**Yale Primary Care HIV Training Track**

**Module 3: Initiation of Antiretroviral Therapy (ART)**

**Preceptor Version**

*Edited 7/16/2019*

**Sources:**

1. “Antiretroviral Therapy Overview.” *National HIV Curriculum*, [www.hiv.uw.edu/go/antiretroviral-therapy](http://www.hiv.uw.edu/go/antiretroviral-therapy). Accessed 7/16/19.
2. “Initiation of Antiretroviral Therapy Adult and Adolescent ARV.” *National Institutes of Health*, U.S. Department of Health and Human Services, 17 Oct. 2017, [https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/10/initiation-of-antiretroviral-therapy. Accessed 7/16/19](https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/10/initiation-of-antiretroviral-therapy.%20Accessed%207/16/19).
3. Zash, Rebecca, et al. “Neural-Tube Defects with Dolutegravir Treatment from the Time of Conception.” *New England Journal of Medicine*, vol. 379, no. 10, 2018, pp. 979–981., doi:10.1056/nejmc1807653.

**Educational Objectives:**

1. Understand when to initiate ART in a patient diagnosed with HIV
2. Understand goals of treatment with ART
3. Describe the major available classes of ART agents
4. Discuss guideline-recommended ART regimens for most patients
5. Discuss guideline-recommended ART regimens for women of child-bearing potential
6. Discuss twelve factors to consider when selecting initial ART regimen

**Question 1.** When should ART be initiated in a patient with HIV?

All patients with HIV should be started on ART, regardless of CD4 T lymphocyte count. This is a grade AI recommendation from the U.S. Department of Health and Human Services, meaning it is a strong recommendation based on data from randomized controlled trials (RCTs). One of the landmark RCTs upon which this recommendation is based is the INSIGHT START trial published in the New England Journal of Medicine in 2015. This multicenter, multi-national study demonstrated that in people living with HIV with CD4 counts > 500 cells/mm3, early ART initiation reduces serious AIDS-related and non-AIDs-related complications compared with delayed ART.

The Department of Health and Human Services specifies in their anti-retroviral therapy guidelines that on a case-by-case basis, ART *may* be deferred due to clinical and/or psychosocial factors, but reinforces that it should be started as soon as possible thereafter.

**Question 2.** What are the goals of treatment with ART?

The primary goal of treatment with ART is reduction of HIV-associated morbidity and mortality. Prompt and sustained viral suppression is key to prolonging life, and reducing complications of HIV. Furthermore, viral suppression reduces the risk of transmission of HIV to others, further reducing population-level suffering.

**Question 3.** What are the classes of ART agents, and what are their mechanisms of action?

1. **Entry inhibitors.** These agents block entrance of HIV into the host cell
   1. Maraviroc is a CCR5 receptor antagonist. It prevents binding of Gp120 with T cell
2. **Nucleoside Reverse Transcriptase Inhibitors.** These agents require intracellular phosphorylation. Once triphosphorylated, they mimic human nucleotides, and can be taken up by HIV reverse transcriptase
   1. T- Tenofovir Disoproxil Fumarate, and Tenofovir Alafenamide
   2. E- Emtricitabine
   3. A- Abacavir
   4. L- Lamivudine
3. **Non-nucleoside Reverse Transcriptase Inhibitors.** These agents bind to HIV reverse transcriptase and cause a conformational change in the molecule, leading to the end of polymerization.
   1. N - Nevirapine
   2. E - Efavirenz, Etravirine
   3. R - Rilpivirine
   4. D - Doravirine
4. **Integrase Strand Transfer Inhibitors.** These agents block the integration of double stranded HIV DNA into the host cell DNA
   1. Dolutegravir
   2. Raltegravir
   3. Bictegravir
   4. Elvitegravir
5. **Protease Inhibitors.** These agents bind to the active site of an HIV protease, and inhibit the protease enzyme activity.
   1. Darunavir
   2. Atazanavir
6. **Pharmocokinetic Boosters.** These agents inhibit the liver enzyme CYP450 3A in order to enhance the activity of other antiretroviral agents.
   1. Cobicistat
   2. Ritonavir (PI)

**Question 4.** Broadly speaking, what classes of ART agents typically comprise an initial ART regimen for a treatment naïve individual with HIV?

1. Two NRTIs. This part of the regimen is called the “backbone”
2. Third active drug from one of three classes: INSTI, NNRTI, or PI + PK (pharmacokinetic booster). This part of the regimen is called the “anchor”

**Question 5.** Which ART regimens are recommended for most treatment naïve patients?

The Department of Health and Human Services classifies the following ART regimens as: “Recommended Initial Regimens for Most People with HIV”

1. Bictegravir + tenofovir alafenamide + emtricitabine
2. Dolutegravir + tenofovir alafenamide/tenofovir disoproxil fumarate + emtricitabine
3. Dolutegravir + abacavir + lamivudine
4. Raltegravir + tenofovir alafenamide/tenofovir disoproxil fumarate + emtricitabine

All the above regimens:

* Are dosed once daily
* Can be initiated *regardless*of initial CD4 count and viral load
* Can be taken with or without food

**Question 6.** How should we approach ART selection in women of child-bearing potential?

First, we should avoid dolutegravir in the following three groups of patients:

* Women of childbearing potential who are planning to get pregnant
* Women who conceived within the past 12 weeks
* Women of childbearing potential who are sexually active, and are using suboptimally effective contraceptive techniques

In May of 2018, the FDA issued a safety alert notifying the public of reports of higher-than expected numbers of neural tube defects observed in women treated with dolutegravir during pregnancy. The Botswana Harvard AIDS Institute Partnership conducts ongoing birth outcome surveillance among infants born to women living with and without HIV. This organization noted neural tube defects in 0.94% (4/426) of infants born to women treated with dolutegravir from the time of conception in Botswana. By comparison, neural tube defects occurred in 0.12% (14/11,300) of infants born to woman who had been exposed to any non-dolutegravir ART from the time of conception in Botswana. These data form the basis for our current avoidance of dolutegravir in certain at-risk groups of women.

Next, we should select an appropriate ART regimen for the women who fall into the above three groups. We should select an ART regimen whose anchor drugs fall into the following two classes:

1. NNRTI (such as efavirenz or doravirine)
2. Protease inhibitor (such as darunavir or atazanavir) with a pharmacokinetic booster (such as cobicistat or ritonavir).

**Question 7.** What patient and drug related factors should you think about when selecting an ART regimen?

Twelve Things to Think About When Selecting Initial Anti-Retroviral Therapy

1. Kidney disease: In patients with an eGFR less than 60 mL/min, avoid tenofovir disoproxil fumarate. In patients with an eGFR less than 30 mL/ min, avoid tenofovir alafenamide. Tenofovir is associated with nephrotoxicity. Specifically, declines in GFR, and type 2 renal tubular acidosis with phosphate wasting. The kidney function of patients on tenofovir should be monitored with a baseline creatinine, creatinine 4 weeks after medication initiation, and then creatinine every 3 months thereafter. Patients on tenofovir should also be monitored with baseline urine analysis, and then a urinalysis every 6 months thereafter to look for proteinuria.

2. Osteoporosis: Tenofovir disoproxil fumarate should be avoided in patients with a diagnosis of osteoporosis, as it has been shown to accelerate bone demineralization.

3. Hyperlipidemia: Avoid the use of protease inhibitors in patients with a diagnosis of hyperlipidemia. Tenofovir disoproxil fumarate, however, has a favorable impact on lipid profile.

4. Structural heart disease: Avoid the use of abacavir in patients with structural heart disease.

5. Cardiac QTc: Avoid efavirenz and rilpiverine in patients with long QTc intervals, as these drugs are known to prolong the cardiac QTc.

6. HLA-B5701 Allele: Avoid abacavir in patients who test positive for the presence of the HLA-B5701 allele. Presence of this allele is strongly associated with a potentially life-threatening hypersensitivity reaction to abacavir.

7. Psychiatric illness: Avoid efaverenz and rilpivirine in patients who struggle with psychosis, or other severe psychiatric illnesses. Efavirenz and rilpiverine have been associated with worsening psychiatric symptoms.

8. Resistance mutations: In patients without an available genotype at the time of ART initiation, choose a regimen known to have a high barrier to the development of resistance mutations. The protease inhibitors (darunavir, specifically), are the least likely to be overcome by resistance mutations. Of the integrase strand transfer inhibitors, dolutegravir is the least likely to be overcome by a resistance mutation. Of the nucleoside reverse transcriptase inhibitor backbones, tenofovir-emtricitabine has the highest barrier to resistance. Therefore, these agents are favored in situations in which a genotype is not available.

When a genotype is available at the time of ART initiation, look for resistance mutations. If a patient has an M184V mutation, avoid lamivudine and emtricitabine. Incidentally, M184V mutation is known to *increase* susceptibility to tenofovir. If a patient has a K103N mutation, avoid efavirenz.

9. Food requirements: Efavirenz should be taken on an empty stomach. Rilpiverine, protease inhibitors, and elvitegravir-based regimens should be taken *with* food.

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10. Pre-treatment viral load and CD4 count: If viral load is at the time of ART initiation is greater than 100,000 copies/mL, avoid these regimens:

* + - Rilpiverine
    - Abacavir-lamivudine + efavirenz, raltegravir, or ritonavir boosted atazanavir
    - Raltegravir + ritonavir boosted darunavir.

If CD4 count at the time of ART intiation is <200, avoid these regimens:

* + - Rilpiverine
    - Raltegravir + ritonavir boosted darunavir.

11. Family planning: If your patient is a woman, and is planning to conceive, or is on suboptimal birth control, avoid dolutegravir.

12. Interactions with other medications: Always enter all of a patient’s current medications, as well as new ART regimen into a medication interaction checker, such as the one found on UpToDate or Micromedex, in order to be sure there are no problematic interactions. Be aware that many common medications interact with ART. Furthermore, be aware that divalent cations such as calcium supplements, dairy products high in calcium, and magnesium supplements, etc, interact with integrase strand transfer inhibitors, reducing their efficacy. As part of your assessment for medication interactions, ask your patient if she/he takes any over the counter vitamins or supplements. Finally, if your patient will be taking an integrase strand transfer inhibitor, counsel against the consumption of calcium-filled foods within a 4 hour period of INSTI dose.

**Review Questions:**

1. Name 4 commonly used NRTIs.
2. Name 4 commonly used NNRTIs.
3. Name 2 commonly used PIs.
4. Name 4 INSTIs.
5. Name the backbone medication class(es) and anchor medication class(es) comprising a standard HIV ART regimen.
6. Name 3 instances in which a certain class of ART should *not* be used in women of child-bearing potential.
   1. \_\_\_\_\_\_\_\_\_\_\_\_\_\_
   2. \_\_\_\_\_\_\_\_\_\_\_\_\_\_
   3. \_\_\_\_\_\_\_\_\_\_\_\_\_
      1. What class of ART should not be used?
7. Name the backbone medication class(es) and anchor medication class(es) recommended for use in most treatment naïve individuals with HIV
8. Name the backbone medication class(es) and anchor medication class(es) recommended for use in women who are pregnant, or who may become pregnant.
9. Which medications are associated with nephrotoxicity?
   1. What are the GFR cutoffs at which we can no longer prescribe these medications?
   2. How should we monitor for the development of nephrotoxicity in these patients?
10. Which medication is associated with decreased bone mineral density?
    1. In which patients should we avoid this medication?
11. Which medication is associated with hypersensitivity reaction?
12. What is the name of the allele associated with increased risk of hypersensitivity reaction?
13. Which medication *may* be associated with increased risk of cardiovascular disease?
14. In which patients should we avoid this medication?
15. Which medications are known to have high barriers to development of resistance mutations?
16. Which medication does the resistance mutation K103N wipe out?
17. Which medications do the resistance mutation M184V wipe out?
18. Which medication’s effect is enhanced by M184V mutation?
19. Which medications are associated with worsening of psychiatric symptoms?
20. True or false: the 4 ART regimens recommended by the Department of Health and Human Services for most treatment naïve individuals living with HIV are dosed once daily.
21. True or false: the 4 ART regimens recommended by the Department of Health and Human Services for most treatment naïve individuals living with HIV are safe in women planning to conceive.
22. True or false: the 4 ART regimens recommended by the Department of Health and Human Services for most treatment naïve individuals living with HIV can be taken with or without food.
23. True or false: the 4 ART regimens recommended by the Department of Health and Human Services for most treatment naïve individuals living with HIV can be started regardless of pre-treatment CD4 count and viral load.