Initiating Antiretroviral Therapy: What to Start and How to Monitor

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Learning Objectives
After attending this presentation, learners will be able to:

- Apply updated guidelines on the initiation of antiretroviral therapy (ART).
- Identify individual characteristics in persons with HIV infection that help to determine the choice of therapy.
- Develop an approach to the clinical and laboratory monitoring of persons on ART.

Financial Relationships With Commercial Entities
Dr. Johnson has served on an advisory board for and received consultation fees to his institution from ViiV Healthcare. (Updated 12/04/19)
Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents: When to Start

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

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

Antiretroviral Therapy: Approved agents in Seven Mechanistic Classes

Entry Inhibitors: Target CD4, Fusion, or CCR5

Integrate Inhibitors

HIV

CD4+ T-Cell

Protease Inhibitors

Reverse Transcriptase Inhibitors: NRTIs (Nucleosides, Nucleotides) and NNRTIs

Integrase Inhibitors

Antiretroviral Timeline: 1987-2019

New Orleans, LA, December 4-7, 2019, Ryan White HIV/AIDS Program CLINICAL CONFERENCE
### New Antiretroviral Agents and Combinations: 2018-2019

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

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

Factors in the Timing and Choice of Initial Antiretroviral Therapy

**Clinical Factors**
- Clinical trial results
- HIV disease stage
- Hepatitis B co-infection
- TB co-infection
- Presence of other OIs
- Substance use
- Mental health conditions
- Other co-morbidities (e.g. CVD)
- Drug-drug interactions
- Drug-food interactions
- Gender
- Plans for pregnancy
- HIV encephalopathy

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

**Other Factors**
- Patient preference
- Provider preference and beliefs
- Adherence potential
- Access to care
- Retention in care
- Financial/insurance issues

New Orleans, LA, December 4-7, 2019, Ryan White HIV/AIDS Program CLINICAL CONFERENCE
Recommendations are Graded Based on the Strength of Evidence

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

Recommended Initial Regimens for Most People with HIV

DHHS Guidelines¹
- INSTI plus 2 NRTIs
  - BIC/TAF/FTC (A1)
  - DTG/ABC/3TC (AI) - if HLA-B*5701 negative
  - DTG plus tenofovir/FTC or 3TC (AI)
  - RAL plus tenofovir/FTC or 3TC (B1 for TDF/FTC or 3TC, BII for TAF/FTC)

IAS-USA Guidelines²
- INSTI plus 2 NRTIs
  - BIC/TAF/FTC (A1a)
  - DTG/ABC/3TC - only for persons who are HLA-B*5701-negative (A1a)
  - DTG plus TAF/FTC (A1a)

Dolutegravir plus 3TC: A new 2-drug Option
- 96 week data show that DTG/3TC has similar efficacy to DTG plus TDF/FTC
- Caveats with this regimen:
  - Baseline HIV RNA level > 500,000 copies/mL (because this regimen has not been studied adequately at high viral loads)
  - HIV genotype results unavailable (given the use of just two drugs, it is essential that the virus is susceptible to both)
  - Individuals with chronic Hepatitis B or if Hepatitis B infection status is unknown (3TC alone is not adequate treatment for Hepatitis B)
- This regimen will be discussed in greater detail during the conference

Individual Characteristics May Affect Initial Choice of ART

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

What Not to Use!

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

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

ARS Question 1

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

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

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

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

RAPID ART Program in San Francisco

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

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

Benefits of Rapid Initiation of ART

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

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

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

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

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

ARS Question 2

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

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

Dolutegravir in Pregnancy

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

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

Potential Adverse Effects of Commonly Used Agents

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

- Weight gain will be discussed more during the conference.

Abacavir Hypersensitivity

Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by signs or symptoms in 2 or more of the following groups:

- Fever
- Rash
- Gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain)
- Constitutional (including malaise, fatigue, or achesness)
- Respiratory (including shortness of breath, cough, or sore throat)
Abacavir Hypersensitivity

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

Drug-Drug Interactions

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

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

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

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


HIV Resistance Tests

- Standard RNA Resistance Tests
- DNA Archive Resistance Tests
IAS-USA Drug Resistance Mutations

<table>
<thead>
<tr>
<th>Drug</th>
<th>amino acid</th>
<th>codon</th>
<th>number of mutations</th>
<th>resistance seen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td></td>
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</tr>
</tbody>
</table>


Adherence to ART is critical. Fixed dose combinations have helped.

How to Monitor Antiretroviral Therapy
Baseline Laboratory Testing

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

Baseline Laboratory Testing

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

Baseline Laboratory Testing: Screening for Co-Infections

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

Virologic Response Definitions

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

Virologic Response Definitions

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

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

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

Laboratory Monitoring on ART: CD4 and HIV RNA

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

The “U = U” Campaign Underscores the Importance of Regular HIV Viral Load Measurement
Potential Savings by Reduced CD4 Monitoring in Stable Patients Receiving Antiretroviral Therapy

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


Other Laboratory Monitoring Tests

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

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

Learning Objectives Revisited

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

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

Question-and-Answer Period