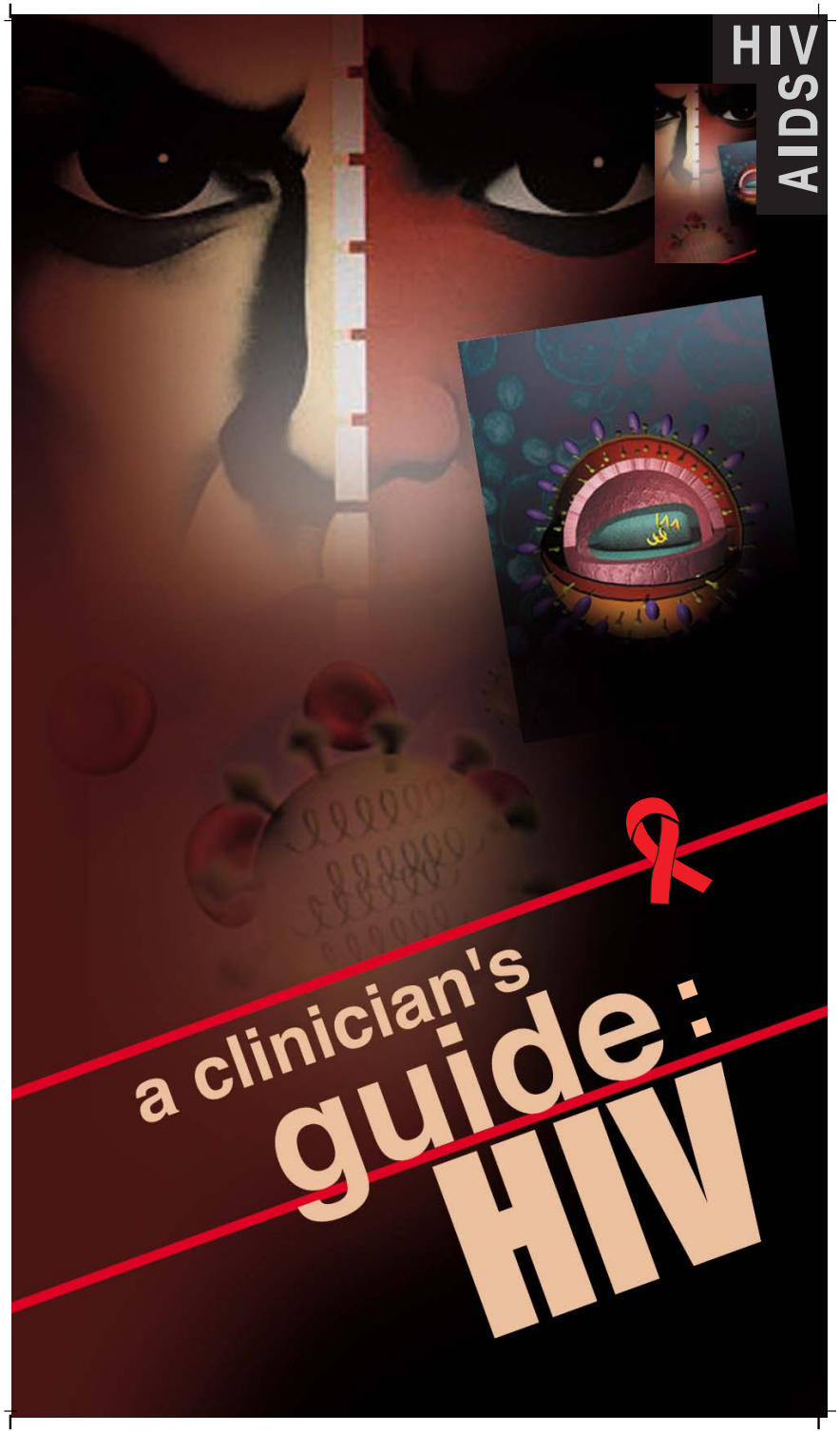
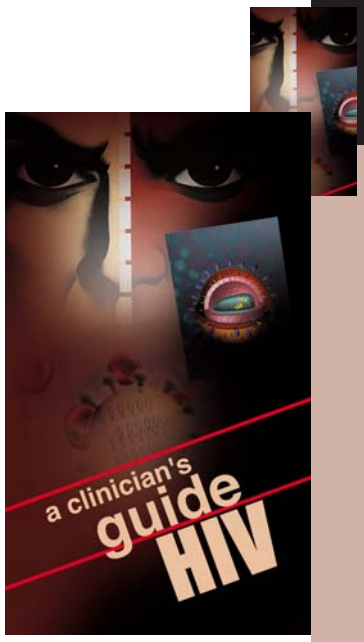

HIV
AIDS
a clinician's
guide:
HIV

HIV AIDS



a clinician's guide:

HIV

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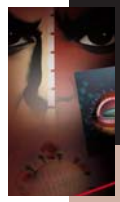

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Preface

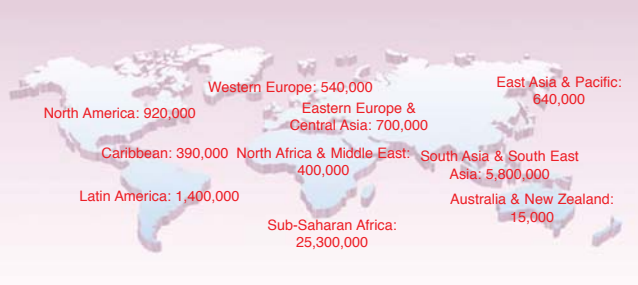
Although it is about 20 years since HIV infection and AIDS gained prominence, HIV therapeutics is an evolving science. Rapid strides made in scientists' understanding of HIV pathogenesis have translated into important clinical benefits for people living with HIV. The introduction of new drugs that potently inhibit HIV replication have successfully reduced morbidity and mortality and improved the quality of life for HIV-positive patients.

Bangladesh is believed to be the country with significant number of people living with HIV. In the years to come, these individuals will definitely place a larger burden on the healthcare services.

Treatment of HIV patients requires a detailed knowledge of the disease, as well as advances in therapeutics. The aim of this booklet is to equip clinicians with current concepts on HIV infection and enable them to treat patients, using both anti-HIV drugs, as well as drugs for treating opportunistic infections.

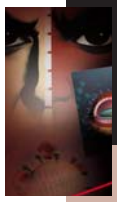
The grim statistics

The number of adults and children estimated to be living with HIV/AIDS at the end of 2000

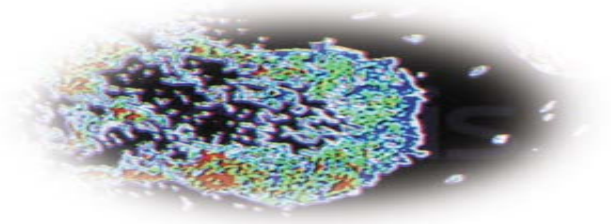


- At the end of 2000, there were 36.1 million adults and children living with HIV/AIDS
- During 2000, 5.3 million children and adults were infected with HIV, and 3 million people died
- The total number of AIDS deaths since the beginning of the epidemic is estimated to be more than 22 million

What is the magnitude of the problem in Bangladesh?



Today, South Africa is the country with the greatest number of HIV-infected individuals in the world, followed by India. Official Indian estimates range from 3.5 to 5 million, and perhaps the actual number may be far more. Moreover, given the similarities between Africa and India, the holocaust that is currently sweeping Africa may well repeat itself in India.



Bangladesh, with a population of 130 million, had about 13,000 adults and children living with HIV infection at the end of 1999, according to UNAIDS estimates. While only about 17 AIDS cases have been reported since 1997, underreporting of cases is likely to occur because of the country's limited voluntary testing and counseling capacity and the stigma and fear of being identified and detected as HIV positive.

The HIV prevalence rate among adults between the ages of 15-49 is still relatively low, at 0.03 percent. As expected, rates are higher in specific groups, such as injecting drug users who have left treatment (1.7 percent) and commercial sex workers (0.5 percent) (National behavioral and serological surveillance 2001).

Although overall HIV prevalence is low, behavior patterns and extensive risk factors that facilitate the rapid spread of the infection are widespread making Bangladesh highly vulnerable to an HIV/AIDS epidemic. These risk factors include:

- A large commercial sex industry with roughly 36,000 workers, each seeing an average of 18.8 clients per week for brothel-based sex workers, and 44 clients per week for hotel-based workers.
- Consistent condom use is low. The majority of brothel-based sex workers report at least some sex without condoms with their clients. Among the clients, such as rickshaw pullers and truckers, about 83% have never used condoms when buying sex.
- Significant prevalence of sexually transmitted diseases (STDs) among sex workers in Central Bangladesh. About 43% of female sex workers and 18.2% of male sex workers have syphilis. STDs facilitate the spread of HIV infection and serve as indicators for low condom use and other high-risk sexual behaviors.
- In Central Bangladesh, among 93.4% of over 500 injecting drug users, needle sharing is routine. These drug injectors are not an isolated population—they are often married and sometimes sell sex and blood.
- Knowledge of HIV is extremely low among the general population. In 1996/97, only 19% of ever-married women and 33% of men had ever heard of AIDS. In 2001, many still could not identify the basic routes of HIV transmission.

These facts clearly reveal the magnitude of the problem in Bangladesh.

How is HIV transmitted?

HIV is transmitted by the following routes:

1. Sexual transmission: This is the commonest route of transmission worldwide as well as in Bangladesh. The presence of sexually transmitted diseases further increases the risk of transmission of HIV.

2. Transfusion of infected blood and blood products: HIV may be acquired through blood transfusion. The probability of acquiring HIV infection after receiving HIV-infected blood is 95%. Haemophiliacs and thalassaemics are at particular risk for acquiring HIV infection.

3. Maternal transmission: HIV may be transmitted from an infected mother to her infant during pregnancy, during delivery or after delivery through breast-feeding.

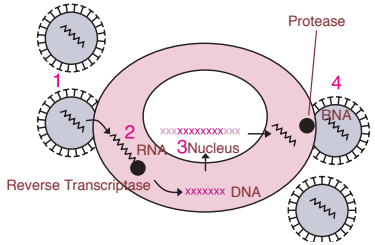
4. HIV-contaminated instruments: Use of HIV-contaminated instruments, e.g. needle sharing among drug users, can transmit HIV. Acupuncture and tattoo may also transmit HIV. Re-usable needles may transmit HIV infection if proper sterilization techniques are not used.

Occupational exposure to HIV may occur. Percutaneous exposure involves needles carrying HIV-infected blood, which accidentally prick the healthcare professional. However, the risk of acquiring HIV via a percutaneous exposure is 0.3%, whereas after a mucocutaneous exposure, the risk is believed to be even lower i.e. about 0.09%.

How does HIV replicate?

HIV is a virus, and needs a living cell within which it can multiply. Once HIV enters the human body, it specifically seeks out a particular type of T-lymphocyte in the blood called the CD4 T-lymphocyte. The various stages of HIV replication are explained below.

Stages of HIV reproduction



1. HIV enters a CD4 cell.

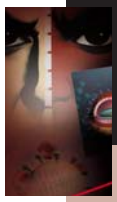
2. HIV is a retrovirus, meaning that its genetic information is stored on single-stranded RNA instead of the double-stranded DNA found in most organisms. To replicate, HIV uses an enzyme known as reverse transcriptase to convert its RNA into DNA.

3. HIV DNA enters the nucleus of the CD4 cell and inserts itself into the cell's DNA. HIV DNA then instructs the cell to make many copies of the original virus.

4. With the help of the protease enzyme, new virus particles are assembled. These newly formed viruses leave the cell, ready to infect other CD4 cells.

Characteristics of HIV replication

Rapid replication of HIV, with concomitant destruction of CD4 cells, occurs continuously throughout the course of HIV infection, including the initial clinically asymptomatic phase of infection. It is estimated that the turnover of the virus is very high - up to 109 virus particles every 1.5 to 2 days.



In patients with advanced HIV disease, as many as 109 new HIV virions are produced each day and as many as 2 x 109 CD4 cells turn over per day.

Sanctuaries of HIV in the body

HIV not only infects the CD4 cells, but also establishes infection in certain sanctuary sites such as the central nervous system, lymphoid tissue and testes. During the early stages of HIV infection, a virus reservoir is established in resting memory CD4+ lymphocytes. Since these cells have a very long half-life, the possibility of a cure for HIV infection with antiretroviral therapy is unlikely.

Which tests are used to diagnose HIV infection?

Tests which are commonly used to diagnose HIV infection are:

1. ELISA: This is the initial, or screening, test for HIV infection. It tests for the presence of antibodies against HIV in the blood. A positive result is usually obtained within 3 months of acquiring the infection.

2. Western Blot: This is a confirmatory test. It detects antibodies against antigens coded by 3 different viral genes.

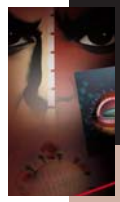
As per NACO (National AIDS Control Organization) guidelines, HIV infection is diagnosed on the basis of blood tests using three different ELISA/Rapid simple tests using different antigen preparations. Cases of AIDS are diagnosed on the basis of two different ELISA/Rapid tests on different antigens and the presence of AIDS-related opportunistic infections. The Western Blot test is used for confirmation of diagnosis when ELISA tests are indeterminate.

3. Polymerase chain reaction (PCR) assays: The PCR technique is used to assay for both HIV RNA and HIV DNA.

HIV infection can be diagnosed in the window period (i.e. when antibodies to HIV have not yet developed and ELISA is negative) by the HIV DNA PCR assay or the p24 antigen test.

The HIV RNA PCR test can measure the amount of HIV RNA in the blood (also referred to as the "viral load"). The viral load indicates the rate of disease progression, with higher viral loads predictive of faster disease progression. HIV RNA PCR is also used to assess the response to anti-HIV therapy.

The viral load may also be measured using another technique known as the branched DNA (bDNA) technique.



What is "Primary HIV Infection"?

The term "primary HIV infection" (also called "acute HIV infection") refers to the illness which occurs when HIV first infects an individual. This stage is characterized by non-specific flu-like symptoms such as fever, lethargy, sore throat, malaise, rash, lymphadenopathy, arthralgias, myalgias, headaches and rarely asymptomatic meningitis. These symptoms usually occur within 2 to 6 weeks after acquiring the virus. Most symptoms usually resolve within 2 to 3 weeks.

Within 2 to 4 weeks after the initial infection, high levels of virus are present in the blood. The immune system now begins to recognize the virus and produce antibodies. HIV antibodies can be detected in the blood usually within 1 to 3 weeks after symptoms appear.

The time period during which the individual is infected with HIV, but has no antibodies in his blood, is called the "window period". During the window period, the HIV-infected person is capable of transmitting the virus to others, and is infectious.

This phase of primary HIV infection is also called the "acute seroconversion syndrome". The term "seroconversion" refers to the appearance of HIV antibodies in the blood.

During the window period, the ELISA test will give a negative result; the only tests for detecting HIV infection at this stage are the PCR test or the p24 antigen test.

What is the natural history of HIV infection?

HIV attacks the CD4 T-lymphocytes

HIV has a special affinity for the CD4 T-lymphocyte. It multiplies rapidly and continuously within these cells. Although the body does replace the lost CD4 cells, the rate of destruction of the CD4 cells far exceeds the body's ability to replace them.

Thus, as HIV infection progresses, there is a progressive decline in the number of CD4 T-lymphocytes. The CD4 count may drop to as low as 50 cells/μ l or even lower, from the normal level of about 1000 cells/μl.

HIV infection leads to immunodeficiency

HIV destroys the CD4 cells, which play a vital role in immune function. The loss of CD4 cells leads to immunodeficiency in HIV-infected patients. In other words, these patients become susceptible to a variety of "opportunistic infections".

Opportunistic infections are commonly encountered when the CD4 count is less than 200 cells/μl. The lower the number of CD4 cells, the more advanced is the stage of the disease.

Thus, HIV causes a progressive and irreversible destruction of the immune system.

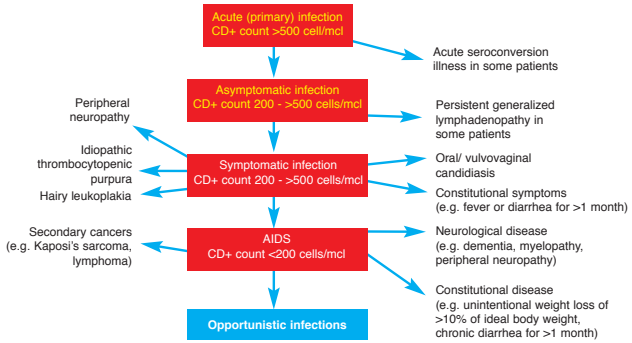
Immunodeficiency causes opportunistic infections

As the immune function declines, the HIV-positive patient is plagued by a variety of opportunistic infections. Virtually no system or organ is spared. Moreover, as immunodeficiency increases, these infections become more difficult to treat, and have a greater tendency to relapse.

Immunodeficiency leads to death

If an HIV-positive patient is left untreated, over the years, his CD4 cells will continue to decline progressively, immune function will deteriorate, and ultimately, he would die because of the opportunistic infections that ravage his body.

Schematic representation of HIV disease progression, including symptoms that may occur at each stage of HIV infection



Common opportunistic infections

1. Tuberculosis, both pulmonary as well as extrapulmonary. This is one of the commonest presentations. Atypical mycobacteria such as Mycobacterium avium complex (MAC) may also cause infection.

2. Oral candidiasis

3. Oesophageal candidiasis

4. Herpes zoster

5. Diarrhea, which may be due to a variety of pathogens:
Protozoal - Amoeba, Giardia, Isospora belli, Cryptosporidium
Helminths -Strongyloides
Viral - Cytomegalovirus

6. Bacterial pneumonia and Pneumocystis carinii pneumonia

7. Toxoplasma encephalitis

8. Cryptococcal meningitis

9. Cytomegalovirus (CMV) retinitis

Cancers such as Kaposi's sarcoma and non-Hodgkin's lymphoma are also seen in these patients.

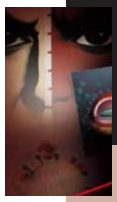
What is the difference between HIV infection and AIDS?

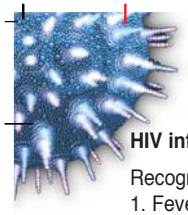
HIV infection

After primary infection, there is a long asymptomatic phase, which may last for several years. Thus, the patient who is infected with HIV, but is asymptomatic or mildly symptomatic, is referred to as "HIV positive". During this phase, the virus is actively multiplying and destroying the CD4 cells.

AIDS

When the CD4 cells decrease to 200 cells/μl, or the patient starts suffering from a characteristic range of severe opportunistic infections(AIDS-defining illnesses), he is said to be suffering from AIDS. It may take 8-10 years to reach this stage, although this may vary between patients.
Thus, AIDS represents an advanced stage of HIV infection, when the patient suffers from a characteristic range of opportunistic infections.

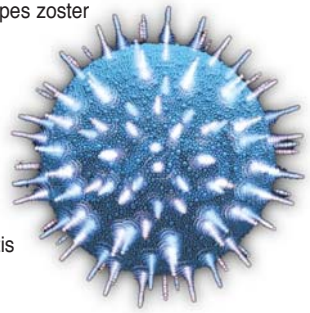




HIV infection and AIDS in South-East Asia

Recognition of Symptomatic HIV infection - Suggestive clinical findings

1. Fever of more than one month's duration
2. Weight loss of more than 10%
3. Diarrhea of more than one month's duration
4. Mucocutaneous manifestations
5. Generalized lymphadenopathy (extra-inguinal)
6. Infections, severe or recurrent
    - Past or present multidermatomal herpes zoster
    - Hairy leukoplakia
    - Warts
    - Molluscum contagiosum
    - Oral thrush
    - Papulonecrotic lesion
    - Folliculitis
    - Vulvovaginitis
7. Others
    - Severe recurrent seborrheic dermatitis
    - Chronic prurigo
    - Reiter's syndrome
    - Kaposi's sarcoma
8. Unexplained neurological manifestations e.g. seizures, motor or sensory deficits, dementia and progressive headache
9. Chronic cough of more than one month's duration or unexplained respiratory distress
10. Cytomegalovirus retinitis
11. Extrapulmonary or disseminated and extensive pulmonary tuberculosis
12. Recurrent pneumonia
13. Invasive cervical carcinoma



WHO clinical case definition for AIDS in South-East Asia

Clinical AIDS in an adult is defined as an individual who has been identified as meeting the two criteria A and B below:

A. Positive test for HIV infection by two tests based on preferably two different antigens.

B. Any one of the following criteria:

1a. Weight loss of 10% body weight or cachexia, not known to be due to a condition unrelated to HIV infection

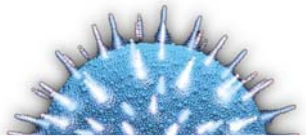
1b. Chronic diarrhea of one month's duration, intermittent or constant

2. Disseminated, miliary or extrapulmonary tuberculosis

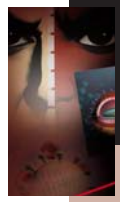
3. Candidiasis of the oesophagus; diagnosable as dysphagia, odynophagia and oral candidiasis

4. Neurological impairment restricting daily activities, not known to be due to a condition unrelated to HIV (e.g. trauma)

5. Kaposi's sarcoma.



How is the HIV-positive patient treated?



What is the treatment approach for an HIV-positive patient?

Basically, the treatment of an HIV-infected patient involves:

A) Inhibiting the replication of the virus using antiretroviral drugs

B) Treatment and prophylaxis of opportunistic infections

C) Psychosocial support

What does antiretroviral therapy do?

Antiretroviral therapy helps in:

1. Inhibiting viral replication
2. Preserving immune function
3. Preventing disease progression
4. Reducing the incidence of opportunistic infections
5. Prolonging survival

What is the goal of antiretroviral therapy?

Currently, the goal of antiretroviral therapy is to bring down viral load to undetectable levels, usually below 50 copies/ml. The time taken to achieve this goal depends on the baseline viral load. In most patients, adherence to a triple drug antiretroviral regimen results in a large decrease (about ten fold) in viral load by 2-8 weeks. The viral load should continue to decline over the following weeks and in most individuals becomes undetectable (<50 RNA copies/ml) by 16-20 weeks.

The durability of the plasma viral load response is critical for the long term clinical outcome of the patient. Data suggest that the initial decline of viral load is predictive of the durability of viral load suppression.

Benefits of antiretroviral therapy

Antiretroviral therapy has been proven to be effective in:

1. Decreasing viral load
2. Increasing CD4 counts
3. Decreasing the incidence of opportunistic infections
4. Preventing disease progression
5. Prolonging survival
6. Enabling the patient to lead a productive life e.g. resuming his job
7. Improving quality of life
8. Possibly reducing the risk of transmission

Classes of antiretrovirals

Antiretrovirals generally target key enzymes that the virus requires in order to replicate: protease and reverse transcriptase.

Thus, protease inhibitors (PIs) target the protease enzyme, whereas reverse transcriptase inhibitors target the reverse transcriptase enzyme. Reverse transcriptase inhibitors are further divided into two types - nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) - based on slight differences in their chemical structure and mode of action.

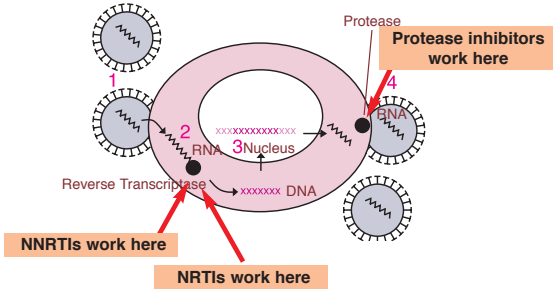
Classification of antiretrovirals

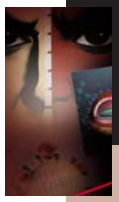
Nucleoside reverse transcriptase inhibitors (NRTIs)	Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Protease inhibitors (PIs)
Zidovudine	Nevirapine	Indinavir
Stavudine	Efavirenz	Nelfinavir
Lamivudine	Delavirdine	Ritonavir
Didanosine		Saquinavir
Zalcitabine		Amprenavir
Abacavir		Lopinavir

How do these drugs act?
An essential step for HIV replication is the conversion of its RNA to DNA. This step is mediated by reverse transcriptase. Both NRTIs and NNRTIs inhibit reverse transcriptase.

After multiplication of the virus is complete, the enzyme protease is required for maturation of these newly produced viruses. Protease inhibitors inhibit this enzyme.

Thus, HIV replication can be inhibited by inhibiting these crucial enzymes.





When should antiretroviral therapy be initiated?
In an asymptomatic patient, current international guidelines recommend that antiretroviral therapy should be initiated when CD4 count goes below 350 cells/ l or HIV RNA is above 30-55,000 copies/ml. All symptomatic patients should be offered antiretroviral therapy irrespective of CD4 counts or plasma viral load.

The best indication to start antiretroviral therapy is when a well-informed patient is ready.

Why is combination therapy recommended?
HIV has the ability to rapidly develop resistance if any one drug is used alone. Hence, a minimum of three drugs have to be used in combination. This triple drug regimen is commonly referred to as HAART, which is an acronym for Highly Active Antiretroviral Therapy.

What are the strategies for using antiretroviral therapy?
Even if triple therapy is used, over a period of time, there is a possibility of the virus developing resistance and the patient failing his initial treatment regimen (manifested by an increase in viral load occurring after viral suppression has been demonstrated). Hence, the initiation of antiretroviral therapy should be viewed as the beginning of a longer term strategy. When choosing an initial regimen, possible future combinations have to be borne in mind.

In other words, clinicians should design a long-term plan for the patient, as discussed below.

How is antiretroviral therapy initiated?
It is recommended to initiate antiretroviral therapy in naive patients (i.e. patients who have not yet been treated with antiretrovirals) using a combination of two NRTIs with either one PI or one NNRTI. For example, zidovudine + lamivudine + nelfinavir or zidovudine + lamivudine + nevirapine or efavirenz.

An alternative initial regimen consists of 2 PIs with 2 NRTIs. The simultaneous initiation of all the drugs is recommended and sequential addition should be avoided.

While choosing the 2 NRTI component of triple drug therapy, the following two-drug combinations should not be used, as they are either antagonistic, or have overlapping toxicities.

1. Zidovudine + Stavudine
2. Zalcitabine + Stavudine
3. Zalcitabine + Didanosine

Recommended Antiretroviral Agents for Initial Treatment of Established HIV Infection

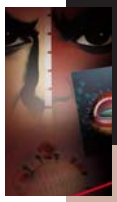
Following table provides a guide to the use of available treatment regimens for individuals with no prior or limited experience on HIV therapy. In accordance with the established goals of HIV therapy, priority is given to regimens in which clinical trials data suggest the following: sustained suppression of HIV plasma RNA (particularly in patients with high baseline viral load) and sustained increase in CD4+ T cell count (in most cases over 48 weeks), and favorable clinical outcome (i.e., delayed progression to AIDS and death). Particular emphasis is given to regimens that have been compared directly with other regimens that perform sufficiently well with regard to these parameters to be included in the "Strongly Recommended" category. Additional consideration is given to the regimen's pill burden, dosing frequency, food requirements, convenience, toxicity, and drug interaction profile compared with other regimens.

It is important to note that all antiretroviral agents, including those in the "Strongly Recommended" category, have potentially serious toxic and adverse events associated with their use.

Antiretroviral drug regimens are comprised of one choice each from columns A and B.

I. Strongly Recommended:

Column A	Column B
Efavirenz	Didanosine + Lamivudine
Indinavir	Stavudine + Didanosine
Nelfinavir	Stavudine + Lamivudine
Ritonavir+ Indinavir	Zidovudine + Didanosine
Ritonavir+ Lopinavir	**Zidovudine + Lamivudine**
Ritonavir+ Saquinavir	



II. Recommended as alternative:

Column A	Column B
Abacavir	Zidovudine + Zalcitabine
Amprenavir	
Delavirdine	
Nelfinavir + Saquinavir	
Nevirapine	
Ritonavir	
Saquinavir	

III. No Recommendation:

Hydroxyurea in combination with antiretroviral drugs

Insufficient Data#

Ritonavir + Amprenavir*
Ritonavir + Nelfinavir*
Tenofovir..

IV. Not Recommended:

All monotherapies, whether from column A or B**

Should not be offered

Column A	Column B
Saquinavir ††	Stavudine + Zidovudine
	Zalcitabine + Didanosine
	Zalcitabine + Lamivudine
	Zalcitabine + Stavudine

† Based on expert opinion.
§ Saquinavir
¶ Pregnant women may be at increased risk for lactic acidosis and liver damage when treated with the combination of stavudine and didanosine. This combination should be used in pregnant women only when the potential benefit clearly outweighs the potential risk.
# This category includes drugs or combinations for which information is too limited to allow a recommendation for or against use.
** Zidovudine monotherapy may be considered for prophylactic use in pregnant women with low viral load and high CD4+ T cell counts to prevent perinatal transmission.
†† Use of Saquinavir is not recommended, except in combination with ritonavir.
.. Data from clinical trials are limited to use in salvage. Data from trials of Tenofovir as initial therapy may be available in the near future.

What are the recommendations for treating a patient who has failed the initial antiretroviral regimen?

If, for example, a patient has started therapy on a PI-based regimen and is no longer responding to this regimen, his second-line regimen may include an NNRTI-based regimen, and vice versa. It is recommended that the second-line regimen should ideally contain three drugs to which the patient has never been exposed. Moreover, these second-line drugs should not be cross-resistant with the first-line drugs - most PIs and all NNRTIs show cross-resistance.

What are the possible advantages and disadvantages of initiating therapy with PI-based versus NNRTI-based regimens?

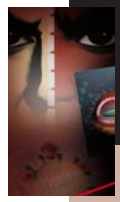
1) PI-based HAART regimen
Possible Advantages
- Targets HIV at two steps of viral replication (reverse transcriptase and protease)
- Resistance requires multiple mutations
- Potency

Possible Disadvantages
- Long-term side effects include lipodystrophy, hyperlipidemia, insulin resistance, osteoporosis, hypertension, nephrolithiasis and gynecomastia
- Compromises future PI regimens when initial regimen fails
- Compliance is poor, due to higher pill burden and stringent food/fasting requirements

2) NNRTI-based HAART regimen (PI-sparing)
Possible Advantages
- Better compliance due to lower pill burden
- Spares the use of PIs for a later date
- No long-term metabolic complications (as seen with PIs) have been reported

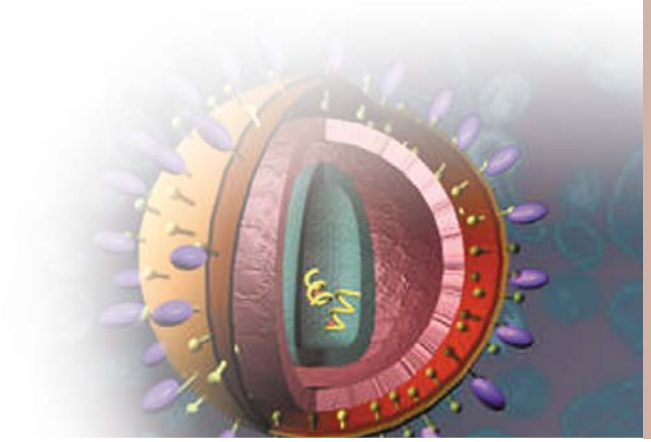
Possible Disadvantages
- Single mutation confers resistance
- Compromises future NNRTI based options

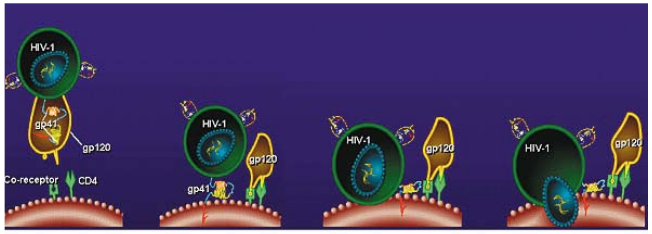
In treatment-experienced patients, there are more data to support the use of PI-based regimens. Some metabolic complications, such as lactic acidosis, have been ascribed to the NRTI component of combination antiretroviral regimens.



How long should the HIV-infected patient continue taking antiretrovirals?
It is important to appreciate that antiretroviral therapy should be continued indefinitely. This is because therapy is suppressive and not curative. The patient should be started on antiretrovirals only if he is committed to lifelong therapy.

Why can't HIV infection be eradicated?
HIV infects various cells and body compartments including the CNS, testes, etc. The virus remains latent in certain cells such as the long-lived resting memory CD4 cells. Antiretroviral therapy is not effective against these cells as they are not actively multiplying. Hence eradication of HIV is presently not considered to be a realistic goal.





How is the HIV-positive patient followed up?

Role of CD4 cell counts

Since HIV specifically targets the CD4 cells, the number of CD4 cells in the blood at a given point in time is a good indicator of immunodeficiency. The lower the number of CD4 cells (from the normal value of approximately 1000 cells/ μl), the more advanced is the stage of the disease.

In other words, the CD4 count tells us the degree of immunodeficiency.

After starting antiretroviral therapy, the CD4 cell count should be monitored regularly. If the patient is responding to therapy, the CD4 cells would increase. Also, the patient experiences fewer opportunistic infections.

Role of HIV RNA PCR tests

The HIV RNA PCR test measures the number of HIV RNA copies per ml of blood. This is referred to as the "viral load". The result of the viral load indicates the amount of virus present in the body. The higher the viral load, the greater would be the rate of multiplication of the virus. Hence, the greater would be the destruction of the CD4 cells.

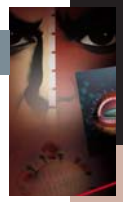
In other words, the viral load can predict the rate of decline of the CD4 cells.

After starting antiretroviral therapy, the viral load should decrease significantly. In fact, potent antiretroviral regimens decrease the viral load so dramatically that the reduction in viral load is measured in terms of log units, and not copies/ml.

Thus, the CD4 cell count and the viral load are used to monitor an HIV-positive patient on antiretrovirals. The lower the viral load, and the higher the CD4 count, the better is the prognosis for the patient.

The CD4 count and the plasma viral load should be measured every 3-6 months.

The patient should also be followed up clinically. Weight gain, as well as a reduction in the number of opportunistic processes are usually noted.



Issues involved in using antiretroviral therapy

There are many issues associated with the use of antiretroviral therapy, such as:

1. Adherence

Adherence is a crucial determinant of therapeutic success with antiretrovirals. The issue of compliance with multidrug antiretroviral regimens has been addressed with the introduction of fixed-dose combinations of antiretrovirals, which combine 2 or all 3 drugs into a single pill. This drastically reduces the overall pill burden and improves compliance with therapy.

In this regard, NNRTI-based regimens have lower pill burdens as compared to PI-based regimens. Moreover, NNRTI-based regimens are not associated with complex restrictions regarding food intake and storage.

2. Drug interactions

The NNRTI class of drugs exhibits a few drug interactions, whereas the NRTI class is not associated with clinically significant drug interactions.

The protease inhibitors most frequently exhibit drug interactions with each other, and also with other drugs e.g. anti-TB drugs, antifungals. This poses a problem for treating the HIV-positive patient, because these are common opportunistic infections, especially in our country.

3. Side effects

The non-nucleoside reverse transcriptase inhibitors are generally associated with short-term hypersensitivity reactions, such as rash. In contrast, the protease inhibitors are associated with some of the most severe long-term side effects. These include:

Lipodystrophy (the arms, legs and face appear to lose weight, whereas the central portion of the body accumulates fat and becomes obese)
Diabetes
Increased cholesterol and triglyceride levels
Hypertension
Osteoporosis
Gynecomastia
Kidney stones (indinavir)

The non-nucleoside reverse transcriptase inhibitors are not associated with significant long term toxicities, but certain patients may develop a rash or elevated liver enzymes during the first few weeks of therapy.

The nucleoside reverse transcriptase inhibitor class of drugs may be associated with anemia (zidovudine), lactic acidosis, peripheral neuropathy or pancreatitis.

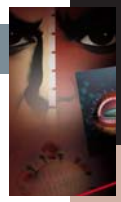
4. Access
The patient should be able to afford antiretroviral therapy for an indefinite period of time.

All the above issues are needed to be discussed with the patient prior to starting treatment.

Before initiating antiretroviral therapy, it is essential to discuss the following points with the patient

- Therapy available today is suppressive, and not curative. But treatment helps the patient to lead a more productive and healthy life.
- The duration of therapy is lifelong. HIV may be regarded as a chronic illness, just like diabetes or hypertension.
- Long term adverse events may occur, but there are drugs to manage these side effects.
- There is a potential for drug interactions with other concomitant medications.
- There may be a number of pills to be swallowed per day, depending on the antiretroviral regimen chosen. However, some of the newer regimens entail taking a total of only 2-5 tablets per day.
- Adherence is critical, else the virus quickly develops resistance. This is especially important with respect to antiretroviral drugs.
- It is important to inform patients that even if they are receiving therapy they should not donate blood and should practice protected sex, since the patient is still capable of infecting others.

Treatment of common opportunistic infections



Tuberculosis

Anti-TB drugs, plus ciprofloxacin (NEOFLOXIN) for resistant cases

Mycobacterium avium complex infections
Clarithromycin (ROLACIN) /Azithromycin (AZITHROCIN) + ethambutol ± rifabutin

Oropharyngeal candidiasis
Fluconazole (OMASTIN) or other antifungals

Herpes simplex/Varicella zoster virus
Acyclovir/ Valacyclovir/ Famciclovir

Diarrhea due to:

Salmonella/Shigella
Ciprofloxacin (NEOFLOXIN)/ Co-trimoxazole (MEGATRIM)

Campylobacter
Erythromycin (ETROCIN)/ Azithromycin (AZITHROCIN)

Clostridium difficile
Metronidazole (FILMET)

Giardia
Metronidazole (FILMET)

Amoeba
Metronidazole (FILMET)+ Iodoquinol or Paromomycin

Isospora belli
Co-trimoxazole (MEGATRIM)

Strongyloides
Albendazole (ALPHIN DS)

Cytomegalovirus
Ganciclovir/ Foscarnet

Herpes simplex virus
Acyclovir/ Valacyclovir/ Famciclovir

Cytomegalovirus retinitis
Ganciclovir/ Foscarnet/ Cidofovir

Pneumonia due to Pneumocystis carinii
Co-trimoxazole (MEGATRIM)

Other bacterial pneumonias
Cefpodoxime,
Clarithromycin (ROLACIN),
Co-trimoxazole (MEGATRIM)

Toxoplasmosis
Pyrimethamine and Sulfadiazine for treatment, and Co-trimoxazole (MEGATRIM) for primary prophylaxis

Cryptococcal meningitis
Amphotericin B + Flucytosine OR Fluconazole (OMASTIN) + Flucytosine followed by Fluconazole (OMASTIN) for maintenance; some studies have used high-dose Fluconazole (OMASTIN) therapy

Non-Hodgkin's lymphoma
Chemotherapy using appropriate protocols

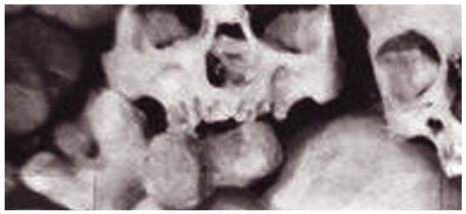
Kaposi's sarcoma
Treatment depends on location and extent of disease

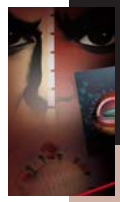
Treatment of pediatric HIV infection

How is pediatric HIV infection diagnosed?
Since maternal HIv antibodies passively diffuse across the placenta, ELISA testing is reliable only after age of 18 months. Therefore, for children aged <18 months, testing using HIV DNA PCR is recommended.

How are CD4 cell counts interpreted in pediatric patients?
CD4 cell counts and percentages are considerably higher in children than in adults. Therefore, a pediatric immunologic staging system has been developed as follows:

Immune Category	Age of Child					
	< 12 months		1-5 years		6-12 years	
	No./mm^3	%	No./mm^3	%	No./mm^3	%
Category I: No suppression	> 1,500	> 25	> 1,000	> 25	> 500	> 25
Category II: Moderate suppression	750-1,499	15-24	500-999	15-24	200-499	15-24
Category III: Severe suppression	< 750	< 15	< 500	< 15	< 15	< 15





When should therapy be initiated in the HIV-1 infected child?
Antiretroviral therapy is recommended for all children with clinical symptoms or evidence of immune suppression, regardless of the age of the child or viral load.

In asymptomatic children aged less than one year, therapy should be started as soon as the child is diagnosed, regardless of clinical or immunologic statue or viral load. In the asymptomatic child aged one year or above, either therapy may be started immediately, or deferred if immune status is normal, but with regular monitoring.

How is the HIV-infected child treated?
Triple therapy with 2 NRTIs (such as zidovudine + lamivudine) in combination with either 1 NNRTI (such as nevirapine) or 1 PI (such as nelfinavir) is recommended.

Prophylaxis for Maternal Transmission of HIV

The risk of vertical transmission of HIV from mother to baby ranges from 7% to 40%. Maternal HIV transmission is the primary means by which infants become infected. Hence, prevention of maternal HIV transmission is of paramount importance.

Maternal HIV transmission can occur in uterus, during labor and delivery, or after birth (via breast-feeding). About 50-70% of maternal HIV transmission occurs in late pregnancy or during labor and delivery.

Various factors are associated with increased maternal transmission of HIV. These are:

1) High maternal viral load
2) Low CD4+ count
3) Lack of HIV neutralizing antibodies
4) Advanced clinical disease
5) Primary infection
6) First-born twins
7) Obstetric factors:
   - Chorioamnionitis
   - Mode of delivery
   - More than 4 hours of ruptured membranes
8) Breast-feeding

Prophylactic therapy with antiretrovirals for mother and baby is recommended to prevent maternal transmission of HIV. Use of formula feeding for the infant reduces the risk of transmission via breast-feeding. Delivery by caesarean section has also been shown to have a beneficial effect, perhaps by decreasing exposure to cervicovaginal secretions.

Both zidovudine and nevirapine (administered as monotherapy for varying periods of time) have proved effective in reducing the risk of maternal transmission.

Post-exposure prophylaxis for healthcare personnel

Healthcare personnel (HCP) whose activities involve contact with HIV-infected patients, or who may come in contact with blood or body fluid from HIV-positive patients in a health care or laboratory setting are at risk for occupational exposure to HIV.

The Centers for Disease Control (CDC) based at Atlanta, USA has issued guidelines for treatment of occupational exposure to HIV (also referred to as 'post-exposure prophylaxis' or PEP). The rationale behind PEP is that antiretroviral treatment started immediately after exposure to HIV may abort infection by inhibiting HIV replication.

The transmission of HIV infection through occupational exposure is rare. The risk of infection via percutaneous exposure is approximately 0.3%. Various factors which influence this estimate are:

1) The size or type of needle
2) Depth or severity of exposure
3) Volume of blood involved and
4) Viral load of the patient

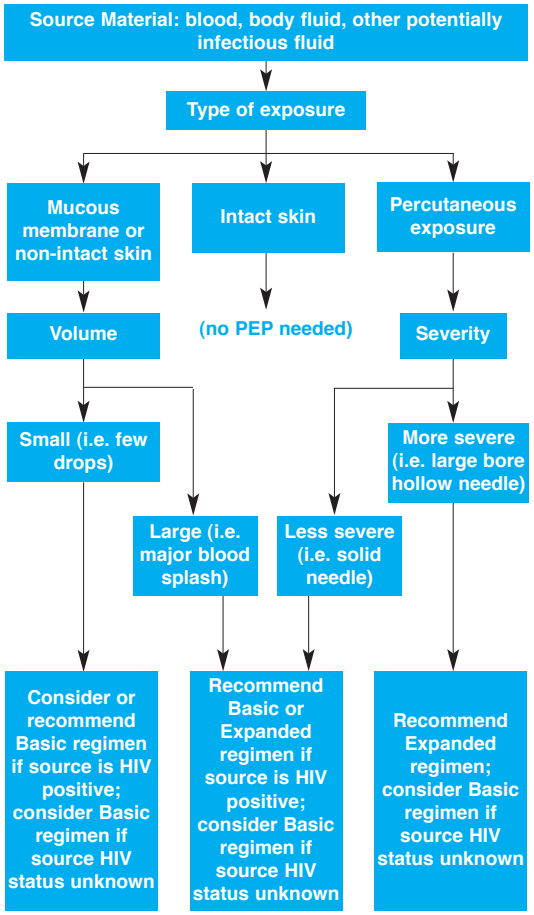
The risk of infection after mucous membrane exposure is about 0.09%. Needlestick injuries are the most common type of occupational exposure.

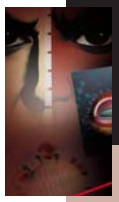
In addition to blood, fluids which may potentially transmit HIV include:
1) Semen
2) Vaginal secretions
3) Fluids with visible blood

Contact with cerebral, synovial, pleural, pericardial and amniotic fluids is also considered as exposure. Exposure to saliva, tears, sweat and non-bloody urine or feces does not entail a risk of infection.

The degree of risk involved in any occupational exposure hinges on the type of substance involved and the route and severity of the exposure. This risk is evaluated as given in the following algorithm.

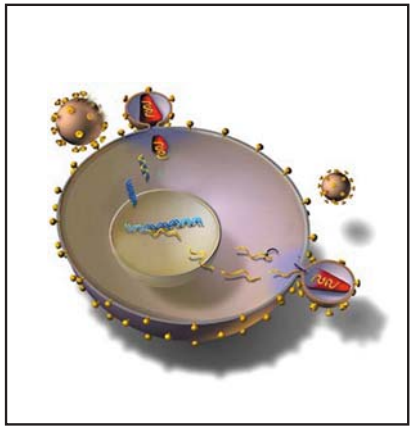
Post-exposure prophylaxis for HCP

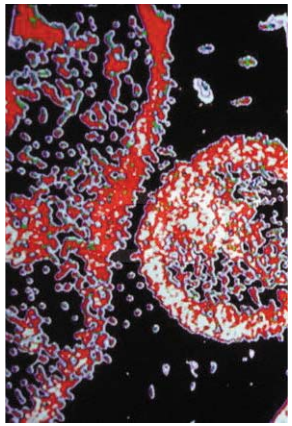




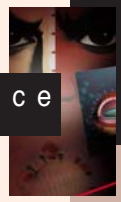
If PEP is indicated, it should be started within 1 to 2 hours of exposure. Details of the recommended regimens are depicted in the table below:

TYPE	DRUG
Basic (28 days)	Zidovudine 300 mg tid + Lamivudine 150 mg bid OR Stavudine 30/40 mg bid + Lamivudine 150 mg bid
Expanded (28 days)	As above, plus Indinavir 800 mg 8 hourly OR Efavirenz 600 mg od at bedtime OR Nelfinavir 750 mg tid
Expanded (28 days)	As above, plus Indinavir 800 mg 8 hourly OR Efavirenz 600 mg od at bedtime OR Nelfinavir 750 mg tid





Antiretrovirals at a glance



Diavix®

- Shows excellent efficacy against HIV replication
- Recommended NRTI by DHHS
- Ensures patients' long-term adherence to therapy
- Lacks potential side effects of stavudine
- Preferred NRTI for patients with renal problem and ulcer

Avifanz®

- Non-competitively blocks reverse transcriptase
- Lower pill burden & dosage frequency compared to PIs
- Fewer drug interactions compared to PIs
- Better than nevirapine for patients with allergy, asthma and hepatic disorder
- Assures a long term treatment plan for the patients
- Offers a better therapeutic option for patients with diabetes and hyperlipidemia

Avifix®

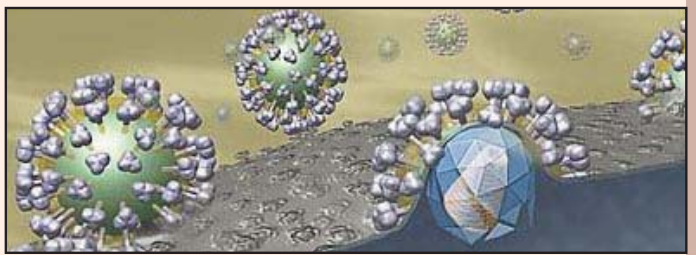
- Offers a unique mode of therapy compared to RTIs
- Viral resistance requires multiple mutation
- Assures a strong anti-HIV action
- Offers a safer therapeutic option for pregnant women & patients with hepatic or psychological problem
- Assures a long term treatment plan for patients

Triovix®

- Blocks viral reverse transcriptase in two ways
- Preferred NNRTI for pregnant women
- Right choice for patients having associated psychological problems

Avilam®

- Offers a component of alternative 'backbone' NRTI regimen
- Shows excellent efficacy against HIV infection



Avifanz®

(Efavirenz)
Tablet

DESCRIPTION

AVIFANZ® is the brand name for Efavirenz. Efavirenz, a synthetic anti-retroviral agent, is a non-nucleoside reverse transcriptase inhibitor. While Efavirenz is pharmacologically related to other non-nucleoside reverse transcriptase inhibitors, Efavirenz differs structurally from these drugs and also differs structurally from other currently available anti-retroviral agents.

INDICATION AND USAGE

AVIFANZ® (efavirenz) in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection. This indication is based on analysis of plasma HIV-RNA levels and CD4 cell counts in controlled studies of up to 24 weeks in duration. At present, there are no results from controlled trials evaluating long-term suppression of HIV- RNA with AVIFANZ®.

DOSAGE AND ADMINISTRATION

Adults: The recommended dosage of AVIFANZ® is 600 mg orally, once daily, in combination with a protease inhibitor and or nucleoside analogue reverse transcriptase inhibitors (NRTIs). AVIFANZ® may be taken with or without food; however, a high fat meal may increase the absorption of AVIFANZ® and should be avoided.

In order to improve the tolerability of nervous system side effects, bedtime dosing is recommended during the first two to four weeks of therapy and in patients who continue to experience these symptoms.

Concomitant Antiretroviral Therapy: AVIFANZ® must be given in combination with other antiretroviral medications.

Pediatric Patients: The following table describes the recommended dose of AVIFANZ® for pediatric patients 3 years of age or older and weighing between 10 and 40 Kg. The recommended dosage of AVIFANZ® for pediatric patients weighing greater than 40 Kg is 600 mg, once daily.

TABLE 7.
Pediatric Dose to be Administered Once Daily

Body Weight		AVIFANZ
Kg	Lbs	Dose (mg)
10 to < 15	22 to < 33	200
15 to < 20	33 to < 44	250
20 to < 25	44 to < 55	300
25 to < 32.5	55 to < 71.5	350
32.5 to < 40	71.5 to < 88	400
_40_	_88_	600

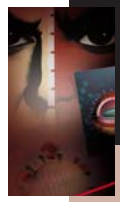
CONTRAINDICATIONS

Efavirenz is contraindicated in patients with known hypersensitivity to the drug or any ingredient in formulation.

WARNING AND PRECAUTIONS

Warning:

Do not use if you are pregnant, plan to become pregnant or while breast-feeding.



Consult your doctor or pharmacist. High fat foods may cause unwanted increases in drug effect. Avoid taking with high-fat foods or take on an empty stomach.

Regular, periodic measurement plasma HIV-1 RNA levels and CD4+ T-cell counts is necessary to determine the risk of disease progression and to determine when to modify anti-retroviral agent regimens. Patients should be advised that Efavirenz has not been shown to reduce the risk of transmission of HIV to others via sexual contact or blood contamination and that practices designed to prevent transmission of HIV should be maintained during anti-retroviral therapy. Efavirenz should always be administered in conjunction with other anti-retroviral agent and should not be used alone in the treatment of HIV infection . Although Efavirenz used in combination with other anti-retroviral agents appears to be well tolerated, patients should be monitored closely for adverse effects during combination therapy. The usual precautions and contraindications of the other anti-retrovirals in the regimen should be considered during combination therapy; Efavirenz should not be added as sole agent to a failing regimen. Whenever a change in anti-retroviral therapy is considered because of therapeutic failure, at least 2 components of the previous regimen should be changed since adding a single new agent may predispose to the development or viral resistance. Use of an entirely new regimen containing at least 3 drugs is preferred. The effect of Efavirenz therapy on subsequent therapy with other non-nucleoside reverse transcriptase inhibitors remains to be determined. Because cross-resistance occurs among non-nucleoside reverse transcriptase inhibitors, most clinicians suggest that individuals who experience disease progression while receiving one of the agents (e.g., Delavirdine, Efavirenz, Nevirapine) should not be switched to another agent in the class. Because Efavirenz has been associated with adverse CNS effect patients should be advised that the drug may impair their ability to perform hazardous activities requiring mental alertness or physical coordination such as operating machinery or driving a motor vehicle. In addition, patients receiving Efavirenz should be informed that there is a potential for additive CNS effects if they use Efavirenz concomitantly with psychoactive drugs or alcohol. Patients should be advised to contact their clinician if they experience delusions, inappropriate behavior, or acute depression while receiving Efavirenz; discontinuance of Efavirenz may be necessary in patients who experience such CNS effects. Efavirenz is metabolized in the liver; the drug should be used with caution in patents with hepatic impairment. Serum hepatic enzyme concentrations should be monitored during Efavirenz therapy in patients who have, or may have, Hepatitis B and/or C virus infection, in patients receiving concomitant ritonavir and in patients receiving concomitant therapy with hepatotoxic drug (s). In patients with serum hepatic enzyme concentrations more than 5 times the upper limit of normal, the benefits of continued Efavirenz therapy versus the risks of hepatotoxicity should be considered. Because increases in serum cholesterol concentration have occurred in individuals receiving Efavirenz, cholesterol monitoring

should be considered in patients receiving the drug. Because of the risk of fetal malformations, Efavirenz should not be used in women who are or may become pregnant unless no other therapeutic options exist.

Precautions:
Efavirenz may cause drowsiness or dizziness. Alcohol may intensify this effect.
Pediatric Precautions
Safely and efficacy of Efavirenz in neonates and children younger than 3 years of age or who weigh less than 13 kg have not been evaluated. Adverse effects reported in children receiving Efavirenz are similar to those reported in adults receiving the drug and including CNS, GI and dermatologic effects. Adverse CNS effects occurred in 9% of children receiving Efavirenz. In clinical studies rash has been reported more frequently in children than adults (40 vs 27.3%) and the incidence of moderate to severe rash has been greater in children than adults. Because of the high incidence of dermatologic reactions in children, antihistamines may be used for the prevention of rash when initiating Efavirenz therapy in children; however, the efficacy of such a strategy has not been determined.

SIDE EFFECTS
CNS effects, including dizziness, impaired concentration, abnormal dreams and insomnia have been reported in about 52% of adults receiving Efavirenz 600 mg once daily. In clinical studies these adverse effects were reported in 26% of adults in the control groups not receiving Efavirenz. In adults receiving Efavirenz, these CNS effects were described as mild (do not interfere with daily activities) in 31.4%, moderate (may interfere with daily activities) in 17.8% or severe (interrupt usual daily activities) in 2.6% cases. Adverse nervous system effects generally begin during the first 1-2 days of Efavirenz therapy, improve with continued therapy and usually resolve after the first 1-2 days of Efavirenz therapy. Adverse CNS effects may be more tolerable if the daily dose of Efavirenz is administered at bedtime, especially during the first 2-4 weeks of therapy and in patients who continue to experience such effects. Fatigue has been reported in up to 7% of adults receiving Efavirenz in clinical studies.
Severe acute depression, sometimes accompanied by suicidal ideation / attempts, has been reported rarely in patients receiving Efavirenz in clinical studies.
Adverse CNS effects reported in less than 2% of patients receiving Efavirenz include ataxia, confusion, impaired coordination, migraine headache, neuralgia, paresthesia, peripheral neuropathy, seizures, speech disorder, tremor, or vertigo. In addition, aggravated depression, agitation, amnesia, anxiety, apathy, emotional liability, euphoria, hallucination, or psychosis has occurred in less than 2% of Efavirenz-treated patients. Adverse CNS effects occurred in 9% of children receiving efavirenz in clinical studies.

Dermatologic and Sensitivity Reactions
Rash has occurred in 27. 3% of adults receiving Efavirenz in clinical studies and in 17% of adults in control groups not receiving the drug. Pruritus or increased sweating has been reported in 1-2% of patients receiving Efavirenz. Allergic reaction, alopecia, eczema, folliculitis, skin exfoliation or urticaria has occurred in lees than 2% of patients receiving the drug.

GI Effects
Nausea or diarrhea has been reported in up to 12% of adults receiving Efavirenz. Vomiting, dyspepsia, abdominal pain, or flatulence has occurred in some Efavirenz-treated adults. Dry mouth or taste change has been reported in up to 2% of patients receiving Efavirenz.

Hepatic Effects
Hepatitis occurred in less than 2% of patients receiving Efavirenz.

Cardiovascular Effects
While the clinical importance remains to be determined, total serum cholesterol concentrations have been increased 10-20% in healthily individuals receiving Efavirenz. Hot flushes, flushing, palpitations, tachycardia, or thrombophlebitis has been reported in less than 2%, of patients receiving Efavirenz.

PHARMACEUTICAL PRECAUTIONS
Store in a cool dry place.
Keep out of reach of children.

COMMERCIAL PACK
Each box contains 1 x 10's tablets in blister strip. Each tablet contains Efavirenz INN 600 mg.

Avilam®

(Lamivudine)
Tablet

DESCRIPTION
AVILAM® (formerly known as 3TC) is the brand name for Lamivudine, a synthetic nucleoside analogue with activity against HIV.

INDICATIONS AND USAGE
AVILAM® in combination with Zidovudine is indicated for the treatment of HIV infection.

DOSAGE AND ADMINISTRATION
Adults and Adolescents (12 to 16 years)
The recommended oral dose of AVILAM for adults and adolescents is 150 mg twice daily administered in combination with Zidovudine. For adults with low body weights (less than 50 kg or 110 lb), the recommended oral dose of AVILAM is 2 mg/kg twice daily administered in combination with Zidovudine. No data are available to support a dosage recommendation for adolescents with low body weight (less than 50 kg).

Pediatric Patients
The recommended oral dose of AVILAM® for pediatric patients 3 months to up to 12 years of age is 4 mg/kg twice daily (up to a maximum of 150 mg twice a day) administered in combination with Zidovudine.

Dose Adjustment
It is recommended that doses of AVILAM® be adjusted in accordance with renal function in patients older than age 16 years (see following table).

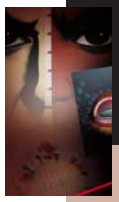


Table : Adjustment of Dosage of AVILAM® in Accordance With Creatinine Clearance

Creatinine Clearance (mL/min)	Recommended Dosage of **AVIFIX**
≥ 50	150 mg twice daily
30-49	150 mg once daily
15-29	150 mg first dose, then 100 mg once daily
5-14	150 mg first dose, then 50 mg once daily
<5	50 mg first dose, then 25 mg once daily

Insufficient data are available to recommend a dosage of AVILAM® in patients undergoing dialysis.

CONTRAINDICATIONS

AVILAM® tablets is contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of the product.

WARNINGS AND PRECAUTIONS

WARNINGS

In pediatric patients with a history of pancreatitis or other significant risk factors for the development of pancreatitis, the combination of AVILAM® and Zidovudine should be used with extreme caution and only if there is no satisfactory alternative therapy. Treatment with AVILAM® should be stopped immediately if there are clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis .

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination, including Lamivudine. A majority of these cases have been in women. Caution should be exercised when administering AVILAM® to any patient, and particularly to those with known risk factors for liver disease. Treatment with AVILAM® should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

PRECAUTIONS

Patients With Impaired Renal Function

Reduction of the dosage of AVILAM® is recommended for patients with impaired renal function.

Patients With HIV and Hepatitis B Virus Co-infection

In clinical trials and postmarketing experience, some patients with HIV infection who have chronic liver disease due to hepatitis B virus infection experienced clinical or laboratory evidence of recurrent hepatitis upon discontinuation of Lamivudine. Consequences may be more severe in patients with decompensated liver disease.

Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Because animal reproductive toxicity studies are not always predictive of human response. Lamivudine should be used during pregnancy only if the potential benefits outweigh the risks.

Nursing Mothers

The US Public Health Service Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast feed their infants to avoid risking postnatal transmission of HIV infection.

SIDE EFFECTS

Adults

Selected clinical adverse events with a ≥5% frequency during therapy with

Lamivudine 150 mg b.i.d. plus Zidovudine 200 mg t.i.d. compared with Zidovudine are listed in the following table.

Selected Clinical Adverse Events (≥ 5% Frequency) in Four Controlled Clinical Trials

Adverse Event	AVIFIX 150 mg b.i.d. plus RETROVIR (n = 251)	RETROVIR (n = 230)
Body as a whole		
Headache	35 %	27 %
Malaise & fatigue	27 %	23 %
Fever or chills	10 %	12 %
Digestive		
Nausea	33 %	29 %
Diarrhea	18 %	22 %
Nausea & vomiting	13 %	12 %
Anorexia and/or decreased appetite	10 %	7 %
Abdominal pain	9 %	11 %
Abdominal cramps	6 %	3 %
Dyspepsia	5 %	5 %
Nervous system		
Neuropathy	12 %	10 %
Insomnia & other sleep disorders	11 %	7 %
Dizziness	10 %	4 %
Depressive disorders	9 %	4 %
Respiratory		
Nasal signs & symptoms	20 %	11 %
Cough	18 %	13 %
Skin		
Skin rashes	9 %	6 %
Musculoskeletal		
Musculoskeletal pain	12 %	10 %
Myalgia	8 %	6 %
Arthralgia	5 %	5 %

Observed During Clinical Practice

The events identified during use of in clinical practice include alopecia, anaphylaxis, hyperglycemia, lactic acidosis and hepatic steatosis, peripheral neuropathy, pruritus, rash, urticaria, and weakness.

OVERDOSE

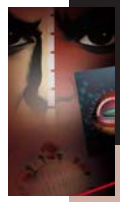
There is no known antidote for Lamivudine. It is not known whether Lamivudine can be removed by peritoneal dialysis or hemodialysis.

PHARMACEUTICAL PRECAUTIONS

Store in a cool dry place. Protect from light.
Keep out of reach of children.

COMMERCIAL PACKS

Each box contains 1 x 10's tablets in Blister strip. Each tablet contains Lamivudine INN 150 mg



Avifix®

(Nelfinavir)
Tablet

DESCRIPTION

Nelfinavir (as mesylate) a human immunodeficiency virus (HIV) protease inhibitor available as film coated tablet in 250 mg strength (as Nelfinavir free base).

INDICATIONS

AVIFIX® is indicated for the treatment of HIV infection when antiretroviral therapy is warranted.

DOSAGE AND ADMINISTRATION

Adults: The recommended dose is 1250 mg (five 250 mg tablets) twice daily or 750 mg (three 250 mg tablets) three times daily. AVIFIX® should be taken with a meal. Antiviral activity is enhanced when AVIFIX® is administered in combination with nucleoside analogues. Therefore, it is recommended that AVIFIX® be used in combination with nucleoside analogues.

Pediatric Patients (2-13 years): The recommended oral dose of AVIFIX® for pediatric patients 2 to 13 years of age is 20-30 mg/kg per dose, three times daily with a meal. The recommended pediatric dose of AVIFIX® to be administered three times daily is described in following table:

Pediatric Dose to be Administered Three Times Daily

Body Weight		Number of Level 1 gm Scoops	Number of Level Teaspoons	Number of Tablets
Kg.	Lbs.			
7 to < 8.5	15.5 to < 18.5	4	1	-
8.5 to < 10.5	18.5 to < 23	5	1 1/4	-
10.5 to < 12	23 to < 26.5	6	1 1/2	-
12 to < 14	26.5 to < 31	7	1 3/4	-
14 to < 16	31 to < 35	8	2	-
16 to < 18	35 to < 39.5	9	2 1/4	-
18 to < 23	39.5 to < 50.5	10	2 1/2	2
greater than or equal to 23	greater than or equal to 50.5	15	3 3/4	3

CONTRAINDICATIONS

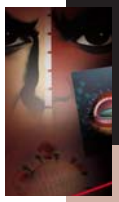
AVIFIX® is contraindicated in patients with clinically significant hypersensitivity to any of its components.

Co-administration of AVIFIX® is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening adverse events.

WARNINGS AND PRECAUTIONS

Warning: AVIFIX® should not be administered concurrently with terfenadine, astemizole, cisapride, triazolam, midazolam, ergot derivatives, amiodarone or quinidine because AVIFIX® may effect the hepatic metabolism of these drugs and create potential for serious and/or life-threatening adverse events.

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus and hyperglycemia have been reported during post-marketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases.



Precautions:

General: Nelfinavir is principally metabolized by the liver. Therefore, caution should be exercised when administering this drug to patients with hepatic impairment.

Hemophilia

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia type A and B treated with protease inhibitors. In some patients, additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship has not been established.

Pregnancy, Fertility and Reproduction
Pregnancy Category B
There are no adequate and well-controlled studies in pregnant women.

Nursing Mothers

The US Public Health Service Centers for Disease Control and Prevention advises HIV-infected women not to breast-feed to avoid postnatal transmission of HIV to a child who may not yet been infected. Studies in lactating rats have demonstrated that Nelfinavir is excreted in milk. It is not known whether Nelfinavir is excreted in human milk.

Pediatric Use

A similar adverse event profile was seen during the pediatric clinical trial as in adult patients. The evaluation of the antiviral activity of Nelfinavir in pediatric patients is ongoing.

The safety, effectiveness and pharmacokinetics of Nelfinavir have not been evaluated in pediatric patients below the age of 2 years

SIDE EFFECTS

The safety of Nelfinavir was studied in over 1500 patients who received drug either alone or in combination with nucleoside analogues. The majority of adverse events were of mild intensity. The most frequently reported adverse event among patients receiving Nelfinavir was diarrhea, which was generally of mild to moderate intensity.

Adverse events occurring in less than 2% of patients receiving Nelfinavir in all phase II/III clinical trials and considered at least possibly related or of unknown relationship to treatment and of at least moderate severity are listed below.

Body as a whole: abdominal pain, accidental injury, allergic reaction, asthenia, back pain, fever, headache, malaise, pain and redistribution/accumulation of body fat .

Digestive System: anorexia, dyspepsia, epigastric pain, gastrointestinal bleeding, hepatitis, mouth ulceration, pancreatitis and vomiting.

Hemic/Lymphatic System: anemia, leukopenia and thrombocytopenia.

Metabolic/Nutritional System: increase in alkaline phosphate, amylase, creating phosphokinase, lactic dehydrogenase, SGOT, SGPT and gamma glutamyl transpeptidase, hyperlipemia,

hyperuricemia, hyperglycemia, hypoglycemia, dehydration and liver function tests abnormal.

Musculoskeletal System: arthralgia, arthritis, cramps, myalgia, myasthenia and myopathy.

Nervous System: anxiety, depression, dizziness, emotional lability, hyperkinesia, insomnia, migraine, paresthesia, seizures, sleep disorder, somnolence and suicide ideation.

Respiratory System: dyspnea, pharyngitis, rhinitis and sinusitis.

Skin/Appendages: dermatitis, folliculitis, fungal dermatitis, maculopapular rash, pruritus, sweating, and urticaria .

Special Senses: acute iritis and eye disorder.
Urogenital System: kidney calculus, sexual dysfunction and urine abnormality.

OVERDOSE

Human experience of acute overdose with AVIFIX® is limited. There is no specific antidote for overdose with AVIFIX®. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid removal of unabsorbed drug. Since Nelfinavir is highly protein bound, dialysis is unlikely to significantly remove drug from blood.

DRUG INTERACTIONS

Nelfinavir is an inhibitor of CYP3A (cytochrome P450 3A). Co-administration of AVIFIX® and drugs primarily metabolized by CYP3A (e.g., dihydropyridine calcium channel blockers) may result in increased plasma concentrations of the other drug that could increase or prolong both its therapeutic and adverse effects. Co-administration of drugs that inhibit CYP3A may increase Nelfinavir plasma concentration.

Based on known metabolic profiles, clinically significant drug interactions are not expected between AVIFIX® and dapsone, trimethoprim/sulfamethoxazole, clarithromycin, erythromycin, itraconazole or fluconazole.

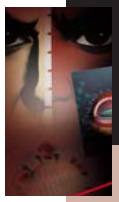
Drugs That Should Not Be Co-administered With AVIFIX®	
Drug Class	**Drugs Within Class Not To Be Co-administered With AVIFIX®**
Antiarrhythmics	Amiodarone, Quinidine
Antihistamines	Astemizole, Terfenadine
Antimigraine	Ergot derivatives
Antimycobacterial agents	Rifampin
Benzodiazepines	Midazolam, Triazolam
GI motility agents	Cisapride

Drugs Which Require a Dose Reduction When Co-administered With AVIFIX®	
Drug Class	**Drugs Within Class Which Require Dose Reduction**
Antimycobacterial agents	Rifabutin

Other Potentially Clinically Significant Drug Interactions With AVIFIX® *	
Anticonvulsants: carbamazepine	May decrease Nelfinavir plasma concentrations**
Anti-HIV protease inhibitors: indinavir	May increase Nelfinavir plasma concentrations
Oral contraceptives: ethinyl estradiol	Plasma concentrations may be decreased by AVIFIX®

* This table is not all inclusive

** AVIFIX® may not be effective due to decreased nelfinavir plasma concentrations in patients taking these agents concomitantly.



Anti-HIV Protease Inhibitors

Indinavir: Co-administration of indinavir with AVIFIX® resulted in an 83% increase in Nelfinavir plasma AUC and a 51% increase in indinavir plasma A.C. Currently, there are no safety and efficacy data available from the use of this combination.

Ritonavir: Co-administration of ritonavir with AVIFIX® resulted in a 152% increase in Nelfinavir plasma AUC and very little change in ritonavir plasma A.C. Currently, there are no safety and efficacy data available from the use of this combination.

Saquinavir: Co-administration of saquinavir (using an experimental soft-gelatin capsule formulation of saquinavir 1200mg) with AVIFIX® resulted in an 18% increase in Nelfinavir plasma AUC and a 4-fold increase in saquinavir plasma A.C. If used in combination with saquinavir hard gelatin capsules at the recommended dose of 600 mg tid, no dose adjustments are needed. Currently, there are no safety and efficacy data available from the use of this combination.

Antifungal Agents

Anti-HIV Reverse Transcriptase Inhibitors

Didanosine: It is recommended that didanosine be administered on an empty stomach; therefore, Nelfinavir should be administered (with food) one hour after or more than two hours before didanosine.

Zidovudine: Co-administration of Zidovudine and Lamivudine with AVIFIX® resulted in a 35% decrease in Zidovudine plasma A.C. A dose adjustment is not needed when Zidovudine is administered with AVIFIX®.

Little or no change in the pharmacokinetics of either drug was observed when AVIFIX® was co-administered with Lamivudine or stavudine.

PHARMACEUTICAL PRECAUTION

Store below 30°C in a dry place. Keep out of reach of children.

COMMERCIAL PACKS

Each box contains 1 x 10's tablets in blister strip.
Each tablet contains Nelfinavir (as mesylate) 250 mg.

Diavix®

(Lamivudine and Zidovudine)
Tablet

DESCRIPTION

DIAVIX® Tablets are combination tablets containing Lamivudine INN 150 mg and Zidovudine USP 300 mg.

INDICATIONS

DIAVIX® is indicated for the treatment of HIV infection.

DOSAGE AND ADMINISTRATION

The recommended oral dose of DIAVIX® for adults and adolescents

(at least 12 years of age) is one tablet (containing 150 mg of Lamivudine and 300 mg of Zidovudine) twice daily.

Dose Adjustment

Because it is a fixed-dose combination, DIAVIX® should not be prescribed for patients requiring dosage adjustment such as those with reduced renal function (creatinine clearance ≤50 mL/min), those with low body weight(<50 kg or 110 lb), or those experiencing dose-limiting adverse events.

Because DIAVIX® is a fixed-dose combination that cannot be adjusted for this patient population, DIAVIX® is not recommended for patients with impaired hepatic function.

CONTRAINDICATIONS

DIAVIX® Tablets are contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of the product.

General

Reduction of doses of Lamivudine is recommended for patients with low body weight (less than 50 kg or 110 lb); therefore, patients with low body weight should not receive DIAVIX®.

PRECAUTIONS

Patients with HIV and Hepatitis B Virus Co-infection

Safety and efficacy of Lamivudine have not been established for treatment of chronic hepatitis B in patients dually infected with HIV and HBV. In non-HIV-infected patients treated with Lamivudine for chronic hepatitis B, emergence of Lamivudine-resistant HBV has been detected and has been associated with diminished treatment response. Emergence of hepatitis B virus variants associated with resistance to Lamivudine has also been reported in HIV-infected patients who have received Lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus. Post-treatment exacerbations of hepatitis have also been reported.

WARNING

Zidovudine, one of the two active ingredients in DIAVIX®, has been associated with hematologic toxicity including neutropenia and severe anemia, particularly in patients with advanced HIV disease.

Prolonged use of zidovudine has been associated with symptomatic myopathy.

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination, including Zidovudine and Lamivudine.

Post-treatment Exacerbations of Hepatitis: In clinical trials in non-HIV-infected patients treated with Lamivudine for chronic hepatitis B, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of Lamivudine. These exacerbations have been detected primarily by serum ALT elevations in addition to re-emergence of hepatitis B viral DNA (HBV DNA). Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from post-marketing experience after changes from Lamivudine-containing HIV treatment regimens to non-Lamivudine-containing regimens in patients infected with both HIV and HBV. The causal relationship to discontinuation of Lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. There is insufficient evidence to determine whether re-initiation of Lamivudine alters the course of posttreatment exacerbations of hepatitis.

DIAVIX® is a fixed-dose combination of Lamivudine and Zidovudine. Ordinarily, DIAVIX® should not be administered concomitantly with either Lamivudine or Zidovudine.

Bone Marrow Suppression

DIAVIX® should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count <1,000 cells/mm^3 or hemoglobin <9.5 g/dL

Frequent blood counts are strongly recommended in patients with advanced HIV disease who are treated with DIAVIX®. For HIV-infected individuals and patients with asymptomatic or early HIV disease, periodic blood counts are recommended.

Lactic Acidosis/Severe Hepatomegaly with Steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported with the use of antiretroviral nucleoside analogues alone or in combination, including Zidovudine and Lamivudine. A majority of these cases have been in women. Caution should be exercised when administering DIAVIX® to any patient, and particularly to those with known risk factors for liver disease. Treatment with DIAVIX® should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

SIDE EFFECTS

Body as a whole: Headache, Malaise & fatigue, Fever or chills.

Digestive: Nausea, Diarrhea, Nausea & vomiting, Anorexia and/or decreased appetite, Abdominal pain, Abdominal cramps, Dyspepsia.

Nervous system: Neuropathy, Insomnia & other sleep disorders, Dizziness, Depressive disorders.

Respiratory: Nasal signs & symptoms, Cough.

Skin: Skin rashes.

Musculoskeletal: Musculoskeletal pain, Myalgia, Arthralgia.

The following events have been chosen for inclusion due to their seriousness, frequency of reporting, causal connection to Lamivudine and/or Zidovudine or a combination of these factors.

Cardiovascular: Cardiomyopathy.

Endocrine and Metabolic: Gynecomastia, hyperglycemia.

Gastrointestinal: Oral mucosal pigmentation, stomatitis.

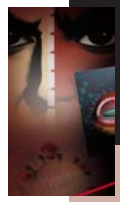
General: Vasculitis, weakness.

Hemic and Lymphatic: Aplastic anemia, anemia, lymphadenopathy, pure red cell aplasia, splenomegaly.

Hepatic and Pancreatic: Lactic acidosis and hepatic steatosis, steatosis, pancreatitis, post-treatment exacerbation of hepatitis B.

Hypersensitivity: Sensitization reactions (including anaphylaxis), urticaria.

Musculoskeletal: Muscle weakness, CPK elevation, rhabdomyolysis.



Nervous: Paresthesia, peripheral neuropathy, seizures.

Respiratory: Abnormal breath sounds/wheezing.

Skin: Alopecia, erythema multiforme, Stevens-Johnson syndrome.

OVERDOSE
There is no experience of overdosage with Lamivudine and Zidovudine combination. However, there are limited data available on the consequences of ingestion of acute overdoses of Lamivudine and Zidovudine in humans. No fatalities occurred, and all patients recovered. No special signs or symptoms have been identified following such overdosage.
If overdosage occurs the patients should be monitored for evidence of toxicity and standard supportive treatment applied as necessary. Since Lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdosage, although this has not been studied. Haemodialysis and peritoneal dialysis appear to have a limited effect on elimination of Zidovudine, but enhance the elimination of the glucuronide metabolite.

PHARMACEUTICAL PRECAUTIONS
Store in a cool dry place. Protect from light.
Keep out of reach of children.

COMMERCIAL PACKS
Each box contains 1 x 10's tablets in Blister strip.
Each tablet contains Lamivudine INN 150 mg and

Triovix®

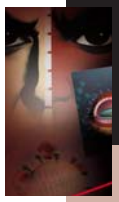
(Lamivudine, Zidovudine & Nevirapine)
Tablet

Description
Each tablet contains Lamivudine INN 150 mg, Zidovudine USP 300 mg & Nevirapine INN 200 mg. A fixed dose combination of Lamivudine, Zidovudine and Nevirapine is recommended for Human Immunodeficiency Virus (HIV-1) infected patients who are able to tolerate standard doses of Lamivudine, Zidovudine and Nevirapine for at least 2 weeks prior to switching over to this fixed dose combination. Patients should have demonstrated adequate tolerability to Nevirapine.

Indications and Usage
A fixed dose combination of Lamivudine, Zidovudine and Nevirapine is recommended for Human Immunodeficiency Virus (HIV-1) infected patients who are able to tolerate maintenance therapy with Nevirapine 200 mg twice daily. All three drugs are to be administered twice daily and each tablet contains half of the daily dose for each component. Twice daily formulation in single tablet for three drugs is convenient for patients to take, ensuring higher rate of compliance.

Dosage and Administration
For treatment of HIV Infection.

Adult Dosage: One tablet twice daily.



This fixed dose combination is not recommended for patients who have not been on initial lower dose of Nevirapine 200 mg once daily for 2 weeks and or have not tolerated this dose. After successful therapy with low dose Nevirapine for two weeks, patients can be switched over to 200 mg b.i.d. dose provided they have not demonstrated any hypersensitivity reaction (rash, abnormal liver function tests) during their initial exposure to Nevirapine. Monitoring of patients for their liver function tests etc. is desirable prior to initiating therapy with Nevirapine and monitoring at frequent intervals once therapy with fixed dose combination is continued.

Dosage Adjustment:
Lamivudine: For patients with low body weight (<50 kg) where dosage adjustment may be required, it preferable not to use this fixed dose combination.

Zidovudine: Because it is a fixed-dose combination, this should not be prescribed for patients requiring dosage adjustment such as those with reduced renal function (creatinine clearance 50 ml/min) or those experiencing dose-limiting adverse events.

Nevirapine: For patients who experience severe rash or rash with constitutional complaints during the initial low dose Nevirapine phase of 14 days with once daily dose of 200 mg, neither, dose should be increased to twice daily nor they should receive triple fixed dose combination until the rash is resolved. Similarly for patients with abnormal liver function tests, Nevirapine therapy should be stopped till liver function return to normal and careful restart is advisable after extended observation. In event of recurrence, Nevirapine therapy can not be restarted in such cases. For patients where Nevirapine therapy has to be restarted after an interruption, someone daily dose of Nevirapine 200 mg for 14 days should be followed with twice daily dose in absence of any hypersensitivity reaction. Studies have not been documented to suggest dosage of Nevirapine in patients with hepatic dysfunction, renal insufficiency or undergoing dialysis.

Contraindications
History of hypersensitivity to Lamivudine, Zidovudine, Nevirapine and to any of excipients available in formulation. Not to be used as initial therapy because initial therapy requires 200 mg once daily of Nevirapine whereas fixed dose combination allows for 200mg twice daily of Nevirapine.

Warnings and Precautions
For these conditions, assess risk to patient and take action as needed: Chronic Hepatitis B, Hepatomegaly with steatosis, lactic acidosis, liver function impairment, severe renal function impairment, peripheral neuropathy.

Side Effects
Lamivudine: Pancreatitis, Paresthesias, Peripheral neuropathy, cough, dizziness, fatigue, gastrointestinal problems, headache,

insomnia, anemia, neutropenia, drug induced skin, rash, hair loss.

Zidovudine: Headache (which may be severe, has been reported in up to 63% of patients receiving Zidovudine and asthenia has been reported in 9-69%) Malaise & fatigue Fever or Chills Nausea (61% cases) Diaphoresis, dyspnea, fever, rash and taste perversion have been reported. Skin rashes, Myalgia has been reported in patients receiving Zidovudine. Myopathy and myositis with pathologic changes similar to that produced by HIV infection, have been associated with prolonged use of Zidovudine. The major adverse effect is bone marrow toxicity resulting in severe anemia and/or neutropenia. Patients with low serum float or vitamin B12 concentrations may be at increased risk for developing bone marrow toxicity during zidovudine therapy. There also are limited data suggesting that bone marrow of patients with fulminant acquired immunodeficiency syndrome (AIDS) may be more sensitive to Zidovudine-induced toxicity than that of patients with less advanced disease (eg, AIDS-related complex [ARC]), Anemia and granulocytopenia usually resolve when zidovudine is discontinued or when dosage is decreased Lactic acidosis (in the absence of hypoxemia) and severe hepatomegaly with steatosis, including some fatalities, have been reported in patients receiving Zidovudine.

Nevirapine: Incidence more frequent, skin rash, diarrhea, gastrointestinal problems, headache, nausea, stomach pain, incidence less frequent: aphthous stomatitis, fever, hepatitis, stevens – Johnson syndrome.

Pharmaceutical Precautions
Store in a cool dry place. Protect from light.
Keep out of reach of children.

Commercial Packs
Each box contains 1 x 10's tablets in Blister strip. Each tablet contains Lamivudine INN 150 mg, Zidovudine USP 300 mg & Nevirapine INN 200 mg.