HIV Therapy and the Importance of Adherence

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Learning Objectives

At the end of this activity, participants should be able to:

- Recognize the different classes of antiretroviral medications and how they inhibit propagation of the virus.
- Define and explain Highly-active Antiretroviral Therapy (HAART).
- Identify the seven preferred regimens for treatment of naïve patients, as stated by the U.S. Department of Health and Human Services (HHS).
- State the goals of HIV therapy.
- Explain the importance of adherence in relation to HAART.

Overview of HIV

Human immunodeficiency virus (HIV) is a retrovirus that attacks the immune system. A retrovirus is an RNA virus that utilizes an enzyme called reverse transcriptase to replicate within the host. As the virus replicates, it causes damage to essential immune cells. These cells are called CD4 cells and they play a major role in the body's ability to defend itself against foreign pathogens. As HIV progresses, it develops into acquired immunodeficiency syndrome (AIDS). AIDS is defined as having a CD4 count less than 200 cells/mm^3 or less than 14 percent of CD4 cells remaining.[1] As the number of viable CD4 cells decline, the risk of developing life threatening complications increases. Common complications associated with AIDS include the development of opportunist infections or cancer.

Epidemiology

HIV and AIDS were first reported during the early 1980s and progressed rapidly throughout the United States (U.S.)[2] By the mid-1980s, the U.S. was experiencing its first AIDS epidemic with more than 130,000 new cases diagnosed each year.[3] Since then, the development of diagnostic screening tools, antiretroviral medications and prevention programs has led to a significant decrease in the number of new cases being reported. By the mid-1990s, new cases were estimated at 50,000 patients per year; more than a 40 percent drop from the height of the epidemic 10 years prior. This rate has remained stable with roughly 47,500 patients diagnosed in 2010.[3]

As incidence, or the rate of new cases, plateaus, prevalence of HIV continues to rise. Currently, the Centers for Disease Control and Prevention (CDC) estimates that 1.2 million people in the U.S. are living with HIV.[3] Prior to the introduction of antiretroviral therapy, patients diagnosed with AIDS were not expected to live more than several years. Now, if treated appropriately, patients are expected to have a lifespan similar to that of a healthy individual.[4]

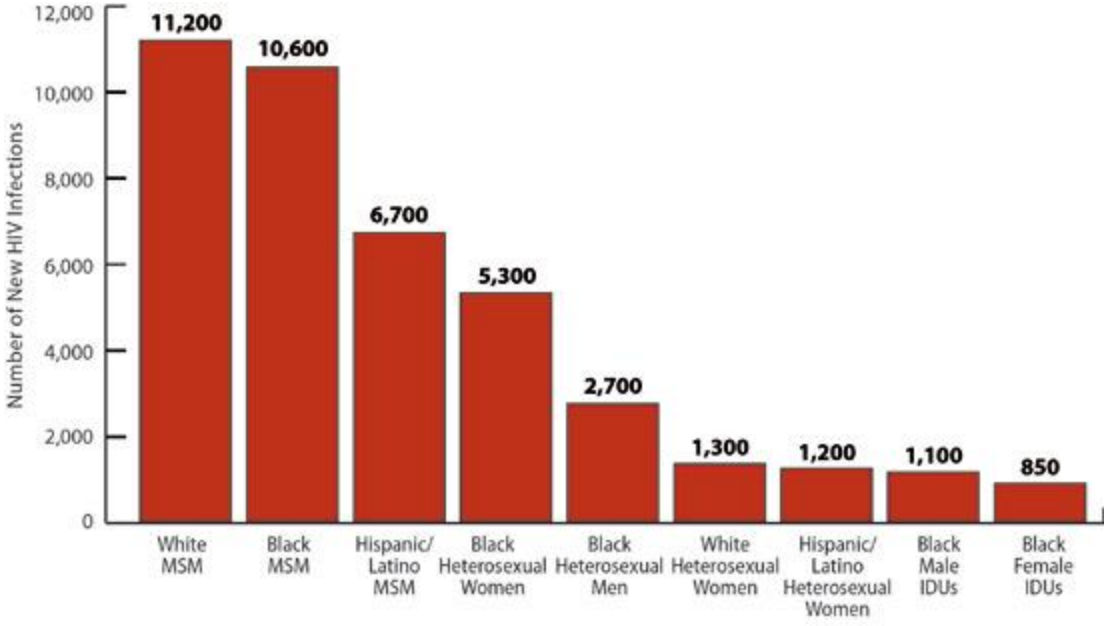
Transmission

HIV is contained in several bodily fluids, including blood, pre-seminal fluid, semen, vaginal secretions, rectal secretions and breast milk. This allows for multiple routes of transmission. Documented sources of transmission include unprotected sex, IV drug use (IDU), blood transfusions and mother-to-child transmission. Unprotected sex includes anal, oral and vaginal intercourse. The risk of acquiring HIV is highest with anal sex, followed by vaginal, and then oral.[5] Although HIV is not found in saliva, it is possible to obtain HIV through oral sex, as this may cause trauma to the mouth and increase exposure to the virus. Transmission from mother to child may

occur one of several ways. The mother can pass HIV to the child during pregnancy, during birth or after birth while breastfeeding. All women who become pregnant should be tested for HIV and appropriate therapy should be initiated as soon as possible if she is found to be positive. Blood transfusions are no longer a serious concern in the U.S. due to rigorous testing of blood products.[5] Aside from risky behavior, several predisposing factors have been identified that increase a patient's risk of acquiring HIV. These factors include elevated viral loads, sexually transmitted infections and men who are not circumcised.

Certain populations appear to be disproportionately affected by HIV, including African Americans, Latinos, and homosexual or bisexual men. In the U.S., white men who have sex with men (MSM) account for the majority of HIV-infected individuals. However, the incidence within young, African American MSM is increasing faster than in any other population. Women account for 20 percent of new infections each year and patients between the ages of 25-34 years old are more likely to have a new diagnosis of HIV.[3] For a more detailed listing of new HIV infections found throughout the U.S., please reference Figure 1.

Figure 1. Estimated New HIV Infections in the U.S., 2010, for the Most Affected Subpopulations[3]



HIV Lifecycle

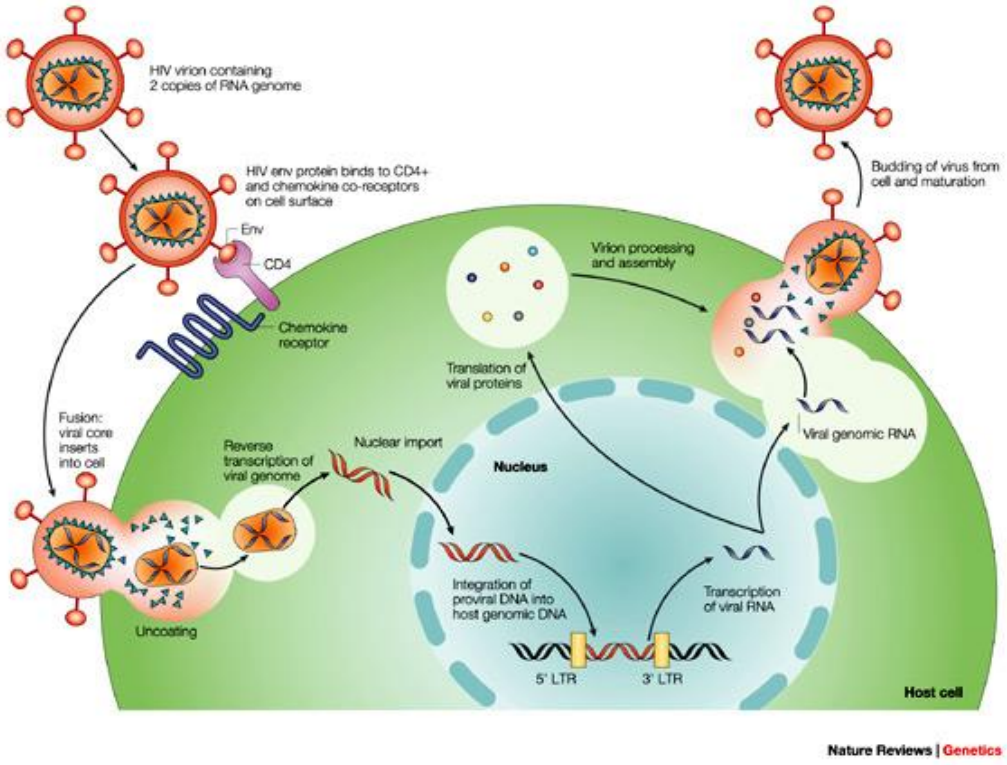
After exposure to body fluids containing HIV, the virus enters the body and replicates. As noted above, exposure to the virus may be through unprotected sex, IV drug use, blood transfusions or mother-to-child transmission.

The process of viral replication is outlined in the steps below.[6] In addition, the HIV lifecycle is represented in Figure 2.

1. **Exposure and Entry:** Host is exposed to the virus and HIV enters the body.
2. **Binding:** Virion binds to CCR5 receptors on host CD4 cells.
3. **Fusion:** Virion fuses with the host cell membrane and the virus enters the cell.

4. **Reverse Transcription:** Viral RNA is converted to DNA within the host by an enzyme called reverse transcriptase.
5. **Integration:** Newly-formed viral DNA is transported to the nucleus where it is incorporated into host DNA by an enzyme called integrase.
6. **Transcription/Translation:** mRNA is produced within the nucleus from viral DNA allowing for the production of essential viral proteins.
7. **Assembly:** Viral proteins are cleaved into active forms by an enzyme called protease and assembled with viral RNA at the outer edge of the cell.
8. **Budding:** Virus uses host cell membrane to envelop assembled viral contents and bud off from the infected CD4 cell.
9. **Propagation:** Newly-developed virion goes on to infect other CD4 cells.

Figure 2. The HIV Lifecycle[7]



Prevention

A variety of prevention methods exist for HIV and should be tailored based on the patient's specific needs. Types of prevention are divided into two main categories: decreased exposure and increased education.

As described above, HIV is transmitted when a person comes in contact with infected bodily fluids. By decreasing the risk of exposure to these fluids, we can prevent HIV from infecting others. Suggested ways to decrease exposure can be found in Table 1 below.

Table 1. Prevention Methods Aimed to Decrease HIV Exposure[8]

Prevent HIV transmission through blood	Refrain from IDU
	Do not share needles
	Use clean needles
	Prevent accidental needle sticks
	Screen blood products
Prevent sexual transmission of HIV	Abstinence
	Decrease number of sex partners
	Use condoms
	Circumcision (males)
	Treat sexually transmitted infections
	Post-exposure prophylaxis (PEP)
	Pre-exposure prophylaxis (PrEP)
Prevent perinatal transmission of HIV	Screen mother for HIV and offer treatment to mothers who are positive
	Test child at birth and provide treatment to children who are positive
	Avoid breastfeeding

If a patient is HIV positive, they can also help prevent transmission of the virus by decreasing their viral load. Viral load is a measure of the amount of virus found in an infected individual's body. The lower the viral load, the less likely a person is to transmit the virus to others. This can be achieved through appropriate use of antiretroviral medications and will be discussed in the next section.

Prevention cannot be achieved without education. Increasing awareness and providing education about HIV helps people understand the significance of the virus and the effects it can have on a person's health. Safe sex education is another important area to address, as this virus is primarily acquired through sexual contact. With safe sex education, it is important to discuss the different routes of sexual transmission associated with HIV (anal, oral and vaginal) and appropriate ways to protect yourself. In sexually active people, condoms are the only proven method to prevent the transmission of HIV. Other forms of birth control, including hormonal contraceptives and spermicide, are not effective. Education about proper condom use should also be provided to those who are sexually active. Many prevention programs across the U.S. aim to increase access to condoms with the idea that this will increase and encourage safe sex practices.

Getting tested is one of the most important prevention methods a person can take. It is estimated that one out of every seven people in the U.S. does not know they have HIV.[3] Testing increases awareness of HIV and encourages people to take an active role in their health. When a person knows their HIV status, it allows them to take the next steps to protect their health and the health of others. Currently, the CDC recommends HIV testing for anyone who is 13-64 years old at least once as part of providing general health care.[9] To find a testing center near you, visit https://gettested.cdc.gov.[10]

STOP AND REFLECT

John Smith, a 23-year-old HIV-positive male, comes into the clinic for his quarterly checkup. During his exam, you discover John has found a new partner and they have become sexually active. Upon questioning, John states he and his partner participate in oral and anal sex. Since John is HIV-positive, he makes sure to use condoms when they partake in anal sex. Based on the information above, what should John be educated about during this appointment?

Introduction to Antiretroviral Therapy (ART)

Antiretroviral therapy (ART) was first introduced to the U.S. during 1987 and has had a significant impact on the outcomes associated with HIV.[2] Prior to ART, patients diagnosed with AIDS were unlikely to survive more than several years. Today, patients who are adequately managed on ART have a life expectancy similar to that of healthy individuals. As the prevalence of patients living with HIV increases, practitioners are beginning to acknowledge the disease as a chronic condition rather than an acute infection.[4] Based on the positive effects ART has had on HIV, the U.S. Department of Health and Human Services (HHS) recommends ART be initiated in all individuals regardless of their CD4 count or viral load status.[11]

Medication Nomenclature, Drug Classes and Formulations

Standard prescription medications have two reference names: a brand name and a generic name. For antiretroviral medications, a third reference name has been generated and is known as a drug code. A drug code is a three-letter abbreviation used to reference antiretroviral medications. This code is often used when physicians prescribe antiretrovirals and it is important to have these codes memorized. It is prudent to pay attention to which code is being referenced, as many of these codes are similar to one another.

To date, there are 26 antiretroviral medications available in the U.S. These medications are divided into six drug classes based on how they inhibit the HIV lifecycle. These classes are listed below. For a more detailed description of antiretrovirals and their site of action please reference Appendix 1.

1. **CCR5 Antagonists (aka Entry Inhibitors or Binding Inhibitors):** Contains one antiretroviral medication
2. **Fusion Inhibitors:** Contains one antiretroviral medication
3. **Nucleoside Reverse Transcriptase Inhibitors (NRTIs):** Contains seven antiretroviral medications
4. **Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs):** Contains five antiretroviral medications
5. **Integrase Inhibitors (INSTIs):** Contains three antiretroviral medications
6. **Protease Inhibitors (PIs):** Contains nine antiretroviral medications

A seventh drug class used in HIV therapy is known as the pharmacokinetic enhancers or boosters. The purpose of this class is not intended for their antiretroviral effects, but to increase the efficacy of other antiretrovirals when they are used in conjunction with one another. This class consists of two drugs: cobicistat and ritonavir. Ritonavir is also considered a protease inhibitor, but it is rarely used in doses high enough to produce an antiretroviral effect. Cobicistat does not exert any antiretroviral activity. When prescribed, these drugs are also given a drug code. Unlike antiretroviral medications, boosters do not receive a three-letter code. Instead, boosters are

abbreviated with a lowercase letter. A table of available antiretrovirals divided by class, brand name, generic name and drug code can be found in Appendix 2.

All medications are available as an oral formulation except Fuzeon (enfuvirtide). Fuzeon is only manufactured as an injectable. This is important to consider when prescribing to patients with a known history of IV drug abuse.

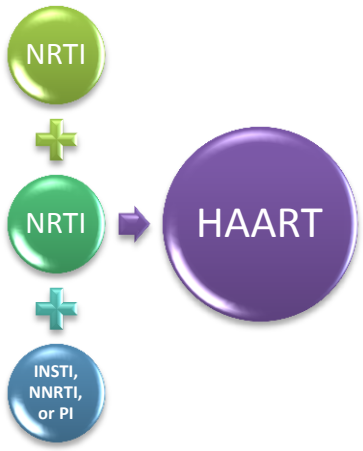
Highly-active Antiretroviral Therapy (HAART)

What is HAART?

Although early therapy with antiretrovirals was promising, it was not without complications. Initially, patients responded well to ART; viral loads decreased and death rates declined. However, this remission was short lived and soon, patients were no longer responding to their original therapy. Researchers found that the virus was able to mutate and develop resistance to antiretroviral medications. In order to prevent this from occurring, a solution was proposed. This solution was HAART.

HAART, or highly-active antiretroviral therapy, was developed in the mid-1990s.[2] This method proposed that patients with HIV should be initiated on multiple antiretrovirals to combat the virus' ability to develop drug resistance. Research data was pooled from multiple studies and determined that the optimal HAART regimen would consist of three antiretroviral medications: two nucleoside reverse transcriptase inhibitors and one non-nucleoside reverse transcriptase inhibitor, integrase inhibitor or protease inhibitor (see Figure 3). Since this discovery, HAART has been the mainstay for HIV therapy.

Figure 3. HAART Regimen



Preferred Regimens for Treatment Naïve Patients

The HHS has determined seven recommended regimens for people newly-diagnosed with HIV (see Table 2). These recommendations follow the criteria for HAART and contain a two-drug NRTI backbone in combination with one drug from another class. Regimens are categorized based on the third drug used in the regimen.

Table 2. HHS Recommended Regimens for Treatment Naïve Patients[11]

Recommended Initial ART Regimen Options for All Patients, Regardless of Pre-ART Viral Load or CD4 Cell Count		
Generic Names	**Brand Names**	**Drug Codes**
NNRTI Based Regimen		
Efavirenz/tenofovir/emtricitabine	**Atripla**	EFV/TDF/FTC
PI Based Regimen		
Atazanavir/ritonavir/tenofovir/emtricitabine	**Reyataz/Norvir + Truvada**	ATV/r + TDF/FTC
Darunavir/ritonavir/tenofovir/emtricitabine	**Prezista/Norvir + Truvada**	DRV/r + TDF/FTC
INSTI Based Regimen		
Dolutegravir/abacavir/lamivudine	**Triumeq**	DTG/ABC/3TC
Dolutegravir/tenofovir/emtricitabine	**Tivicay + Truvada**	DTG + TDF/FTC
Elvitegravir/cobicistat/tenofovir/emtricitabine	**Stribild**	EVG/cobi/TDF/FTC
Raltegravir/tenofovir/emtricitabine	**Isentress + Truvada**	RAL + TDF/FTC

Determining which regimen to use is based on patient specific characteristics. Things to consider include side effects, dosing frequency, pill burden, food requirements, patient comorbidities, pregnancy, drug interactions and accessibility to medication.

Side Effects Associated with Preferred Regimens

Antiretroviral medications are associated with numerous side effects. This is a major factor to consider when selecting a regimen for patients to adhere to. In this section, we will discuss commonly encountered side effects associated with select antiretrovirals found in the HHS guidelines. It is important to note that this is not an all-encompassing list and each antiretroviral has a unique side effect profile.

Efavirenz, the NNRTI found in Atripla, is known to cause central nervous system (CNS) disturbances, including dream disorders and insomnia. These effects typically persist for the first two to four weeks and improve with continued use of the medication.[12] Many patients find the CNS side effects difficult to manage and may discontinue the medication. It is important to reassure patients that these side effects will dissipate over time. Efavirenz is also teratogenic and should not be used in women who are, or plan to be, pregnant.

Protease inhibitors such as atazanavir or darunavir are known to cause gastrointestinal (GI) side effects, including nausea, vomiting and diarrhea. To alleviate these symptoms, it is important to instruct the patient to take the medication with food.

Abacavir, a NRTI found in Triumeq®, is associated with dangerous hypersensitivity reactions. Prior to prescribing products that contain abacavir, patients are required to undergo an HLA-B genetic test. Patients with the HLA-B * 5701 genetic mutation are at increased risk for this reaction and should not be prescribed this medication. All medications containing abacavir should be dispensed with a warning card that describes the hypersensitivity reaction and what to do if this occurs. Products that contain abacavir include Epzicom®, Triumeq®, Trizivir® and Ziagen®.

Monitoring Parameters and Goals of Therapy

Two lab values are used to monitor the HIV status of a patient. These values include the CD4 count and viral load. Additional labs may be required based on the medication prescribed.

CD4 count is used to assess the immune function of a patient's body. A normal CD4 count ranges between 8,000-12,000 cells/mm.[6] In patients with HIV, this number falls below normal and increases the risk for infection. When CD4 counts drop below a certain level, a physician may want to prescribe additional medication to prevent infections from occurring.

Viral load is used to assess the amount of virus in patient's body. When a patient is on HAART, this value helps to determine if the treatment is effective. If the viral load does not decrease after an adequate trial of HAART, then a physician may want to consider a different medication regimen. The goal of HAART is to reduce viral loads so that they are undetectable in the blood (< 20 copies/mL).[11]

Since there is not a cure for HIV, the goals of therapy are aimed at preserving the immune system and decreasing transmission. Below are the HHS goals of therapy.[11]

- Reduce HIV-associated morbidity and prolong the duration and quality of survival
- Restore and preserve immunologic function
- Maximally and durably suppress plasma HIV viral load
- Prevent HIV transmission

The Role of Adherence in HAART

Although HAART was developed to prevent the emergence of resistant viral strains, this is highly dependent upon patient adherence. In order to effectively reduce viral load and prevent resistance from occurring, patients must be 95 percent adherent to their medication regimen.[13] Causes for nonadherence may be related to the patient or medication. Suggested causes are outlined in Table 3 below.

Table 3. Causes for Nonadherence

Medication Related	Patient Related
Complex dosing regimen	Worried about stigma associated with HIV
High pill burden	Patients with a history for drug abuse
Side effects	Patients known to skip doctor appointments
Drug-drug interactions	Elderly
Food restrictions	Very young
Cost	

Why is Drug Resistance a Problem?

The problem with resistant HIV strains is multifactorial. Drug resistance can result in:

- Virologic Failure
- Cross-resistance to other antiretroviral medications
- Diminished antiretroviral options
- Less favorable antiretroviral options
- Transmission of resistant strains

Maintaining adherence can prevent these complications from occurring and preserve the limited number of antiretrovirals we have in the U.S.

Providing Solutions for Nonadherence

It is important to acknowledge and address when a patient is nonadherent to their antiretroviral regimen. To combat the issue of high pill burden, many drug companies are manufacturing combination products. To date, there are 11 FDA-approved HIV combination products. Four of these products contain an entire HAART regimen, including Atripla®, Complera®, Stribild® and Triumeq®.

Cost is another factor to address. Many of these medications are expensive. If a patient does not have insurance or an insurance company does not want to pay for the medication, there are governmental support programs that may be able to subsidize the cost. In Michigan, the program to use is the Michigan HIV/AIDS Drug Assistance Program (MIDAP).[14]

STOP AND REFLECT
How many doses of HAART can a patient miss in one month to maintain a 95 percent adherence rate?

Conclusions

HIV is a disease that attacks the immune system. When left untreated, HIV can progress to AIDS and lead to life-threatening complications. Since the initiation of HAART, the incidence of HIV has decreased and life expectancy for those who are infected has increased. Adherence is essential to the success of HIV therapy and considerable efforts should be made to maintain appropriate adherence rates. Although the number of antiretrovirals available in the U.S. is limited, many drug companies are producing combination products to combat adherence issues. Staying up-to-date on new medications and medication abbreviations is important to deliver optimal patient care.

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Appendix 1. HIV Antiretroviral Sites of Action

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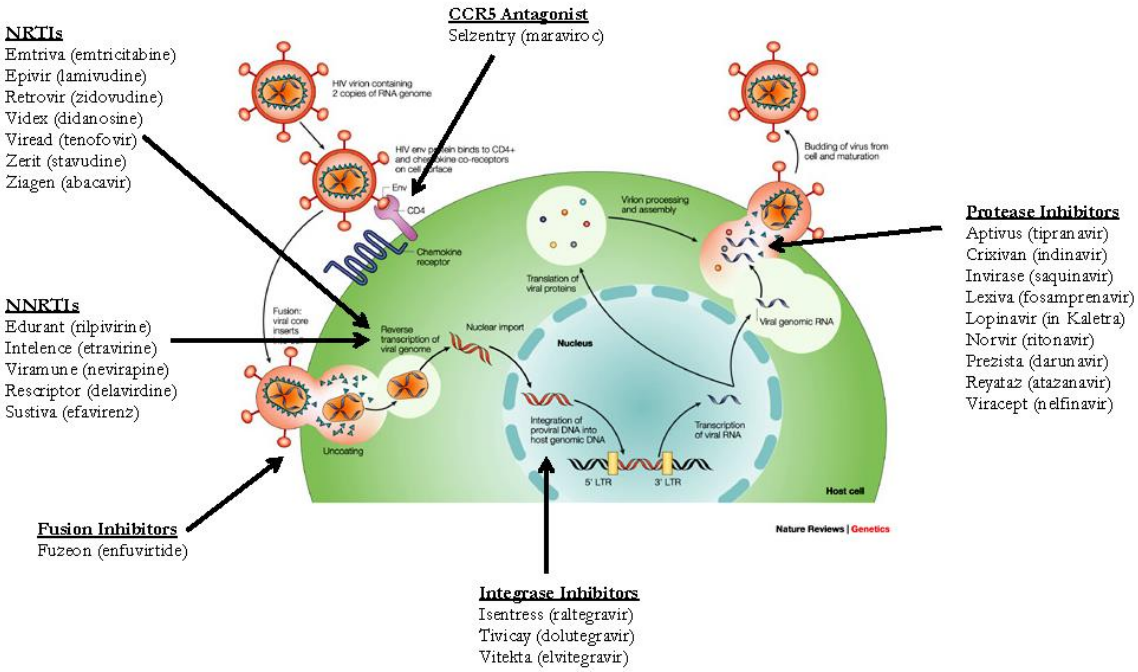

Image Source: Rambaut, A., Posada, D., Crandall, K.A., Holmes, E.C., Key aspects of the HIV life cycle. *Nature Reviews Genetics*, 2004 (5), pp. 52-61.

Appendix 2. Approved Antiretroviral Agents by Class

Appendix 2. Approved HIV Antiretroviral Agents by Class		
Brand Name	**Generic Name**	**Drug Code**
CCR5 Antagonist		
Selzentry	Maraviroc	MCV
Fusion Inhibitor		
Fuzeon	Enfuvirtide	ENF or T-20
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
Emtriva	Emtricitabine	FTC
Epivir	Lamivudine	3TC
Videx	Didanosine	DDI
Retrovir	Zidovudine	ZDV or AZT
Viread	Tenofovir	TDF
Zerit	Stavudine	d4T
Ziagen	Abacavir	ABC
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
Edurant	Rilpivirine	RPV
Intelence	Etravirine	EVR
Rescriptor	Delavirdine	DLV
Sustiva	Efavirenz	EFV
Viramune	Nevirapine	NVP
Integrase Inhibitors		
Isentress	Raltegravir	RAL
Tivicay	Dolutegravir	DTG
Vitekta	Elvitegravir	EVG
Protease Inhibitors		
Aptivus	Tipranavir	TPV
Crixivan	Indinavir	IDV
Invirase	Saquinavir	SQV
Lexiva	Fosamprenavir	FPV
Norvir	Ritonavir[1]	RTV
Prezista	Darunavir	DRV
Reyataz	Atazanavir	ATV
Viracept	Nelfinavir	NFV
-	Lopinavir[2]	LPV
Pharmacokinetic Enhancers (Boosters)		
Norvir	Ritonavir[1]	r
Tybost	Cobicistat	c or COBI
Combination Products		
Atripla*	Efavirenz/tenofovir/emtricitabine	EFV/TDF/FTC
Combivir	Zidovudine/lamivudine	ZDV/3TC
Complera*	Rilpivirine/tenofovir/emtricitabine	RPV/TDF/FTC
Epzicom	Abacavir/lamivudine	ABC/3TC
Evotaz	Atazanavir/cobicistat	ATV/c
Kaletra	Lopinavir/ritonavir	LPV/r
Prezcobix	Darunavir/cobicistat	DRV/c
Stribild*	Elvitegravir/cobicistat/tenofovir/emtricitabine	EVG/c/TDF/FTC
Triumeq*	Dolutegravir/abacavir/lamivudine	DTG/ABC/3TC
Trizivir	Zidovudine/lamivudine/abacavir	ZDV/3TC/ABC
Truvada	Tenofovir/emtricitabine	TDF/FTC

1. *Ritonavir is a protease inhibitor and a "booster."*
2. *Lopinavir is not manufactured as a single drug. It is only found in Kaletra.*

**Indicates "all-in-one" combination products*