

# HIV 102: Care & Treatment

Written by: Jose Castro, MD  
University of Miami, Miller  
School of Medicine, Miami, FL

Editorial Contributions by:  
Jules Levin

580 BROADWAY, SUITE 1010, NEW YORK, NY, 10012 1-888-26-NATAP (212) 219-0106 fax (212) 219-8473 info@natap.org http://www.natap.org

## Origins of HIV

The origin of HIV has been controversial and of interest in the public and the scientific community since this disease was identified at the beginning of the 80's. What is known is that HIV is a virus that belongs to a family of virus called lentivirus. This type of virus invades the immune system, where defenses to outside diseases are crucial. The virus breaks down the immune system by killing CD4 cells (also called T-cells), which are important for the proper functioning of the immune system, and leads to diseases long after HIV enters the human body. The Lentivirus belongs to a larger group, the retrovirus. These viruses are found in different animals, such as cats, sheep, horses and cattle. However, the most interested lentivirus in terms of investigation about the origins of HIV is the Simian Immunodeficiency Virus (SIV) that affects the monkeys.

Currently it is clear that HIV is a descendant from the SIV because certain strains of SIV are similar to HIV. In particular, in 1999 a group of Scientifics discovered that certain chimpanzees had a type of SIV, in this case called SIV-cpz that is almost identical to HIV.

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How this virus jumped from one species to another, from chimps to humans, is not clear, yet. However, it is well known that certain viruses can pass from one species to another. (a common, current example is the influenza virus). When this jump occurred is also unclear. But it is clear that there were already cases of HIV/AIDS several decades before the epidemic came to light. For example there is a proven case of HIV infection in a man who lived in what currently is the Democratic Republic of Congo in 1959. There is some support for a hypothesis that estimates that the first case of HIV happened in Western Africa around 1930.

## Historical Perspective on Treatment

The first years of the HIV epidemic were characterized, by among other things, the high rates of death for patients diagnosed with AIDS. For several years the only option was to maintain and prolong life by treatment to prevent opportunistic infections. In 1987 there was great enthusiasm as new treatments directed against HIV were thought to be possible for the first time. It was during these early years, between 1987 and 1990, that the antiretroviral (HIV drugs) era started. The therapy at first was with 1 drug, which is called monotherapy. The first drug for HIV therapy was AZT monotherapy. In the mid-1990s thanks to large-scale studies, it was showed that dual therapy with two nucleosides was superior to sequential monotherapy. The 2-drug combination of AZT+3TC was popular. It was also around that time that a new class of antiretrovirals, called protease inhibitors (PI's) was being evaluated in several research studies. Between December of 1995 and March of 1996, three PI's were approved (Crixivan, Invirase, Ritonavir) . Shortly after, it was clear that the combined use of three drugs was necessary to achieve the best results. Three drugs were needed to fully suppress HIV replication. The HAART era was born. HAART stands for highly active antiretroviral therapy. HAART is the name used to describe a 3-drug HIV therapy regimen. By the middle of 1996, the first drug of another new class (NNRTI) was approved, in this case nevirapine. (NNRTI stands for non-nucleoside reverse transcriptase inhibitors)

In a few years, it was clear that the fear of HIV and the view that it was an inescapable death sentence was being replaced by a new era where these new medicines (HAART) transformed HIV into a chronic disease with new challenges: long term side effects of the medicines and the presence of resistance to the antiretroviral drugs.

Subsequently, newer medicines have been developed not only with potency in mind but also with fewer side effects and improved convenience in taking them. When AZT was first discovered and used for HIV treatment it was taken by IV infusion every 6 hours. At the beginning of the HAART era in 1995 protease inhibitors had to be taken every 8 hours or 3 times a day. This has been vastly improved, as potent HIV drugs can be taken once a day or every 12 hours. And these new drugs are safer, more tolerable, and have less side effects.

Researchers are now trying to develop *The Future HIV Therapy*, and as we will discuss later, the challenge is to develop drugs with minimal side effects, convenient administration and drugs that attack HIV in different ways, which is often referred to as a 'novel mechanism of action'. And there are many researchers devoted to discovering and developing new drugs and new ways to attack HIV with novel therapies.

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Please consult your physician before making any treatment decisions.

## How is HIV transmitted?

**From the beginning of the Epidemic it has been clear that HIV is transmitted mostly in these ways:**

**Sexual transmission:** Sexual intercourse without protection is vaginal, anal or oral contact without the use of a condom or another barrier that prevents contact with the other persons' bodily fluids (the fluids that can transmit HIV, such as semen). It is important to remember that the transmission of HIV is facilitated by the presence of cuts and sores (including the microscopic ones) in the vagina, penis, anus, and mouth. So, any condition that increases the risks of cuts or sores in these zones (such as sexual transmitted diseases including syphilis and herpes) increases the risks of transmission of HIV.

**Vertical transmission** (from mother to fetus) and perinatal (around the birth).

**Blood:** includes transfusions of blood and other blood products and the use of materials contaminated with these products.

**Bodily fluids or secretions** from an HIV-infected person such as breast milk and semen may lead to HIV being transmitted.

**Injection drug use:** sharing needles and other related paraphernalia used to inject drugs including the water, cooker, and cotton in the cooker.

Outside of the USA the main form of transmission of this virus is through the sexual route (and is then, one of the newest sexually transmitted diseases), but in certain areas of the world, transmission through contaminated needles remains as one of the most important.

## Medical Care for HIV

**Medical care of patients with HIV has the following components:**

- ◆ History and Physical Examination
- ◆ Laboratory tests
- ◆ Preventive care and mental health
- ◆ Follow up

(patients should visit their care providers on a regular basis to receive proper follow-up care and evaluations including proper lab testing to monitor for maintenance of health and to check for any emerging problems or concerns).

The medical evaluation starts with the initial **History** of the patient and a **Physical Examination** of the patient. Here, all the general medical information is collected, as well as specific information related to HIV disease. This includes a detailed review of the presence of symptoms from each of all the "human systems". In this part, your provider will ask you in detail about the presence of symptoms in all the "systems", for example: cardiovascular system (heart), respiratory system (lungs), gastrointestinal (digestive), genitourinary system (relating to or affecting the genital and urinary organs, such as burning or pain with urination, itching, unusual discharge, swelling, rash). The objective is to identify symptoms that could have been overlooked by the patient. As well, a psycho-social evaluation should be conducted to understand the behavior patterns and lifestyle of the patient. **Understanding these should help the doctor or care provider advise the patient regarding many things including how to prevent transmission of HIV and in selecting the best HIV treatment.**

The clinician (doctor or care provider) should use a vocabulary that

can be easily understood by the patients. Patients should provide the best information (if possible copies) of prior medical evaluations and care. It is also important to disclose information about the use of non-prescription drugs (including herbs and vitamins) and types of sexual practices. In order to discuss these issues a degree of trust is needed between the patient and the doctor that can only be achieved with time.

It is important to discuss new symptoms in each visit. The specific components of the History and Physical in patients with HIV infection are listed in **Table # 1**.

The patient also should expect a complete physical exam in the first visit (and one each year) with emphasis in the areas more frequently affected by HIV and its complications. The patient's weight should be registered in each visit.

**Table 1. The History and Physical for Patients**

History of present illness
Past immunizations
Occupational history and hobbies
Pets/animal exposures
Allergies
Travel history/place of birth
Mental health
Past hospitalizations and past and current illnesses
Full review of systems: the cardiovascular system (heart), respiratory system (lungs), gastrointestinal (digestive), genitourinary system (relating to or affecting the genital and urinary organs, such as burning or pain with urination, itching, unusual discharge, swelling, rash).

**Specific evaluations:**

**Ophthalmologic (the eyes) evaluation:** Patients with CD4 counts < 50 cells/mm<sup>3</sup> should be seen by the ophthalmologist initially and every 6 months. Patients with persistent visual symptoms should also have this evaluation, regardless of the CD4.

**Oral evaluation (dental):** All patients should have one evaluation and cleaning at least once a year.

**Laboratory evaluations**

During the evaluation of patients with HIV infection there are some tests that are ordered for the management of the disease and others as part of screening as suggested in **table # 2**. In general, the tests includes:

**Immunologic evaluations:** The CD4 test should include the absolute number and the percentage of CD4 cells. The CD4 cells are also called T-cells and are a reflection of the health of the immune system. A good number of CD4 or T-cells means the immune system is capable of fighting off foreign pathogens, viruses, and bacteria, and maintaining one's health. A normal CD4 count ranges from approximately 600 to 1200. When a patient's number of CD4s get too low HIV therapy should be started. The purpose of HIV therapy is to increase and maintain one's CD4 count at a healthy level.

**Virologic evaluations:** The first test to measure the HIV viral load (amount of virus in the blood) should be the standard test not the ultrasensitive. Later, during treatment, the viral load should be measured prior to vaccinations and not during intercurrent illness, because when a person has a flu or illness the viral load might be artificially elevated.

**Screening for tuberculosis:** all patients should be ruled out for tuberculosis.

**Screening for STD's:** sexually transmitted diseases including gonorrhea, syphilis, etc.

**Papanicolaou test.** This is a test that is done in women and its purpose is to screen for cervical cancer (a common gynecological cancer). This test should be done at least every year in all HIV infected women. This test consists of the analysis of cells obtained from the vagina.

**Blood pressure, fasting blood sugar and fasting lipid profile:** it is important to evaluate a patient's risk for **heart disease and diabetes**. Certain factors increase risk such as cigarette smoking, poor diet, lack of exercise, genetic or family predisposition, and of course the patient's lab results can predict a risk for heart disease and diabetes. Lab tests should be performed before going on HIV therapy to see the levels of important lipids by doing what's called

a 'lipid panel': cholesterol (bad cholesterol is LDL-C & good cholesterol is HDL-C), triglycerides, and glucose (sugar). Lipids should be regularly monitored 3-6 months after starting HAART and every year whether on HAART or not. A patient's 'lipid profile' can be considered when selecting a HAART regimen. Lipid-lowering drugs can be used if lipids are elevated and HIV therapy can be changed. Very often if a parent had diabetes or heart disease a person has an increased risk for developing heart disease or diabetes.

African-Americans have a higher risk for heart disease. Latinos are at greater risk for diabetes than whites. Again, diet and family history play a big role in developing heart disease and diabetes. Having diabetes significantly increases the risk for heart disease. **Hypertension** is high blood pressure and it is associated with heart disease and diabetes. African-Americans are at a higher risk for hypertension. High blood pressure makes your heart work harder. You can feel healthy and not know you have it, but high blood pressure can cause: heart attack, kidney problems, eye problems, and death.

**Table 2. Laboratory Tests for Patients**

**Immunologic assessment (baseline and every 3 to 4 months)**

CD4 lymphocyte count and percentage, to produce reliable results, the same testing laboratory should be used.

**Virologic assessment**

- Quantitative HIV RNA testing for viral load assessment (baseline and every 3 to 4 months); the same testing method should be used
- Genotypic resistance should be performed 1) prior to initiating treatment in ARV therapy-naïve patients to determine whether they were infected with drug-resistant virus, and 2) in patients experiencing virologic failure or incomplete viral suppression while receiving ARV therapy.

**Tuberculosis evaluation (baseline and annually)**

- PPD skin test for patients with no previous history of TB or no previous positive PPD
- Chest x-ray for patients known to have a history of TB or known to be PPD positive

**Screening for sexually transmitted diseases\***

- RPR or VDRL for syphilis with verification of positive test by confirmatory treponemal tests such as FTA-abs or MHA-TP (baseline and annually)
- For females
  - Culture or DNA amplification test for gonorrhea (baseline and at least annually)
  - Immunofluorescence, or DNA amplification test for Chlamydia (baseline and at least annually)

**Pap smears for HIV-infected women**

- Obtain at baseline and then 6 months after baseline. Repeat annually, as long as results are normal.
- Abnormal Pap smears should be repeated every 3 to 6 months until there have been two successive normal Pap smears†

**Complete blood count, including differential (baseline and every 3 to 4 months)**

**Serum creatinine, BUN, total protein, albumin (baseline and every 3 to 4 months)**

**Fasting blood glucose, fasting lipid profile (for patients receiving HAART: before initiating HAART, 3-6 months after initiation, and annually thereafter; for patients not receiving HAART: at baseline and annually)**

**Serum liver enzymes (baseline and every 3 to 4 months for patients receiving HAART)**

**Urinalysis (baseline and at least annually)**

**Additional baseline tests**

- Hepatitis A antibody screening for the following populations who have not been previously vaccinated: men who have sex with men, injection drug users, those from endemic area, and those with liver disease
- Hepatitis B serology
- Hepatitis C serology §
- Toxoplasma gondii antibody screening
- Varicella antibody screening for adults without history of chickenpox

\*Patients who continue to engage in unsafe sexual practices are at increased risk for other STDs. Patients with any other STDs, whether ulcerative or not, are at higher risk for HIV transmission. Recent increases in STDs among men who have sex with men (MSM) warrant screening of asymptomatic sexually active patients.

§ A qualitative HCV RNA PCR should be obtained when no hepatitis antibodies are detectable in a patient with elevated serum liver enzymes and risk factors for HCV.

† Abnormal pap smears should be followed with HPV typing and/or colposcopy.

## Preventive & Mental Health

Patients with HIV infection should have all the other age-appropriate preventive screening tests that are done for all HIV-negative individuals. These measures include vaccinations (except vaccines containing live-virus) and age-sex specific tests (mammogram, colonoscopy, rectal exam, etc). Because of the numerous breakthroughs in new HIV drugs in the past 10 years, HIV can be a chronic manageable disease similar to diabetes. To achieve this goal it is important to receive good and regular care.

It is also important to routinely discuss with your care provider behaviors and activities that decrease or increase the risks of HIV transmission. It is important to remind patients that even with an “undetectable” (below limit of detection) viral load (in the blood), HIV can be transmitted because, among other reasons, there is no correlation between the “viral load” in the blood and in the genital secretions. In other words, an HIV-infected person could have undetectable or <50 copies/ml of HIV viral load (in the blood) but they could still have HIV in semen or vaginal secretions, which might facilitate transmission of HIV through sex. As well, there is always a risk, even if HIV viral load is <50 copies (undetectable) by sharing syringes for injection drug use.

In patients who are sexually active or that use substances (illicit drugs), it is important to review and emphasize frequently practices that can decrease the risk of HIV transmission.

The general topics that can be expanded for discussion between doctor and patient in more detail depend on the life circumstances and behaviors of a particular patient and include: sexual education, evaluation and counseling for drug use, evaluation and counseling for tobacco use, counseling for family planning, domestic violence and psychosocial evaluation.

The first principle of patient-related strategies is to **negotiate a treatment plan** that the patient understands and to which he or she commits. **A trusting and open relationship** between the doctor or care provider and the health team and the patient is important.

Before writing the first prescription, clinicians should assess the patient’s readiness to take medication, which might take two or three office visits and patience. If a patient is not ready to take therapy they might miss doses and this can have serious consequences. So it is important that the patient is ready to make the commitment required for successful therapy. Patient education should include explaining the goals of therapy, and include a review of expected outcomes that are based on baseline viral load and CD4+ T cell counts (for example, the **MACS study data from the DHHS Guidelines, see below**). It is also important for the doctor to discuss the reason for adherence, and a plan for how to be adherent. The MACS study data in the Guidelines provide statistics on the probability for progression to AIDS or death according to CD4 count, viral load, and socio-demographic factors including age and a history of injection drug use. This information can be helpful in deciding when to begin therapy. Perhaps, the most important factor for success in taking therapy for HIV (HAART) is adherence (discussed in Adherence section). Patients must understand that the first HAART regimen has the best chance for long-term success. Clinicians and health teams should develop a plan for the specific regimen, including how medication timing relates to meals and daily routines.

A patient should expect to receive easy to understand explanations from their doctor or care provider.

Education of family and friends and their recruitment as participants in the adherence plan can be useful. Community interventions, including adherence support groups or the addition of adherence concerns to other support group agendas that a patient may be attending, can aid adherence. Community-based case managers and peer educators can assist with adherence education and strategies for each patient.

## Treatment for HIV & Antiretrovirals

Currently, infection with HIV can be seen as a **chronic infection** that can allow almost a normal life, different from 20 years ago, when the infection for HIV was seen as a rapidly fatal infection. The difference between these two different outcomes of the same infection from the same virus has been the **availability of effective therapy**. Historically, this change happened in a relatively short time and is associated with an ever growing number of medications and classes of medications available. The development of antiretroviral therapy has been one of the most dramatic developments in the History of Medicine. Immediately below is a discussion of the many anti-HIV drugs available to put together a regimen for therapy. In the next section in this newsletter is a discussion of **when to begin therapy** and some guidance on **things to consider** when putting together a regimen. The **goal of therapy** is to sustain health and longevity of life. In choosing a regimen there are a number of considerations. Selecting the drugs to be in a regimen is an individual choice made in discussion with the clinician (doctor, care provider) and important considerations include **potency** of the regimen and **tolerability** and **convenience**. A key to long-term success with therapy is **adherence**. These topics are discussed in more depth in the next section of this newsletter. As well, when to begin therapy is an individual choice made in discussion with the doctor (clinician) and patient.

### Antiretroviral Medications

These are the HIV drugs used to treat HIV-infection. **The goal of therapy is to reduce HIV viral load (the amount of HIV in the blood) to levels undetectable by the HIV viral load tests and to maintain durable suppression**, which has been shown to result in restoration and preservation of immunologic function, improvement of quality of life, and reduction of HIV-related sickness and death.

The HIV viral load test (Standard) measures viral load above 400 copies/ml and the ultrasensitive test measures viral load above 50 copies/ml. It is better to have an “undetectable viral load” or a viral load below the limit of detection (< 400 or <50 copies/ml depending on the test). It is preferable to have a viral load below 50 copies/ml, as this is more effective in providing durable suppression of HIV and in sustaining health. When viral load is <50 copies/ml and a patient is completely adherent to taking medications, this will prevent the development of drug resistance to the medications in the regimen, which will result in durable suppression of HIV and better health and longevity of life.

The standard HIV therapy regimen is a 3-drug combination that consists of a protease inhibitor (PI) along with 2 nucleosides or a non-nucleoside reverse transcriptase inhibitor (NNRTI) plus 2 nucleosides. Nucleosides are often called nukes for short. Usually the protease inhibitor is accompanied by a low dose of ritonavir to boost the drug levels of the protease inhibitor, which makes the protease inhibitor much more effective for suppressing HIV viral load. HIV therapy, the 3-drug regimen, is often called HAART. This stands for **Highly Active Antiretroviral Therapy**.

## Currently Approved Drugs

There are four classes of antiretrovirals:

- ♦ Nucleoside and nucleotide analogs (NRTI's (for short called 'nukes')
- ♦ Non-nucleoside reverse transcriptase inhibitors (NNRTI's)
- ♦ Protease inhibitors (PI's)
- ♦ Fusion inhibitors

**Table 3. Current Antiretroviral Medications**

NRTI		PI	
Abacavir	ABC	Atazanavir	ATV
Didanosine	DDI	Fosamprenavir	FPV
Emtricitabine	FTC	Indinavir	IDV
Lamivudine	3TC	Lopinavir	LPV
Stavudine	D4T	Nelfinavir	NFV
Zidovudine	ZDV	Ritonavir	RTV
Tenofovir	TDF	Saquinavir	SQV
		Tipranavir	TPV
<b>NNRTI</b>		Prezista	PZT
Delavirdine	DLV		
Efavirenz	EFV	<b>Fusion Inhibitor</b>	
Nevirapine	NVP	Enfuviride	T-20

## "Nukes"

### Nucleoside and nucleotides analogues or "Nukes"

**How this class of drug works in stopping HIV.** Nucleosides and nucleotides are the names of some of the elements that form the genetic code (for all species). When one organism (HIV in this case) is replicating (reproducing itself) it will need to replicate its own genetic code inside a cell in the human body. Nukes (NRTI's) are medications that are similar enough to the natural nucleoside and nucleotides to fool the virus and halt the replication process. The NRTIs are temporarily incorporated into the replicating genetic material of HIV and when this happens HIV replication is interrupted. The specific way they do it is the inhibition or disruption of the activity of the viral enzyme (enzyme are proteins that have certain specific functions) called Reverse Transcriptase. This enzyme is central to viral replication and when its function is disrupted, replication stops.

In general, nukes as a class are easy to take and a once a day dose is enough for the majority of them. Tolerability is in general good. Some may from time to time initially produce gastrointestinal side-effects (nausea, vomiting, diarrhea), but this usually passes quickly. These medications may at times also cause long-term side effects (after continuous long use). Examples of these long term side effects include: bone marrow toxicity (blood cells production), lactic acidosis (accumulation of a type of body acid), neuropathy (nerve damage), pancreatitis (pancreas inflammation), renal damage and some types of lypodystrophy (body shape changes: fat loss, also called lipoatrophy, in the face and extremities, and fat gain in the belly). When lipo-dystrophy does occur it can be quite disturbing to a patient. But there are ways to limit the possibility of it happening or to treat it if it occurs. The best approach is to try to prevent it.

### Combination and Individual Nucleosides and Nucleotides

The three immediately below are combinations of two nucleos(t)ides in one pill. These are popular and convenient ways to take 2 nukes. Any of these three nuke combinations can be taken in combination with a protease inhibitor or NNRTI. Such a combination is the most popular therapy approach for a first-line therapy. An alternative or second approach is 3 nukes in one pill taken twice a day called Trizivir, which contains AZT+3TC+abacavir.

- ♦ Epzicom: is abacavir (600 mg) + 3TC (300 mg) in one pill taken once a day.
- ♦ Truvada: is tenofovir (300 mg) + FTC (200 mg) in one pill taken once a day.
- ♦ Combivir: is AZT (300 mg) + 3TC (150 mg) in one pill taken twice a day.

Another convenient first-line therapy option that just became available in June 2006 is Atripla, which is one pill taken once a day and it contains 3 medications in the one pill: Sustiva 600 mg (NNRTI) + tenofovir 300 mg + FTC 200 mg (2 nukes).

### Abacavir (Ziagen)

It is one of the most potent NRTI's. Initial studies showed that this drug could reduce viral load (a measure of the amount of virus in the blood, which reflects the viral replication activity) by 1.4 logs in 4 weeks (potent for a nuke). Other important characteristics are: good central nervous system penetration and its long intracellular half-life (gets into & stays in cells for a long time) that allows the drug to be dosed once daily (300 mgs once a day). Also it has a lower incidence of lipoatrophy compared to other members of the nuke class of HIV drugs. Abacavir is approved to be taken once daily and twice daily. (what is lipoatrophy: this term refers to a condition where fat loss may occur in various parts of the body including the face, rear end, legs, chest, and arms. This can result in appearing to be skinnier). Several studies found that patients with fat loss while on other nukes saw improvement after they switched to abacavir.

On the other hand, it is important to mention that this medicine can cause an allergic reaction called "Hypersensitivity Reaction Syndrome" that can occur in up to 4 to 6% of patients, almost exclusively in the first 6 weeks. If this syndrome occurs, the medicine has to be stopped immediately and should not be re-administered in the future as it can be fatal.

This medicine is available individually or co-formulated in one tablet with 3TC (Epzicom) or with AZT + 3TC (Trizivir).

### AZT (Zidovudine, Retrovir)

It was the first antiretroviral (drug) approved for the treatment of HIV in 1987. Its effectiveness and potency has been demonstrated in studies, as have all HIV drugs. Initially AZT was prescribed every 6 hours, but later studies showed that intracellular half-life allowed dosing every 12 hours. Currently it is prescribed 300 mgs every 12 hours alone, or as part of Combivir (with 3TC) or Trizivir (with Abacavir and 3TC.), in the same tablet. AZT can affect the production of the cells that form the blood (bone marrow toxicity), and anemia (fatigue) can occur in a small percentage of patients; and that the gastrointestinal side effects can be of moderate intensity (nausea and vomiting) in the beginning of therapy and it usually passes quickly.

### ddC (Zalcitabine, Hivid)

It was the third NRTI approved, in 1992. Its use has been very limited by: toxicity (peripheral neuropathy), cross resistance with other NRTI's and its administration three times a day. This drug will be taken off the market in December 2006.

### ddl (Didanosine, Videx)

ddl is a potent HIV drug. One of the main problems with this medication was related to its tolerability (size of the table, taste). In 2000, the new acid resistant formulation was approved for which tolerability is much better. The main side effects are related to its gastrointestinal side effects (pancreatitis up to 10%) and peripheral neuropathy. It is also important to know that these side effects can present more often or be more severe if ddl is co-administered with: d4T, hydroxyurea or tenofovir. Among its main advantages are the once a day administration (due to a long intracellular life) and its resistance profile: it is more difficult to develop resistance to ddl, and ddl is effective when resistance is developed to other nucleosides. Speak to your doctor about dosing, and how it should be taken.

### D4T (Stavudine, Zerit)

D4T is a potent nuke with a good resistance profile. In general, its initial tolerance is better than to AZT. It was one of the most prescribed NRTI's but in the last few years its use has decreased due to long term toxicity concerns (lipodystrophy and neuropathy) and the availability of other NRTI's with a more favorable resistance and side effects and toxicity profile. Lipoatrophy (fat loss) occurs more frequently with d4T than with most of the other NRTI's. The recommended dose is related to the weight and varies from 20, 30 or 40 mgs twice a day. A once a

day formulation was approved but was never commercially available.

### **FTC (Emtricitabine, Emtriva)**

Chemically FTC is very similar to another NRTI (3TC, Lamivudine). It is given once a day (one 200 mg tablet) and is well-tolerated. It has a long intracellular half-life and it is also important to remember that this medication has also activity against the virus of hepatitis B. This drug was recently approved (2003) and can be administered alone (in a 3-drug regimen) or with tenofovir (nucleotide) as Truvada (one pill that has two NRTI's, tenofovir+FTC, that is given once a day) or as Atripla, the recently approved medication which is one pill taken once a day that contains 3 medications: Sustiva 600 mg (NNRTI) + tenofovir 300 mg + FTC 200 mg. The most common side effect of FTC is a dark discoloration of the palms, which infrequently occurs.

### **3TC (Lamivudine, Epivir)**

It is a well-tolerated NRTI that has a long intracellular half-life. It is approved to be given 150 mgs twice a day or 300 mgs once a day. Similarly to FTC, it also has activity against hepatitis B virus. It can be administered alone, or co-formulated with AZT (combivir), with abacavir (Ziagen) or with AZT + abacavir (Trizivir). Similar to FTC, a single mutation is enough for HIV to acquire high-level resistance.

### **Tenofovir (Viread)**

It is one the newest NRTI's (it is actually a nucleotide) as it was approved a few years ago. It also is one of the most prescribed because of its potency, its easy to take and tolerate, its once a day administration (one 300 mg tablet a day), and safety. It has a low incidence of lipodystrophy (body changes). Its potency is similar to abacavir. Abacavir and tenofovir are the most potent nukes. As well, patients with lipodystrophy (fat loss) who switched while on other NRTIs to tenofovir saw improvement. The main side effects include potential renal (kidney) toxicity (especially if its dose it is not adjusted based on the patient's renal function, if a patient has severe kidney dysfunction), which very infrequently occurs, and the potential for a number of drug interactions (some were unexpected), such as the ones with ddI and atazanavir (a protease inhibitor). It can be administered alone or as Truvada (when co-formulated with FTC).

## **NNRTIs (Non-nucleoside inhibitors of the reverse transcriptase)**

The similarity of these drugs with the NRTI is where they both act: the enzyme reverse transcriptase (RT). The difference is that these medications are not structurally related to the natural NRTI's. These medications attach to the RT (reverse transcriptase enzyme) and this attachment produces a change in the shape of the enzyme that will inactivate it.

All three currently available NNRTI's (nevirapine, delavirdine and efavirenz) were approved by the FDA between 1996 and 1998. Despite that they were not as popular in earlier days as the protease inhibitors. Combinations of 2 NRTI's + 1 NNRTI are at least similar or some may think maybe superior to combinations of 2NRTI's + 1 PI in treatment-naïve patients. Use of a NNRTI-based HAART regimen has become more popular today. This is, in part, because their use is simple and in general well tolerated. The main problem of the NNRTI's as a class is their resistance profile characterized by extensive cross-resistance. (resistance to one almost always means resistance to all three currently approved); resistance to a NNRTI can develop with one drug resistance mutation, while several drug mutations are required to develop before resistance can occur to a protease inhibitor.

### **Nevirapine (Viramune)**

It was the first NNRTI approved, actually nevirapine +AZT + ddI was probably the oldest HAART combination. The effectiveness of regimens that contain nevirapine have been demonstrated in several studies, including superiority to some PI containing regimens. The most important side effect of nevirapine is that it can cause elevation of the liver enzymes, even to the range of hepatitis (inflammation of the liver). It has been shown that females with a higher CD4 count (above 250 cells/mm<sup>3</sup>) have the highest risk for hepatotoxicity at the initiation of therapy, as well as persons infected with the hepatitis C virus. The

risk of this elevation of the liver enzymes is greatest during the first 8 weeks, when extra-vigilance is recommended. The other well-known side effect of nevirapine is rash, which occasionally can be severe. It is important to remember that nevirapine is a powerful inducer (an inducer is a substance that accelerates the process of breakdown of other substances by the human body) of the metabolism, including its own one. For that reason it is given once a day for the first 14 days and later twice a day. Nevirapine is lipid-friendly, meaning it is not likely to increase cholesterol and triglycerides.

### **Efavirenz (Sustiva, Stocrin)**

It was the third approved NNRTI, but the first that proved to be at least as effective or more than PI's in studies in treatment-naïve patients (as part of combination regimen, HAART). Since the study '006' (compared with indinavir) there have been several studies that have shown that the efavirenz containing regimens in treatment-naïve patients are highly potent and effective. The most common side effects include central nervous system (CNS) symptoms, such as: abnormal dreams, dizziness and sleepiness. That is the reason why it is recommended to take efavirenz before bedtime. It is also important to warn patients to avoid driving or the operation of machines. In general these symptoms go away in the majority of patients after the first two weeks. Efavirenz is also an inducer (inducers are molecules that can speed up the breakdown of substances like medication inside the body. If a medication is broke down more rapidly it will be dosed more frequently), but its dose does not need to be adjusted as with nevirapine. However it can interact with a number of medications (drug interactions). Rash and elevations of liver function tests are also potential side effects with efavirenz, but hepatitis is less frequent than with nevirapine. In fact, a number of HIV drugs have the potential to elevate liver function tests (liver enzymes like ALT). Efavirenz is contraindicated during pregnancy. Efavirenz is recommended by the DHHS as the first choice when initiating therapy in treatment-naïve patients with an NNRTI.

### **Delavirdine (Rescriptor)**

It was the second NNRTI approved by the FDA in 1997. Due to the high pill burden and to its three times a day dosage, this drug currently is rarely used, despite that it probably is as effective as the other two NNRTI's. Rash is probably more likely than with the other NNRTI's. Delavirdine also interacts with many medications.

## **Protease Inhibitors**

Protease is a viral protein that literally cuts the forming virus (a long protein) in specific points so the cut up pieces can be put together for the final assembly of HIV. Studies of molecular structure of HIV done in the early 90's allowed the design of specific drugs that could occupy the position where the HIV viral protein enters in the protease and prevents it from cutting up the virus so it cannot assemble into a new viable virus. In 1995, the PI's revolutionized the treatment of HIV and the new era of HAART was born, when studies showed the effectiveness of the newly approved PI's. The first PIs to become available were these in 1995-96: indinavir, ritonavir and saquinavir.

In addition to the common gastrointestinal side effects (nausea, vomiting, diarrhea) and the high pill burden (the number of pills taken), it became clear that some of these medications had also long term side effects. One was an alteration in the blood lipids (cholesterol, triglycerides) and abnormalities in the distribution of the body fat (lipodystrophy), except for atazanavir (Reyataz), which usually does not result in elevated cholesterol and triglycerides and perhaps sugar. These medications also had a number of interactions with other medications, and the extreme case is full-dose ritonavir (PI). Today, a low-dose of ritonavir is commonly used to boost the levels of other protease inhibitors, but full-dose of ritonavir is not used anymore. The use of low-dose ritonavir improves the effectiveness of the therapy by raising the blood levels of the other protease inhibitor, which increases the potency of the therapy and improves its convenience in taking this therapy. Before the use of ritonavir boosting, PIs had to be taken three times or twice a day in order to keep PI blood levels high enough to suppress HIV replication, but boosting with ritonavir significantly increases PI blood levels and make this last longer so this allows PIs to be taken only once or twice a day and the number of pills taken is reduced.

### **Amprenavir and fosamprenavir (Agenerase and Lexiva)**

Fosamprenavir is a potent and tolerable HIV drug. Fosamprenavir is the pro-drug of amprenavir (a pro-drug is a substance similar to the drug but has to be broken down inside the body to become active). Some medications are administered as prodrugs for a number of reasons, for example to facilitate absorption. Of the two drugs, amprenavir was approved first, but due to the high pill burden (8 capsules twice a day) and poor absorption it was recently removed from the market. Fosamprenavir is better tolerated and accepted because of its low pill burden. Similar to many PI's, fosamprenavir can be boosted with ritonavir for higher blood level of the drug. (1 fosamprenavir 750 mg capsule + 100 mg of ritonavir twice a day or all four capsules once a day: speak to doctor about how to dose fosamprenavir according to your situation). Additional advantages of fosamprenavir include relatively fewer drug interactions, administration independent of the fed status (you can take fosamprenavir with or without food) and relatively lipid-friendly when compared with the majority of all other PI's. Finally, it is not recommended to take Kaletra along with fosamprenavir because they have a negative interaction.

### **Atazanavir (Reyataz)**

It is the first once a day protease inhibitor approved (2004). Atazanavir is a potent HIV drug and is popular because it is considered more tolerable and easy to take. Its main appealing characteristics are: the minimal or no influence on the lipids, its once a day administration, low pill burden (two capsules once a day), overall minimal gastrointestinal side effects and it can be "boosted" with ritonavir when high levels of atazanavir are needed (treatment "experienced" patients, who often have HIV drug resistance). Even for treatment-naïve patients atazanavir boosted with low-dose ritonavir is usually preferred for important reasons: it produces higher atazanavir blood levels making atazanavir more potent and more effective in preventing drug resistance. Recent studies show taking atazanavir with a low-dose of ritonavir is more effective in preventing drug resistance, which results in a more durably effective therapy. Atazanavir is dosed at 400 mg (2 pills) once a day when taken without ritonavir boosting, and 300 mg (2 pills) once a day when boosted with 100 mg (1 pill) of ritonavir taken once a day. The main side effect is the asymptomatic (without symptoms) elevation of the bilirubin (a natural pigment, present in the blood). Occasionally, the skin and mucosas in the eye can turn into a yellowish discoloration (icterus or jaundice). In this situation, the recommendation is the patient can switch the medication to another one. The discoloration should disappear when atazanavir is stopped. Studies have reported that the effectiveness of atazanavir is similar to nelfinavir and Sustiva. In "treatment-experienced" (have failed prior regimens) patients, the recommendation is to use "boosted" atazanavir at the dose of 300 mg once a day plus 100 mg of ritonavir (2 atazanavir capsules and 1 ritonavir capsule once a day). A study that compared atazanavir and Kaletra in experienced patients showed similar effectiveness, except when there are more than 5 HIV drug mutations, when Kaletra is superior. The FDA just approved a 300mg capsule that can replace the two 150mg capsules of Atazanavir.

Atazanavir has a significant number of interactions with other medications (we refer to the term "interaction" when the pharmacological effect [drug levels in the blood] of one medication is altered if given in the presence of a second medication). One of the most important (due to the availability of over the counter formulations) is with medications used for the treatment of reflux (stomach distress) or peptic ulcer disease (antacids, H2 blockers and H2 proton pump inhibitors). This means a patient should NOT take these medications along with atazanavir. Also important are the interactions with tenofovir, and rifampin (antibiotic used for the treatment of some infections, such as tuberculosis). When tenofovir is used in a 3-drug regimen (HAART) with atazanavir it is important to use atazanavir with ritonavir boosting because of the interaction between tenofovir and atazanavir, which results in a decrease in the amount of atazanavir available in the blood.

### **Indinavir (Crixivan)**

It is one of the oldest and most studied PI's. Its effectiveness is well recognized, however its use has declined in favor of the newer PI's with better tolerance, convenience and effectiveness. One of the main problems with indinavir is nephrolithiasis (kidney stones) that could affect up to 25% of the patients. Indinavir can be used three times a day (less convenient than most of the current available PI's given once a day or twice a day), but indinavir boosted by low-dose ritonavir is twice a day. If Crixivan is used today, it is usually used boosted with low-dose ritonavir. However if used with ritonavir the frequency of side effects increases, in particular kidney stones.

### **Lopinavir/ritonavir (Kaletra)**

Kaletra is popular because it is a very potent and effective therapy. It was the first approved protease inhibitor that was co-formulated with low dose ritonavir (in the same capsule). It was approved about 7 years ago so it has been in use and studied for a relatively long time; therefore, it has a longer track record for effectiveness and safety. Kaletra was originally approved to be taken twice a day, but about a year ago a new formulation of the drug allowed it to be taken once a day. It remains the only PI co-formulated (in the same capsule) with low-dose ritonavir. This low ritonavir dose (33.3 mgs/capsule) increases the levels of lopinavir over 100 times. Previously, the usual dose was 3 capsules twice a day (total of 800/200 mgs/day), but recently the new formulation with a tablet has been approved (each table 200/50 mgs) decreasing the number of pills to two twice a day (or all 4 once a day). Among its advantages are the high blood levels of the drug, which allows for a high level of potency for patients starting their first HIV therapy, and for patients who have PI drug resistance. Kaletra is also potent for patients with resistance to protease inhibitors because of the high level of drug in the blood. On the other hand, in addition to the common gastrointestinal problems seen at the beginning of the therapy, the main concern is the development of various degrees of dyslipidemia (elevated lipids: cholesterol, triglycerides) over time.

### **Nelfinavir (Viracept)**

It was the fourth PI that was approved, and for many years was the most used. Initially it was approved for administration three times per day but later it was used as 5 (250 mgrs) tablets twice a day. Lately, a new formulation of 625 mgs tablet has been approved. With this new presentation the dose is two 625 mgs tablets twice a day. This medication, however, can not be boosted with ritonavir. So, Viracept use has declined. The most common side effect is diarrhea that in some cases can be severe. The drug is otherwise well tolerated. Other important characteristic of nelfinavir is its resistant profile with overall low cross-resistance to other PI's.

### **Ritonavir (Norvir)**

It was one of the first PI's approved. Currently it is mostly used as a "booster" to increase the blood level of the other PI's. Due to its poor tolerability (severe diarrhea, oral paresthesias [numbness]) it is hardly used in full dose (as a PI), instead a low dose (from 100 to 400 mgs a day) is used to boost or increase levels of other PI's. The low dose of ritonavir is in general well tolerated. The reason why ritonavir can "boost" the levels of other drugs is because ritonavir can inhibit the metabolism (breakdown) of other drugs, and in that way will allow the drug it is boosting to remain active for longer period of time, as well as significantly increasing the levels. This allows other PIs to be taken once or twice a day and significantly reduces the risks for developing drug resistance.

### **Saquinavir (Invirase)**

It was the first PI approved in 1995 for the treatment of HIV and currently is the only one that was available in different formulations. The original formulation was a hard capsule (Invirase), but due to its poor absorption it was replaced by the soft capsules (Fortovase), with better absorption (and blood levels). Fortovase soft-gel capsules have been however discontinued by the new Invirase 500 mgs capsules for which the pill burden has decreased (two 500 mg capsules twice a day plus ritonavir 100 mg). A once daily regimen of saquinavir is being studied now. This medication is well tolerated with few gastrointestinal side effects and appears is potent. Large studies using the

500 mg capsules plus ritonavir 100 mg are ongoing comparing it to other leading HIV therapies. Several studies have already been conducted and show that this therapy is potent and tolerable.

### **Tipranavir (Aptivus)**

This was the last PI approved in the U.S prior to the approval in June 2006 of TMC-114. It is co-administered with ritonavir (500 mg of tipranavir + 200 mg of ritonavir twice a day). Tipranavir is potent and used specifically for patients who have been through several protease inhibitors and have extensive drug resistance to protease inhibitors. When using tipranavir it is important to bear in mind that it is particularly important to use additional drugs in the regimen to which the patient is not resistant. There should be at least 2 drugs in the regimen to which the patient has no resistance (to which the patient is fully sensitive).

Results from studies were very impressive that used tipranavir plus Fuzeon in patients who never before used either drug despite high degrees of drug resistance. The main side effects are gastrointestinal, probably in part due to the relatively high dose of ritonavir, and the potential for hepatotoxicity. Fuzeon was the first entry inhibitor to become available. It is described later in the newsletter.

### **TMC-114 (darunivir, Prezista)**

This is the newest protease inhibitor, approved by the FDA in June 2006. Studies show it is particularly potent and effective for patients who have used a number of protease inhibitors and have extensive resistance to them. Studies find the drug to be tolerable and safe as no particular extreme side effects or toxicities have been observed in studies conducted to date. This PI is also co-administered with low-dose ritonavir (600 mg of TMC-114 + 100 mg of ritonavir twice daily). For patients with resistance to tipranavir or extensive PI resistance, TMC114 is expected to be a very helpful new addition to therapy options. As mentioned above regarding tipranavir, it is very important to use TMC-114 along with at least 1 and preferably with 2 drugs to which the patient is fully sensitive. This applies to all drug regimens. But I mention this here in this situation because often these patients have extensive drug resistance or are not sensitive to many drugs when they get to the point of needing tipranavir or TMC-114. Resistance testing can be useful in identifying drugs that the patient is sensitive to. Patients in this situation of course will be fully sensitive to new classes of drugs that they have not used before such as integrase inhibitors or Fuzeon. Studies of TMC-114 once daily are planned comparing it to Kaletra in treatment-naïve patients.

### **Fusion Inhibitors: Entry Inhibitors Inhibitors of viral entry: 'entry inhibitors'**

Three steps are needed for HIV to enter the cell. The first step is the attachment of HIV to the CD4 molecules on surface of the cell, a macrophage or T lymphocyte. The second is the binding of HIV with one of the two "co-receptors" (called CCR5 or CXCR4) also present on the human cell surface; and the final step is the fusion of the virus into the cell, which results in the virus' contents getting dumped into the interior of the cell, where HIV reproduces itself. Each of these steps can be inhibited, and the classes of drugs used are called: attachment inhibitors, co-receptor antagonists, and fusion inhibitors. All three are called, as a group, entry inhibitors. At this time only a fusion inhibitor (Fuzeon) is available. A co-receptor antagonist (inhibitor) drug called Maraviroc is expected to finish its study soon and become available. Attachment inhibitors are being studied in patients and we hope they will become available in the near future.

### **T-20 (Enfuvirtide, Fuzeon)**

This drug is the prototype of the fusion inhibitors, the first to be approved by the FDA, and is very potent. This molecule is relatively large, like insulin, and similarly has to be administered as a subcutaneous injection (under the skin). It was approved in the U.S. and Europe in 2003. Fuzeon is effective for patients who have experienced viral failure and resistance to previous therapy regimens. It can be used in combination with tipranavir or TMC-114 and other drugs when trying to put a combination of drugs together. The adverse events as-

sociated with use of Fuzeon are mainly related to its subcutaneous administration: approximately 2/3 of the patients have local reactions, mostly mild local induration (little red bumps on the skin at the place of injection). Fuzeon is used mainly by patients with advanced HIV and limited therapy options because of the way its administered and the local skin reactions. Of note, there is a new injection device for Fuzeon that makes the drug easier to use and causes less skin reactions. Researchers have found a second generation fusion inhibitor that may only have to be dosed once a week or perhaps less often and may have less skin reactions when injected. This drug is in early stage of development and has not yet been studied in patients.

## **Medications under development**

There are a number of new drugs researchers have recently found that are in later stages of development and some that are in very early stage of development. As well, research continues to try and uncover new drugs for HIV treatment. The pipeline for new drugs appears very healthy and this provides much hope that HIV will become more easily manageable and patients ought to be able to live long and be productive. Of particular note, at this time two new classes of drugs are in later stages of development and are expected to be available within about 1 year: an integrase inhibitor, and an entry inhibitor which is actually a co-receptor antagonist. The Merck integrase inhibitor MK-0518 is in late stage of development (phase III study). It is particularly potent, appears to be tolerable with few side effects, and will be administered twice a day. Pfizer's co-receptor inhibitor drug Maravaroc is also potent and in the final stage of development, and is expected to be available soon. These drugs and additional new ones in development are described below. Also noteworthy are two NNRTIs being studied in patients: TMC-125 and TMC-278, discussed below.

### **New NRTI's (nukes)**

#### **ACH-126,433 (Elvucitabine)**

It is a new nucleoside that is effective against HIV and HBV. Some studies have shown that this drug retains potency in presence of several NRTI mutations, so it is expected that this drug would be useful for patients who have used currently available nukes. This medication has such a long half-life (this means it stays in the blood a long time) there may be a plan to study once a week administration. Some preliminary studies have also shown less mitochondrial toxicity than some of the currently available NRTI's. A concern from the preliminary studies is the development of neutropenia and rash. There are studies under way that will explore lower doses to avoid those side effects.

#### **SPD-754 (Previously BCH-10652, now called AVX754)**

Chemically this drug is similar to 3TC, however it retains activity in presence of several NRTI mutations (up to 5). Again, we hope this drug would be useful for patients who have used and developed resistance to currently available nukes. In preliminary studies this drug was potent and seems to be well tolerated and is well-absorbed. A related product is characterized by serious dermatological (skin) problems, but so far in animal studies (monkeys) this product has produced only very mild skin problems. This drug is being studied in patients with 3TC and FTC resistance.

**GS 7340** is a NRTI and a pro-drug of tenofovir. The objective of this drug is to improve the intracellular levels of tenofovir. Animal studies have shown very high concentrations of the drug in the lymph nodes, and that means that perhaps the drug's potency will be superior to tenofovir.

There are several additional nucleosides in early stages of development.

### **New NNRTI's**

Etravirine (**TMC-125**) is a NNRTI being developed by Tibotec (Johnson & Johnson) that has been shown in early study in patients to be effec-

tive and potent for patients with resistance to currently used NNRTIs nevirapine and efavirenz. TMC-125 is taken twice a day. Studies remain ongoing and we can expect to see further results in 2007. An Expanded Access Program for TMC-125 started in September of 2006. This program provides access to patients who need TMC-125 to compose an effective regimen.

**TMC-278** is a new NNRTI, also being developed by Tibotec (J&J), but is in earlier stage of development than TMC-125 and also appears to be potent and effective. This NNRTI is taken once a day and is in studies to be a first-line therapy and might perhaps also be used after NNRTI resistance develops to another NNRTI.

### New Protease Inhibitors

**BrecaNavir** is a protease inhibitor that looks promising. In an early small study in patients with extensive protease inhibitor experience and resistance the drug was potent and safe. Larger phase II study is ongoing. **SPI-256** and **PL-100** are two promising protease inhibitors in early stages of pre-clinical (haven't been studied in patients yet) development that appear preliminarily to be potent and may be effective for HIV that is resistant to other protease inhibitors.

### Attachment Inhibitors

This is a new class of HIV drugs, and therefore could be effective for patients with HIV drug resistance. **TNX-355** is a post-attachment inhibitor in development. The drug is potent as it reduced HIV viral load by 1.5 log in a 14-21 day study, and it appears so far to be safe and well tolerated. Unfortunately, the drug is administered by injection or infusion, which will limit its usefulness. But the drug can be useful for patients who have already been through a number of therapies and have very limited therapy options to add to a HAART regimen. Bristol-Myers Squibb has an attachment inhibitor development program and has presented patient study results for a series of drugs on their way to trying to develop a drug with optimal characteristics. **BMS-4588043** was studied for 10 days in treatment-naïve patients and resulted in 1 log reductions in viral load. But high doses of 1800 mg were required, so study was stopped as they evaluate other potential drugs with better characteristics. An attachment inhibitor such as this could be useful for firstline therapy as well as for patients with HIV drug resistance.

### Maturation Inhibitors

**PA-457** is the first maturation inhibitor being studied. In an early small study the drug was potent as it reduced HIV viral load by 0.75 to 1.5 log reductions in viral load, and appears effective for patients with HIV drug resistance. More studies are ongoing. Additional maturation inhibitor drugs are in very early stages of research.

### Co-receptor Antagonists

As explained above, in order for HIV to gain entry into cells in the body and to re-produce itself, HIV requires attachment to the CD4 receptor on the cell and also attachment to some other receptors, called "co-receptors". The most important of these co-receptors are named CXCR4 and CCR5. The HIV virus that mainly uses the CXCR4 receptor is known as "X4" and virus that uses CCR5 is called "R5" virus. In general, most HIV viruses that patients have are R5 (approximately 80% of all viruses). R5 virus is more common in patients with relatively higher CD4's and low viral loads and X4 virus is more common in patients with advanced HIV disease. An entry inhibitor drug is called a R5 inhibitor (or antagonists) because it has antiviral activity against R5 viruses, that is they prevent attachment of HIV to the R5 co-receptor. Drugs that inhibit attachment of HIV to the X4 co-receptor are called X4 inhibitors or antagonists. Three CCR5 inhibitors were in development until recently, but development of an X4 inhibitor is more difficult although researchers are trying to develop X4 drugs. Two of the CCR5 inhibitor drugs ran into some trouble during studies while in development, but the 3rd CCR5 inhibitor drug called **Maraviroc** is moving along well and almost ready for use by patients.

Study of the GlaxoSmithKline CCR5 inhibitor was stopped because hepatitis toxicity was discovered in a small number of patients. Schering Plough's **Vicriviroc** is a potent CCR5 inhibitor and its study in treatment-naïve patients was stopped because of a poorly designed study. There were no signs of safety concerns in the study in treatment-naïve patients, but there were viral failures and it was thought that this might have been due to low dosing of the drug. The study in treatment-experienced patients continues although there was a finding of some cancers developing in a small number of patients. The patients had very advanced HIV disease so the study continues because it was thought that the development of cancers could be due to advanced HIV disease and not to Vicriviroc. Study of this drug in treatment-naïves is expected to be started up again with better designed dosing using higher doses.

R5 inhibitor drugs are not expected to be effective (have antiviral activity) for patients with X4 HIV. There is a blood test that can help tell you whether you have R5 or X4 virus, but this test has some flaws; it is called a 'tropism' assay. They are trying to find a better test.

**Maraviroc** It is a CCR5 inhibitor that has been shown to be potent against HIV, and currently is in phase III studies, the final stage of development prior to FDA approval and availability in the pharmacy. The drug is expected to be available in the pharmacy for patients around the middle of 2007. Pfizer, the company developing Maraviroc, is planning an Expanded Access Program around the end of 2006 for patients who need the drug to compose an effective therapy regimen. No safety concerns have been reported from the phase III study or from earlier studies in patients. This is a new class of HIV drugs and therefore is expected to be potent and effective both for patients with treatment-experience and for treatment-naïve patients.

**Vicriviroc (SCH-D)** This drug is a potent R5 inhibitor and its study in treatment-naïve patients was on hold for better design, but as mentioned above the study in patients with advanced HIV continues. The company is planning to move ahead now with new studies.

### Integrase Inhibitors

The development of integrase inhibitors is a major advancement in therapy. Merck has been developing an integrase inhibitor for 10 years. Integrase is one of the most important proteins required for HIV to reproduce itself in the human cell. After HIV enters the cell the integrase enzyme helps the genetic material of the HIV virus merge with the genetic material of the cell. There are two integrase inhibitors being studied now in patients. **MK-0518** is being developed by Merck. It is very potent and appears safe and tolerable. It can be used for treatment-experienced patients with drug resistance, and by treatment-naïve patients. Results were reported from a study of patients who had extensive HIV drug resistance, and the drug was very effective; the average viral load reduction for patients was potent 2 logs and a high percent of patients were able to achieve undetectable viral load. As well, in patients who never before had HIV therapy preliminary 24 weeks study results showed MK-0518 to be very potent and safe. Since integrase is a new class of drugs, integrase inhibitors should be effective and potent for patients with drug resistance to all 4 classes of HIV drugs—NRTIs, NNRTIs, protease inhibitors, and fusion inhibitors (Fuzeon, T-20). For this reason, integrase inhibitors are expected to be very helpful for patients with drug resistance. **MK-0518** is dosed twice a day and is expected to be available near the end 2007. Integrase inhibitors will be very good to combine with other new drugs such as tipranavir, Fuzeon, and TMC-114 for patients with extensive HIV drug resistance. Merck is providing MK-0518 through an Expanded Access Program that started in September 2006 for patients who need the drug to put together an effective regimen.

Another integrase inhibitor is **GS-9317** from Gilead Sciences. This drug also appears to be very potent but is in an earlier stage of development than MK-0518. Results were recently reported from a 10-day study which showed viral load was reduced also by a potent 2 logs with this drug. A large phase II study of this drug started in 2006. This drug may be used with a low dose rironavir so it can be dosed once a day and for greater effectiveness.

## Starting Therapy

### When to start?

When to start antiretroviral therapy has been a matter of debate since the beginning of the HAART era in 1996. In general, the recommendations on when to begin therapy have varied from one point when there was high hope for the eradication (and cure) of the virus (start early), to the other when the concerns were considered more important regarding missing doses and getting resistance and long term side effects of medications (delay therapy).

Currently, according to the recommendations of the DHHS (the Department of Health and Human Services), all **patients with HIV or AIDS-related symptoms should begin therapy.**

For asymptomatic patients (no apparent symptoms) with a **CD4 below 350** cells/mm<sup>3</sup>: for patients with **CD4 count <200**, they should begin therapy; for patients with a CD4 count between **200 to 350 cells**, they should be offered therapy along with a full discussion about the pros and cons of beginning therapy.

For patients with a CD4 count **>350** if the HIV viral load is **<100,000** copies/ml they should defer therapy. But, for patients with a CD4 count of **>350** and a viral load of **>100,000** the recommendations say "some clinicians will treat, but most recommend deferring therapy".

The DHHS Guidelines also say this. After considering available data in terms of the relative risk for progression to AIDS at certain CD4+ T cell counts and viral loads, and the potential risks and benefits associated with initiating therapy, most specialists in this area believe that the evidence supports initiating therapy in asymptomatic HIV-infected persons with a CD4+ T cell count of 200-350 cells/mm<sup>3</sup>.

It is important to bear in mind that the Federal DHHS Guidelines are only recommendations meaning the decision of when to begin therapy ultimately rests with the clinician and patient. This decision should be made after a careful discussion between doctor and patient considering the pluses and minuses of starting therapy now or deferring the start, and in consideration of the individual patient's situation. You may want to consider that in the past two years several studies have found that starting therapy early, when CD4 count is above 350 and even above 500, response to therapy is better and patients in general maintain health better. There are several considerations to bear in mind. Once therapy is started there is a risk for developing side effects, although in recent years newer therapies have been able to reduce the risks for side effects. Full adherence is required to prevent drug resistance, so if starting therapy earlier a patient will have to maintain adherence (see Adherence section).

As you can see, the CD4 count is generally considered more useful in predicting HIV progression than viral load in making the decision when to start therapy. When in doubt, another variable to take in consideration is the CD4/CD8 ratio. In a large study, it was found that a patient had increased risk of death if they started therapy when the CD4/CD8 ratio was 15% or less.

The DHHS Guidelines now recommend **resistance testing** for patients about to start therapy for the first time, since one can acquire drug resistant HIV from the person who transmitted HIV to them. The presence of drug resistant HIV can reduce response to certain HIV drugs, so resistance testing can be useful in selecting a more effective regimen. Resistance testing is also used for patients who have been through several therapy regimens and have HIV drug resistance. The tests can be useful for identifying drugs that may be more effective and which drugs may be less effective.

### Table 4. Indications for Initiating Antiretroviral Therapy for the Chronically HIV-1 Infected Patient

The DHHS Guidelines say --- The optimal time to initiate therapy is unknown among persons with asymptomatic disease and CD4+ T cell count of >200 cells/mm<sup>3</sup>. This table provides general guidance rather than absolute recommendations for an individual patient. All decisions regarding initiating therapy should be made on the basis of prognosis as determined by the CD4+ T cell count and level of plasma HIV RNA indicated in table 4 in the DHHS Guidelines, the potential benefits and risks of therapy, and the willingness of the patient to accept therapy. (Table 4, shows the probability of progressing to AIDS or death over a certain number of years based on the patient's CD4 count, viral load, and other sociodemographic information). This can be used to help in making the decision of when to begin therapy.

Clinical Category	CD4 Cell Count*	Plasma HIV RNA	Recommendation
AIDS-defining illness or severe symptoms*	Any Value	Any Value	Treat
Asymptomatic**	CD4+ T cells <200/mm <sup>3</sup>	Any Value	Treat
Asymptomatic	CD4+ T cells <200/mm <sup>3</sup> but ≤350/mm <sup>3</sup>	Any Value	Treatment should be offered following full discussion of pros and con with each patient (see text)
Asymptomatic	CD4+ T cells >350mm <sup>3</sup>	≥100,000	Most clinicians recommend differing therapy, buy some clinicians will treat (see text)
Asymptomatic	CD4+ T cells >350/mm <sup>3</sup>	<100,000	Defer therapy

\* AIDS-defining illness per Centers for Disease Control, 1993. Severe symptoms include unexplained fever or diarrhea > 2-4 weeks, oral candidiasis, or >10% unexplained weight loss.

A collaborative analysis of data from 13 cohort studies from Europe and North America found that lower CD4 count, higher HIV viral load, injection drug use, and age over 50 were all predictors of progression to AIDS or death in antiretroviral-naïve patients beginning combination antiretroviral therapy.

## What to start with?

The main objectives of HAART are:

- (1) to reduce morbidity (reduce chances to become ill, improve health and sustain health)
- (2) mortality (reduce chances to die prematurely) related to HIV infection,
- (3) to improve the quality of life,
- (4) to restore and preserve the immunological function
- (5) the maximal viral suppression.

It has been shown that the initial treatment regimen, the first HAART regimen, has the best chance for long-term success because the patient has no prior treatment-experience and is not likely to have HIV drug resistance. Studies show that if a patient is fully adherent to a good HAART regimen this regimen can be effective for many years. Studies have so far gone out as far as 10 years since that is how long HAART has been available, and these studies show patients can remain and in fact many patients do remain having undetectable HIV on the same regimen for the entire 10 years. Clearly, full and complete adherence is essential to achieving this. Once HIV drug resistance develops it becomes more difficult to durably suppress HIV. As previously mentioned, **resistance testing** can be useful in selecting the initial therapy regimen in case the patient was infected with HIV from a person who had HIV drug resistance. For example, if the resistance test finds you have resistance to NNRTIs then you can start therapy with a protease inhibitor regimen. As well, **resistance testing** to guide the choice of therapy in a patient failing a particular regimen has been shown to be of benefit.

Each HIV drug has its own set of benefits and its own set of side effects. In consideration of the discussion above, it is very important to individualize the regimen while taking into account many factors, including: potential side effects of the HIV drugs, drug interactions with other prescription medications (including herbs the patient may be taking), patient potential for good adherence, an illness existing at the same time, potential pregnancy, and the degree of effectiveness and potency needed from a regimen for this individual patient's situation. In selecting a therapy regimen it is helpful to consider what fits well with the patient's daily routine, lifestyle, and personal concerns regarding side effects. With the available number of approved medications, there are many potential combinations, however some regimens have performed better than others in large studies in patients. Taking that evidence into consideration, the Department of Health and Human Services (DHHS) Panel has made judgments about available regimens and makes recommendations about certain specific initial regimens from which there is good evidence originated from large well controlled studies. These recommendations are often updated as new drugs become available. After a new drug becomes available studies are conducted and when the results are available and evaluated the recommendations may be changed.

## There are three categories of potential initial regimens:

NNRTI based, PI based and triple NRTI's are the 3 categories for types of regimens. This classification is based on the regimens that have generated the largest amount of relevant information including results from studies. The PI and NNRTI regimens include two NRTI's, the reason being is that two NRTI's have been the most used backbone in all studies. The triple NRTI regimen is Trizivir and it includes 3 nukes in one pill: abacavir, AZT, and 3TC. The DHHS recommendations use the term "preferred" for the initial treatment of HIV infected patients when studies have demonstrated optimum efficacy and durability with acceptable tolerability and ease of use. "Alternative" are the regimens recommended for patients for which studies have demonstrated effectiveness but are considered alternative because of disadvantages in terms of antiviral activity, durability, tolerability, or ease of use, compared to "preferred" regimens. Recommendations regarding the two NRTI backbone as part of preferred or alternative regimens are made by the DHHS panel based on antiviral activity, durability, short and long term toxicities, drug interactions, resistance profile and dose convenience. A summary of the specific recommendations is shown in table # 6.

DHHS Guidelines recommend for firstline therapy or 'Initial Treatment' efavirenz (Sustiva) as a 'Preferred Regimen' for a NNRTI based therapy. Kaletra was the only 'Preferred Regimen' for a protease inhibitor based therapy. On October 10, 2006 the HHS Guidelines added to the list of Preferred Protease Inhibitor Regimens: atazanavir boosted with low dose ritonavir taken once-a-day, fosamprenavir boosted with low-dose ritonavir taken twice-a-day. Kaletra taken twice-a-day remains also a Preferred Protease Inhibitor Regimen.

Atazanavir (Reyataz) is a popular first selection for a protease inhibitor based therapy because it is easy to tolerate and convenient and does not increase lipids (cholesterol and triglycerides), as well as being potent. Kaletra is popular because of its high potency and high drug levels. Both Kaletra and atazanavir have unique resistance profiles. Since Kaletra was approved 7 years ago and atazanavir 2 years ago, there is more information and research on Kaletra from studies. Efavirenz is the most popular choice as a firstline NNRTI therapy because of its potency, once daily administration, and safety profile. PIs tend to have a preferred resistance profile compared to NNRTIs.

The new October 10 Guidelines list of 'Alternative Regimens' includes nevirapine as a NNRTI based therapy, and for a PI based therapy atazanavir taken once-a-day, fosamprenavir taken twice-a-day, fosamprenavir boosted by low-dose ritonavir taken once-a-day, and Kaletra taken once-a-day.

There is another organization called the International AIDS Society (IAS) that includes doctors and researchers from outside the USA. They also issue Guidelines for Treatment. For first-line therapy choices they recommend consideration of all these ritonavir-boosted protease inhibitors: Kaletra, saquinavir/r, amprenavir/r, atazanavir/r. In the USA, the DHHS Guidelines appear to carry more weight.

## Diabetes and HIV

Among HIV+ individuals impaired glucose tolerance and diabetes are more prevalent, and many HIV+ individuals remain undiagnosed. It is important to be tested and evaluated for impaired glucose tolerance (IGT) and diabetes if you are HIV+.

### Diabetes risk factors include:

- ❖ Age over 45
- ❖ Overweight
- ❖ Family history of diabetes in a first-degree relative
- ❖ Habitual physical inactivity
- ❖ African-Americans & Hispanic have high risk
- ❖ Hypertension (blood pressure 140/90 mmHg)
- ❖ Elevated lipids defined as high-density lipoprotein cholesterol (HDL) concentration 35 mg/dL and/or triglycerides 250 mg/dL

### Suggested screening tests for impaired glucose tolerance and diabetes:

- (1) fasting blood glucose is recommended
- (2) 2-hour post-glucose challenge test is a 2nd choice
- (3) elevated body mass index (BMI >30) and fasting triglycerides and cholesterol may predict diabetes

## Antiretroviral Regimens Recommended for Treatment of HIV-1 Infection in Antiretroviral-Naïve Patients

These are the DHHS recommended Guidelines. Patients along with their care provider or doctor can decide which therapy might be most effective for a patient, as well as deciding when to begin therapy. Patients should have an informed discussion with their care provider regarding the best decision for their personal situation regarding when to begin therapy and what regimen to select. The DHHS Guidelines are recommendations by the panel of doctors and researchers considered to be experts brought together to make these recommendations, but the Guidelines are just that—Guidelines—so, the doctor or care provider in discussion with the patient can ultimately decide which therapy suits the patient better.

**Table 5. Initial Treatment, Preferred Regimens and Alternative to Preferred Regimens**

Preferred Components	<b>NNRTI</b> efavirenz (All)	<b>PI-</b> atazanavir + ritonavir (All) fosamprenavir + ritonavir (2x/day) (All) lopinavir/ritonavir (2x/day) (All) (co-formulated)
Preferred Components	tenofovir/emtricitabine (co-formulated) (All); or zidovudine/lamivudine (co-formulated) (All)	
<b>Plus</b>		
Alternative to Preferred Components	<b>NNRTI</b> nevirapine (BII)	<b>PI-</b> atazanavir (BIII) fosamprenavir (BIII) fosamprenavir + ritonavir (1x/day) (BIII) lopinavir/ritonavir (1x/day) (BIII) (co-formulated)
Alternative to Preferred Components	abacavir/lamivudine (co-formulated) (BII) didanosine (emtricitabine or lamivudine) (BII)	
		(NNRTI or PI Options - in alphabetical order)

### When to switch a regimen

The definition of success or failure of a therapy the patient is taking depends on several factors for each individual patient and is related to specific objectives of the therapy for that person. For example, in patients on their first antiretroviral regimen (HAART), the objectives are more strict or you could say simple than in more experienced patients. For patients on their first or initial regimen and probably their next one or maybe two regimens the usual goal is complete viral suppression (to achieve HIV viral load below 50 copies/ml) with a correspondent increase in CD4. As patients go through more regimens, they start to lose more therapeutic options and the objective of the therapy may change from complete viral suppression to the protection against diseases associated with AIDS by maintaining the CD4 to the highest possible level. Although the key goal of therapy is always to reduce HIV viral load to <50 copies/ml when possible, it might be more acceptable to have a less rigorous goal for patients who have previously experienced viral failure on drug regimens and for whom it might be difficult to find a regimen that can reduce viral load to <50 copies/ml. However, with the new availability of a number of new drugs (TMC114, TMC125, MK-0518, Maraviroc, Fuzeon, and Tipranavir) the goal of therapy should be to achieve <50 copies/ml. Even for patients with drug resistance this is more easily attainable now with these new drugs available. The IAS Guidelines say: "In the setting of treatment experience, resistance testing should be performed while the patient is taking the failing regimen. Trials with newer antiretroviral agents have shown that it is possible to achieve plasma HIV-1 RNA levels below 50 copies/mL even in highly treatment-experienced patients. If at least 2 drugs cannot be identified, strong consideration should be given to maintaining the current regimen until new drugs become available, assuming immunologic and clinical stability".

In a more detailed explanation, treatment failure is defined from the following points of view:

**Virologic failure:** Viral load above 400 copies/ml after 24 weeks of

the initiation of the regimen, or above 50 copies/ml after 48 weeks, or with repeated viral loads over 400 copies/ml after the successful suppression below 400 copies/ml. The detection of viral load above the level of detection while taking the medications is defined as virologic rebound. Some care providers or doctors prefer a more rigorous definition of virologic failure. They require that viral load should reach <50 copies/ml after starting a therapy, and if this does not occur within about 8 weeks or perhaps 12 weeks, a change or adjustment in therapy should be considered.

**Immunologic failure:** is defined as the failure to increase CD4 from 25 to 50 cells/mm<sup>3</sup> above the baseline after the first year, or for a drop of the CD4 below the baseline while in medications. In general, it is expected that HAART should increase a patient's CD4 count by a few hundred or even more. Some patient's have had a very good response to therapy by using a potent regimen and had a CD4 increase from 100 to 1000 or more.

**Clinical failure:** is defined by the occurrence or recurrence of opportunistic infections 3 months or later after the initiation of antiretroviral therapy, which means the immune system has not improved. Conditions associated with 'immune reconstitution' are excluded from this definition. This is a situation where the immune system has improved so well that it is responding to an underlying infection the patient has. You can ask your doctor about this.

A regimen can be failing from the virologic point of view but can still produce clinical and immunological (adequate CD4 levels) benefit, in particular in treatment-experienced patients. Or, it is possible, although not likely, that a patient can have virologic success (HIV viral load decrease to <50 copies/ml), but CD4 count does not increase.

Among the possible causes of treatment failure are: prior use of sub-optimal therapies (for example the use of monotherapy in the past), poor adherence to the medications due to poor tolerability and side effects, negative interaction among medications resulting in reduction of HIV drug blood levels, poor potency and pre-existing HIV drug resistance.

## Treatment Options for Patients with Drug Resistance

If a patient has been through one or more HAART regimens, what are the options? Due to advances in research there are a number of good treatment options.

A protease inhibitor regimen can be used after a patient has failed a NNRTI therapy, and there are several to consider. NNRTI therapy can be used after a patient has failed a PI therapy.

If a patient has been on several regimens and developed drug resistance to several drugs, there are a number of therapy options. **T-20 (Fuzeon)**, a fusion inhibitor (entry inhibitor), can be useful. It is a very potent drug and is equally potent regardless of drug resistance to other drugs. It is administered by subcutaneous injection, which can cause soreness at the injection sites. 50% of patients reported mild tenderness at the sites of injection for Fuzeon. About 20% reported moderate pain. And about 1-2% reported severe pain requiring analgesics or limiting usual activities. **TMC-114** is a new protease inhibitor just approved for use in June of 2006. It is very potent for patients with prior protease inhibitor use and drug resistance, and appears safe and tolerable. **Tipranavir** is also a very potent protease inhibitor for patients with prior protease inhibitor use and drug resistance, and can be associated with hepatotoxicity in some patients. Of particular interest as a therapy option for patients with prior experience with several regimens and resistance to several HIV drugs is the **Merck integrase inhibitor (MK-0518)**. It is in the final stage of study in patients and is expected to be available in the latter part of 2007. Patients with drug resistance will be fully sensitive to this drug since it's from a new class of HIV drugs, and so far it appears safe and tolerable. In September 2006 Merck opened an **Expanded Access Program (EAP)**, to provide early access to MK-0518 for patients who need a new therapy to compose an effective regimen. You can speak to your doctor about this. As mentioned, MK-0518 is very potent as it reduced HIV viral load by about 2 logs in studies for patients with extensive drug resistance. **TMC-125** is a new NNRTI that appears effective for patients with HIV drug resistance to the currently available NNRTIs. Tibotec opened an **Expanded Access Program** in September 2006 for patients who need TMC-125 to put together an effective regimen. **Maraviroc** is another treatment option. It is an entry inhibitor that is potent and in the final stage of development. This drug is another treatment option for patients with drug resistance. It is from a new class of drugs and so patients with resistance to currently used drugs should be sensitive to this drug. You will have to perform a test to see if you are sensitive to the drug, called a tropism assay. Pfizer, the developer of Maraviroc, is planning an Expanded Access Program around the end of 2006 for patients who may need this drug for an effective therapy regimen.

### 3 keys for turning HIV in to a chronic manageable disease

- Start therapy at the appropriate time  
-don't delay it too long.
- Select a HAART regimen that the HIV positive individual is comfortable with.
- Complete and full adherence!

## Adherence

### Adherence: very important for success of HIV therapy

The two ingredients most important for the success of HAART are (1) to select an adequately potent and tolerable therapy that fits the patient, and (2) full and complete adherence. With these two ingredients satisfied a patient can have many years of success on the same regimen and achieve health and longevity. A normal lifespan is possible. Those are the key ingredients to making HIV a chronic manageable disease. Studies have followed patients for ten years on HAART, as long as HAART has been around, and found that patients who achieve <50 copies/ml quickly (the quicker the better) and sustain this for 2 years remain undetectable for 10 years. The first few months on therapy is the key. The goal is to reach <50 copies/ml in the first few weeks on therapy and with complete adherence remain there for the first 2 years. If a patient achieves this and continues with good adherence HIV can become a chronic manageable disease. Again, pick the right regimen and stick to complete adherence.

The success of all regimens depends on the ability of the medications to reduce the viral replication to the minimal level of replication. Studies have shown that an almost perfect adherence (> 95%) is needed to maintain viral replication to that level. For example, if you are taking HAART twice a day, the regimen is taken 14 times in a week, and 95% of 14 is 13.3. Over a 2 week span the regimen is taken 28 times and 95% is 26.6.

It also has been shown that a minimal decrease in adherence (from 95% to 90%) can result in a marked reduction in the rates of suppression of viral replication.

At first sight it would appear that antiretroviral therapy is a challenge. Specially considering that HIV treatment is a long term commitment. It is also important to consider that therapy is essential to prevent HIV disease from progression. So deciding when to begin therapy is an important decision. It is important to take into consideration that it is expected that patients and doctors should work together in identifying possible barriers against adherence and therefore maintain the benefits of therapy. There are certain strategies that have been used in other chronic conditions that may be of help in improving adherence in the treatment of HIV infection.

### Improving adherence

Some patients with HIV have a chaotic lifestyle. These circumstances are more prevalent among those with mental health problems, drug use and homelessness. Thus, it is not surprising that drug adherence in these groups is perceived as challenging.

Adherence could be improved by counseling before and during the initiation of antiretroviral therapy. This type of counseling should include information about the correct use of antiretrovirals, dietary restrictions and side effects management while patients are followed during the first weeks of treatment. Adherence support groups are often available and can also be very helpful. When beginning therapy be prepared by knowing what the challenges are and be ready to make the commitment.

Another concern is **stopping therapy**. This is often called "treatment interruptions" or "drug holidays". Because patients can get tired of taking HIV therapy every day for years and maintaining full adherence, sometimes patients want to stop therapy or take an interruption or drug holiday. It is important to bear in mind that results from several studies were reported in 2006 and they found that interrupting therapy can result in serious negative consequences including the development of drug resistance and health problems. If a patient has a desire to interrupt therapy, it is important to discuss this with the doctor or clinician and not to do it on their own.

### HIV infection and chronic viral (B/C) hepatitis or co-infection

Hepatitis is inflammation of the liver, and could be acute (it just occurred) or chronic (infection for more than 6 months). Among the most common causes of chronic hepatitis is hepatitis caused by B and C viruses (viral hepatitis). The discussion about this kind of hepatitis is important during the discussion of HIV infection because they share routes of transmission. In addition to the relatively high frequency of HIV+ individuals having co-infection with hepatitis C or hepatitis B, viral hepatitis is a serious condition that may limit or complicate the treatment for HIV. We will review these two conditions. Of particular importance is that HIV can accelerate hepatitis C or B disease to progress significantly more quickly because HIV suppresses the immune system. For individuals with the hepatitis C virus (HCV) but without HIV it can take 20 to 30 years to develop serious hepatitis complications related to the liver, and most individuals infected with only HCV don't develop serious complications. But, when a person is co-infected with both HIV and HCV serious complications related to hepatitis can develop in as quickly as 5 to 10 years.

Hepatitis C is mostly transmitted by sharing paraphernalia used for injection drug use. This includes sharing the syringe with another person but it appears there may also be a risk of transmission by sharing the other paraphernalia, which includes the cotton, cooker, and the water. Several recent studies have found a risk associated with sexual transmission of HCV among HIV+ individuals, particularly men who have sex with men, who practice risky sexual behaviors or have STDs. When a sexual partner has an STD, which of course includes syphilis and HIV, the risk of sexual transmission of HCV appears to increase. Having multiple sex partners, having anal sex, and other sex that might break mucosa (thin protective layer in the anus and vagina) such as 'fisting' appears to increase the risk for sexual transmission of HCV.

### Hepatitis B

The infection caused by hepatitis B virus (HBV) is a serious condition that is very common worldwide. This infection can cause chronic viral hepatitis. With time this chronic hepatitis can lead to cirrhosis, liver failure and or liver cancer. HIV and HBV share common routes of transmission (sexual contact, contaminated needles, and transfusion of blood products). Up to 90% of HIV infected patients have serologic markers of past HBV infection, but only about 5 to 10% have active chronic co-infection with both HIV and HBV.

HIV infection negatively affects hepatitis B. First, it decreases chances of resolving the initial hepatitis B (therefore progressing to chronic viral hepatitis with the later risks of complications); second, it accelerates the progression of hepatitis disease. And since HIV can accelerate HBV it is important not to delay therapy for HBV for very long.

After the beginning of the HAART era, the treatment of HBV and HCV in coinfecting patients is even more important due to expecting HIV-infected individuals to live long healthy lives. With respect to the treatment of this infection, lately there have been several important advances.

Currently there are several medicines available for treatment of hepatitis B. On one hand is alpha- interferon (pegylated interferon), although its role in coinfecting patients is less clear. On the other hand, since the reproduction of the hepatitis virus in the human has a step in which it uses its reverse transcriptase (similar to HIV), nucleosides may be used. Pegylated interferon has been studied in HIV-negative individuals with HBV, but not in HIV+ individuals. Study results show pegylated interferon can have the unique ability to improve the immune system's response to HBV, as well as an antiviral effect that reduces HBV viral load.

Currently available orally administered nucleosides for HBV treat-

ment are 3TC, adefovir, tenofovir, FTC, telbivudine and entecavir which was approved in 2005. As well, there are several additional orally administered drugs in different stages of development, so it is expected that there would be new medicines available in the near future.

At this time the most popular approach in therapy for a patient who is co-infected with both HIV and HBV, and has made the decision to begin HIV therapy (HAART) is to include FTC or 3TC along with tenofovir. Truvada is a one pill 'fixed dose' combination that combines in it both FTC and tenofovir so this is a popular choice due to potency and convenience. FTC, 3TC and tenofovir all are active against both viruses HIV and HBV. For patients with FTC or 3TC drug resistance, tenofovir appears to be the most potent drug against HBV.

Entecavir has been shown in studies to be the most potent HBV drug in HBV treatment-naïve patients, but is only active against HBV. It is not active against HIV. So it is not as convenient to use, but it can be considered. How would it be used? In one of two ways. If a patient is not ready to start HAART you can begin HBV therapy only with entecavir. And when starting HAART you can add it to entecavir. If it's decided to begin HIV and HBV therapy, you can start a HAART regimen and also take entecavir. An important aspect of HBV treatment is drug resistance. Entecavir has been studied so far for three years and there has been no resistance found in patients on entecavir. Other HBV drugs have been seen to lead to drug resistance. Lamivudine has the highest rates of drug resistance. Tenofovir appears to have lower rates of resistance and appears to be very potent. Tenofovir is only approved for HIV therapy, but studies are ongoing now to get tenofovir approved for HBV therapy.

Telbivudine is a potent new drug for hepatitis B treatment that was approved in the USA in October 2006. This drug is active only against hepatitis B, it is not active against HIV; but resistance can develop.

Combination therapy of two orally administered anti-HBV drugs as well as a combination of pegylated interferon plus 3TC have been examined in a few studies. The results do not in general find that combination therapy has an additive effect in reducing HBV viral load any more than just using 1 drug. More studies are planned to continue examining various approaches to combination therapy. But the studies so far conducted find that combination therapy can have an important affect by reducing the chances of developing drug resistance. For this reason alone combination therapy has a significant benefit.

### Hepatitis C

The frequency of Hepatitis C infection varies considerably among the different types of patient groups co-infected with HIV. The highest rate of infection is among those whose risk factor for infection was the use of contaminated blood products (hemophiliacs, transfusion) and intravenous drug use. HCV has become one of the most important challenges in HIV infected persons. About 30% of HIV-infected individuals in the USA also have HCV. But among persons infected with HIV through injection drug use up to 90% may be co-infected with HCV. HCV has become perhaps the leading cause of hospitalization and death among HIV-infected individuals. It is very important to be tested for HCV and if HCV+ to discuss care and therapy with the doctor or care provider and perhaps a hepatitis specialist.

One of the differences between Hepatitis B and C virus is that infection with Hepatitis C leads to chronic viral hepatitis C in more than 80% of the cases, with potential for the same complications previously mentioned (cirrhosis and/or liver cancer). While 85-90% of persons infected with HBV clear it spontaneously and do not get chronically infected.

There is ample evidence that shows that HIV infection negatively affects hepatitis C progression, shortening the time of progression to cirrhosis and increasing the frequency of complications. Also, the presence of HIV increases the rate of complications during the treatment for Hepatitis C. Like in HBV, since HIV can accelerate HCV

disease progression it is important to consider starting HCV therapy, and not to delay initiating therapy for too long.

### Treatment for Hepatitis C: the future looks promising

Currently, the standard of care and most effective therapy for Hepatitis C is **pegylated interferon and ribavirin** both for mono-infected and co-infected patients, although the success rate is lower for co-infected individuals. Pegylated interferon is administered once a week by subcutaneous injection (under the skin) and ribavirin are pills taken daily.

This therapy is often difficult to tolerate. The most common side effects of interferon are decrease in red and white blood cells which can cause fatigue, depression, irritability, and flu-like symptoms. Ribavirin, on the other hand, may cause a particular type of anemia, associated with fatigue. Due to the potential complications and that many patients taking the therapy experience side effects of treatment, it is important to determine the likelihood of success at week 12 of treatment. If there is little or no response to therapy by 12 weeks after starting you can consider stopping therapy for now. If there is response to treatment (a decrease in at least 2 logs in HCV viral load) it is justified to continue treatment. After 24 weeks from starting therapy HCV viral load should be tested again to see if it's undetectable. If it is undetectable it is ok to continue therapy for a total of 48 weeks or longer. Periodic monitoring of HCV viral load while on therapy is recommended, and if it's not undetectable you can consider stopping therapy due to the possibility of side effects or toxicity. If a patient shows some response to therapy that approaches 2 logs by week 12 it may be justified to continue until week 16-24 to see if a successful response is mounted rather than give up too easily. If such a late response occurs extending therapy to 18 months might be more successful than 1 year in achieving the goal of therapy: elimination of HCV, often called eradication or "cure".

### New Therapies in Development

It is important to know that there are some promising new drugs for HCV under development, so it is expected that there would be new medicines available in the near future for the treatment of this condition. Several new orally administered drugs (administered by pill) for HCV treatment are in early stage of development. They are being studied in patients now and appear promising. These drugs are expected to be easier to take, more convenient, more tolerable, and have less side effects. But these drugs will be used in combination therapy, along with pegylated interferon, and perhaps ribavirin. At this time the furthest along in development is the **HCV protease inhibitor called VX-950**. It is very potent. It is a pill taken every 8 hours. In a 14-day study VX-950 was very potent in showing a 4.4 log reduction in HCV viral load. In a 28-day study the combination of VX-950 and Pegasys showed a potent reduction in HCV viral load of 5.5 logs. A large phase II study was started in early 2006 testing the combination of VX-950 along with pegylated interferon (Pegasys) and ribavirin. A new approach to therapy will be evaluated in this study. The success of treatment with 12, 24, and 48 weeks of therapy will be evaluated. A **second HCV protease inhibitor SCH503034** has also started a large phase II study in early 2006 along with pegylated interferon (Pegintron) plus ribavirin. In a 14-day study this drug showed less potency, a 1.4 log reduction in HCV viral load.

As in HIV, drug resistance will play a role in the new HCV multiple drug combination therapies being studied. HCV protease inhibitors are associated with drug resistance. The phase II and III studies planned for the two HCV protease inhibitors will inform us on how to use these new therapies. Additional studies will be conducted over the next several years with all the new drugs to inform us how to use them.

There are a number of additional HCV drugs in earlier stages of development. Of particular note, Merck reported in June 2006 the initial results of a study of its **HCV polymerase inhibitor drug MK-0608** in chimpanzees. The drug appears very potent by showing a 5.7 log

reduction in HCV viral load after only 7 days of treatment in the chimpanzees. Studies in humans are planned and if the potency seen in chimps holds up in humans this drug could be the most potent. In March 2006 Roche reported results from a 14-day study of its orally administered polymerase inhibitor R1626. It showed a 1.2 log reduction in HCV viral load in HCV+ patients, and studies in patients for this drug are being planned. Viropharma reported in March 2006 the results of a 14-day study of its HCV polymerase inhibitor drug HCV-796, which showed a 1.4 log reduction in HCV viral load in HCV+ patients. All these drugs could be used one day together in combination therapy for HCV.

**Albuzeron** is a type of interferon being studied and is administered every 2 weeks or perhaps every 4 weeks by subcutaneous injection. So far in early studies it appears similar in potency and safety to regular pegylated interferon.

**NM-283** is a HCV polymerase inhibitor that appeared potent in studies and was furthest along in development, but development hit a snag. Due to side effects and toxicity a lower dose is being evaluated now. **Viramidine** is a new drug being studied as a substitute for ribavirin because there is less risk for anemia associated with it compared to ribavirin, but this drug also hit a snag in development. So, new studies may have to be developed.

There are a number of additional drugs in early stages of development.

It is important to bear in mind that for the foreseeable future pegylated interferon and perhaps ribavirin will be required to be used in combination with these new drugs.

It is very important to be tested for HCV. It is recommended that everyone with HIV be tested for HCV and HBV. Because HIV can significantly accelerate HCV disease progression it is very important to receive care and be closely monitored, and consider therapy. Do not let HCV disease get out of control as this can be very serious to one's health.

### Closing Remarks

As a person who has lived with HIV for 23 years, I feel fortunate to be alive in the era where HIV can be considered a chronic manageable disease, like diabetes, and not necessarily a death sentence. That does not mean that HIV is easy to manage, but if managed properly, one may live a normal lifespan. The key to accomplishing this is making good treatment decisions from the start.

This newsletter, *HIV 102*, along with other NATAP publications such as: *HIV 101*, *Do you have HCV / HIV Coinfection*, and the *HIV / HCV Coinfection Handbook*, are designed to help all people understand treatment. These publications are produced in both English and Spanish.

In addition to having HIV, I had hepatitis C but successfully treated it with peginterferon plus ribavirin therapy. It is very important to be evaluated for hepatitis B and hepatitis C as early as possible if you have HIV because HIV can accelerate hepatitis disease progression.

Anyone with HIV can turn it into a situation where you live life fully. Having HIV does not have to prevent one from seeking and achieving a rewarding, full life.

Good luck,



## NATAP Provides

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NATAP Websites: <http://www.natap.org> & <http://www.hepcadvocacy.org>  
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