Approach to a Patient Newly Diagnosed with HIV, Including ART Basics

Rajesh T. Gandhi, M.D.

Disclosures: grant support from Gilead, Roche, EBSCO
Objectives

• Apply current guidelines to initial evaluation of a newly diagnosed HIV-infected patient

• Discuss Antiretroviral Therapy (ART) Basics, including When, What and How to start

• Identify steps for monitoring patients on ART
Case

• 45 yo MSM is tested for HIV as part of a life insurance evaluation
• HIV ELISA and Western blot are positive
• No previous HIV testing

• He asks you 3 questions:
  – When should I start therapy for HIV?
  – How should I be treated?
  – How can you tell if the medicine is working?
Approach to the HIV+ Patient: 4 Steps

Step 1: History, Examination and Lab Tests

Step 2: Opportunistic infection prophylaxis (if indicated)

Step 3: Antiretroviral therapy: when and what to start; common side effects of ART

Step 4: Monitoring a patient on ART
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

Judith A. Aberg, Joel E. Gallant, Khalil G. Ghanem, Patricia Emmanuel, Barry S. Zingman, and Michael A. Horberg

1Division of Infectious Diseases and Immunology, New York University School of Medicine, Bellevue Hospital Center, New York; 2Southwest CARE Center, Santa Fe, New Mexico; 3Johns Hopkins University School of Medicine, Baltimore, Maryland; 4Department of Pediatrics, University of South Florida Health, Tampa; 5Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, New York and 6Mid-Atlantic Permanente Research Institute, Rockville, Maryland
Step 1: History

• Risk behaviors; approx. date of infection
• Symptoms
• Exposures: tuberculosis, endemic fungi, sexually transmitted infection (STIs)
• Psychiatric history (prevalence of depression twice as high in HIV+ women as in infected men)
• Family history: cancer; myocardial infarction in 1st degree relative (male <55 yo, female <65 yo)
• Tobacco, alcohol, illicit drug use; sexual history
• Medications, including alternative meds
• Disclosure
Physical Exam

- Skin
- Fundoscopic exam → ophthalmologist if CD4 <50
- Oropharynx
- Lymph nodes → consider biopsy if dominant, focal node or rapid enlargement
- Anogenital exam
  - Cervical pap
  - Rectal exam; anal, prostate masses
Dermatologic Findings

Herpes Zoster

Prurigo nodularis

Kaposi Sarcoma

Images courtesy of Drs. Anisa Mosam & Richard Johnson

www.idimages.org
Oropharyngeal Findings

Aphthous ulcers

Oral candidiasis

Oral hairy leukoplakia

Source: Medscape
Lab Tests

- Routine tests
- Screening tests for infection
- HIV-specific tests
Which test should you order in all HIV+ patients?

A. G6PD
B. HIV tropism
C. HLA-B5701
D. HIV genotype
E. HIV phenotype
Lab Evaluation: Routine Tests

- Chemistries, BUN/Cr, liver function tests
- CBC/diff
- Fasting lipids and glucose
- G6PD: blacks; males from Mediterranean, India, SE Asia
- Urinalysis (U/A)

Aberg J et al, CID, 2013
Lab Evaluation: Screening for Infection

- Serologic testing for infections that can reactivate: toxoplasma IgG, cytomegalovirus (CMV) IgG
- Hepatitis serologies (A, B, C)
- Tuberculin skin test (TST) or interferon-gamma release assay (IGRA)
  - TST >5 mm is positive in HIV+ patients
  - If negative and patient’s CD4 count is <200, repeat TST or IGRA after immune reconstitution
- STI screen: syphilis; gonorrhea, chlamydia

Aberg J et al, CID, 2013
HCV Testing

- HCV antibody (Ab) at care initiation and then annually for high-risk MSM, IDU
  - Increasing sexual transmission of HCV in HIV+ MSM
  - At Fenway Health in Boston, HCV incidence 1.6/100 person-yrs

- If HCV Ab negative but suspicion high (elevated LFTs, recent exposure), check HCV RNA
  - Window period until seroconversion may be up to 12 wks

Lab Evaluation: HIV-specific Tests

- CD4 cell count
- HIV RNA ("viral load")
- HIV drug resistance test (genotype)
  - Transmitted Drug Resistance: 16%
  - NNRTI 8%; NRTI 7%; PI 4.5%
  - [www.iasusa.org/content/hiv-drug-resistance-mutations](http://www.iasusa.org/content/hiv-drug-resistance-mutations)
- HLA-B5701: if considering abacavir.
  - Positive in 8% of US whites. ≈2% of US African-Americans and Hispanics

1Kim D et al, CROI 2013, Abs #149; 2E Phillips, CID, 2006
Which test should you order in all HIV+ patients?

A. G6PD
B. HIV tropism
C. HLA-B5701
D. HIV genotype
E. HIV phenotype

D. HIV genotype
Step 1: History, Examination and Lab Tests

Step 2: Opportunistic infection prophylaxis (if indicated)*

Step 3: Antiretroviral therapy

Step 4: Monitoring

*More on this in other sessions
• 45 yo MSM with newly diagnosed HIV
• Past medical history
  – Gastroesophageal reflux disease (GERD)
  – Allergic rhinitis
• Medications: omeprazole, fluticasone
• Cr 0.5. Total cholesterol 210, LDL 165, HDL 35
• CD4 count 181, HIV RNA 178,000
• HIV genotype: no resistance mutations
• HLA-B5701 positive
• Pneumocystis pneumonia (PCP) prophylaxis (trim/sulfa DS daily) if:
  − CD4 count <200 (CD4 percentage <14)
  − History of thrush

• Mycobacterium avium complex prophylaxis (azithromycin 1200 mg weekly) if CD4 count <50
Approach to the HIV+ Patient: 4 Steps

Step 1: History, Examination and Lab Tests

Step 2: Opportunistic infection prophylaxis (if indicated)*

Step 3: Antiretroviral therapy: when and what to start

Step 4: Monitoring
When to Start

ART recommended for all HIV+ individuals. Strength of recommendation varies based on CD4 count:

<table>
<thead>
<tr>
<th>CD4 Cell Count</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 350</td>
<td>AI</td>
</tr>
<tr>
<td>350-500</td>
<td>AII</td>
</tr>
<tr>
<td>&gt;500</td>
<td>BIII</td>
</tr>
</tbody>
</table>

AI: strong recommendation, data from randomized clinical trials
AII: strong recommendation, non-randomized or observational cohort studies
BIII: moderate recommendation, expert opinion
What to start?

HIV drugs target virus lifecycle

1) Virus Entry
2) Reverse transcriptase
3) Integration
4) Transcription
5) Translation
6) Cleavage
7) Packaging
8) Maturation
9) Re-infection

CD4 receptor
CCR5 coreceptor
Therapies now available for HIV

1) Virus Entry
2) Reverse transcriptase
   RNA → DNA
3) Integration
   Nucleoside reverse transcriptase inhibitors (NRTIs): e.g. tenofovir, abacavir, 3TC, FTC
   Nonnucleoside reverse transcriptase inhibitors (NNRTIs): e.g. efavirenz, rilpivirine
   Protease inhibitors (PIs): e.g. atazanavir, darunavir
4) Transcription
5) Translation
6) Cleavage
7) Packaging
8) Maturation
9) Re-infection
   CD4 receptor (CXCR4, CCR5)
   Fusion (entry) inhibitor: enfuvirtide (T-20
   CCR5 receptor antagonist: maraviroc

Integrate strand transfer inhibitors (INSTI): e.g. raltegravir, dolutegravir, elvitegravir

Fusion (entry) inhibitor: enfuvirtide
CCR5 receptor antagonist: maraviroc

Therapies now available for HIV
Antiretroviral Therapy: >25 Options

**Nucleoside and nucleotide RTIs**
- Zidovudine, AZT (*Retrovir*)
- Abacavir, ABC (*Ziagen*)
- Lamivudine, 3TC (*Epivir*)
- Didanosine, ddI (*Videx*)
- Stavudine, d4T (*Zerit*)
- Tenofovir, TDF (*Viread*)
- Emtricitabine, FTC (*Emtriva*)
- AZT/3TC (*Combivir*)
- AZT/3TC/ABC (*Trizivir*)
- ABC/3TC (*Epzicom*)
- TDF/FTC (*Truvada*)

**CCR5 receptor blocker**
- Maraviroc (*Selzentry*)

**Integrase inhibitor**
- Raltegravir (*Isentress*)
- Elvitegravir (*EVG*)
- Dolutegravir (DTG) (*Tivicay*)

**NNRTIs:**
- Delavirdine (DLV)
- Nevirapine, NVP (*Viramune*)
- Efavirenz, EFV (*Sustiva*)
- Etravirine (*Intelicence*)
- Rilpivirine (*Edurant*)

**Fusion inhibitors:**
- Enfuvirtide, ENF or T20 (*Fuzeon*)

**Protease inhibitors:**
- Indinavir, IDV (*Crixivan*)
- Saquinavir, SQV (*Invirase*)
- Nelfinavir, NFV (*Viracept*)
- Amprenavir, APV (*Agenerase*)
- Atazanavir, ATV (*Reyataz*)
- Fosamprenavir, FPV (*Lexiva*)
- Lopinavir/ritonavir (*Kaletra*)
- Tipranavir (*Aptivus*)
- Darunavir (*Prezista*)

**Combination (1 pill once daily)**
- EFV/FTC/TDF (*Atripla*)
- RPV/FTC/TDF (*Complera*)
- EVG/cobicistat/FTC/TDF (*Stribild*)
- DTG/ABC/3TC
Common Initial Treatments for HIV

Two NRTIs
- Tenofovir/FTC
- Abacavir/3TC

Plus

NNRTI:
- Rilpivirine (RPV)* (if VL <100K, CD4>200)
- Efavirenz (EFV)*

or

Boosted PI:
- Darunavir/r (DRV/r)

or

Integrase inhibitor
- Raltegravir, Elvitegravir/cobi*
- Dolutegravir (DTG)**

*Coformulated with tenofovir/FTC; **Coformulated with ABC/3TC
“How should I be treated?”

Choosing an Antiretroviral Regimen: Two decisions

- **Step 1**: Decide which NRTI to use
- **Step 2**: Decide on which drug to use within the NNRTI, PI or INSTI class
# TDF/FTC or ABC/3TC

<table>
<thead>
<tr>
<th>NRTI</th>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF/FTC</td>
<td>• Single pill options available (with EFV, RPV, EVG/cobi)</td>
<td>• Nephrotoxicity (particularly in those receiving other nephrotoxic agents, PIs)</td>
</tr>
<tr>
<td></td>
<td>• Active vs. HBV</td>
<td>• Increased loss of bone mineral density</td>
</tr>
<tr>
<td>ABC/3TC</td>
<td>• Not nephrotoxic</td>
<td>• Must confirm HLA-B5701 negative</td>
</tr>
<tr>
<td></td>
<td>• Coformulated with DTG</td>
<td>• Some studies, but not all, show association with myocardial infarction</td>
</tr>
</tbody>
</table>
**Individualizing Therapy: Choosing Between NRTIs**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Preferred Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Disease</td>
<td>ABC/3TC</td>
</tr>
<tr>
<td>CV disease</td>
<td>Favor TDF/FTC</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Favor TDF/FTC</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Favor ABC/3TC</td>
</tr>
<tr>
<td>Pre-ART VL &gt;100 K</td>
<td>If using with EFV or ATV/r →TDF/FTC</td>
</tr>
<tr>
<td>Cost</td>
<td>3TC patent expired in 2010 ABC patent expired in 2012</td>
</tr>
</tbody>
</table>
### Individualizing Therapy: Choosing a 3rd drug: NNRTI, PI, INSTI

<table>
<thead>
<tr>
<th>Factor</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need to start ART before resistance results known (acute HIV, OI) or uncertain adherence</td>
<td>Avoid NNRTI; Favor drug with low TDR rate, high resistance barrier: PI, possibly DTG</td>
</tr>
<tr>
<td>Pre-ART VL &gt;100 K, CD4 &lt;200</td>
<td>Avoid RPV</td>
</tr>
<tr>
<td>Food requirements</td>
<td>EFV: empty stomach</td>
</tr>
<tr>
<td></td>
<td>RPV with meal (&gt;390 kcal); EVG/cobi/TDF/FTC: with food</td>
</tr>
<tr>
<td></td>
<td>DTG: no food requirements</td>
</tr>
<tr>
<td>One pill, once daily desired</td>
<td>DTG/ABC/3TC; EFV/TDF/FTC; EVG/c/TDF/FTC; RPV/TDF/FTC</td>
</tr>
<tr>
<td>Psychiatric illness</td>
<td>Consider avoiding EFV -- can worsen psychiatric symptoms</td>
</tr>
<tr>
<td>HCV Therapy</td>
<td>RAL, DTG: fewer drug interactions</td>
</tr>
</tbody>
</table>
## Common Drug Interactions

### Non-HIV medication | ARV
---|---
Proton-pump inhibitors, H2 blockers | ↓ atazanavir, rilpivirine absorption
Divalent cations | Caution with INSTIs

### ARV | Non-HIV medication
---|---
Protease inhibitors, cobicistat | ↑ levels of CYP3A4 metabolized drugs, e.g. many statins, rifampin, PDE5 inhibitors
Efavirenz | ↓ methadone, buprenorphine

Useful site: [http://www.hiv-druginteractions.org](http://www.hiv-druginteractions.org)
Drug Interactions: Exogenous Steroids

- Injectable steroids: levels increased by PIs
  - 10% of patients on PIs who received a steroid injection developed clinical evidence of steroid excess or adrenal insufficiency\(^1\)

- Inhaled fluticasone\(^2\) & budesonide\(^3\): systemic levels increased by PIs
  - Beclomethasone is a safer alternative\(^4\)

\(^1\)Hyle E et al, JAIDS, 2013
\(^3\)http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm336367.htm
\(^4\)Boyd S et al, JAIDS, 2013
“What about side effects?”

- Rash: NNRTI, bactrim
- Indirect hyperbilirubinemia due to atazanavir
  - Usually asymptomatic. Similar to Gilbert’s; benign
- Nephrotoxicity: complication of tenofovir
- Body-fat abnormalities, especially with older ARVs
- Immune reconstitution inflammatory syndrome
  - Worsening or unmasking of opportunistic conditions soon after initiation of ART due to restoration of antigen-specific immunity
  - e.g. TB, MAI lymphadenitis, zoster, PCP, PML, KS
Approach to the HIV+ Patient: 4 Steps

Step 1: History, Examination and Lab Tests

Step 2: OI prophylaxis (if indicated)

Step 3: Antiretroviral therapy

Step 4: Monitoring a Patient on ART

“How can you tell if the medicine is working?”
How Often Do You Check CD4 Counts in Stable* Patients on ART?

*Stable: VL < 50 for many years; CD4 count > 500

A. Every 3 months
B. Every 6 months
C. Once a Year
D. Never
Monitoring after Starting ART

• Chemistries, BUN/Cr, LFTs: wk 2-8 after starting ART, then every 3-6 mo.
• CBC/diff: every 3-6 mo.
• Fasting glucose or HbA1c: every 3-6 mo. if previously abnormal; every 12 mo. if normal
• Lipids: if abnormal, every 6 mo; normal: every 12 mo.

Urinalysis and Renal Monitoring

- U/A at initiation of care and then at least annually (every 6 months if receiving tenofovir)
- Estimate glomerular filtration rate with serum Cr or measure creatinine clearance
- Cobicistat, dolutegravir, trimethoprim can inhibit creatinine secretion \(\rightarrow\) ↑ serum Cr without affecting renal function
- Tenofovir nephrotoxicity
  - **Glomerular**: decreased kidney function
  - **Tubular**: Fanconi’s syndrome: glucosuria (with normal blood glucose), proteinuria (≥1+), urinary phosphate wasting
  
  Tourret J et al, JASN, 2013
Monitoring after Starting ART

• HIV RNA:
  – 2-4 wks after starting ART; then every 4-8 wks until undetectable.
  – First 2 yrs of ART: every 3-4 mo.
  – After 2 yrs of suppression, can extend to every 6 mo

• CD4 count:
  – 3 mo. after initiating ART
  – First 2 yrs of ART: every 3-6 mo
  – After 2 yrs of virologic suppression, CD4 300-500: every 12 mo.; CD4 >500, optional

Approach to HIV+ Patient: 4 Steps

**Step 1: History, Examination, Labs**

- 45 yo M with HIV
- GERD, allergic rhinitis.
- Meds: omeprazole, fluticasone (interact with several commonly used regimens)
- CD4 cell count 181, HIV RNA 178,000
- HIV Genotype: no resistance mutations
- HLA-B5701 positive
Step 2: OI Prophylaxis
• CD4 count 181: PCP prophylaxis indicated

Step 3: ART – individualizing therapy
• Abacavir contraindicated (pt is HLA-B5701 positive)
• Normal renal function (Cr 0.5) so TDF OK
• VL >100,000, CD4 <200: don’t use RPV

Step 4: Monitoring
Case – Bringing it all back home

- Trim/sulfa initiated for PCP prophylaxis
- Initiated TDF/FTC + DTG
- Monitor HIV RNA monthly until undetectable (best indicator that ART is working); monitor safety labs (including U/A), CD4 cell count
- Once VL suppressed for > 2 years, if CD4 count >500, additional CD4 testing is optional
Thank you for your attention!