

Anti-Retrovirals: Fighting the Good Fight

Vallery Huston, PharmD
Schnucks Specialty Pharmacy Manager

Conflict of Interest

- I have no actual or potential conflict of interest in relation to this activity.

Objectives

- For pharmacists:
 - Describe the mechanism of action for the new anti-retroviral agents
 - Discuss the therapeutic use of the new anti-retroviral agents
- For technicians:
 - Discuss the dosage form and route of administration for each new anti-retroviral agent.
 - Discuss the therapeutic use of the new anti-retroviral agents.

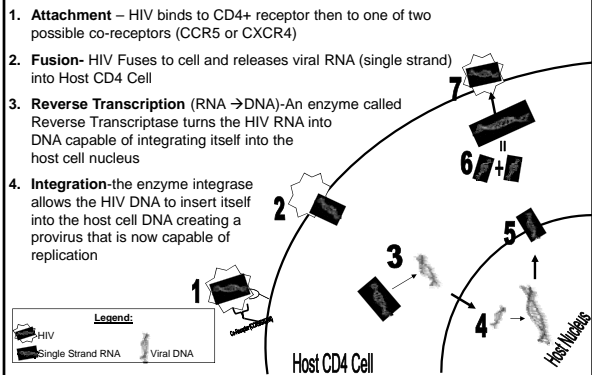
How Many Classes of HIV specific Anti-Retrovirals Currently Exist?

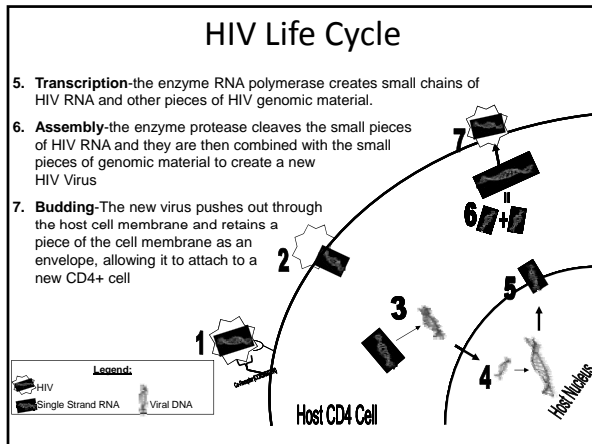
1. 3 Classes
2. 4 Classes
3. 5 Classes
4. I hate going to classes!

HIV/AIDS

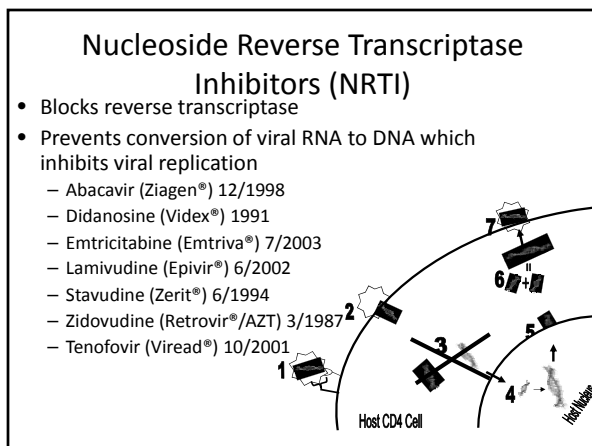
- HIV-Human Immunodeficiency Virus
 - Virus that is transmitted via body fluid contact
- AIDS-Acquired Immune Deficiency Syndrome
 - Syndrome that occurs when the immune system has been weekend by the HIV virus
 - Defined as a CD4+ count <200 cells/mm³
 - Or
 - An AIDS defining illness

HIV Life Cycle



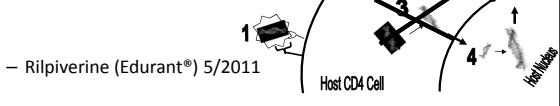


- ### Anti-Retroviral Classes
- Nucleoside reverse transcriptase inhibitor (NRTI)
 - Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)
 - Protease Inhibitor (PI)
 - Entry Inhibitors (EI)
 - Integrase Inhibitors (II)



Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

- Blocks reverse transcriptase
- Prevents conversion of viral RNA to DNA Binds at a different site than NRTIs: synergistic effects when two classes are taken together
- Elevated LFTs and Rash Class Side Effect
 - Delavirine (Rescriptor®) 4/1997
 - Efavirenz (Sustiva®) 2/2002
 - Nevirapine (Viramune®) 06/1996
 - Etravirine (Intencele®) 1/2008



Rilpiverine (Edurant®)

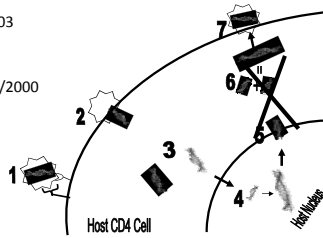
- Rilpiverine 25mg tablet once daily
- **Must** be taken with a 400 cal meal or absorption is decrease by 40% (Proton Pump Inhibitors Contraindicated)
- FDA approval 5/2011
- ECHO/THRIVE: rilpiverine not inferior to efavirenz at a VL < 100,000
- Available in triple drug combination Complera™
- A HAART Regimen including rilpiverine is an alternative treatment regimen per the October 2011 HIV treatment guidelines

Based on the October 2011 HIV Treatment guidelines, a HAART Regimen which includes an NRTI backbone along with Darunavir is which of the following?

1. Alternative Regimen
2. Preferred Regimen
3. Acceptable Regimen
4. An inappropriate Regimen

Protease Inhibitors (PI)

- Inhibits protease
- Prevents viral cleavage and subsequent viral assembly
- Metabolic abnormalities are a class side effect
- Darunavir (Prezista®) 6/2006
 - Atazanavir (Reyataz®) 6/2003
 - Fosamprenavir (Lexiva®) 10/2003
 - Indinavir (Crixivan®) 3/1996
 - Timpranavir (Aptivus®) 6/2005
 - Lopinavir+ritonavir (Kaletra®) 9/2000
 - Nelfinavir (Viracept®) 3/1997
 - Ritonavir (Norvir®) 6/1999
 - Saquinavir (Invirase®) 10/1995



Darunavir (Prezista®)

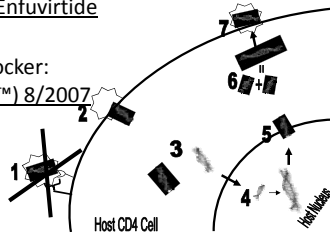
- Darunavir 800mg tablet once daily
Or
- Darunavir 600mg tablet twice daily
- FDA approval 6/2006
- Must be taken with food
- High genetic barrier to resistance
 - Effective in ARV experienced patients
 - Effective for previously non-adherent patients with multiple drug mutations
- Minimal metabolic abnormalities when compared to other protease inhibitors
- A HAART Regimen including darunavir is a preferred treatment regimen per the October 2011 treatment guidelines

The anti-retroviral maraviroc is an Entry inhibitor. It works by antagonizing the co-receptor the HIV virus attaches to. Which specific co-receptor must the HIV virus have in order for maraviroc to be effective?

1. CCR5
2. CXCR4
3. GP41
4. GP120

Entry Inhibitor (EI)

- Prevents the entry of the HIV virus into the host CD4+
- Mechanisms of action:
 - Prevent viral fusion: Enfuvirtide (Fuzeon®) 3/2003
 - CCR5 Co-receptor Blocker: Maraviroc (Selzentry™) 8/2007

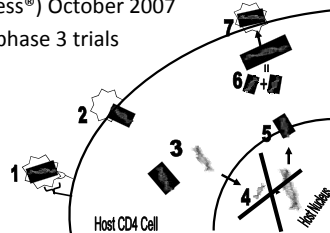


Maraviroc (Selzentry™)

- Maraviroc 150 mg tablet twice daily
- Maraviroc 300mg tablet twice daily
Or
- Maraviroc 300mg two tablets twice daily
- CCR5 Receptor Antagonist (Trofile Test: 4 weeks)
- **Works for CCR5 receptor only virus**, CXCR4 and dual tropic virus will not work
- Many p450 drug interactions, MUST modify dosing with strong p450 substrates including HIV protease inhibitors.
- A HAART Regimen including maraviroc is an acceptable treatment regimen per the October 2011 treatment guidelines

Integrase Inhibitors (InstI)

- Inhibit enzyme integrase
- Prevents viral DNA insertion into host cell DNA
 - Raltegravir (Isentress®) October 2007
 - Elvitegravir (EVG) phase 3 trials



Raltegravir (Isentress®)

- Raltegravir 400mg tablet twice daily
- First of integrase inhibitor class
- Low genetic barrier to resistance
- Good side effect profile
- A HAART Regimen including raltegravir is a preferred treatment regimen per the October 2011 treatment guidelines

Elvitegravir (EVG)

- Investigational HIV-1 integrase inhibitor in Phase 3 development
- Elvitegravir 150mg once daily
- Non-inferior to efavirenz based regimen
- Should be taken with food
- Once daily dosing is beneficial when compared to raltegravir
- Place in therapy still to be determined

Cobicistat

- New novel investigational pharmacoenhancer "booster"
- Phase 3 studies
- Similar concept to protease inhibitor ritonavir
- No intrinsic HIV activity
- Decreases risk of developing protease inhibitor mutations
- Watching renal function closely

How Many Single Tablet Regimens are currently available?

1. One
2. Two
3. Three
4. Four

Single Tablet Regimens (STR)

- A large focus of research
- Combining drugs from multiple classes of ARVs to improve adherence
- Studies show once daily regimens significantly decrease hospital stays
 - Atripla® 07/2006
 - Complera™ 8/2011
 - Elvitegravir/Cobicistat/Tenofovir/Emtricitabine: Phase 3 trials, summer 2012

tenofovir/emtricitabine/rilpiverine (Complera™)

- FDA approval 08/2011
- One tablet once daily
- Must be taken with a meal of at least 400 cal
- An alternative regimen for the treatment of HIV based on the October 2011 treatment guidelines

Elvitegravir/Cobicistat/tenofovir/emtricitabine

- Phase 3 trials
- Available Summer 2012
- Phase three trials show non-inferiority to tenofovir/emtricitabine/efavirenz

References

1. Anderson PL, Kakuda TN, Fletcher CV, Chapter 134. Human Immunodeficiency Virus Infection. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 8th ed. New York: McGraw-Hill; 2011. <http://www.accesspharmacy.com/content.aspx?aiD=8006952>. Accessed February 5, 2012.
2. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services, October 14, 2011; 1-167. Available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf> Accessed February 12, 2012
3. U.S. Food and Drug Administration, Drugs @ FDA, FDA Approved Drug Products. Available at: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>. Accessed February 13, 2012
4. Edurant® [Package Insert]. Raritan, NJ: Tibotec Pharmaceuticals; 2011; 2011
5. Prezista® [Package Insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2006
6. Complera™ [Package Insert]. Foster City, CA: Gilead Sciences; 2011
7. Selentry® [Package Insert]. Research Triangle Park, NC: ViiV Healthcare; 2010
8. Isentress® [Package Insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2007

References

9. Cohen C, Eilon R, Ruane P, et al. Randomized, phase 2 evaluation of two single-tablet regimens elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate versus efavirenz/emtricitabine/tenofovir disoproxil fumarate for the initial treatment of HIV infection. *AIDS*. Mar 27 2011; 25(6): F7-12.
10. Gilead Sciences Inc. Gilead's investigational antiretroviral Quad regimen meets 48-week primary objective in pivotal phase 3 clinical study. 102. Foster City, CA. August 15, 2011
11. Gilead Sciences Inc. Gilead's second pivotal phase 3 clinical study of the investigational antiretroviral Quad regimen meets 48-week primary objective. Foster City, CA. September 19, 2011
12. German P, Warren D, West S, Hui J, Kearney BP. Pharmacokinetics and Bioavailability of an Integrase and Novel Pharmacoenhancer-Containing Single-Tablet Fixed-Dose Combination Regimen for the Treatment of HIV. *J Acquir Immune Defic Syndr*. November 1 2010; 55(3):323-329
13. Molina JM, Lamarca A, Andrade-Villanueva J, et al. Efficacy and safety of once daily elvitegravir versus twice daily raltegravir in treatment-experienced patients with HIV-1 receiving a ritonavir-boosted protease inhibitor: randomized, double-blind, phase 3, non-inferiority study. *Lancet Infect Dis*. October 18, 2011
14. German P, Lui C, Warren D, et al. Effect of cobicistat on glomerular filtration rate (GFR) in subjects with normal and impaired renal function [Poster H2-804]. Paper presented at: 51st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); September 17-20, 2011; Chicago, IL.
15. Lepist E-I, Murray BP, Ting L, Roy A, Bannister R, Ray AS. Effect of cobicistat and ritonavir on proximal renal tubular cell uptake and efflux transporters [Poster A1-1724]. Paper presented at: 51st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); September 17-20, 2011; Chicago, IL.

Anti-retrovirals: Fighting the Good Fight!

Vallery Huston, Pharm.D.

0121-0000-12-020-L02-P

0121-0000-12-020-L02-T

Self-assessment Questions:

1. Based on the October 2011 HIV Treatment guidelines, a HAART Regimen which includes an NRTI backbone along with Darunavir is which of the following?
 - a. Considered an Alternative Regimen for the treatment of HIV-1 infection
 - b. Considered a Preferred Regimen for the treatment of HIV-1 infection
 - c. Considered an Acceptable Regimen for the treatment of HIV-1 infection
 - d. Considered an Inappropriate regimen for the treatment of HIV-1 infection
2. The anti-retroviral maraviroc is an Entry inhibitor. It works by antagonizing the co-receptor the HIV virus attaches to. In order for maraviroc to be effective a persons HIV infection must only be which of the following co-receptor types?
 - a. CCR5
 - b. CXCR4
 - c. GP41
 - d. GP120
3. Raltegravir is in the anti-retroviral class called Integrase inhibitors. Which of the following statements best describes the mechanism of action of Integrase inhibitors?
 - a. Prevents small HIV particles from integrating into a larger HIV particle in the host cell.
 - b. Prevents integration of the HIV virus into the host cell.
 - c. Prevents insertion of viral RNA into the host cell nucleus
 - d. Prevents insertion of viral DNA into the host cell nucleus
4. Rilpiverine is a once daily anti-retroviral approved for use in May of 2011. Which of the following best describes the class of anti-retroviral rilpiverine belongs to as well as how rilpiverine should be taken?
 - a. Rilpiverine is a Protease inhibitor and must be taken with a large meal
 - b. Rilpiverine is a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) and must be taken with a large meal.
 - c. Rilpiverine is a Protease inhibitor and must be taken on an empty stomach.
 - d. Rilpiverine is a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) and must be taken on an empty stomach.
5. Elvitegravir is a new investigation drug in phase 3 trials. If approved it will belong to which class of anti-retrovirals?
 - a. Nucleoside Reverse transcriptase inhibitor
 - b. Protease inhibitor
 - c. Entry Inhibitor
 - d. Integrase inhibitor