start
- Higher on ART CD4
- High pre-ART VL\(\rightarrow\) lower on-ART VL
- Severity of disease
- Early ART start\(\rightarrow\) (<30 days)

Treatment:
- Mild: NSAIDs
- More severe: steroids
- Surgical drainage

TB IRIS: Role of Steroids

Prednisone as IRIS Treatment
Meintjes et al, AIDS 2010
- RCT of placebo vs. prednisone (1.5mg/kg/day x 2 weeks\(\rightarrow\)0.75mg/kg/day x 2 weeks)
- n=110, HIV + non-life threatening IRIS in South Africa
- Endpoint: days of hospitalization and outpatient therapeutic procedures (equiv 1 hospital day)

\(\rightarrow\) Placebo 3 days (IQR 0-9), Prednisone 0 days (IQR 0-3). No increase infections

Prednisone as IRIS Prevention: PredART Trial

RCT double-blind of placebo vs. prednisone (40mg/day x 2 weeks → 20mg/day x 2 weeks) at time of ART start

- n=240, HIV+ naïve pt, CD4 ≤ 100, TB Rx start within 30 days
- Endpoint: TB-IRIS
- Placebo: 46.7% with IRIS, Prednisone 32.5%, RR 0.70 (0.51-0.96; p=0.02)
- Placebo: median time to IRIS 8 days vs. prednisone 10 days, HR 0.61 (p=0.02)

2019 DHHS OI Guidelines: Recommends pre-emptive prednisone for patients at high risk of developing TB-IRIS

Conclusions

1. Screen all PLHIV for TB at diagnosis or entry into care
   - Screen high risk patients annually
2. TST or IGRA can be used to screen for LTBI
3. Treat LTBI: It prevents TB and reduces mortality
4. 9 months of INH is the preferred LTBI treatment regimen; alternatives exist, but beware of drug-drug interactions
5. CO-TREATMENT OF HIV AND TB SAVES LIVES
   - Start ART ASAP and >2 weeks in TB/HIV pts with CD4<50
6. Rifamycins have multiple interactions with ART
7. Prednisone has a role in prevention and treatment of TB-IRIS

Recent Developments in TB Prevention

Final Analysis of a Trial of M72/AS01e Vaccine to Prevent Tuberculosis

- Population: 3289 HIV-negative adults in Africa
- Exposure: 2 doses of the M72/AS01e candidate vaccine vs 2 doses of placebo, 1 month apart
- Result: Mean 2.7 years' follow-up:
  - Pulmonary TB: 0.3 versus 0.6 cases per 100 person-years.
  - Overall 36-month efficacy was 49.7%.

Thank you!

Special thanks to the following for their contributions to this presentation:

- Gabriel Chamie
- Diane Havlir
- Annie Luetkemeyer
- Carina Marquez