

## A REVIEW ON PATHOLOGY OF AIDS AND ITS TREATMENT REGIMENS

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### ABSTRACT

People suffering from HIV have differing needs depending their personal circumstances and stage of infection. A comprehensive package of care covers the entire journey from diagnosis to death, which with antiretroviral treatment may span several decades. HIV drugs cannot cure HIV but they can help you stay healthy by preventing the virus from reproducing.

**Keywords:** HIV, AIDS, Immunity, drug resistance.

### INTRODUCTION

HIV is highly adept at developing resistance to medications. To prevent this happening, it is essential that the drugs be taken every day in the correct way, and that patients undergo regular monitoring. If resistance does emerge then the drug combination must usually be changed. Most people who take antiretroviral treatment experience side effects. In some cases these can be severe, and in rare instances they can be life threatening. Many side effects are treatable or can be stopped by switching drugs. When HIV cannot reproduce, it cannot infect new cells in your body and thereby allow immune system to recover its strength.

### HIV Drugs and the HIV Lifecycle<sup>1</sup>

#### The basics

Forms of HIV treatment and care can be grouped into three broad categories according to when they are usually first needed.

#### Early Stage-

- HIV testing
- Counseling and Psychosocial support
- Prevention of onward transmission
- Protection from stigma and discrimination

#### Later Stages-

- Prevention and treatment of Opportunistic Infections
- Managing nutritional effects
- Palliative care
- Antiretroviral therapy
- Complementary and alternate medicine

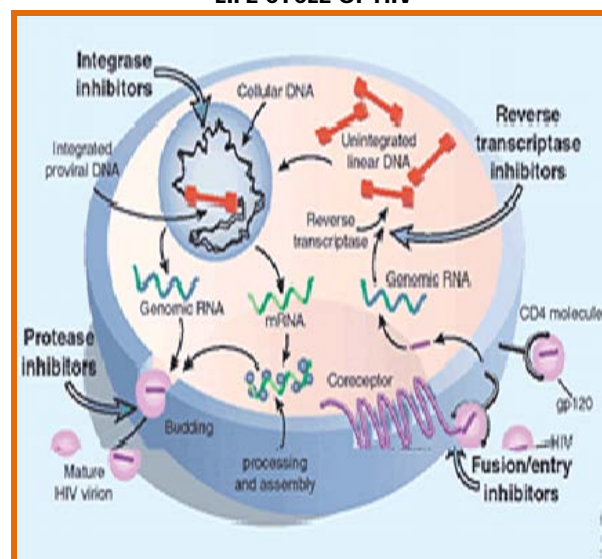
#### End of life stage-

- End of life care
- Preparing for death
- Support for surviving family and orphans

HIV must go through a number of different steps in order to make copies of itself. This is called the HIV lifecycle. All

HIV drugs work by interrupting a step in HIV's lifecycle, thereby stopping HIV "in its tracks."

### LIFE CYCLE OF HIV



Once HIV is in the body, it targets and infects a certain type of white blood cell called a CD4 cell. HIV then takes over or "hijacks" these cells and turns them into factories that produce thousands of copies of the virus. The steps HIV goes through to complete this process are as follows:

1. **Binding and Fusion:** HIV begins to enter a CD4 cell by binding (or attaching) itself to a specific point, called a CD4 receptor, on the cell's surface. HIV must then bind to a second co-receptor, either the CCR5 co-receptor or the CXCR4 co-receptor. This allows the virus to join with the CD4 cell in a process called fusion. After fusion, HIV releases its RNA (genetic material) and enzymes (proteins that cause chemical reactions) into the CD4 cell.
2. **Reverse Transcription:** HIV's RNA contains the "instructions" that will reprogram the CD4 cell so that it produces more viruses. In order to be effective, HIV's RNA must be changed into DNA. An HIV enzyme called reverse transcriptase changes the HIV RNA into HIV DNA.



3. **Integration:** Next, the newly formed HIV DNA enters the nucleus (command center) of the CD4 cell. Another HIV enzyme called integrase combines or integrates HIV's DNA with the CD4 cell's DNA.
4. **Transcription:** Once the virus has become part of (is integrated into) the CD4 cell, it commands the CD4 cell to start making new HIV proteins. The proteins are the building blocks for new HIV viruses. They are produced in long chains.
5. **Assembly:** An HIV enzyme called protease cuts the long chains of HIV proteins into smaller pieces. As the smaller protein pieces come together with copies of HIV's RNA, a new virus is put together (assembled).
6. **Budding:** The newly assembled virus pushes ("buds") out of the original CD4 cell. This new virus is now able to target and infect other CD4 cells.

### Classification of drugs used<sup>2</sup>

- 1) Nucleoside Reverse Transcriptase Inhibitors (NRTIs)
- 2) Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)
- 3) Protease Inhibitors (PIs)
- 4) Fusion Inhibitors (FIs)
- 5) Integrase Inhibitors (II)
- 6) CCR5 Antagonists

First treatment regimen will probably contain:

- An NNRTI plus 2 NRTIs or
- An integrase inhibitor plus 2 NRTIs or
- A PI plus 2 NRTIs (the PI should be combined, or "boosted," with a small dose of a second PI called Norvir (ritonavir); this makes the first PI work better)

These combinations will attack HIV at different parts of its lifecycle to pack a strong punch against the virus. The guidelines rank specific drug combinations as preferred, alternative and acceptable.

### Preferred Regimens<sup>3</sup>

Study results of these combinations showed they were powerful and long-lasting, did not have a lot of side effects, and were easy to use. Preferred regimens included:

- NNRTI-based regimen : Atripla (efavirenz + tenofovir + emtricitabine)
- PI-based regimens :Prezista (darunavir) and low-dose Norvir and Truvada (tenofovir + emtricitabine)
  - Reyataz (atazanavir) and low-dose Norvir and Truvada
- Integrase inhibitor-based regimen
  - Isentress (raltegravir) and Truvada
- Preferred regimen for pregnant women

- Kaletra (lopinavir/ritonavir) twice-daily and Combivir (zidovudine + lamivudine)

### Alternative Regimens<sup>4</sup>

These combinations have been proven useful in clinical trials, but may have disadvantages, such as less effectiveness or more side effects. Alternative regimens include:

- NNRTI-based regimens
  - Sustiva (efavirenz) and Epzicom (abacavir + lamivudine) or Combivir
  - Viramune (nevirapine) and Combivir
- PI-based regimens
  - Invirase (saquinavir) and low-dose Norvir and Truvada
  - Kaletra once or twice daily and Epzicom or Combivir or Truvada
  - Lexiva (fosamprenavir) and low-dose Norvir (once or twice daily) and Epzicom or Combivir or Truvada
  - Reyataz and low-dose Norvir and Epzicom or Combivir

### Acceptable Regimens

These combinations can be used in certain circumstances, but are not as good as preferred or alternative regimens. Acceptable regimens include:

- NNRTI-based regimen
  - Sustiva and Videx EC (didanosine) and Emtriva (emtricitabine) or EpiVir (lamivudine)
- PI-based regimen
  - Reyataz (without Norvir) and Epzicom or Combivir

### Approved HIV Drugs<sup>5</sup>

Different classes of HIV drugs block different steps of HIV's lifecycle. There are currently five classes of HIV drugs approved by the US Food and Drug Administration (FDA):

- **Entry Inhibitors:** These drugs stop (inhibit) HIV from entering a CD4 cell. There are different types of entry inhibitors: fusion inhibitors and CCR5 antagonists. One of each type is approved:
  - Fusion inhibitor: Fuzeon (enfuvirtide or T-20)
  - CCR5 antagonist: Selzentry (maraviroc)
- **Integrase Inhibitors:** These drugs interfere with HIV's integrase enzyme. There is one approved integrase inhibitor:
  - Isentress (raltegravir)



- **Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTIs or “nukes”):** These drugs interfere with HIV’s reverse transcriptase enzyme. There are many approved NRTIs:

- Emtriva (emtricitabine or FTC)
- Efavirenz (Sustiva)
- Zidovudine (Retrovir or AZT)
- Didanosine (Videx or ddI)
- Tenofovir (Viread)
- Stavudine (Zerit or d4T)
- Abacavir (Ziagen)

- **Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs or “non-nukes”)**

Like NRTIs, these drugs interfere with HIV’s reverse transcriptase enzyme. There are a number of approved NNRTIs:

- Efavirenz (Sustiva)
- Delavirdine (Rescriptor)
- Nevirapine (Viramune)

- **Protease Inhibitors (PIs)**

These drugs interfere with HIV’s protease enzyme. There are many approved PIs:

- Tipranavir (Aptivus)
- Indinavir (Crixivan)
- Saquinavir (Invirase)
- Lopinavir plus ritonavir (Kaletra)
- Fosamprenavir (Lexiva)
- Ritonavir (Norvir)
- Darunavir (Prezista or TMC-114)
- Atazanavir (Reyataz)
- Nelfinavir (Viracept)

- **Fixed-Dose Combinations**

Although not a separate class, there are fixed-dose formulations that combine two or more HIV drugs from one or more classes in just one pill. This can make dosing easier. There are five combination pills approved:

- Atripla (Sustiva plus Emtriva plus Viread)
- Combivir (Retrovir plus Efavirenz)
- Epzicom (Efavirenz plus Ziagen)
- Trizivir (Retrovir plus Efavirenz plus Ziagen)
- Truvada (Emtriva plus Viread)

### Combining HIV Drugs<sup>6</sup>

Doctors often combine drugs from different classes in order to attack HIV at more than one step in its lifecycle. This is because HIV can make mistakes, called mutations, when it reproduces. Certain mutations prevent certain

HIV drugs from working. When this happens, we say that HIV has become resistant to a particular HIV drug.

If you take only one drug (monotherapy) or take a few drugs that all belong to one class, it is easy for HIV to develop mutations that make it resistant to that drug or drug class. However, if you take a combination of drugs from different classes, HIV has a much harder time mutating enough to develop drug resistance.

What does this mean to you? It means that combination therapy with drugs that block HIV at different steps of its lifecycle can prevent most of the production of new HIV. Most importantly, it means slower disease progression and longer life for people living with HIV (HIV+ people).

### The Bottom Line

Currently five classes of HIV drugs target four steps of HIV’s lifecycle. Attacking HIV on multiple fronts by combining drugs from different classes is the best way to slow or stop HIV reproduction. It is also the best way to prevent the development of drug resistance. The approval of new classes of HIV drugs—and new drugs in the classes already available—will continue to provide more treatment options for HIV+ people in the future.

### Nucleoside Reverse Transcriptase Inhibitors (NRTIs)<sup>7</sup>

These inhibitors so called “nukes”, interfere with the function of reverse transcriptase, which HIV uses to replicate. They were first approved to treat HIV in 1987. The Table 1 depicts some of the NRTI’s and their description.

### General Description of Drugs

#### Emtriva

*Common side effects:* Nausea, diarrhea, headaches, skin rash, skin discoloration

*Serious side effects:* Buildup of lactic acid in the blood, enlarged liver, lipodystrophy

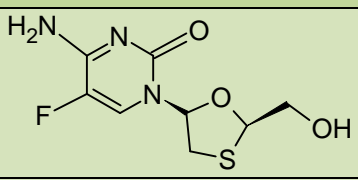
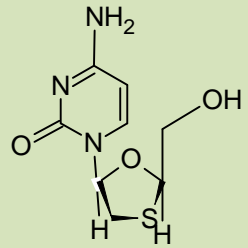
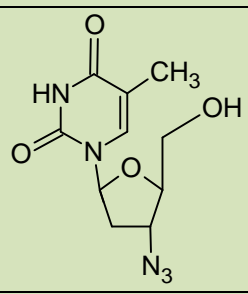
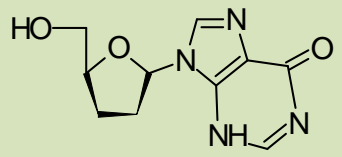
*Special Considerations:* Get tested for hepatitis B (HBV) before taking Emtriva. Emtriva fights HBV as well as HIV. If you are co-infected with HBV and HIV, stopping Emtriva may cause your HBV to get worse.

*Company:* Gilead

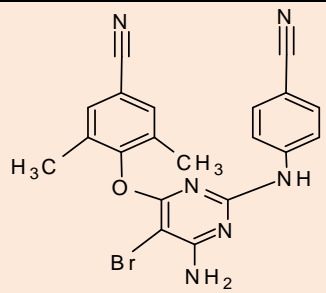
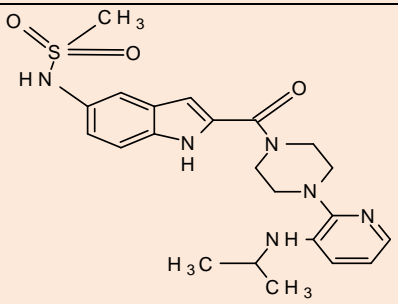
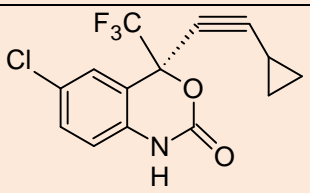
EMTRIVA is a synthetic nucleoside analog with activity against human immunodeficiency virus type 1 (HIV-1) reverse transcriptase. The chemical name of emtricitabine is 5-fluoro-1-(2R,5S)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. Emtricitabine is the (-) enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5-position. It has a molecular formula of C<sub>8</sub>H<sub>10</sub>FN<sub>3</sub>O<sub>3</sub>S and a molecular weight of 247.24.



**Table 1:** Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Brand Name	Other Name	Generic Name (s)	Structure	Number of Doses a Day
EMTRIVA	FTC	Emtricitabine		1
EPIVIR	3TC	Lamivudine		1 or 2
RETROVIR	AZT	Zidovudine		2
VIDEX EC	ddl	Didanosine		1

**Table 2:** Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Brand Name	Other Name	Generic Name (s)	Structure	Number of Doses a Day
INTELENCE	TMC-125	Etravirine		2
RESCRIPTOR	n/a	Delavirdine		3
SUSTIVA	n/a	Efavirenz		1

**Epivir**

*Common side effects:* Nausea, diarrhea, headaches, fatigue

*Serious side effects:* Anemia, neutropenia, buildup of lactic acid in the blood, enlarged liver, lipodystrophy

*Special Considerations:* Get tested for hepatitis B (HBV) before taking Epivir. Epivir fights HBV as well as HIV. If you are co-infected with HBV and HIV, stopping Epivir may cause your HBV to get worse.

*Company:* GlaxoSmithKline

EPIVIR is a synthetic nucleoside analogue with activity against HIV-1 and HBV. The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)-enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)-2',3'-dideoxy, 3'-thiacytidine. It has a molecular formula of  $C_8H_{11}N_3O_3S$  and a molecular weight of 229.3.

**Retrovir**

*Common side effects:* Nausea, vomiting, loss of appetite, headaches, fatigue, insomnia

*Serious side effects:* Anemia, neutropenia, myopathy, buildup of lactic acid in the blood, enlarged liver, Lipodystrophy.

*Company:* GlaxoSmithKline

RETROVIR is a pyrimidine nucleoside analogue active against HIV. RETROVIR IV Infusion is a sterile solution for intravenous infusion only. Each mL contains 10 mg zidovudine in Water for Injection. Hydrochloric acid and/or sodium hydroxide may have been added to adjust the pH to approximately 5.5. RETROVIR IV Infusion contains no preservatives. The chemical name of zidovudine is 3'-azido-3'-deoxythymidine. The molecular formula is  $C_{10}H_{13}N_5O_4$  and molecular weight 267.24.

**Videx Ec**

*Common side effects:* Nausea, diarrhea, headaches, insomnia

*Serious side effects:* Peripheral neuropathy, pancreatitis, buildup of lactic acid in the blood, enlarged liver, lipodystrophy

*Company:* Bristol-Myers Squibb

Videx is a reverse transcriptase inhibitor, effective against HIV and used in combination with other antiretroviral drug therapy as part of highly active antiretroviral therapy (HAART). Children >1 year and Adults should receive 2 tablets per dose and children <1 year should receive 1 tablet per dose for adequate buffering and absorption; tablets should be chewed; didanosine has also been used as 300 mg once daily on empty stomach. The chemical name of Videx is 9-[(2R,5S)-5-(hydroxymethyl)oxolan-2-

yl]-6,9-dihydro-3H-purin-6-one. It has a molecular formula of  $C_{10}H_{12}N_4O_3$  and a molecular weight of 236.227.

**NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)<sup>8</sup>**

These inhibitors block reverse transcriptase by binding to the reverse transcriptase enzyme. With the enzyme blocked, HIV cannot reproduce. They were first approved to treat HIV in 1997. The following table depicts some of the NNRTI's and their description. In Table 2 descriptions of Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) are given.

**General Description of Drugs****Intence**

*Common side effects:* Rash, diarrhea, nausea, headache

*Serious side effects:* Hypersensitivity (rash, flulike symptoms and sometimes organ problems, including liver failure), Stevens-Johnson syndrome (severe skin rash accompanied by fever, fatigue, muscle or joint aches, blisters, facial and tongue swelling)

*Special Considerations:* Contact your health care provider immediately if symptoms of severe skin reactions develop to discuss possibly stopping Intence

*Company:* Tibotec Therapeutics

INTELENCE is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1). The chemical name for etravirine is 4-[[6-amino-5-bromo-2-[(4-cyanophenyl)amino]-4-pyrimidinyl]oxy]-3,5-dimethylbenzonitrile. Its molecular formula is  $C_{20}H_{15}BrN_6O$  and its molecular weight is 435.28.

**Rescriptor**

*Common side effects:* Nausea, diarrhea, headaches, fatigue, skin rash, fever, elevated liver enzymes.

*Serious side effects:* Stevens Johnson Syndrome, liver problems

*Company:* Agouron-Pfizer

Rescriptor is a non-nucleoside reverse transcriptase inhibitor. It is used as part of highly active antiretroviral therapy (HAART) for the treatment of human immunodeficiency virus (HIV) type 1. It is presented as the mesylate. The recommended dosage is 400 mg, three times a day. The chemical name of Rescriptor is *N*-[2-[(4-[3-(propan-2-ylamino)pyridin-2-yl]piperazin-1-yl)carbonyl]-1*H*-indol-5-yl]methanesulfonamide. The empirical formula is  $C_{22}H_{28}N_6O_3S$  and molecular weight is 456.562.

**Sustiva**

*Common side effects:* Nausea, diarrhea, headaches, fatigue, skin rash, insomnia, increased liver enzymes.

*Serious side effects:* Nervous system side effects (disorientation, dizziness, anxiety, depression, mood changes, abnormal dreams), rare psychiatric symptoms





(suicidal thoughts, aggression), Stevens-Johnson syndrome (severe skin rash accompanied by fever, fatigue, muscle or joint aches, blisters, facial and tongue swelling)

*Special Considerations:* Women who are pregnant or may get pregnant should not use Sustiva-containing regimens

*Company:* Bristol-Myers Squibb

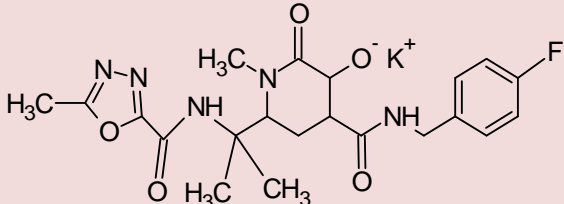
Sustiva is a non-nucleoside reverse transcriptase inhibitor used to treat HIV-1 infection in combination with at least two other antiretroviral agents. It is given orally as 600

mg daily, usually at bedtime to limit central nervous system effects. It should not be used as single-agent therapy.

### Integrase Inhibitors<sup>9</sup>

These are a new drug class that blocks the action of integrase, an enzyme that integrates genetic material from the virus into its target cell. They were first approved to treat HIV in 2007. The following Table 3 depicts Integrase inhibitor and its description.

**Table 3:** Integrase Inhibitors

Brand Name	Other Name	Generic Name (s)	Structure	Number of Doses a Day
ISENTRRESS	n/a	Raltegravir		2

### General Description of Drugs

#### Isentress

*Common side effects:* Diarrhea, nausea, headaches

*Serious side effects:* Liver toxicity, elevated levels of a muscle enzyme called creatine kinase

*Special Considerations:* Should be used with caution by people who are at increased risk for muscle problems like myopathy and rhabdomyolysis

*Company:* Merck

ISENTRRESS is indicated in combination with other anti-retroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients. The use of other active agents with ISENTRESS is associated with a greater likelihood of treatment response. The safety and efficacy of ISENTRESS have not been established in pediatric patients. ISENTRESS contains raltegravir potassium, a human immunodeficiency virus integrase strand transfer inhibitor. The chemical name for raltegravir potassium is *N*-[(4-Fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-2-[1-methyl-1-[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino]ethyl]-6-oxo-4-pyrimidinocarboxamide monopotassium salt. The empirical formula is C<sub>20</sub>H<sub>20</sub>FKN<sub>6</sub>O<sub>5</sub> and the molecular weight is 482.51.

#### Protease Inhibitors<sup>10</sup>

These drug target the HIV protease enzyme called HIV-1 protease, which the virus uses to complete viral replication. By binding to this enzyme, PI's inhibit its activity and therefore prevent viral replication. They were first approved to treat HIV in 1995. The Table 4 depicts some of the PI's and their description.

### General Description of Drugs

#### Aptivus

*Common side effects:* Nausea, vomiting, diarrhea, abdominal pain, fatigue, headaches, increased cholesterol and triglycerides.

*Serious side effects:* Liver problems, lipodystrophy, sulfa allergy, increased bleeding, Stevens-Johnson syndrome (severe skin rash accompanied by fever, fatigue, muscle or joint aches, blisters, facial and tongue swelling)

*Special Considerations:* Should not be taken by people with moderate-to-severe hepatitis B or C.

*Company:* Boehringer-Ingelheim

Tipranavir is a nonpeptidic protease inhibitor. It is administered with ritonavir in combination therapy to treat HIV infection and is given as two 250 mg capsules together with 200 mg of ritonavir. It is very potent and is effective in Salvage therapy for patients with some drug resistance. The chemical name of aptivus is *N*-{3-[(1*R*)-1-[(2*R*)-6-hydroxy-4-oxo-2-(2-phenylethyl)-2-propyl]-3,4-dihydro-2*H*-pyran-5-yl]propyl]phenyl}-5-(trifluoromethyl)pyridine-2-sulfonamide. It has a molecular formula of C<sub>31</sub>H<sub>33</sub>F<sub>3</sub>N<sub>3</sub>O<sub>5</sub>S and a molecular weight of 602.66.

#### Crixivan

*Common side effects:* Nausea, vomiting, diarrhea, abdominal pain, heartburn, headaches, fatigue, insomnia, skin rash, dry skin, hair loss, elevated bilirubin, increased cholesterol, triglycerides, and glucose, increased liver enzyme levels.

*Serious side effects:* Kidney stones (drink 48 ounces of water daily to lower risk of kidney stones), anemia,



lipodystrophy, increased bleeding in people with hemophilia.

*Company:* Merck

CRIVAN is an oral capsule used for the treatment of HIV (Human Immunodeficiency Virus). It can help reduce our chances of getting illnesses associated with HIV. It can also help lower the amount of HIV in our body (called "viral load") and raise our CD4 (T) cell count. It may not have these effects in all patients. It is usually prescribed with other anti-HIV drugs such as ZDV (also called AZT), 3TC, ddI, ddC, or d4T. It works differently from these other anti-HIV drugs. It is administered as 800 mg every 8 hours.

### **Invirase**

*Common side effects:* Nausea, diarrhea, abdominal pain, gas, headaches, fatigue, insomnia, mental confusion, increased cholesterol, triglycerides, and glucose, increased liver enzyme levels.

*Serious side effects:* Lipodystrophy, increased bleeding in people with hemophilia.

*Special Considerations:* n/a

*Company:* Roche.

### **Lexiva**

*Common side effects:* Nausea, vomiting, diarrhea, abdominal pain, gas, headaches, skin rash, numbness or tingling around the mouth, increased cholesterol, triglycerides, and glucose, increased liver enzyme levels.

*Serious side effects:* Liver problems, Stevens-Johnson syndrome (severe skin rash accompanied by fever, fatigue, muscle or joint aches, blisters, facial and tongue swelling), lipodystrophy, sulfa allergy, increased bleeding in people with hemophilia.

*Company:* GlaxoSmithKline

LEXIVA is a prodrug of amprenavir, an inhibitor of HIV protease. The chemical name of fosamprenavir calcium is (3S)-tetrahydrofuran-3-yl (1S,2R)-3-[[[4-(aminophenyl)sulfonyl](isobutyl)amino]-1-benzyl-2-(phosphonoxy)propyl]carbamate monocalcium salt. Fosamprenavir calcium is a single stereoisomer with the (3S)(1S,2R) configuration. It has a molecular formula of  $C_{25}H_{34}CaN_3O_9PS$  and a molecular weight of 623.7.

### **Norvir**

*Common side effects:* Nausea, diarrhea, abdominal pain, loss of appetite, headaches, heartburn, fatigue, weakness, insomnia, numbness and tingling around the mouth, increased cholesterol, triglycerides, and glucose, increased liver enzyme levels.

*Serious side effects:* Liver problems, lipodystrophy, increased bleeding in people with hemophilia  
*Special Considerations:* Taking Norvir with certain allergy medications, sedatives, heart medications, and migraine medications can increase the risk of their side effects

*Company:* Abbott

NORVIR is an inhibitor of HIV protease with activity against the Human Immunodeficiency Virus (HIV). Ritonavir is chemically designated as 10-Hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R\*,8R\*,10R\*,11R\*)]. Its molecular formula is  $C_{37}H_{48}N_6O_5S_2$ , and its molecular weight is 720.95.

### **ENTRY INHIBITORS<sup>11</sup>**

These inhibitors also known as fusion inhibitors, are a class of antiretroviral drugs that interfere with the binding, fusion and entry of an HIV virion to a human cell. They were first approved to treat HIV in 2003. The Table 5 depicts some of the Entry inhibitors and their description.

### **General Description of Drugs**

#### **Selzentry**

*Common side effects:* Cough, fever, colds, rash, muscle and joint pain, stomach pain, dizziness.

*Serious side effects:* Liver toxicity, cardiovascular problems, low blood pressure.

*Special Considerations:* A tropism test is needed before Selzentry is used to determine if treatment with the drug will be useful.

*Company:* Pfizer

SELZENTRY is an anti-HIV medicine called a CCR5 antagonist. SELZENTRY is used with other anti-HIV medicines in adults with CCR5-tropic HIV-1 infection who are already taking anti-HIV medicines and the medicines are not controlling their HIV infection.

**COMBINATION PILLS<sup>12</sup>** Description of important combination pills is given in Table 6.

### **General Description of Drugs**

#### **Atripla**

*Common side effects:* Same as those for the individual drugs that make up Atripla: dizziness, trouble sleeping, drowsiness, nausea, headache, vomiting, trouble concentrating, and/or rash

*Serious side effects:* Buildup of lactic acid in the blood, enlarged liver, lipodystrophy, kidney problems, severe depression.

*Company:* Bristol-Myers Squibb and Gilead

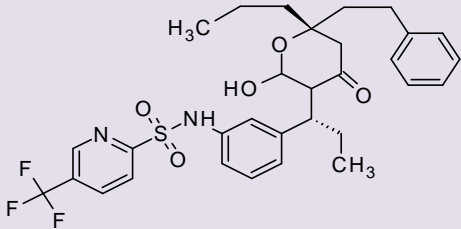
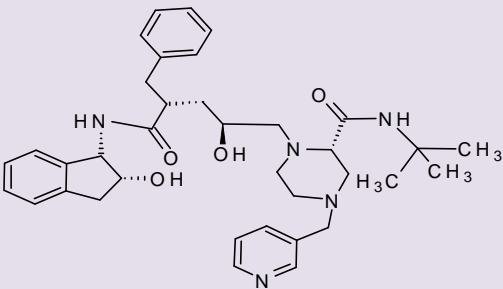
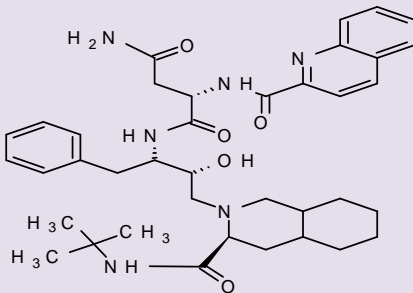
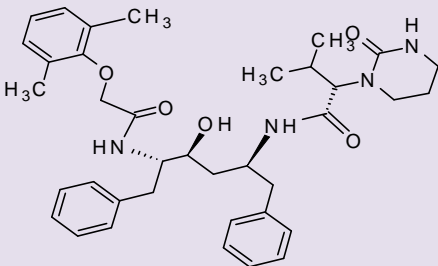
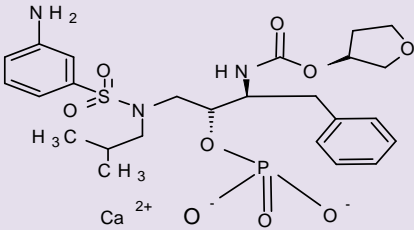
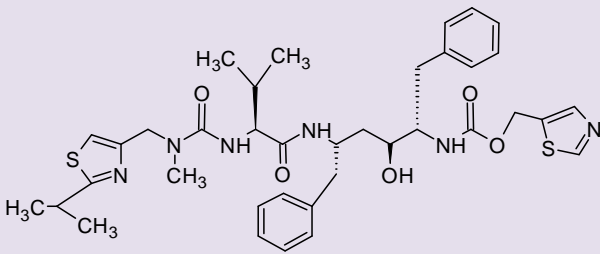
ATRIPLA is a fixed-dose combination tablet containing efavirenz, emtricitabine, and tenofovir disoproxil fumarate (tenofovir DF). ATRIPLA tablets are for oral administration. Each tablet contains 600 mg of efavirenz, 200 mg of emtricitabine, and 300 mg of tenofovir DF (which is equivalent to 245 mg of tenofovir disoproxil) as active ingredients. The tablets include the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate,



microcrystalline cellulose, and sodium lauryl sulfate. The tablets are film-coated with a coating material containing

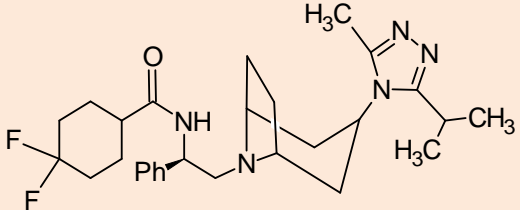
black iron oxide, polyethylene glycol, polyvinyl alcohol, red iron oxide, talc, and titanium dioxide.

**Table 4:** Protease Inhibitors

Brand Name	Other Name	Generic Name (s)	Structure	Number of Doses a Day
APTIVUS	n/a	Tipranavir		2+ boosted with Norvir
CRIVAN	n/a	Indinavir		3
INVIRASE	n/a	Saquinavir		2+ boosted with Norvir
KALETRA	n/a	Lopinavir+ Ritonavir		1 or 2
LEXIVA	n/a	Fosamprenavir		2
NORVIR	n/a	Ritonavir		1 or 2



**Table 5:** Entry Inhibitors

Brand Name	Other Name	Generic Name (s)	Structure	Number of Doses a Day
SELZENTRY	n/a	Maraviroc		2 + 2 boosted dose

**Table 6:** Combination Pills

Brand Name	Other Name	Generic Name (s)	Class of Drug	Number of Doses a Day
ATRIPLA	Sustiva + Truvada + Viread	Efavirenz + Emtricitabine + Tenofovir	2 NRTI's + 1 NNRTI	1
COMBIVIR	Retrovir + Eпивir	Zidovudine + Lamivudine	2 NRTI's	2
EPZICOM	Eпивir + Ziagen	Lamivudine + Abacavir	2 NRTI's	1

**Table 7:** Drugs under Clinical Trials

Brand Name	Other Name	Generic Name (s)	Class of Drug	Number of Doses a Day
ELV	ACH-126443, L-Fd4C	Elvicitabine	NRTI	5 and 10 mg once daily and 20 mg once every other day.
EVG	GS-9137	Elvitegravir	Integrase Inhibitor	150mg once daily + 100mg Norvir .
RCV	(+)/(-)-FTC	Racivir	NRTI	Once daily as part of a combination regimen. Clinical trials have evaluated racivir dosages of 200, 400, and 600 mg once daily.
AMDX	DAPD	Amdoxovir	NRTI	300mg and 500mg, both of which are taken twice a day

**Combivir**

*Common side effects:* Same as those for the individual drugs that make up Combivir: nausea, vomiting, loss of appetite, headaches, fatigue, insomnia

*Serious side effects:* Anemia, neutropenia, myopathy, buildup of lactic acid in the blood, enlarged liver, lipodystrophy

*Company:* GlaxoSmithKline

COMBIVIR Tablets are combination tablets containing lamivudine and zidovudine. Lamivudine and zidovudine are synthetic nucleoside analogues with activity against HIV-1. COMBIVIR Tablets are for oral administration. Each film-coated tablet contains 150 mg of lamivudine, 300 mg of zidovudine, and the inactive ingredients colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

**Epzicom**

*Common side effects:* fever and rash, followed by headaches, stomach upset, feeling sick or tired, sore throat, cough, and shortness of breath

*Serious side effects:* Liver problems, lipodystrophy including increased fat around the abdomen, breasts, and back of the neck, as well as decreased fat in the face, arms, and legs, and diabetes.

*Company:* GlaxoSmithKline

Epzicom is an HIV medication. Epzicom prevents HIV from altering the genetic material of healthy CD4 cells. This prevents the cells from producing new virus and decreases the amount of virus in the body. Epzicom is a combination of two drugs: 600mg of Ziagen (abacavir) and 300mg of Eпивir (lamivudine). Epzicom is a tablet taken once a day. It can be taken with or without food.



**DRUGS UNDER CLINICAL TRIALS<sup>13</sup>** Description of important combination pills is given in Table 7.

### General Description of Drugs

#### ELV<sup>14</sup>

*Common side effects:* Mild to moderate macropapular rash, Mild headache and gastrointestinal distress

*Serious side effects:* Bone marrow toxicity.

*Company:* Achillion Pharmaceuticals

Elvucitabine is an L-cytosine nucleoside analogue reverse transcriptase inhibitor (NRTI) currently under investigation in Phase I/II clinical trials for the treatment of HIV infection and chronic hepatitis B. The chemical name of elvucitabine is 4-Amino-5-fluoro-1-[(2S,5R)-5-(hydroxymethyl)-2,5-dihydrofuran-2-yl]pyrimidin-2-one.

Elvucitabine is a beta-L-(-) nucleoside analogue developed to improve upon the antiviral activity of lamivudine, an FDA-approved beta-L-(-) nucleoside analogue. Elvucitabine inhibits wild-type HIV and HIV expressing the M184V mutation associated with lamivudine resistance. It has a molecular formula of  $C_9H_{10}FN_3O_3$  and a molecular weight of 226.

#### EVG<sup>15</sup>

*Common side effects:* No additional short-term side effects associated with elvitegravir use were documented.

*Serious side effects:* Additional studies evaluating the short- and long-term safety of elvitegravir are planned and ongoing.

*Company:* Gilead Sciences

Elvitegravir is an experimental integrase inhibitor designed to block the activity of the integrase enzyme and to prevent HIV DNA from entering healthy cell DNA undergoing Phase III clinical trial. The chemical name of elvitegravir is 6-[(3-Chloro-2-fluorophenyl)methyl]-1-[(2S)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxoquinoline-3-carboxylic acid. Elvitegravir holds promise for HIV-positive patients who have taken other anti-HIV drugs in the past. Because elvitegravir targets HIV differently than currently available drugs, chances are that most people living with the virus—regardless of their treatment history—will likely benefit from using elvitegravir. It has a molecular formula of  $C_{23}H_{23}ClFNO_5$  and a molecular weight of 447.883

#### RCV<sup>16</sup>

*Common side effects:* mild headache and fatigue occurring no more frequently than with placebo.

*Serious side effects:* no severe adverse effects attributed to therapy were noted.

*Company:* Pharmasset

Racivir is an oxathiolane nucleoside reverse transcriptase inhibitor similar to emtricitabine and lamivudine. Racivir

is a 50:50 mixture of emtricitabine and its positive enantiomer that displays potent and selective activity against both HIV-1 and hepatitis B virus (HBV) in cell culture and in animal models. Racivir is now being studied in phase II/III clinical trials as part of combination therapy for the treatment of HIV-1 infection. The chemical name of Racivir is 4-Amino-5-fluoro-1-[(2S,5R)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]pyrimidin-2(1H)-one. It has a molecular formula of  $C_8H_{10}FN_3O_3S$  and a molecular weight of 247.25.

#### AMD<sup>17</sup>

*Common side effects:* amdoxovir causes kidney (rarely) and eye problems (lenticular opacities).

*Serious side effects:* no severe adverse effects attributed to therapy were noted.

*Company:* RFS Pharma

Amdoxovir is a nucleoside reverse transcriptase inhibitor undergoing research for the treatment of HIV. Amdoxovir is now being studied in phase II clinical trials as part of combination therapy for the treatment of HIV-1 infection. Amdoxovir will need to be used in combination with other drugs, including another NRTI and at least one protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI). The chemical name of Amdoxovir is [(2R,4R)-4-(2,6-Diaminopurin-9-yl)-1,3-dioxolan-2-yl]methanol. It has a molecular formula of  $C_9H_{12}N_6O_3$  and a molecular weight of 252.23.

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