Updates in HIV Therapy

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Disclosure

- I, Gabriella Douglass, have no financial relationships to disclose.
Objectives

Following this presentation the participants will be able to:

- Describe the role of a pharmacist and pharmacist technician in the care of patients with HIV.
- Select an appropriate initial combination regimen for antiretroviral naïve patients.
- Devise an appropriate plan for short-term therapy interruption of antiretroviral therapy.
- Recognize and assess clinically significant drug interactions between antiretroviral agents and co-prescribed drug therapy.
- Recognize the need for opportunistic infection prophylaxis and select an appropriate regimen.
- Recommend appropriate therapy for occupational and nonoccupational HIV exposure.
CDC Fast Facts

• >1.2 million people in the United States living with HIV infection
  • ~ 1 in 8 (12.8%) unaware of their infection

• HIV incidence stable in recent years, ~50,000 new HIV infections per year

• By risk group, men who have sex with men (MSM) are most seriously affected

• By race, African Americans face the most severe burden

Rates of Diagnoses of HIV Infection Among Adults and Adolescents, by Area of Residence, 2013
United States and 6 Dependent Areas

N= 47,957       Total rate = 18.0

Trends in Annual Age-Adjusted* Rate of Death Due to HIV Infection, United States, 1987–2010

Note: For comparison with data for 1999 and later years, data for 1987–1998 were modified to account for ICD-10 rules instead of ICD-9 rules.

*Standard: age distribution of 2000 US population

Trends in the Percentage Distribution of Deaths due to HIV Infection by Geographic Region, United States, 1987–2010

Note: For comparison with data for 1999 and later years, data for 1987–1998 were modified to account for ICD-10 rules instead of ICD-9 rules.

HAART Era

Era before highly active antiretroviral therapy (mono- and dual therapy)

Era of highly active antiretroviral therapy (triple therapy)

Our Role

• Be a part of the health care team.
• Optimize the patient’s medication therapy.

Efficacy
• Appropriate Antiretroviral therapy (ART)
• Monitoring response
• Monitoring adherence

Safety
• Adverse effects
• Drug interactions
• Opportunistic infection prophylaxis

Education
• Patient
• Pre and Post-exposure prophylaxis
Efficacy
Case 1

- A 35 year old male with a history of IDU presents to your clinic to discuss treatment for his newly diagnosed HIV infection. His CD4 count is 600 cells/ml and his viral load is 12,000 copies/ml. Which of the following would be the most appropriate option for treatment of this patient at this time?
  - A. Recommend initiating ART at this time because the clinical benefits of ART are greater when started early.
  - B. Recommend initiating ART at this time because the patient is young and has a history of IDU.
  - C. Recommend deferring ART at this time because the patient’s viral load is above 500 cells/ml.
  - D. Recommend deferring ART at this time because of the risk of treatment toxicity and development of resistance.
Appropriate ART

- Choosing an appropriate regimen
  - Who qualifies for ART?
  - When do we start ART?
  - How do we choose appropriate ART?

Answers found here: https://aidsinfo.nih.gov/
Appropriate ART

- Who qualifies and when do we start?
  - “ART is recommended for all HIV-infected patients regardless of pre-treatment CD4 count. However, the strength of the recommendation will be changed to AI (strong recommendation based on data from randomized controlled trials) for all patients.”

Source: AIDSinfo Statement by the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents Regarding Results from the START and TEMPRANO Trials Date: July 28, 2015
Appropriate ART

- Pivotal trials for Early vs. Deferred treatment
  - START Trial
    - Serious AIDS or non-AIDS events reported in 42 participants in the early ART arm and 96 participants in the deferred ART arm [hazard ratio, 0.43, 95% CI (0.30–0.62), \( P < .001 \)]
  - TEMPRANO ANRS 12136 Study
    - Risk of primary events was lower with immediate ART than with deferred ART, with a hazard ratio of 0.56 in favor of early ART (CI, 0.33–0.94).

Case 1

- A 35 year old male with a history of IDU presents to your clinic to discuss treatment for his newly diagnosed HIV infection. His CD4 count is 600 cells/ml and his viral load is 12,000 copies/ml. Which of the following would be the most appropriate option regarding treatment for this patient at this time?
  - A. Recommend initiating ART at this time because the clinical benefits of ART are greater when started early.
  - B. Recommend initiating ART at this time because the patient is young and has a history of IDU.
  - C. Recommend deferring ART at this time because the patient’s viral load is above 500 cells/ml.
  - D. Recommend deferring ART at this time because of the risk of treatment toxicity and development of resistance.
Comorbidities and other Conditions
- Cardiovascular disease, hyperlipidemia, renal disease, osteoporosis, psychiatric illness, neurologic disease, drug abuse or dependency
- Pregnancy or pregnancy potential
- Coinfections: HCV, HBV, TB

Regimen characteristic
- Resistance
- Adverse effects
- Drug interactions
- Convenience
- Cost

Patient Factors
- Viral load and CD4 count
- Genotype results
- HLA-B*5701 status
- Patient preferences
- Anticipated adherence

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>Abacavir, Didanosine, Emtricitabine, Lamivudine, Stavudine, Tenofovir, Zidovudine</td>
</tr>
<tr>
<td>NNRTI</td>
<td>Delavirdine, Efavirenz, Etravirine, Nevirapine, Rilpivirine</td>
</tr>
<tr>
<td>Protease Inhibitor (PI)</td>
<td>Atazanavir, Darunavir, Fosamprenavir, Indinavir, Lopinavir, Nelfinavir, Saquinavir, Tipranavir</td>
</tr>
<tr>
<td>Integrase Inhibitor (INSTI)</td>
<td>Dolutegravir, Elvitegravir, Raltegravir</td>
</tr>
<tr>
<td>Entry inhibitor</td>
<td>Fusion Inhibitor, Enfuvirtide, CCR5 Antagonist, Maraviroc, PK booster, Ritonavir, Cobicistat</td>
</tr>
</tbody>
</table>
A 47 year old female patient presents to clinic to begin her first ART. Her past medical history is significant for a hysterectomy, hyperlipidemia, diabetes, and hypertension. She takes pravastatin 40 mg at bedtime, metformin 1000 mg twice a day, lisinopril 20 mg daily, and HCTZ 25 mg daily. No ART resistance identified on genotype testing. Hepatitis serology and STI testing is negative. HLA-B*5701 is also negative. Results of most recent lab work: HIV RNA: 79,900 copies/ml, CD4 count 198, CMP: normal, CBC: normal; A1c, BP and lipids at goal. NKDA. Which of the following is the most appropriate initial ART for this patient?

- A. Efavirenz/tenofovir/emtricitabine
- B. Dolutegravir/abacavir/lamivudine
- C. Elvitegravir/cobicistat/tenofovir/emtricitabine
- D. Atazanavir/ritonavir plus tenofovir/emtricitabine
Appropriate ART

- **Recommended regimens for antiretroviral-naive patients:**
  - **Integrase Strand Transfer Inhibitor-Based Regimens:**
    - Dolutegravir/abacavir/lamivudine
    - Dolutegravir plus tenofovir/emtricitabine
    - Elvitegravir/cobicistat/tenofovir/emtricitabine
    - Raltegravir plus tenofovir/emtricitabine
  - **Protease Inhibitor-Based Regimen:**
    - Darunavir/ritonavir plus tenofovir/emtricitabine

Monitoring Response

- **CD4 count**
  - Indicator of immune function
  - Used in determining need for opportunistic infection prophylaxis
  - Important in determining response to ART

- **HIV RNA (viral load)**
  - Marker of response to ART
  - Goal of ART: HIV RNA below limit of detection

Monitoring Adherence

Assessing Adherence

- Viral load suppression
- Patient’s self report
- Pharmacy records
- Pill counts
- Therapeutic drug monitoring
- Electronic measurement devices

Monitoring Adherence

- **Identify barriers:**
  - Assess patient’s cognitive competence and impairment.
  - Assess behavioral and psychosocial challenges
  - Identify and address language and literacy barriers.
  - Assess beliefs, perceptions, and expectations about taking ART
  - Ask about medication taking skills and foreseeable challenges with adherence
  - Assess structural issues

Therapy Interruption

**Reasons:**
- Drug toxicity
- Intercurrent illnesses that preclude oral intake
- Surgical procedures
- Interrupted access to drugs

Therapy Interruption

- “HIV patients are about 25% more likely to experience a medication error while in the hospital than are patients admitted without HIV infection.”

- Search revealed that 79.3% of ART cannot be crushed, sprinkled, or administered through a PEG or NG tube
  - Ones they identified that can be crushed or sprinkled:
    - Delavirdine, efavirenz, etravirine, stavudine, nelfinavir, saquinavir.

Therapy Interruption

Short-Term Therapy Interruption

Unanticipated (Severe or Life-Threatening Toxicity or Unexpected Inability to Take Oral Medications)

All components of the drug regimen should be stopped simultaneously.

Temporary discontinuation of all drug components is indicated. The regimen should be restarted as soon as the patient can resume oral intake.

Planned

Similar half lives?

Yes

Food required for absorption?

Yes

Stop the NNRTI first and the other ARV drugs 2 to 4 weeks later. Alternatively, replace the NNRTI with a boosted protease inhibitor for 4 weeks.

No

No

All drugs may be given with a sip of water, if allowed; otherwise, all drugs should be stopped simultaneously.

Yes

Food required for absorption?

Yes

All drugs may be given with a sip of water, if allowed; otherwise, all drugs should be stopped simultaneously.

No

Therapy Interruption

- Regimens that Should be Taken with Food:
  - Atazanavir/ritonavir or cobicistat
  - Darunavir/ritonavir or cobicistat
  - Elvitegravir/cobicistat/tenofovir/emtricitabine
  - Rilpivirine/tenofovir/emtricitabine

- Regimens that Should be Taken on an Empty Stomach:
  - Efavirenz-based regimens

## ART Formulations

<table>
<thead>
<tr>
<th>Solution</th>
<th>Powder</th>
<th>IV</th>
<th>Subcutaneous</th>
</tr>
</thead>
</table>
| • All NRTIs except Tenofovir  
• Nevirapine  
• Darunavir  
• Fosamprenavir  
• Lopinavir/ritonavir  
• Ritonavir  
• Tipranavir | • Tenofovir  
• Atazanavir  
• Nelfinavir  
• Raltegravir | • Zidovudine | • Enfuvirtide |

Safety

Adverse Effects
**Cardiovascular**
- Bleeding (PIs)
- MI (abacavir, didanosine, and PIs)
- Conduction abnormalities (PIs)
- Dyslipidemia (stavudine, zidovudine, abacavir, efavirenz, elvitegravir combo, and PIs)
- Bone marrow suppression (zidovudine)

**Gastrointestinal**
- Cholelithiasis (atazanavir)
- GI intolerance (PIs, pancreatitis with didanosine)
- Hepatic Effects
  - NRTIs: lactic acidosis/hepatomegaly
  - NNRTIs: hepatotoxicity (nevirapine: watch CD4 count)
  - PIs: hepatotoxicity; indirect hyperbilirubinemia (atazanavir and indinavir)
  - Maraviroc: hepatotoxicity

**Endocrine/Metabolism**
- Diabetes Mellitus/Insulin Resistance (zidovudine, didanosine, stavudine, indinavir, and lopinavir)
- Lipodystrophy (lipoatrophy: stavudine > zidovudine; lipohypertrophy: efavirenz, PIs, and raltegravir)

**Skin/Musculoskeletal**
- Bone Density Effects (tenofovir)
- Hypersensitivity Reaction (abacavir and nevirapine)
- Rash (emtricitabine, NNRTIs, atazanavir, darunavir, fosamprenavir, lopinavir, tipranavir, raltegravir, elvitegravir, maraviroc)
- Myopathy (zidovudine and raltegravir)

**Other**
- Nervous System (Peripheral neuropathy: stavudine > didanosine)
- Psychiatric Effects (efavirenz and INSTIs)
- Renal Effects
  - Tenofovir: renal insufficiency, Fanconi syndrome
  - Indinavir, atazanavir: urolithiasis
  - Cobicistat: inhibits Cr secretion without reducing renal glomerular function.

Safety

Drug Interactions
Drug Interactions

- ART drug classes:
  - PIs
  - NNRTIs

- Pharmacokinetic boosters
  - Ritonavir
  - Cobicistat

- Dose adjustments may be required

- Coadministration may be contraindicated

- What should we do?
Drug Interactions

- Pharmacokinetic Interactions Affecting Hepatic Metabolism
  - CYP450 – NNRTIs, PIs, CCR5 antagonist, and elvitegravir
  - UGT 1A1 – dolutegravir and raltegravir

- Pharmacokinetic Interactions Affecting Drug Absorption
  - Acid reducing agents – atazanavir and rilpivirine
  - Polyvalent cations - integrase inhibitors (INSTI)

Drug Interactions

- Statins
- Rifampin, rifapentine
- Azole antifungals
- Benzodiazepines
- Anticonvulsants
- Hepatitis C agents
- Hormonal contraceptives
- Methadone
- PDE5 inhibitors
- Metformin (dolutegravir)
- St. John’s Wort
- Ranolazine
- Antiarrhythmics
- Anticoagulants
Case 2

- A 47 year old female patient presents to clinic to begin her first ART. Her past medical history is significant for hysterectomy, hyperlipidemia, diabetes, and hypertension. She takes pravastatin 40 mg at bedtime, metformin 1000 mg twice a day, lisinopril 20 mg daily, and HCTZ 25 mg daily. No ART resistance identified on genotype testing. Hepatitis serology and STI testing is negative. HLA-B*5701 is also negative. Results of most recent lab work: HIV RNA: 79,900 copies/ml, CD4 count 198, CMP: normal, CBC: normal; A1c, BP and lipids at goal. NKDA. Which of the following is the most appropriate initial ART for this patient?
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  - D. Atazanavir/ritonavir plus tenofovir/emtricitabine
Safety

Opportunistic Infection Prophylaxis
Case 3

A 47 year old female patient presents to clinic to begin her first ART. Her past medical history is significant for hysterectomy, hyperlipidemia, diabetes, and hypertension. She takes pravastatin 40 mg at bedtime, metformin 1000 mg twice a day, lisinopril 20 mg daily, and HCTZ 25 mg daily. No ART resistance identified on genotype testing. Hepatitis serology and STI testing is negative. HLA-B*5701 is also negative. Results of most recent lab work: HIV RNA: 79,900 copies/ml, CD4 count 198, CMP: normal, CBC: normal; A1c, BP and lipids at goal. NKDA. Which of the following is the most appropriate option for opportunistic infection prophylaxis for this patient?

- A. She does not need OI prophylaxis at this time
- B. TMP/SMX DS 1 tablet daily
- C. Azithromycin 1200 mg weekly
- D. Fluconazole 100 mg daily
PCP Prophylaxis

- **Primary prophylaxis**
  - CD4 < 200 or < 14%
  - Oropharyngeal candidiasis
  - AIDS-defining illness
  - CD4 b/t 200-250 & inability to monitor CD4 at least q3 months
  - d/c: if CD4 > 200 for ≥ 3 months with ART

- **Pharmacotherapy**
  - TMP/SMX DS or SS: 1 tablet daily
  - Alternatives
    - Dapsone
    - Atovaquone
    - Pentamidine

Toxoplasmosis Prophylaxis

- **Primary Prophylaxis**
  - CD4 < 100 & Toxoplasma IgG positive
  - d/c: if CD4 increased to > 200 for ≥ 3 months with ART

- **Pharmacotherapy**
  - TMP/SMP – 1 DS tablet daily
  - Alternatives
    - Dapsone + pyrimethamine + leucovorin
    - Atovaquone +/- pyrimethamine + leucovorin

- Note: pyrimethamine is no longer available in retail pharmacies in the United States. It is only available through a special pharmacy program (http://www.daraprimdirect.com/how-to-prescribe)

MAC Prophylaxis

- **Primary Prophylaxis**
  - CD4 < 50
  - d/c: CD4 > 100 for ≥ 3 months with ART

- **Pharmacotherapy**
  - Azithromycin 1200 mg PO once weekly
  - Clarithromycin 500 mg PO BID
  - Azithromycin 600 mg PO twice weekly

- **Alternatives**
  - Rifabutin

Case 3

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Education
Patient Education

- Pathophysiology and natural history of HIV infection and progression to AIDS.
- Goals, MOA, and duration of ART.
- Adverse effects and interactions with ART and ways to manage adverse effects.
- Drug resistance and the importance of adherence.
- Laboratory monitoring of therapeutic response to ART.
- Modes of HIV transmission and effective techniques for prevention of transmission.
Case 4

A 32 year old female presents for a well woman checkup. She is not infected with HIV. She shares with you that her male partner is HIV-infected and is currently on antiretroviral treatment. She states they use condoms most of the time. Which of the following is the best option to reduce the patient’s risk of HIV infection?

A. Replace condom use with once daily tenofovir/emtricitabine

B. Continue condom use and start once daily tenofovir/emtricitabine

C. Continue condom use only, the patient is in a heterosexual relationship and therefore does not qualify for pre-exposure prophylaxis with tenofovir/emtricitabine

D. Discontinue condom use, she does not need pre-exposure prophylaxis since her partner is on ART
# Pre-exposure prophylaxis

## Table 1: Summary of Guidance for PrEP Use

<table>
<thead>
<tr>
<th></th>
<th>Men Who Have Sex with Men</th>
<th>Heterosexual Women and Men</th>
<th>Injection Drug Users</th>
</tr>
</thead>
</table>
| Detecting substantial risk of acquiring HIV infection | HIV-positive sexual partner  
Recent bacterial STI  
High number of sex partners  
History of inconsistent or no condom use  
Commercial sex work | HIV-positive sexual partner  
Recent bacterial STI  
High number of sex partners  
History of inconsistent or no condom use  
Commercial sex work  
In high-prevalence area or network | HIV-positive injecting partner  
Sharing injection equipment  
Recent drug treatment (but currently injecting) |
| Clinically eligible  | Documented negative HIV test result before prescribing PrEP  
No signs/symptoms of acute HIV infection  
Normal renal function; no contraindicated medications  
Documented hepatitis B virus infection and vaccination status |                                                                                           |                                                                                        |
| Prescription         |                                                                                          |                                                                                          | Day supply                                                                           |
| Other services       | Follow-up visits at least every 3 months to provide the following:  
HIV test, medication adherence counseling, behavioral risk reduction support, side effect assessment, STI symptom assessment  
At 3 months and every 6 months thereafter, assess renal function  
Every 6 months, test for bacterial STIs | Do oral/rectal STI testing  
Assess pregnancy intent  
Pregnancy test every 3 months | Access to clean needles/syringes and drug treatment services |

STI: sexually transmitted infection

Case 4

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D. Discontinue condom use, she does not need pre-exposure prophylaxis since her partner is on ART
Case 5

A pharmacist is working in an HIV clinic. The pharmacist is interacting with an HIV positive female who is non-adherent to her ART and has a viral load of 250,000 copies/ml. While the patient is conversing with the pharmacist, saliva sprays from the patient’s mouth and comes into contact with the pharmacist’s eye. Does the pharmacist need occupational post-exposure prophylaxis?

A. Yes

B. No
**Occupational Exposure Risk**

- Most cases have resulted from needle stick injury
  - Estimated 0.3% risk of transmission
  - Mucotaneous exposure (e.g., tainted blood splash in eye, mouth, nose) has risk of ~0.09%

- Significant risk factors for seroconversion after needle stick:
  - Deep injury
  - Injury with a device visibly contaminated with blood
  - Advance HIV disease in index patient
Exposures

- Infectious
  - Blood, semen, pre-seminal fluid, rectal fluids, vaginal fluids, and breast milk

- Not Infectious
  - Feces, nasal secretions, saliva, sputum, sweat, tears, urine, and vomitus unless visibly bloody
Post-Exposure Prophylaxis

- PEP should be started as soon as possible after the exposure, preferably within hours.
- PEP should be taken for 4 weeks.
- Recommended regimen: Raltegravir 400 mg PO twice daily plus Emtricitabine/Tenofovir 1 tab PO daily.
- HIV testing at baseline, 6 weeks, 12 weeks, and 6 months after exposure.
  - If 4th-generation p24 Ag/HIV Ab test is used: HIV testing at baseline, 6 weeks, 12 weeks, and 4 months after exposure.

Case 5

A pharmacist working in an HIV clinic. The pharmacist is interacting with an HIV positive female who is not adherent to her ART and has a viral load of 250,000 copies/ml. While the patient is conversing with the pharmacist, saliva sprays from the patient’s mouth and comes into contact with the pharmacist’s eye. Does the pharmacist need occupational post-exposure prophylaxis?

A. Yes
B. No
QUESTIONS
UPDATES in HIV Therapy

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