Ongoing Management of the HIV Patient in the Ambulatory Care Setting: Strategies for Achieving Long-term Viral Suppression

Proceedings of a Midday Symposium and Live Webinar at the 50th ASHP Midyear Clinical Meeting and Exhibition

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www.cemidday.com

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Ongoing Management of the HIV Patient in the Ambulatory Care Setting: Strategies for Achieving Long-term Viral Suppression

Agenda

11:30 a.m. – 11:40 a.m.
Welcome and Introductions
Jason J. Schafer, Pharm.D., M.P.H., BCPS, AAHIVP

11:40 a.m. – 11:50 a.m.
HIV Epidemiology and Engagement in Care
Jason J. Schafer, Pharm.D., M.P.H., BCPS, AAHIVP

11:50 a.m. – 12:10 p.m.
Acute HIV Infection
Joseph A. DeSimone, Jr. M.D., FIDSA, AAHIVS

12:10 p.m. – 12:30 p.m.
Switching ART
Joseph A. DeSimone, Jr. M.D., FIDSA, AAHIVS

12:30 p.m. – 12:50 p.m.
Hepatitis C Co-infection
Jason J. Schafer, Pharm.D., M.P.H., BCPS, AAHIVP

12:50 p.m. – 1:00 p.m.
Faculty Discussion and Audience Questions
All Faculty

Faculty

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Associate Professor, Department of Pharmacy Practice
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Disclosure Statement

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- Jason J. Schafer, Pharm.D., M.P.H., BCPS, AAHIVP, declares he received a research grant from Merck.
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Activity Overview

The epidemic of human immunodeficiency virus (HIV) infection in the United States has changed dramatically in the last 30 years. The widespread use of antiretroviral therapy, in particular, can significantly suppress HIV replication, restore a patient’s immune function, and has resulted in a significant decline in HIV-related morbidity and mortality. As a result, patients on long-term therapy that maintain viral suppression can now manage their infection as a chronic illness and are likely to experience a near-normal life expectancy. Despite the remarkable advances in the management of patients living with HIV infection in the United States, challenges to successful HIV care remain.

This educational activity will apply emerging evidence and current practice guidelines to address contemporary challenges in achieving long-term viral suppression among HIV positive patients commonly encountered in the ambulatory care setting.

Learning Objectives

At the conclusion of this application-based educational activity, participants should be able to

- Outline the diagnosis and management of acute HIV infection.
- Select patients who are appropriate candidates for switching antiretroviral regimens to improve convenience, safety or tolerability.
- Demonstrate the current approach to managing patients with HIV and hepatitis C co-infection.

Additional Educational Opportunities about HIV Coming in 2016

- Web-based activity - Based on today’s live symposium (1.5 hours of CE, please note that individuals who claim CE credit for the live symposium or webinar are ineligible to claim credit for the web-based activity)

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On-Demand Activity ACPE #: 0204-0000-15-473-H02-P

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Ongoing Management of the HIV Patient in the Ambulatory Care Setting: Strategies for Achieving Long-term Viral Suppression

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Clinical Pharmacy Specialist, HIV Ambulatory Care
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Dr. Schafer received his Doctor of Pharmacy degree from Duquesne University and completed a pharmacy practice residency at the Mercy Hospital of Pittsburgh and a second residency specializing in infectious diseases at the Ohio State University Medical Center. He received his Master of Public Health degree from the Jefferson School of Population Health. He is a board-certified pharmacotherapy specialist (BCPS) and is certified by the American Academy of HIV Medicine (AAHIVM) as a practicing HIV Pharmacist (AAHIVP).

Dr. Schafer’s clinical practice site is an HIV specialty ambulatory care clinic in Philadelphia where he provides medication therapy management services. He also provides service to the AAHIVM on its Pharmacist and Credentialing Committees.

Dr. Schafer has published numerous articles on HIV medicine and pharmacotherapy in the medical literature including the *ASHP Guidelines on Pharmacist Involvement in HIV Care*. He has also been active in ASHP most recently serving as the Infectious Diseases Network Facilitator and as Director at Large for the Section of Clinical Specialists and Scientist’s Executive Committee.

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Ongoing Management of the HIV Patient in the Ambulatory Care Setting:
Strategies for Achieving Long-term Viral Suppression

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Philadelphia, Pennsylvania

Joseph A. DeSimone, Jr., M.D., FACP, FIDSA, is Professor of Medicine and Program Director for the Infectious Diseases Fellowship Program at the Sidney Kimmel Medical College, at Thomas Jefferson University in Philadelphia, Pennsylvania.

Dr. DeSimone graduated from Hahnemann University School of Medicine where he also completed both his Internal Medicine residency and Infectious Diseases fellowship. He is a fellow of the Infectious Diseases Society of America (FIDSA) and a Practicing HIV Specialist (AAHIVS).

He is responsible for teaching infectious diseases and HIV to medical students, internal medicine residents, and infectious diseases fellows at Thomas Jefferson University. Dr. DeSimone has provided clinical care for HIV-infected patients at Thomas Jefferson University for over 15 years and currently cares for over 300 HIV-infected patients in his practice.

He has acted as the principal or co-principal investigator for dozens of clinical trials investigating antiretroviral therapy for persons with HIV infection. Dr. DeSimone has authored numerous publications in peer-reviewed journals and abstract presentations at national meetings. He has received numerous teaching awards while at Thomas Jefferson University including the Dean’s Award for Excellence in Education from the Sidney Kimmel Medical College and Induction into the Gold Humanism Honor Society.
Ongoing Management of the HIV Patient in the Ambulatory Care Setting: Strategies for Achieving Long-term Viral Suppression

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Learning Objectives

• Outline the diagnosis and management of acute HIV infection.
• Select patients who are appropriate candidates for switching antiretroviral regimens to improve convenience, safety or tolerability.
• Demonstrate the current approach to managing patients with HIV and hepatitis C co-infection.
HIV Epidemiology and Engagement in Care

Jason J. Schafer Pharm.D., M.P.H, BCPS, AAHIVP
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HIV Infection in the U.S.
AIDS Diagnoses and Deaths in the United States, 1985-2012

Centers for Disease Control and Prevention, HIV/AIDS Surveillance.

HIV Infection in the US
Patient engagement in the continuum of HIV Care

- Of the 1.2 million people living with HIV in the U.S. in 2011, an estimated 86% were diagnosed.
- 14% (or 1 in 7 people living with HIV) were unaware of their infection
- Patient engagement decreases at each stage in the continuum

CDC National HIV Surveillance System and Medical Monitoring Project

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92% of new HIV infections are attributable to people with HIV who are not in medical care, including those who are not diagnosed.


- Closing the gaps
  - Improvements in HIV testing and diagnosis
  - Emerging strategies for linking and retaining patients in care
  - Evolving recommendations for when to initiate antiretroviral therapy
  - Achieving and maintaining viral suppression

Acute HIV Infection
Joseph A. DeSimone, Jr. MD, FACP, AAHIVS
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Director, Infectious Diseases Fellowship Program
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Philadelphia, Pennsylvania

Patient Case-August 2015
• PT is a 37 YO AA female; ER 8/17/15.
• 5 days abdominal pain, dysuria, foul-smelling urine, vomiting.
• Observed overnight, dx pyelonephritis, sent home with oral cephalosporin.
• While in observation unit, offered HIV screening per ED protocol.
• HIV Antigen(Ag)/Antibody (Ab) 4th-generation enzyme immunoassay (EIA) reactive.
• Reports prior negative HIV testing.
• New monogamous male sexual partner 6 months ago after 7 years of abstinence. Partner serostatus unknown.

In patients with a reactive 4th-generation HIV Ag/Ab result, what test should be performed next?

a. HIV-1 Western blot
b. HIV-2 Western blot
c. HIV viral RNA quantitative assay (viral load)
d. HIV-1/HIV-2 discriminatory immunoassay
e. CD4 cell count
If reactive HIV-1/2 Antigen/Antibody Combination Immunoassay...

Perform HIV-1/2 Antibody Differentiation Immunoassay

- HIV-1 (+) / HIV-2 (-) = HIV-1 Antigens Detected
- HIV-1 (-) / HIV-2 (+) = HIV-2 Antibodies Detected
- HIV-1 Antigens and HIV-2 Antibodies Detected
- HIV-1 and HIV-2 Infection

HIV-1/HIV-2 differentiation assay (Multispot)

The HIV-1/HIV-2 differentiation assay (Multispot) results are both non-reactive. What should be done next for PT?

a. HIV-1 Western blot  
b. CD4 cell count  
c. HIV viral RNA quantitative assay (viral load)  
d. Inform the patient that she is definitely infected with HIV  
e. Inform the patient she is definitely not infected with HIV

See enlargement, p. 34
Acute (Primary, Early) HIV Infection

- Systemic: fever, weight loss
- Cervical: lymph nodes
- Pharynx:
- Mouth: sore, ulcer
- Esophagus:
- Muscles: myalgia
- Liver and spleen: enlargement
- Central:
- Malaise
- Headache
- Neuropathy
- Lymph nodes:
- Lymphadenopathy
- Skin:
- Rash
- Gastric:
- Nausea
- Vomiting

Awareness of Serostatus Among People with HIV, and Estimates of Transmission

- ~20% Unaware of Infection
- ~80% Aware of Infection

People Living with HIV/AIDS: 1,200,000

New Sexual Infections Each Year: ~50,000

~69% of New Infections

~51% of New Infections

PT comes to office 5 days later to learn of confirmed diagnosis. HIV viral load is >10 million copies; CD4 count is 600 cells/mm³. Should this patient be treated with ART and when?

a. Yes, immediately (today)
b. Yes, in 4 weeks (after genotype available)
c. No, since CD4 count is >500 cells/mm³.
d. Not yet, since she needs time to process her new diagnosis.
e. Not sure

<table>
<thead>
<tr>
<th>Theoretical Rationale for and Potential Disadvantages of Initiating ART during Acute Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rationale for ART during acute HIV infection:</td>
</tr>
<tr>
<td>- Reduction in the risk of viral transmission</td>
</tr>
<tr>
<td>- Preservation of HIV-specific immune function, including the growth of the survival of CD4 cells that are involved in the initial response to HIV infection</td>
</tr>
<tr>
<td>- Suppression of the initial burst of viral replication with a decrease in the magnitude of viral dissemination, which reduces reservoir size and may preserve gut-associated lymphoid tissue</td>
</tr>
<tr>
<td>- Potential reduction in the emergence of viral variants with the suppression of viral replication</td>
</tr>
<tr>
<td>- Potential to reduce the severity and duration of illness during symptomatic acute HIV infection</td>
</tr>
<tr>
<td>- Potential to reduce the risk of HIV superinfection (i.e., infection with a second strain of HIV)²</td>
</tr>
</tbody>
</table>

Potential disadvantages of ART during acute HIV infection:

- Development of drug resistance if therapy fails due to monotherapy or insufficient suppression of viral replication
- Adverse effects or quality of life as a result of drug toxicity
- Failure to gain control of disease ART

Providing same day, observed ART to newly diagnosed HIV+ outpatients is associated with improved virologic suppression

Christopher D. Pilcher, Hiroyu H. Hatano, Aditi Dasgupta, Diane Jones, Sandra Torres, Fabiola Calderon, Erin Demicco, Wendy Hartogensis, Clarissa Ojena-Norvell, Elzin Geng, Monica Gandhi, Diane Havlir

University of California, San Francisco
San Francisco General Hospital

**Milestones of care: SFGH, 2006-2013**

<table>
<thead>
<tr>
<th>Years</th>
<th>Referral</th>
<th>1st Clinic Visit</th>
<th>1st PCP Visit</th>
<th>ART Prescribed</th>
<th>Viral load suppressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006-2009 CD4-guided ART</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010-2013 Universal ART</td>
<td></td>
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RAPID Demonstration Project
July 2013-December 2014

• Overall feasibility of a health systems intervention for same-day outpatient ART for newly diagnosed HIV infection
• Deployed in context of extensive existing services for navigation, linkage and retention
• Initially targeted to new patients with acute HIV infection (HIV Ab – within 6 months)
• Extended in 2014 to include active opportunistic infection (OI), CD4<200 cells/mm³

RAPID
Intervention Components

• Facilitation of same day appointments
• Flexible scheduling for providers (on-call back-up)
• ART regimens pre-approved for use prior to genotyping or lab testing
• Available as 5-day starter packs
• Accelerated process for health insurance initiation
• Recommendation for 1st dose to be taken observed in the clinic

New SFGH patients, RAPID era: 2013-4

<table>
<thead>
<tr>
<th>Indicator</th>
<th>RAPID Cohort (n=39)</th>
<th>Universal ART (n=47)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sociodemographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age: mean(range)</td>
<td>32 (21-47)</td>
<td>35 (19-68)</td>
<td>NS</td>
</tr>
<tr>
<td>Male: n (%)</td>
<td>39 100%</td>
<td>43 92%</td>
<td>NS</td>
</tr>
<tr>
<td>Non-white ethnicity</td>
<td>23 59%</td>
<td>34 72%</td>
<td>NS</td>
</tr>
<tr>
<td>Homeless</td>
<td>11 28%</td>
<td>13 25%</td>
<td>NS</td>
</tr>
<tr>
<td>Uninsured</td>
<td>39 100%</td>
<td>47 100%</td>
<td>NS</td>
</tr>
<tr>
<td>Staging</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute (Ab &lt;6m)</td>
<td>21/30 70%</td>
<td>8/31 26%</td>
<td>0.001</td>
</tr>
<tr>
<td>Log₁₀VL</td>
<td>4.9 (2.8-6.6)</td>
<td>4.5 (1.6-6.1)</td>
<td>NS</td>
</tr>
<tr>
<td>CD4 mean (range)</td>
<td>474 (1391)</td>
<td>417 (11-1194)</td>
<td>NS</td>
</tr>
</tbody>
</table>

V₁= viral load
Uptake of same-day ART

% on ART

Days after ART offer/clinician visit

RAPID program era 2013-4: acceptability and safety

<table>
<thead>
<tr>
<th>Indicator</th>
<th>RAPID (n=39)</th>
<th>Universal (n=47)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acceptability</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall ART uptake</td>
<td>39 (100%)</td>
<td>40 (85%)</td>
<td>NS</td>
</tr>
<tr>
<td>Engaged in care (appt &lt;6 mos)</td>
<td>35 (90%)</td>
<td>40 (83%)</td>
<td>NS</td>
</tr>
<tr>
<td>Transferred care</td>
<td>8 (21%)</td>
<td>11 (23%)</td>
<td>NS</td>
</tr>
<tr>
<td>Provider switched</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ART simplification</td>
<td>10 (26%)</td>
<td>0 (0%)</td>
<td>0.001</td>
</tr>
<tr>
<td>ART Toxicity</td>
<td>2 (5%)</td>
<td>0 (0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Genotype-driven modification</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*all outcomes determined as of last followup (up to 18 months post referral)

Engagement Timeline, SFGH

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Conclusions

• It was feasible to implement same-day ART initiation for outpatients with newly diagnosed HIV in a well resourced, public health clinic setting.
• Same day ART was highly acceptable to both patients and providers.
• Same day ART was associated with improved rates of virologic suppression.
• No excess toxicity or other adverse effects of starting ART immediately at the first visit were seen.
• Expansion of the RAPID model citywide in 2015.


Patient Case

• PT defers treatment at time of diagnosis.
• Returns to office one year later.
• Asymptomatic.
• Viral load 200,000 copies/mL; CD4 600 cells/mm³.
• Estimated GFR 110 mL/min/1.73m².
• Takes no other meds.

Is treatment with ART recommended for PT?

a. Yes
b. No
c. Not sure
**START Study: Initiation of ART in Early Asymptomatic HIV Infection**

Multicontinental Study (n=4685)
- HIV-positive adults
- Treatment-naive
- CD4 >500 cells/mm³

Randomization 1:1
- Immediate ART (n=2326)
- Deferred ART (n=2359)

Primary outcome a composite outcome of 2 major components:
- Any serious AIDS-related event
- Any serious non-AIDS-related event

Grading of events:
- AIDS (acquired immunodeficiency syndrome)
- Non-AIDS (related to other causes)

Deferral of ART:
- CD4 declined to <350 cells/mm³ or AIDS-related event

Immediate ART was superior to deferral of ART:
- Both for serious and non-serious AIDS events
- Majority (88%) of the primary endpoints occurred in patients with a CD4 >500 cells/mm³
- Similar significant reductions were noted across all patient subgroups
- No increase in adverse events associated with immediate versus deferred ART

**START Study Outcomes: Composite Primary Endpoint and its Components**

- Immediate ART was superior to deferral of ART:
  - Both for serious and non-serious AIDS events
  - Majority (88%) of the primary endpoints occurred in patients with a CD4 >500 cells/mm³
  - Similar significant reductions were noted across all patient subgroups
  - No increase in adverse events associated with immediate versus deferred ART

- **When to Start Therapy: Balance Now Favors Early ART**
  - Drug toxicity
  - Preservation of limited Rx options
  - Risk of resistance (and transmission of resistant virus)

- ↑ potency, durability, simplicity, safety of current regimens
- ↓ emergence of resistance
- ↓ toxicity with earlier therapy
- ↑ subsequent treatment op. ons
- Risk of uncontrolled viremia at all CD4 levels
- ↓ Transmission

Permission from Practice Point Communications.
Recommendations for Initiating ART:
Considerations

• “Patients starting ART should be willing and able to commit to treatment and should understand the benefits and risks of therapy and the importance of adherence.”
• Patients may choose to postpone ART
• Providers may elect to defer ART, based on an individual patient’s clinical or psychosocial factors, but ART should be started as soon as it is feasible to do so.

Per the DHHS 2015 guidelines, which of the following is currently recommended as a first-line regimen for this patient?
a. Efavirenz/tenofovir disoproxil/emtricitabine (EFV/TDF/FTC)
b. Rilpivirine/tenofovir disoproxil/emtricitabine (RPV/TDF/FTC)
c. Atazanavir/ritonavir (ATV/r) plus TDF/FTC
d. Elvitegravir/cobicistat/TDF/FTC (EVG/cobi/TDF/FTC)
e. Darunavir/ritonavir (DRV/r) plus abacavir/lamivudine (ABC/3TC)

U.S. DHHS Guidelines, April 2015: What to Start

Recommended Regimens

- Integrase strand transfer inhibitor (INSTI)-based
  - Dolutegravir/abacavir/lamivudine (DTG/ABC/3TC)*
-- DTG plus tenofovir disoproxil fumarate/emtricitabine (TDF/FTC)
-- Elvitegravir/cobicistat/TDF/FTC (EVG/cobi/TDF/FTC)
-- Raltegravir (RAL) plus TDF/FTC
- Ritonavir-boosted protease inhibitor (PI/r)-based
  - Darunavir/ritonavir (DRV/r) plus TDF/FTC

*Only for pts who are HLA-B*5701 negative. Only for pts with pre-ART CD4 < 35 cells/mm³.

- Non-nucleoside reverse transcriptase inhibitors (NNRTIs) and Atazanavir/ritonavir (ATV/r), previously classified as “recommended,” are now “alternative regimens”

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Alternative Regimens

**NNRTI** based
- EFV/TDF/FTC
- RPV/TDF/FTC

**PI** based
- ATV/COBI + TDF/FTC
- DRV/COBI + ABC/3TC
- DRV/ABC + TDF/FTC
- DRV/COBI + TDF/FTC

*Only for pts with pre-ART HIV-1 RNA < 100,000 copies/mL and CD4+ > 200 cells/mm3.
†Only for pts with pre-ART CrCl ≥ 70 mL/min.
‡Only for pts who are HLA-B*5701 negative.

• An alternative regimen may be the preferred regimen for some patients

U.S. DHHS Guidelines, April 2015:
What to Start

ACTG 5257: Cumulative Incidence of Virologic or Tolerability Failure

SINGLE: DTG + ABC/3TC Superior to EFV/TDF/FTC in ART-Naive Pts to Wk 144

- Open-label extension, excluding pts with hepatitis B virus (HBV)
- Emergent resistance in those with VF: 0/39 (DTG) vs 7/33 (EFV)

Virologic Success*  Virologic Nonresponse  No Virologic Data
Pts (%)

Favors DTG + ABC/3TC
95% CI for Difference† 15%

DTG + ABC/3TC QD (n = 414)
EFV/TDF/FTC QD (n = 419)

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FLAMINGO: DTG Superior to DRV/r in ART-Naive Pts to Wk 96

Molina et al. HIV Drug Therapy Glasgow 2014; Glasgow, UK. Slides O153.

Comparing the Integrase Inhibitors

<table>
<thead>
<tr>
<th>Agent</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| Raltegravir (RAL) | • Longest experience  
|             | • Fewer drug interactions than EVG, DTG            | • Twice daily dosing (for now)  
|             |                                                   | • No coformulation                  |
| Eptinavir (EVG) | • Single-tablet regimen (STR)  
|             | • Once-daily dosing                               | • Requires Cobi boosting           
|             |                                                   | • Cobi-drug interactions similar to RTV |
| Dolutegravir (DTG) | • The only non-TDF-containing STR  
|             | • Once-daily dosing                               | • Cumulated with ABC/3TC only      
|             | • Lower barrier to resistance                     |                                    
|             | • Few drug interactions                           |                                    
|             | • Active against some RAL- and EVG-resistant virus |                                    |

Together, the results of STARTMRK, GS 102 and 103, SINGLE, FLAMINGO, and ACTG 5257 suggest that integrase inhibitor–based regimens are the preferred starting regimens in the majority of patients.

CE IN THE MIDDAY

Switching ART
PT starts EVG/c/TDF/FTC. One year later: Viral load undetectable; CD4 count 900 cells/mm³; GFR now 70 mL/min/1.73 m²; HLA B-5701 is positive.

Next step?

a. Observe on EVG/c/TDF/FTC until GFR drops below 30 mL/min/1.73 m²
b. Switch EVG/c/TDF/FTC to Raltegravir (RAL) plus TDF/FTC
c. Switch EVG/c/TDF/FTC to DTG/ABC/3TC
d. Switch EVG/c/TDF/FTC to EVG/c/TAF/FTC

TAF (tenofovir alafenamide)

- Tenofovir disoproxil (TDF) associated with severe renal adverse events in 1-2%
- Conflicting data on reversibility of renal impairment after discontinuation of TDF
- TAF is tenofovir (TFV) prodrug with 91% less circulating plasma tenofovir exposure and increased intracellular concentration

See enlargement, p. 36
Study 109: Switch to Tenofovir Alafenamide-Containing Single-Tablet Regimen

Phase 2 study (56 weeks)
Treatment-experienced
Open-label
Non-inferiority (12% margin)
HIV RNA <50 copies/mL
eGFR >50 mL/min

Primary Endpoint
Week 48
HIV RNA <50 Copies/mL (FDA Snapshot)

Randomization 2:1
Continue Tenofovir DF-Based Regimen (n=477)
Switch to E/C/F/TAF (n=959)

Primary Endpoint
Week 48
HIV RNA <50 Copies/mL (FDA Snapshot)

E/C/F/TAF:
elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide.
TAF 10mg.
Tenofovir DF-based regimens:
• Elvitegravir/COBI/FTC/TDF (n=459).
• Efavirenz/FTC/TDF (n=376).
• Boosted atazanavir + FTC/TDF (n=601).

Median CD4: 662–675 cells/mm³.
Median eGFR: 106–108 mL/min.

Study 109: Virologic Outcomes at Week 48 Following Switch to Tenofovir Alafenamide-Containing Single-Tablet Regimen

Remaining HIV RNA <50 Copies/mL

*Net over inferiority criteria (treatment difference: 4.1 [1.6–6.7]).

Study 109: Other Outcomes and Summary

- Discontinuations due to adverse events
  - E/C/F/TAF: 0.9%
    - Renal events (n=2), other events (n=7)
  - TDF-based regimen: 2.5%
    - Renal events (n=1), other events (n=6)
- Patients who switched to E/C/F/TAF versus TDF-based regimen were
  - Significantly more likely to maintain virologic suppression (P<0.001)
  - Significant improvements in spine and hip BMD (P<0.001)
  - Significant improvements in proteinuria and other markers of renal function (P<0.001)
Study 112: Switch to E/C/F/TAF in Patients With Renal Impairment

- **Phase 3 study (56 weeks)**
- **Treatment-experienced**
- **Open-label**
- **VIR+A<50 copies/mL**
- **eGFR 30-69 mL/min**

### Primary Endpoint

**Week 24**

Change From Baseline in eGFR

**Switch to E/C/F/TAF**

(n=242)

### Mean Change in eGFR at Week 48

- **Cockcroft-Gault**
- **Actual GFR at Week 24**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>59</td>
<td>58</td>
<td>53</td>
</tr>
<tr>
<td>52</td>
<td>47</td>
<td>43</td>
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</table>

<table>
<thead>
<tr>
<th>Patients</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>59</td>
<td>58</td>
<td>53</td>
</tr>
<tr>
<td>52</td>
<td>47</td>
<td>43</td>
</tr>
</tbody>
</table>

### Actual GFR at Week 24

- (iohexol Clearance)

### Mean Change in eGFR at Week 48

- (Cockcroft-Gault)

### Study 112: Change in GFR After Switch to E/C/F/TAF in Patients With Renal Impairment

- **Actual GFR was unaffected by E/C/F/TAF switch, regardless of previous regimen**
  - eGFR remained unchanged through week 48
- **Significant improvements after E/C/F/TAF switch (P<0.05)**
  - Spine and hip bone mineral density
  - Urinary tubular proteins and fractional excretion of uric acid
  - Albuminuria and proteinuria
  - Cholesterol fractions in patients not on a TDF-based regimen at time of switch

### Study 112: Change in GFR and Other Outcomes After Switch to E/C/F/TAF

- These 48-week data support the renal and bone safety of E/C/F/TAF in HIV patients with renal impairment (eGFR 30-69 mL/min)
### Recent Switch Studies: Suppressed

<table>
<thead>
<tr>
<th>Trial</th>
<th>From</th>
<th>To</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS-123[1]</td>
<td>RAL + TDF/FTC</td>
<td>EVG/TDF/FTC/Cobi</td>
<td>✔️</td>
</tr>
<tr>
<td>SPIRIT[5]</td>
<td>PIR + 2 NRTI</td>
<td>RPV/TDF/FTC</td>
<td>✔️</td>
</tr>
<tr>
<td>SPIRAL[6]</td>
<td>PIR + 2 NRTI</td>
<td>RAL + 2 NRTI</td>
<td>✔️</td>
</tr>
<tr>
<td>SALT[7]</td>
<td>ATV/r + 2 NRTI</td>
<td>ATV/r + 3TC</td>
<td>✔️</td>
</tr>
<tr>
<td>OLEPI</td>
<td>LPV/r + 2 NRTI</td>
<td>LPV/r + 3TC</td>
<td>✔️</td>
</tr>
<tr>
<td>SWITCHMIRK[8]</td>
<td>LPV/r + 2 NRTI</td>
<td>RAL + 2 NRTI</td>
<td>✗</td>
</tr>
<tr>
<td>HARNESS[9]</td>
<td>3rd agent + 2 NRTI</td>
<td>RAL + ATV/r</td>
<td>✗</td>
</tr>
<tr>
<td></td>
<td>LPV/Alpinavir</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patient Case

- MA is a 34 year old woman with HIV/HCV infections diagnosed in 2005
- Never treated for HCV because she refuses to take interferon (IFN)
- She is aware of the new HCV medications and asks if she can be treated

- ART History:
  - Raltegravir/emtricitabine/tenofovir (2009 – 2013; reports missing PM doses)
  - Elvitegravir/cobicistat/emtricitabine/tenofovir (2013 – present)

- HIV Labs
  - HIV viral load < 20 copies/mL (x 2 years), CD4 cell count: 550-650 cells/mm³

- HCV Labs
  - Genotype 1a, HCV viral load = 3,400,000 copies/mL, Metavir score = 2

- Other Labs
  - AST = 45 IU/L, ALT = 75 IU/L, Scr = 1.3 mg/dL

How would you approach treating this patient’s HCV infection?

a. Start HCV treatment now
b. Delay HCV treatment until liver disease is more advanced
c. D/C ART, treat HCV, then restart ART

Hepatitis C Infection

Treatment is NOT what it used to be...

SVR Rates for Approved Therapies in HCV GT 2 Patients
HIV/HCV Co-infection

Treating Co-infection is NOT what it used to be...

SVR according to genotype for HIV/HCV co-infected patients receiving Peg-interferon plus ribavirin for 48 weeks

- Genotype 1
- Genotype 2/3

*SVR (%)
*60-85% receiving ART
*60-65% with undetectable HIV RNA

SVR Rates for Approved Therapies in HCV GT 1 Patients Co-infected with HIV

HIV/HCV Co-infection

Similar response rates in HIV/HCV co-infected patients compared to HCV mono-infected patients

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**HIV/HCV Co-infection**

- HIV co-infection accelerates fibrosis progression among HCV-infected persons
- Controlling HIV may mitigate progression to some extent, but ART is not a substitute for HCV treatment
- Co-infected patients have more liver-related and overall mortality than HCV-monoinfected patients
- Achieving SVR reduces the incidence of liver-related death and improves survival in co-infected patients

**Stopart** Can Adversely Affect HIV and Non-HIV Related Outcomes

- CD4+ guided ART interruption was associated with significantly greater risk of disease progression and death compared to continuous ART
  - RR 2.5 (95% CI: 1.8-3.6; p<.001)
- Includes increased CVD, liver, and renal-related deaths:

<table>
<thead>
<tr>
<th>Complications</th>
<th>No. of Events</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe complications</td>
<td>114</td>
<td></td>
</tr>
<tr>
<td>• CVD, liver, renal deaths</td>
<td>31</td>
<td>1.4</td>
</tr>
<tr>
<td>• Nonfatal CVD events</td>
<td>62</td>
<td>1.4</td>
</tr>
<tr>
<td>• Nonfatal hepatic events</td>
<td>14</td>
<td>1.4</td>
</tr>
<tr>
<td>• Nonfatal renal events</td>
<td>7</td>
<td>2.5</td>
</tr>
</tbody>
</table>

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HIV/HCV Co-infection

**Recommended HCV Treatment Regimens in Patients**
with or without HIV Co-infection

<table>
<thead>
<tr>
<th>Population</th>
<th>SMV + SOF</th>
<th>LDV/SOF</th>
<th>OMV/PTV/RTV + ODV</th>
<th>DCV + SOF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1a, no cirrhosis</td>
<td>12 wks ± RBV</td>
<td>12 wks</td>
<td>24 wks ± RBV</td>
<td>12 wks</td>
</tr>
<tr>
<td>Genotype 1a, cirrhosis</td>
<td>24 wks ± RBV</td>
<td>12 wks</td>
<td>24 wks + RBV</td>
<td>24 wks ± RBV</td>
</tr>
<tr>
<td>Genotype 1b, no cirrhosis</td>
<td>12 wks</td>
<td>12 wks</td>
<td>12 wks</td>
<td>12 wks</td>
</tr>
<tr>
<td>Genotype 1b, cirrhosis</td>
<td>24 wks ± RBV</td>
<td>12 wks</td>
<td>12 wks</td>
<td>24 wks ± RBV</td>
</tr>
</tbody>
</table>

**Confirmed absence of Q80K polymorphism**

DCV=daclatasvir


Which HCV treatment strategy do you recommend?

a. Keep ART and start sofosbuvir/ledipasvir
b. Change ART and start sofosbuvir/ledipasvir
c. Keep ART and start daclatasvir + sofosbuvir
d. Change ART and start simeprevir + sofosbuvir
e. Keep ART and start paritaprevir/ritonavir/ombitasvir plus dasabuvir (PrOD)


• All co-infected patients are candidates for HCV therapy
• HIV disease must be stable before initiating HCV treatment
• Interrupting HIV treatment to manage HCV infection is not recommended
• Recommended ART regimens for co-infected patients are the same as those recommended for patients without HCV
• Co-infected persons should be treated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications

HIV/HCV Co-infection
AASLD/IDSA Guidance. It’s all about the interactions!

See enlargement, p. 37

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HIV/HCV Co-infection

AASLD/IDSA/IAS–USA guidelines

Key Takeaways

• Drug interaction resources
  – AASLD/IDSA/IAS–USA hepatitis C guidelines
  – U.S. DHHS Adult and Adolescent HIV guidelines
  – www.hiv-druginteraction.org
  – www.hep-druginteractions.org

• Early HIV diagnosis, initiation of ART and engagement in care are essential to achieving long-term viral suppression.

• Switching ART in response to adverse events can be performed successfully but must be done carefully to maintain viral suppression.

• Successful treatment of both HIV and HCV in co-infected patients requires the management of significant drug interactions.
Perform HIV-1/2 Antigen/Antibody Combination Immunoassay

Perform HIV-1/2 Antibody Differentiation Immunoassay

HIV-1 (+) HIV-2 (-)
HIV-1 Antigens Detected
HIV-1 Infection

HIV-1 (-) HIV-2 (+)
HIV-2 Antigens Detected
HIV-2 Infection

HIV-1 (+) HIV-2 (+)
HIV Antibodies Detected
Dual HIV-1 and HIV-2 Infection

HIV-1 (-) or Indeterminate HIV-2 (-)

Perform HIV-1 Nucleic Acid Test

Note: new algorithm may not be uniformly adopted in all settings. If a rapid 3rd generation test is used with a positive test result, confirmation is needed with a more specific test (e.g., Western Blot).


CDC and APHL: Recommended Laboratory HIV Testing Algorithm for Serum or Plasma Specimens

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Difference in 96-wk cumulative incidence
(97.5% CI)

- ATV/r*
- RAL*
- DRV/r*

Favors ATV/r vs RAL 15% (10% to 20%)
Favors ATV/r vs DRV/r 7.5% (3.2% to 12%)
Favors RAL

SINGLE: DTG + ABC/3TC Superior to EFV/TDF/FTC in ART-Naive Pts to Wk 144

- Open-label extension, excluding pts with hepatitis B virus (HBV)
- Emergent resistance in those with VF: 0/39 (DTG) vs 7/33 (EFV)

Virologic Success* Virologic Nonresponse No Virologic Data
Pts (%) Favors EFV/TDF/FTC 95% CI for Difference
Wk 48 96 144 Wk 48 96 144 Wk 48 96 144
7.4% 8.0% 8.3% 2.5% 2.3% 2.0% 14.6%

Favors DTG + ABC/3TC

95% CI for Difference†

*HIV-1 RNA < 50 copies/mL as defined by FDA Snapshot algorithm.
†-10% noninferiority margin.


Tenofovir Alafenamide (TAF): Novel Prodrug of Tenofovir

- 91% lower plasma TFV levels minimize renal and bone effects while maintaining high potency for suppressing HIV

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HIV/HCV Co-infection
AASLD/IDSA Guidance…It’s all about the interactions!

**Tenofovir Absorption**

**Gut Lumen**

**Blood Stream**

**Tenofovir DF**

**Enterocytes**

**P-gp**

**BCRP**

**Ledipasvir**

**Ritonavir**

**Cobicistat**

**Gut Lumen**

**Tenofovir Absorption**

**BCRP: Breast Cancer Resistance Protein**
Ongoing Management of the HIV Patient in the Ambulatory Care Setting:
Strategies for Achieving Long-term Viral Suppression

Abbreviations

**HIV Drug Classes**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART</td>
<td>antiretroviral therapy</td>
</tr>
<tr>
<td>CCR5</td>
<td>C-C chemokine receptor 5</td>
</tr>
<tr>
<td>INSTI</td>
<td>integrase strand transfer inhibitor</td>
</tr>
<tr>
<td>NNRTI</td>
<td>nonnucleoside reverse transcriptase inhibitor</td>
</tr>
<tr>
<td>NRTI</td>
<td>nucleoside (or nucleotide) reverse transcriptase inhibitor</td>
</tr>
<tr>
<td>PI</td>
<td>protease inhibitor</td>
</tr>
<tr>
<td>PI/r</td>
<td>ritonavir-boosted protease inhibitor</td>
</tr>
</tbody>
</table>

**HIV Drugs**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Drug Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>3TC</td>
<td>lamivudine</td>
</tr>
<tr>
<td>ABC</td>
<td>abacavir</td>
</tr>
<tr>
<td>ATV</td>
<td>atazanavir</td>
</tr>
<tr>
<td>ATV/r</td>
<td>atazanavir/ritonavir</td>
</tr>
<tr>
<td>COBI</td>
<td>cobicistat</td>
</tr>
<tr>
<td>DRV</td>
<td>darunavir</td>
</tr>
<tr>
<td>DRV/r</td>
<td>darunavir/ritonavir</td>
</tr>
<tr>
<td>DTG</td>
<td>dolutegravir</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>efavirenz</td>
</tr>
<tr>
<td>EVG</td>
<td>elvitegravir</td>
</tr>
<tr>
<td>FTC</td>
<td>emtricitabine</td>
</tr>
<tr>
<td>LPV</td>
<td>lopinavir</td>
</tr>
<tr>
<td>LPV/r</td>
<td>lopinavir/ritonavir</td>
</tr>
<tr>
<td>MVC</td>
<td>maraviroc</td>
</tr>
<tr>
<td>RAL</td>
<td>raltegravir</td>
</tr>
</tbody>
</table>
Ongoing Management of the HIV Patient in the Ambulatory Care Setting: Strategies for Achieving Long-term Viral Suppression

RPV  rilpivirine
RTV  ritonavir
TAF  tenofovir alafenamide
TDF  tenofovir disoproxil

**Hepatitis C Virus Drugs**

BOC  boceprevir
DAA  direct-acting antiviral
DCV  daclatasvir
DSV  dasabuvir
IFN  interferon
LDV  ledipasvir
OMV  ombitasvir
PegIFN  peginterferon
PrOD  paritaprevir/ritonavir/ombitasvir plus dasabuvir
PTV  paritaprevir
RBV  ribavirin
SMV  simeprevir
SOF  sofosbuvir
TVR  telaprevir

**Miscellaneous**

Ab  antibody
Ag  antigen
EIA  enzyme immunoassay
GT  genotype
HBV  hepatitis B virus
### Ongoing Management of the HIV Patient in the Ambulatory Care Setting: Strategies for Achieving Long-term Viral Suppression

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV</td>
<td>hepatitis C virus</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>NAAT</td>
<td>nucleic-acid amplification testing</td>
</tr>
<tr>
<td>SVR</td>
<td>sustained virologic response</td>
</tr>
<tr>
<td>VF</td>
<td>virologic failure</td>
</tr>
<tr>
<td>VL</td>
<td>viral load</td>
</tr>
</tbody>
</table>
Assessment Test

This assessment test has been provided as a study aid only. Follow the prompts at the end of the presentation to claim credit. Credit must be claimed within 60 days of completing the activity.

1. Most new HIV infections can be attributed to HIV infected patients who are:
   a. Engaged in care and receiving ART.
   b. Engaged in care, but not receiving ART.
   c. Not engaged in care, but have received an HIV diagnosis.
   d. Not engaged in care and have not been diagnosed with HIV.

2. Which of the following confirmatory tests is currently recommended for a patient with a reactive HIV Ag/Ab 4th-generation assay?
   a. HIV-1 Western blot.
   b. HIV-2 Western blot.
   c. HIV-1/HIV-2 discriminatory immunoassay.
   d. CD4 count.

3. Which of the following is correct regarding acute HIV infection?
   a. Patients with acute HIV are never symptomatic.
   b. Patients with acute HIV will consistently have reactive immunoassays for HIV-1 or HIV-2.
   c. Patients with acute HIV are unlikely to transmit the infection to others.
   d. Patients with acute HIV usually require nucleic acid testing to confirm the diagnosis.

4. Based on results from the recently-reported INSIGHT START trial, antiretroviral therapy should be offered to patients at which of the following times?
   a. Only when the CD4 count is <200 cells/µL.
   b. Only when the CD4 count is <350 cells/µL.
   c. Only when the CD4 count is <500 cells/µL.
   d. Upon learning of the diagnosis, regardless of CD4 count.

5. Which of the following is a recommended first-line antiretroviral regimen per the latest DHHS guidelines (April 2015)?
   a. Efavirenz plus TDF/FTC.
   b. Rilpivirine plus TDF/FTC.
   c. Dolutegravir/ABC/3TC.
   d. Atazanavir/r plus TDF/3TC.

6. Tenofovir alafenamide (TAF) differs from tenofovir disopoxil (TDF) in which way?
   a. TAF results in lower tenofovir concentrations in the CD4 cell.
   b. TAF results in higher TDF concentrations in the plasma.
   c. TAF results in more bone loss.
   d. TAF results in less decrease in GFR.
7. Ledipasvir increases the concentrations of tenofovir DF through which of the following mechanisms?
   a. Inhibition of cytochrome P450 3A4 enzymes.
   b. Induction of uridine glucuronosyl transferase 1A1.
   c. Inhibition of organic cation transporting protein.
   d. Inhibition of p-glycoprotein.

8. Which of the following accurately describes the likelihood of achieving a sustained virologic response (SVR) for HCV infection when a patient is co-infected with HIV?
   a. SVR rates are similarly low among patients receiving interferon based regimens and newer regimens containing direct acting antivirals.
   b. Achieving SVR is unlikely in patients with HIV co-infection due to significant drug interactions with ART and direct acting antivirals.
   c. The likelihood of achieving an SVR is similar among patients with and without HIV co-infection when regimens containing direct acting antivirals are used.
   d. Longer durations of therapy with directed acting antiviral agents are often needed to achieve SVR in patients with HIV co-infection.

9. Which of the following is an acceptable strategy for initiating treatment for HCV in a patient with HIV co-infection?
   a. Discontinue ART prior to initiating HCV therapy to avoid drug-drug interactions and restart ART once HCV therapy is complete.
   b. Delay HCV treatment until more safe and effective direct acting antivirals exist for patients with HIV receiving ART.
   c. Initiate HCV therapy, switching ART as necessary to avoid significant drug interactions.
   d. Monitor the progression of liver disease in co-infected patients and only initiate therapy in those who become cirrhotic.

10. HCV associated liver disease is a leading cause of “non-opportunistic” deaths in HIV patients.
    a. True.
    b. False.