Optimizing Treatment Strategies in the Management of HIV/AIDS: Individualizing Therapy for Improved Patient Outcomes

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• None
Outline

- Statistics: HIV in the U.S.
- Strategies for Improving HIV Care Continuum Outcomes
- Antiretroviral therapy (ART) in 2017
  - Recommendations for Initial Therapy
  - Strategies for Switching Patients with Viral Suppression
  - Virologic Failure
  - Drug-Drug Interactions

Learning Objectives

1. Analyze recent safety and efficacy data on new HIV therapies to individualize therapy and improve patient outcomes
2. Identify important patient characteristics, including age, comorbidities, and drug-drug interactions, in the selection of initial individualized HIV therapy
3. Examine HIV switching strategies that may benefit patients who have exhibited first- or second-line treatment failure
Learning Objectives, cont.

4. Apply HIV management approaches to improve outcomes, lower costs, and make informed reimbursement decisions
5. Review patient characteristics to identify patients with HIV and currently on stable treatment who may benefit from a different regimen
6. Discuss current and evolving strategies used by managed care organizations (MCOs) to facilitate high quality care for members with HIV

Statistics: HIV in the U.S.
HIV Disease in the U.S.

• More than 1,200,000 people with the U.S. are living with HIV
• Approximately 39,500 new diagnoses in 2015
• Decline in new HIV diagnoses by 19% from 2005 → 2014

http://www.cdc.gov/hiv/statistics/overview/ataglance.html

New HIV Diagnoses in the United States for the Most-Affected Subpopulations, 2015

http://www.cdc.gov/hiv/statistics/overview/ataglance.html
ART for HIV Prevention and Treatment

- With effective ART, HIV-related morbidity and mortality have decreased
- ART is also an effective form of HIV prevention
- ART is now recommended as soon as an HIV diagnosis is made


START study: Benefit of immediate ART
Strategies for Improving HIV Care Continuum Outcomes

Estimated percentage of persons living with HIV infection, by outcome along the HIV care continuum — United States, 2011

* Linkage to care measures the percentage of people diagnosed with HIV in a given calendar year who had one or more documented viral load or CD4+ test within three months of diagnosis. Because it is calculated differently from other steps in the continuum, it cannot be directly compared to other steps and is therefore shown in a different color. See Table 1 on page 4 for more details.

IAPAC GUIDELINES FOR OPTIMIZING THE HIV CARE CONTINUUM FOR ADULTS AND ADOLESCENTS

Evidence-Based Recommendations from an IAPAC Panel

OPTIMIZING THE HIV CARE ENVIRONMENT

1. Laws that criminalize the conduct of or entry into anal sex or other sexual acts against men who have sex with men (MSM), transsexual individuals, substance users, and sex workers are not recommended and should be repealed where they have been enacted. [A IV]

2. Laws that criminalize the conduct of people living with HIV (PLHIV) based on perceived exposure to HIV, and without any evidence of intent to do harm, are not recommended and should be repealed where they have been enacted. [A IV]

3. HIV-related restrictions on voting, stay, and residence in any country for PLHIV are not recommended and should be repealed. [A IV]

4. Strategies to monitor and eliminate stigma and discrimination based on race, ethnicity, gender, age, sexual orientation, and/or behavior in all settings, but particularly in healthcare settings, using standardized measures and evidence-based approaches, are recommended. [B III]

5. Proactive steps are recommended to identify and manage clinical mental health disorders (e.g., anxiety, depression, traumatic stress, and/or mental health factors related to HIV diagnosis, disclosure of HIV status, and/or HIV treatment). [A II]

6. Enabling PLHIV to take responsibility for their care (e.g., self-management, peer-driven care) is recommended. [A II]

7. Shifting and sharing HIV testing, dispensing of pre-exposure prophylaxis (PrEP), and other appropriate tasks among professional and paraprofessional health worker cadres is recommended. [A II]

7a. Use of lay health workers to provide pre-test education and testing and to enhance PLHIV engagement in HIV care is recommended. [B I]

7b. Task shifting/sharing from physicians to appropriately trained healthcare providers, including nurses and associate clinicians, is recommended for ART initiation and management. [B II]

8. Community engagement in every step across the HIV care continuum is recommended. [B III]

INCREASING HIV TESTING COVERAGE AND UNAVAILABILITY TO CARE

9. Routine offering on-site HIV testing to all individuals who present at health facilities is recommended. [A I]

10. Community-based HIV testing is recommended to reach those who are less likely to attend facility-based HIV testing. [A I]

11. Confidential voluntary HIV testing in large workplace and institutional settings (military, police, mining/mining companies, and educational/recreational) should be considered. [B III]

12. HIV self-testing is recommended with the provision of guidance about the proper method for administering the test and direction on what to do once the results have been obtained. [B II]
13. The use of epidemiological data and network analyses to identify individuals at risk of HIV infection for HIV testing is recommended. [B III]

14. The offer of HIV testing to partners of newly diagnosed individuals is recommended. [A II]

15. Immediate referral to HIV care is recommended following an HIV-positive diagnosis to improve linkage to ART. [A I]

16. For high-risk individuals who test HIV negative, offering PEP is recommended in addition to the provision of free condoms, education about risk reduction strategies, post-exposure prophylaxis (PEP), and voluntary medical male circumcision. [A I]

17. The use of case managers and patient navigators to increase linkage to care is recommended. [B III]

18. Increasing HIV treatment coverage

19. First-line ART regimens with the highest levels of efficacy, least adverse event profiles, and delivered in fixed-dose, once-daily dosed combinations are recommended. [B III]

20. Viral load testing at least every six months is recommended as the preferred tool for monitoring ART response. [B II]

21. HIV drug resistance testing is recommended at entry into care or prior to ART initiation, and when virologic failure is confirmed. [B II]

21a. Where routine access to HIV drug resistance testing is restricted, population-based surveillance is recommended. [B II]

22. Community-based ART distribution is recommended. [A II]

22a. The use of community-based pharmacies should be considered. [C III]

**INCREASING RETENTION IN CARE, ART ADHERENCE, AND VIRAL SUPPRESSION**

23. Systematic monitoring of retention in HIV care is recommended for all patients. [A II]

23a. Retention in HIV care should be considered as a quality indicator. [B III]

23b. Measuring retention in HIV care using electronic health record and other health system data is recommended. [B III]

23c. Use of clinic databases/surveillance systems for HIV clinical monitoring and population-level tracking is recommended. [B II]

24. Routine ART adherence monitoring is recommended in all patients. [A II]

24a. Viral suppression is recommended as the primary adherence monitoring metric. [B III]

24b. Routine collection of self-reported adherence data from patients is recommended. [A II]

24c. Pharmacy refill data are recommended for adherence monitoring. [B II]

25. Information and communication technologies aimed at supporting patient self-care are recommended. [B II]

25a. Mobile health technology using weekly interactive components (e.g., two-way SMS) is recommended. [B II]

25b. Alarm devices are recommended as reminders for PLHIV with memory impairment. [A I]

26. Patient education about and offering support for medication adherence and keeping clinic appointments are recommended. [A I]

26a. Pillbox organizers are recommended, particularly for HIV-infected adults with lifestyle-related barriers to adherence. [B II]

27. Neither directly administered nor directly observed ART are recommended for routine clinical-care settings. [A I]

27a. Directly administered ART is recommended for people who inject drugs and released prisoners at high risk of ART non-adherence. [B II]

28. Proactive engagement and re-engagement of patients who miss clinic appointments and/or are lost to follow-up, including intensive outreach for those not engaged in care within one month of a new HIV diagnosis, is recommended. [B II]

28a. Case management to retain PLHIV in care and to locate and re-engage patients lost to follow-up are recommended. [B II]

28b. Transportation support for PLHIV to attend their clinic visits is recommended. [B II]
Suggested HIV Checklist for Managed Care Plans

- Designate HIV specialists as PCPs to make referrals unnecessary.
- Employ a multidisciplinary care philosophy that vests authority in everyone.
- Make care managers effective.
- Constantly measure and improve quality.
- Mine your data to identify people at risk of falling out of care
- Build trust with your members to engage them.

Dalzell M. HIV: A Fragile Population Enters Managed Care. Managed Care. 2013

ART in 2017
Recommendations for Initial Therapy
Case Presentation

53 yo African American male presents for initial evaluation of HIV disease
HIV transmission risk factor is unprotected receptive anal intercourse
PMH: HBP; has not taken BP meds in a few years
½ ppd smoker and uses cocaine most weekends

Baseline clinical / lab data: BP elevated at 175/91; the rest of his exam is unremarkable.
CD4 352, HIVRNA 18650. Baseline genotype reveals no mutations. HLA-B*5701 testing is negative. HBV and HCV are negative. Baseline renal and hepatic function are normal.
T chol 221, LDL 135, TG 142, HDL 38.

Patient says he thinks he can stick with HIV therapy, and wants a once per day medication

Goals of ART

• Reduce HIV reduction of HIV-related morbidity and mortality
• Improve quality of life
• Restore and preserve immune function
• Control HIV replication

Recommended Antiretroviral Regimen Options for Treatment-Naive Patients (July 2016)

- Abacavir/dolutegravir/lamivudine (only if HLA-B*5701 negative)
- Dolutegravir plus either emtricitabine/tenofovir DF or emtricitabine/tenofovir AF
- Cobicistat/elvitegravir/emtricitabine/tenofovir DF (only if creatinine clearance \([CrCl] \geq 70\) mL/min)
- Cobicistat/elvitegravir/emtricitabine/tenofovir AF (only if \(CrCl \geq 30\) mL/min)
- Raltegravir plus either emtricitabine/tenofovir DF or emtricitabine/tenofovir AF
- Darunavir/ritonavir plus either emtricitabine/tenofovir DF or emtricitabine/tenofovir AF


International Antiviral Society–USA Guidelines Recommended initial regimens

- Abacavir/dolutegravir/lamivudine*
- Dolutegravir plus emtricitabine/tenofovir AF
- Cobicistat/elvitegravir/emtricitabine/tenofovir AF
- Raltegravir plus emtricitabine/tenofovir AF

*must be HLA-B*5701 negative

DHHS alternative regimens

- Efavirenz/emtricitabine/tenofovir DF or efavirenz + emtricitabine/tenofovir AF
- Rilpivirine/tenofovir DF/emtricitabine or rilpivirine/emtricitabine/tenofovir AF (requires HIV-1 RNA < 100,000 copies/mL and CD4+ cell count > 200 cells/mm³)

- (Atazanavir/cobicistat or atazanavir/ritonavir) + (emtricitabine/tenofovir DF or emtricitabine/tenofovir AF)
- (Darunavir/cobicistat or darunavir/ritonavir) + abacavir/lamivudine*
- Darunavir/cobicistat + (emtricitabine/tenofovir DF or emtricitabine/tenofovir AF)

*must be HLA-B*5701 negative

IAS – Regimens when INSTIs are not an option

- Efavirenz/emtricitabine/tenofovir DF
- Rilpivirine/tenofovir DF/emtricitabine or rilpivirine/emtricitabine/tenofovir AF*
- Darunavir/cobicistat or darunavir/ritonavir + (emtricitabine/tenofovir AF, emtricitabine/tenofovir DF, or abacavir/lamivudine**)

*If HIV-1 RNA < 100,000 copies/mL and CD4+ cell count > 200 cells/mm³
** must be HLA-B*5701 negative
What drives clinicians’ (and patients’) choices?

- Achieving viral suppression
- Minimizing toxicity
- Minimizing pill burden, dosing frequency
- Drug–drug interactions
- Baseline resistance (need PR, RT, possibly integrase resistance testing); potential for development of resistance
- Cost
- Comorbidities
- Food Restrictions

Clinical trials assessing virologic suppression comparing Integrase inhibitors (INSTIs) to Protease Inhibitors (PIs)

- ACTG A5257 (Atazanavir/ritonavir vs. darunavir/ritonavir vs. raltegravir – each arm administered with tenofovir DF/emtricitabine)
  Three arms equally efficacious, less toxicity in raltegravir arm
- Study 103 (Elvitegravir/cobicistat/emtricitabine/tenofovir DF vs. atazanavir/ritonavir + emtricitabine/tenofovir DF)
  Elvitegravir/cobicistat regimen noninferior to atazanavir/ritonavir regimen
- WAVES (Elvitegravir/cobi/emtricitabine/tenofovir DF vs. atazanavir/ritonavir plus emtricitabine/tenofovir DF)
  Women only
  Elvitegravir/cobicistat regimen superior to atazanavir/ritonavir regimen

Minimizing Toxicity

• Renal function
• Bone mineral density
• Lipid effects
• Other side effects

Minimizing pill burden, dosing frequency

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Number of Pills</th>
<th>QD or BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir/dolutegravir/lamivudine</td>
<td>1</td>
<td>QD</td>
</tr>
<tr>
<td>Dolutegravir plus either emtricitabine/tenofovir DF or emtricitabine/tenofovir AF</td>
<td>2</td>
<td>QD</td>
</tr>
<tr>
<td>Cobicistat/elvitegravir/emtricitabine/tenofovir DF</td>
<td>1</td>
<td>QD</td>
</tr>
<tr>
<td>Cobicistat/elvitegravir/emtricitabine/tenofovir AF</td>
<td>1</td>
<td>QD</td>
</tr>
<tr>
<td>Raltegravir plus either emtricitabine/tenofovir DF or emtricitabine/tenofovir AF</td>
<td>3</td>
<td>BID</td>
</tr>
<tr>
<td>Darunavir/ritonavir plus either emtricitabine/tenofovir DF or emtricitabine/tenofovir AF</td>
<td>3</td>
<td>QD</td>
</tr>
</tbody>
</table>

Note: regimens that are underlined are both DHHS and IAS first-line regimens
## Baseline resistance

- Transmitted resistance mutation present in 17.4% of MSM; 15.5% in non-MSM (CDC; US sample, 11 jurisdictions, 10,894 samples)
- Transmitted resistance mutation present in 11.2% of treatment-naïve patients screening for clinical trials (Gilead sciences; international sample predominantly US and Europe; 6,704 samples)
- Majority of transmitted resistance is NNRTI resistance
- Transmitted resistance to INSTIs is low


## Cost

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Estimated cost per 30 day supply</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir/dolutegravir/lamivudine</td>
<td>$2659</td>
</tr>
<tr>
<td>Dolutegravir plus either emtricitabine/tenofovir DF or emtricitabine/tenofovir AF</td>
<td>$3182</td>
</tr>
<tr>
<td>Cobicistat/elvitegravir/emtricitabine/tenofovir DF</td>
<td>$2957</td>
</tr>
<tr>
<td>Cobicistat/elvitegravir/emtricitabine/tenofovir AF</td>
<td>$2861</td>
</tr>
<tr>
<td>Raltegravir plus either emtricitabine/tenofovir DF or emtricitabine/tenofovir AF</td>
<td>$3033</td>
</tr>
<tr>
<td>Darunavir/ritonavir plus either emtricitabine/tenofovir DF or emtricitabine/tenofovir AF</td>
<td>$3380</td>
</tr>
</tbody>
</table>

Drug pricing information: Goodrx.com
Cost, cont.

- ART is cost-effective
- Increased out-of-pocket costs are related to worse adherence to medications for chronic diseases; clinicians should try to minimize out-of-pocket costs
- Availability of generic ART may increase pill burden/frequency and decrease adherence
- Appropriate laboratory monitoring (e.g., decreasing unnecessary CD4 cell count monitoring) can be cost-saving

### Comorbidities

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Drug consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric Illness</td>
<td>Avoid NNRTIs</td>
</tr>
<tr>
<td>Osteopenia or Osteoporosis</td>
<td>Avoid TDF</td>
</tr>
<tr>
<td>High cardiac risk</td>
<td>Consider avoiding ABC; recent study from CROI also pointed to increased CVD risk with darunavir/r</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Avoid RTV- or cobi-boosted PIs, ABC, EFV, ELV/c, (TAF)</td>
</tr>
<tr>
<td>HBV</td>
<td>Need to use emtricitabine/tenofovir DF or AF OR Lamivudine + tenofovir DF or AF OR emtricitabine or lamivudine with entecavir or another anti-HBV drug</td>
</tr>
<tr>
<td>HCV</td>
<td>Be mindful of drug interactions with HCV agents</td>
</tr>
</tbody>
</table>

Adapted from Paul Sax, MD

### Case Presentation

53 yo African American male presents for initial evaluation of HIV disease  
HIV transmission risk factor is unprotected receptive anal intercourse  
PMH: HBP; has not taken BP meds in a few years  
½ ppd smoker and uses cocaine most weekends

Baseline clinical / lab data: BP elevated at 175/91; the rest of his exam is unremarkable.  
CD4 352, HIVRNA 18650. Baseline genotype reveals no mutations. HLA-B*5701 testing is negative. HBV and HCV are negative. Baseline renal and hepatic function are normal.  
T chol 221, LDL 135, TG 142, HDL 38.

Patient says he thinks he can stick with HIV therapy, and wants a once per day medication
ART in 2017
Strategies for Switching Patients with Viral Suppression

Switch strategies when suppressed

• Tolerability/toxicity
• Preserve treatment options
• Avoid drug-drug interactions
• Simplify regimen (improve adherence)
• Decrease cost
• Alter food requirements
• Avoid parenteral administration
• Optimize ART use in pregnancy or in the case of pregnancy

Switch strategies when suppressed

• Goals: maintain viral suppression
• Do not compromise future treatment options

• Proactive – avoid adverse effects, improve potential for optimal adherence
• Reactive – after an adverse event

What to keep in mind prior to switch

• Possible archived resistance mutations
  • Initial acquisition of drug-resistant virus or selection of resistance mutations during failure of previous regimen
• Duration of suppression prior to switch
• Patient’s adherence
Switch Strategies with Good Supporting Evidence

- Within-class switches
- Between-class switches
- Ritonavir-boosted PI plus 3TC/FTC

Switch Strategies Under Evaluation

- Ritonavir-boosted PI plus INSTI
- Cobicistat/elvitegravir/emtricitabine/tenofovir AF plus darunavir
- Dolutegravir plus 3TC or FTC
- Dolutegravir + rilpivirine

Additional Citation: Llibre. CROI 2017 Abstract 44LB.

ART in 2017
Management of the Treatment-Experienced Patient: Virologic Failure
Definitions

- **Virologic failure**: The inability to achieve or maintain suppression of viral replication to an HIV RNA level <200 copies/mL.

- **Incomplete virologic response**: Two consecutive plasma HIV RNA levels ≥200 copies/mL after 24 weeks on an ARV regimen in a patient who has not yet had documented virologic suppression on this regimen. A patient’s baseline HIV RNA level may affect the time course of response, and some regimens will take longer than others to suppress HIV RNA levels.

- **Virologic rebound**: Confirmed HIV RNA ≥200 copies/mL after virologic suppression.

- **Virologic blip**: After virologic suppression, an isolated detectable HIV RNA level that is followed by a return to virologic suppression.

Causes of Virologic Failure

**Patient-Related Factors**

**ART Regimen-Related Factors**
Assessment of Virologic Failure

Suboptimal Adherence
• Assess adherence
• Identify and address the underlying cause(s)
• Simplify the regimen if possible

Medication Intolerance
• Assess the patient’s tolerance
  • Symptomatic treatment (e.g., antiemetics, antidiarrheals)
  • A switch from one ARV in a regimen to another agent in the same drug class
  • A switch from one drug class to another class

Pharmacokinetic Issue

Suspected Drug Resistance

Management of Virologic Failure in Different Clinical Scenarios

• First Regimen Failure (general guidelines)
  • Failing an NNRTI plus NRTI regimen → boosted PI plus NRTIs, INSTI, ETV
  • Failing a boosted PI plus NRTI regimen → continue w/adherence support if no resistance or change to non-PI based regimen if there is a tolerability/drug interaction/resistance issue
  • Failing an INSTI plus NRTI regimen → boosted PI plus NRTIs or INSTI

• Second-Line Regimen Failure and Beyond
  • Drug resistance with treatment options allowing for full virologic suppression
    • ≥ 2, preferably 3 active agents
  • Multidrug resistance without treatment options allowing for full virologic suppression
    • Consider trial, expanded access
ART in 2017
Drug-Drug Interactions

Mechanisms of Drug-Drug Interactions

**Drug absorption:**
- Acid-reducing agents
- Polyvalent cations can bind to INSTIs
- Drugs that induce/inhibit CYP3A4 or efflux transporter P-glycoprotein [P-gp] in the intestines

**Pharmacokinetic interactions that affect hepatic metabolism**
- Via the cytochrome P450 enzyme system
- Via the uridine diphosphate (UDP)-glucuronosyltransferase (UGT) 1A1 enzyme: Metabolism of INSTIs dolutegravir (DTG) and raltegravir (RAL)

- PK enhancer (booster)
- Ritonavir/cobicistat
- Both potent CYP 3 A4 inhibitors
- RTV and COBI effect other CYP/UGT metabolizing enzymes/drug transporters differently – cannot extrapolate RTV interactions to COBI interactions

### INSTIs Protease Inhibitors

- Acid Reducers
- Anticoagulants/ antiplatelets
- Anticonvulsants
- Antidepressants/ anxioytics/ antipsychotics
- Antifungals
- Antimycobacterials
- Cardiac medications
- Corticosteroids
- HCV DAAs
- Herbals
- Hormonal contraceptives
- Statins
- Immunosuppressants
- Narcotics/treatment for opioid dependence
- Neuroleptics
- PDE5 Inhibitors
- Sedative/Hypnotics
- Misc (colchicine, flibanserin, metformin, polyvalent cation supplements, salmeterol)

### NNRTIs

- Acid Reducers
- Anticoagulants/ antiplatelets
- Anticonvulsants
- Antidepressants/ anxioytics/ antipsychotics
- Antifungals
- Antimalarials
- Antimycobacterials
- Antimycobacterials/ Antitoxoplasmosis/ Antipneumocystis drugs
- Cardiac medications
- Corticosteroids
- HCV DAAs
- Herbals
- Hormonal contraceptives
- Statins
- Immunosuppressants
- Narcotics/treatment for opioid dependence
- PDE5 Inhibitors

### NRTIs

- Acid Reducers
- Anticoagulants/ antiplatelets
- Anticonvulsants
- Antidepressants
- Antifungals
- Antimalarials
- Antimycobacterials
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- Cardiac medications
- Corticosteroids
- HCV DAAs
- Herbals
- Hormonal contraceptives
- Statins
- Immunosuppressants
- Narcotics/treatment for opioid dependence
- PDE5 Inhibitors
- Anticonvulsants (TAF)
- Antimycobacterials (TAF)

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### Conclusions

1. Effective, well tolerated ART should be individualized for the best chance of long-term success of the initial ART regimen.

2. Multiple patient factors and drug-drug interactions must be considered when making therapeutic decisions and an HIV expert should be involved in designing regimens for treatment-experienced patients.

3. Retention in HIV care is crucial to reap the long-term benefits of ART both for decreasing HIV-related morbidity and mortality and for decreasing HIV transmission.
Thank you for your attention

Questions? amonroe@jhmi.edu