New Goals and New Drugs for People With Heavy Anti-HIV Drug Experience

Writer: Mark Mascolini
Editor: Jules Levin
Medical Reviewer: Robert Heglar, MD,
Care Resources, Ft Lauderdale, FL.
Production: Jessie Gibson
Photo right: Jenny Mandeville

More than 20 drugs that fight HIV, the virus that causes AIDS, are available in the United States. Of note, doctors are studying several new anti-HIV drugs—called anti-retrovirals—that attack HIV in different ways. *In fact there is a wave of new HIV drugs available now for people with drug resistance* (Table 1). That's unusual because new anti-HIV drugs usually come one at a time. This is good news for people who have already tried several types of anti-HIV drugs but still cannot stop HIV from making new copies of itself and infecting more cells in the body .

This book is a guide to using these new drugs and to taking advantage of this opportunity. The availability of so many new drugs is exciting because it may allow people who have tried many anti-HIV drugs and have lots of HIV drug resistance to put together an effective anti-HIV regimen. An effective regimen is one that can get HIV viral load below 50 copies (in 1 milliliter of blood) and keep it there. With strict adherence one may be able to keep HIV viral load undetectable (under 50 copies) for 10 years or longer.

Table 1. Recently introduced anti-HIV drugs

Drug	Type of drug	Availability
Fuzeon (enfuvirtide)	Entry/fusion inhibitor	Approved by FDA 3 years ago
Aptivus (tipranavir)	Protease inhibitor	Approved by FDA 1.5 years ago
Prezista (darunavir, TMC114)	Protease inhibitor	Approved by FDA in June 2006
Raltegravir (MK-0518)	Integrase inhibitor	Not yet approved; expanded access program open (see below)
Etravirine (TMC125)	Nonnucleoside	Not yet approved; expanded access program open (see below)
Maraviroc	CCR5 antagonist	Expanded access program open (see below)

In the past year, HIV experts changed their advice on treatment goals for people who have already tried several drug combinations without success. A group called the IAS-USA now says that when doctors can give these people at least two strong drugs, the goal should be a viral load that cannot be measured in the blood [1]. In other words, a test that counts fewer than 50 copies of HIV can count no copies.

This is an important change in treatment advice. It means HIV experts now think many people who have already tried several anti-HIV drug combinations should have the same treatment goal as people starting their first anti-HIV drugs: no HIV in the blood. Studies show that HIV-infected people who achieve this goal:

- Can live a long and healthy life without AIDS.
- Can reach a healthy level of infection-fighting CD4 cells.
- Can keep taking the same anti-HIV drug combination for many years.
- Have a lower chance that their HIV will develop resistance to anti-HIV drugs.

This book explains the new goals of anti-HIV therapy for people with lots of anti-HIV drug experience. It also describes many of the new drugs that can help fight HIV in these people. But first make sure you understand the terms used in this book. If you find it hard to understand these terms, your doctor or nurse or someone who works at an AIDS service organization can help.

Important Terms

CD4 cells are white blood cells that play an important part in fighting all types of infections and cancers. HIV attacks CD4 cells, which then die. Healthy people have a CD4 count around 750 or higher. When the CD4 count falls below 500, the ability to fight infections drops. A CD4 count under 200 is very risky—it means a person has AIDS.

Viral load is a measure of how much HIV can be found in the blood. A viral load under 50 means HIV is under control. This under-50 viral load is the goal of all first-time and second-time anti-HIV combinations. Now new anti-HIV drugs make it possible for many people who have already used several kinds of anti-HIV drugs to reach a viral load under 50.

Viral replication is the term used to describe how HIV makes many copies of itself in CD4 cells. These copies go on to infect other CD4 cells. Stopping viral replication is the main goal of anti-HIV therapy. Keeping the HIV viral load below 50 controls viral replication.

Virologic failure means failure to stop viral replication and keep the viral load under 50 with anti-HIV drugs.

Resistance describes what happens when HIV changes its make-up (or gene code) to escape control by anti-HIV drugs. Each anti-HIV drug causes specific changes (**mutations**) in the gene code if the viral load is not under 50 when a person is taking that drug.

You can get resistant HIV in two ways:

1. When you first get infected with HIV, the HIV you pick up may already be resistant to some anti-HIV drugs or to whole groups of drugs.

2. Resistance may develop (1) when you are taking anti-HIV drugs that don't push your viral load under 50, or (2) if you miss several doses of your anti-HIV drugs or don't take them on time, or (3) if you stop taking your drugs without telling your doctor.

Table 2. Anti-HIV drugs now available in the United States (early 2007)

Group 1: Nucleosides (NRTIs)

Brand name	*Common name*	*Short name*
Emtriva	Emtricitabine	FTC
Epivir	Lamivudine	3TC
Retrovir	Zidovudine	AZT, ZDV
Videx	Didanosine	ddI
Viread	Tenofovir	TDF
Zerit	Stavudine	d4T
Ziagen	Abacavir	ABC

Group 2: Nonnucleosides (NNRTIs)

Brand name	*Common name*	*Short name*
Rescriptor	Delavirdine	DLV
Sustiva	Efavirenz	EFV
Viramune	Nevirapine	NVP

Group 3: Protease inhibitors (PIs)

Brand name	Common name	Short name
Agenerase	Amprenavir	APV
Aptivus	Tipranavir	TPV
Crixivan	Indinavir	IDV
Invirase	Saquinavir	SQV
Kaletra	Lopinavir + ritonavir	LPV/RTV
Lexiva	Fosamprenavir	FPV
Norvir	Ritonavir	RTV
Prezista	Darunavir (TMC114)	DRV
Reyataz	Atazanavir	ATV
Viracept	Nelfinavir	NFV

Group 4: Entry inhibitors

Brand name	*Common name*	*Short name*
Fuzeon	Enfuvirtide	ENV, T-20

Combination drugs

Brand name	*Common name*	*Short name*
Atripla	Efavirenz + tenofovir + emtricitabine	EFV + TDF + FTC
Combivir	Zidovudine + lamivudine	AZT + 3TC
Epzicom	Abacavir + lamivudine	ABC + 3TC
Trizivir	Zidovudine + lamivudine + abacavir	AZT + 3TC + ABC
Truvada	Tenofovir + emtricitabine	TDF + FTC

Resistance tests tell your doctor whether HIV has developed resistance to the drugs you are taking. For a person who has already tried many anti-HIV drugs, resistance tests may help a doctor decide which different anti-HIV drugs will still work.

HIV experts call for resistance tests before a person starts a first anti-HIV combination and before switching to a new combination.

Multidrug resistance means HIV has developed resistance to more than one anti-HIV drug—and often to more than one group of anti-HIV drugs.

Active drugs are drugs to which HIV is not resistant.

Salvage therapy, also called rescue therapy, describes an anti-HIV drug combination planned for people with multidrug resistance.

Adherence describes how well a person takes anti-HIV drugs. “Complete adherence” means taking all your drugs at the right time every day. Complete adherence is the best way to prevent resistance and to make sure your anti-HIV drug combination works.

Why Stopping Viral Replication Is So Important

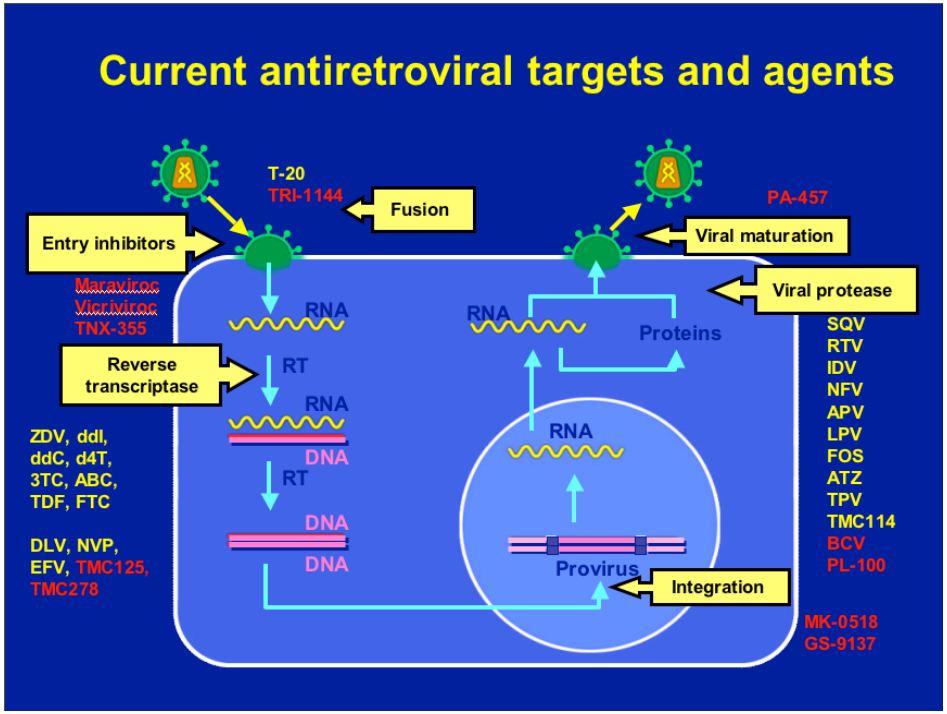
Viral replication is not a good thing. The goal of anti-HIV therapy is to get the viral load (counted as copies of HIV RNA in a milliliter of blood) below 50. Doing so helps prevent resistance to anti-HIV drugs, HIV-related illness, and death.

Another goal of anti-HIV therapy is to raise the CD4 cell count as high as possible. So there are two goals of anti-HIV therapy: to raise the CD4 count as high as possible and to push the viral load below 50. Many people with HIV push their CD4 count as high as counts of HIV-negative people, which is above 750. Some people with HIV may not reach a normal CD4 count and still be safe from HIV-related illness.

But if your viral load is detectable (above 50), it means you have continuing viral replication. Having a viral load above 50 is not good over the long term. You may not feel bad in the short term with a low level of viral replication. But over the long term ongoing viral replication will lead to drug resistance in people taking anti-HIV drugs. Ongoing viral replication can also increase the risk of health problems.

Until recently, people with lots of resistance to anti-HIV drugs had a hard time reaching a viral load below 50. But today the many new HIV drugs available make it possible for more people with lots of resistance to get their viral load under 50 with active drugs. That’s why the IAS-USA changed the goal of therapy for people with lots of drug resistance [1].

Figure 1. Different groups of anti-HIV drugs work at different points inside and outside CD4 cells. Combining drugs that work at different points is one way to stop multidrug-resistant HIV. (Approved drugs in yellow; drugs still being studied in red. See Table 2 for short names of drugs.)



(Adapted with permission from Roche.)

Complete adherence is the key to reaching this under-50 goal (Figure 1). Anti-HIV drugs that are easier to take and cause fewer side effects make adherence easier. So it's important to select easy-to-take anti-HIV drugs, if possible (Figure 1). That can be challenging because the first goal is to find a combination of active drugs strong enough to get the viral load under 50 and keep it there. Fortunately several new, powerful anti-HIV drugs are easier to take and have few side effects. So it's sometimes possible to find a strong anti-HIV drug combination that is also safe and easy to take.

Goals of Salvage (or Rescue) Therapy

Only a few years ago, HIV experts believed the goal of salvage therapy should be to keep the CD4 cell count as high as possible and to avoid AIDS diseases. They knew that most people with multidrug resistance would not be able to reach a viral load under 50 with a new combination of anti-HIV drugs.

Today—with more strong anti-HIV drugs available—HIV experts think many people with multidrug resistance CAN reach a viral load under 50. And these experts say HIV doctors should try to plan active drug combinations that can achieve this goal.

Advice from HIV experts in the United States and elsewhere [1,2] suggests some important steps in planning and taking anti-HIV drug combinations when a person has multidrug resistance:

1. Combine *three*, or at least *two*, active anti-HIV drugs that will work against multidrug-resistant HIV.

2. *The drugs needed will often be new drugs made specifically to fight resistant HIV or drugs in an anti-HIV drug group that a person has not used before.* (See "Anti-HIV Drugs in New Drug Groups" and "Anti-HIV Drugs in Current Drug Groups" later in this book for a list of such drugs.)

3. Resistance tests—and often advice from experts—are usually needed to pick active drugs that will fight resistant virus.

4. Complete adherence to your doctor's drug-taking instructions is very important in making this new drug combination work.

What happens if your HIV doctor can't find two or three active drugs that will fight the resistant virus in your body? (Again, an active drug is a drug to which HIV has not become resistant.) Most HIV experts say it's best not to give a drug combination that contains just one active anti-HIV drug. If that happens, HIV has a much better chance of becoming resistant to that one drug. And if HIV becomes resistant to that drug, it will be weaker or completely useless in future combinations.

It's usually much better to wait until two or three active drugs can be combined. And with so many new anti-HIV drugs being studied, chances are good that new drugs will be available soon.

While you are waiting for new drugs, your doctor will try to combine current anti-HIV drugs that will keep your CD4 cell count as high as possible and prevent AIDS diseases. Sustiva (efavirenz) and Viramune (nevirapine) should not be part of such a combination [1]. But Emtriva (emtricitabine) or Epivir (lamivudine) may be useful for this kind of treatment [1]. Your doctor will probably also use other drugs that do not directly fight HIV. Instead, they prevent AIDS diseases that may develop at lower CD4 cell counts.

What About Drug Holidays?

Over the past 10 years, HIV doctors have studied drug holidays in people with virologic failure and multidrug resistance. A drug holiday means stopping all anti-HIV drugs for a certain time. Some experts thought drug holidays might make a person's HIV change back to a less resistant form. Then starting anti-HIV drugs again might work better.

But this plan didn't work. Several studies show that people who took drug holidays with multidrug resistance did no better when they restarted anti-HIV drugs than people who never took a holiday [3-6]. In fact, the people who took anti-HIV drug holidays sometimes ran a higher risk of getting an AIDS disease.

Other studies show that it's usually better for people with virologic failure to continue a partly effective regimen than to stop all anti-HIV drugs [7-10]. When a person stops all anti-HIV drugs, the CD4 cell count falls and the viral load goes up.

Sometimes your doctor may stop all anti-HIV drugs to focus on treating another serious disease. The anti-HIV drugs will start again when treatment controls the other disease. You should never stop anti-HIV drugs on your own. You should not even stop one of several drugs you may take. Taking all your anti-HIV drugs on time is very important in preventing resistance.

Anti-HIV Drugs and How They Work

As Table 2 shows, right now (early 2007) we have four groups of anti-HIV drugs approved by the Food & Drug Administration (FDA): nucleosides, nonnucleosides, protease inhibitors, and entry inhibitors. Some new drugs in these groups work against resistant HIV.

Five new groups of anti-HIV drugs may become available over the coming months and years.

- Integrase inhibitors
- CCR5 inhibitors
- CD4 inhibitors
- CXCR4 inhibitors
- Maturation inhibitors

The first integrase inhibitor, raltegravir, is available now through a special program (called an "Expanded Access Program") from Merck. The first CCR5 inhibitor (or CCR5 antagonist), maraviroc, is also available through an expanded access program from Pfizer (see "How to Get New Anti-HIV Drugs" below). After FDA approval availability transfers to the pharmacy.

Doctors group anti-HIV drugs by how they work against HIV. Drugs may affect a part of HIV itself. Or they may affect a part of the CD4 cell that HIV infects. Table 3 and Figure 2 list the nine main groups of anti-HIV drugs and explain where and how they work.

Table 3. How different anti-HIV drug groups work

Current drug groups

Drug group	*Affect HIV or CD4 cell?*	*How they work*
Nucleosides (NRTIs)	HIV	Act against reverse transcriptase, an HIV enzyme that reads HIV's gene code1
Nonnucleosides (NNRTIs)	HIV	Act against reverse transcriptase, an HIV enzyme that reads HIV's gene code1
Protease inhibitors (PIs)	HIV	Act against protease, an HIV enzyme that cuts HIV proteins into the size needed to make new HIV particles2
Entry inhibitors	HIV	Act against gp41, a protein on HIV's coat that HIV uses to enter CD4 cells

New drug groups

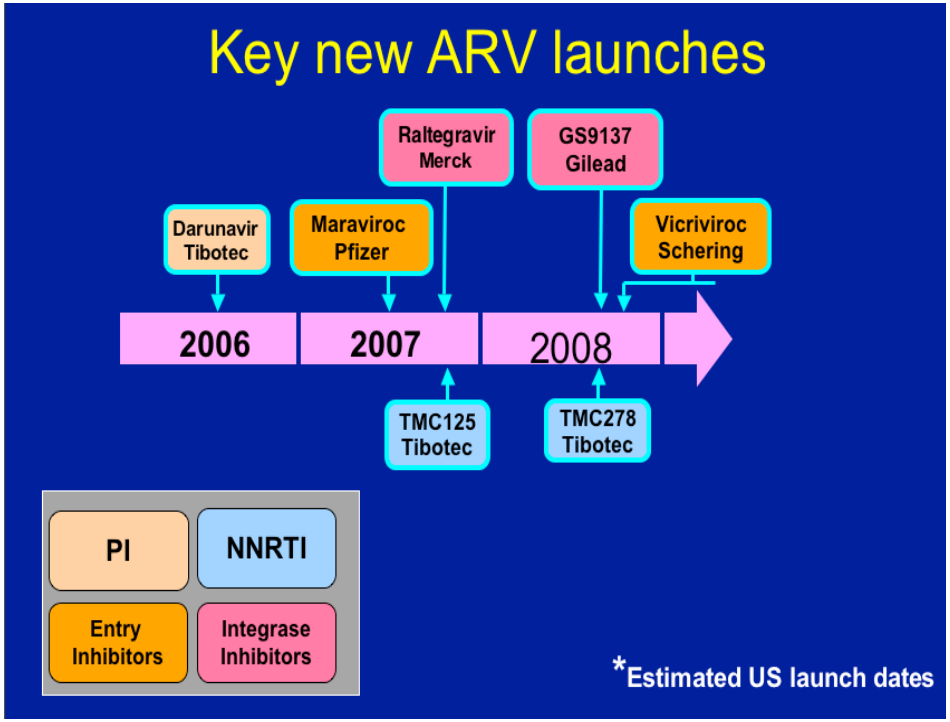
Drug group	Affect HIV or CD4 cell?	How they work
CCR5 inhibitors	CD4 cell	Act against CCR5, a protein on the CD4 cell surface that some HIVs use to get inside these cells
CXCR4 inhibitors	CD4 cell	Act against CXCR4, a protein on the CD4 cell surface that some HIVs use to get inside these cells
CD4 inhibitors	CD4 cell	Act against CD4, a protein on the CD4 cell surface that all HIVs use to get inside these cells
Integrase inhibitors	HIV	Act against integrase, an HIV enzyme that HIV needs to get inside the CD4 cell core or "nucleus"
Maturation inhibitors	HIV	Act against cutting of HIV proteins into the size needed to make new HIV particles2

1Nucleosides and nonnucleosides act against reverse transcriptase in completely different ways.

2Protease inhibitors and maturation inhibitors act against HIV protein cutting in completely different ways.

It takes many steps for HIV to get inside CD4 cells and to make copies of itself that pop out of the cell surface. The nine anti-HIV drug groups in Table 3 all work in different ways or at different points in this many-step path (Figure 2).

Figure 2. This chart shows when several new anti-HIV drugs may be approved for use in the United States. Prezista (also called TMC114) was approved by the FDA in June 2006.



When HIV changes itself to become resistant to one drug in a group, it may also become resistant to other drugs in that group. Let's say a person is taking an anti-HIV drug combination that includes the nonnucleoside Sustiva (efavirenz). Then that person starts missing doses. HIV will probably change to become resistant to Sustiva. That HIV will also probably be resistant to the nonnucleoside Viramune (nevirapine), even though that person has never taken Viramune.

This resistance pattern is important for three reasons:

1. It means your doctor usually needs a resistance test to tell whether HIV resistant to one drug in a drug group is also resistant to other drugs in that group.

2. It means you should not skip drug doses or stop taking your drugs unless your doctor tells you to. Skipping doses or taking drug holidays can make HIV resistant to drugs you are not even taking.

3. It means anti-HIV drugs from a drug group you have never taken will probably work against the HIV in your body. A drug in a new group will probably work against HIV even if the HIV is resistant to other classes of drugs you have taken in the past.

For example, if you have HIV resistant to nucleosides, nonnucleosides, and protease inhibitors, a combination including a CCR5 inhibitor and an integrase inhibitor would have a very good chance of stopping that multidrug-resistant HIV.

How to Get New Anti-HIV Drugs

You can get new anti-HIV drugs—including those in new drug groups—in three ways:

1. Enter a study testing the new drug.

Many studies of new drugs split people into two groups: Some people get the new drug plus other anti-HIV drugs. Other people get other anti-HIV drugs but not the new drug.

In this kind of study—a "randomized trial"—a person cannot be sure of getting the new drug immediately. But people who do not get the new drug immediately will often get it after several months in the study, if they do not respond to the combination of FDA-approved drugs.

Not everyone can get into new drug studies. For example, people with severe liver disease may not be able to join. You and your doctor can find out which studies you can join by searching through one of the following Web sites:

http://clinicaltrials.gov/

http://www.aidsinfo.nih.gov/ClinicalTrials/Default.aspx?MenuItem=ClinicalTrials (English)

http://www.aidsinfo.nih.gov/ClinicalTrials/Default_es.aspx?MenuItem=ClinicalTrials (Español)

http://www.acria.org/clinical_trials/

2. Get the new drug through "expanded access."

When a drug is close to approval, the drug's maker may make it available to people who have a great need for new anti-HIV drugs. In other words, access to the drug is "expanded" beyond formal studies.

Only certain people can get new drugs this way. For example, a person may need to have HIV resistant to three other groups of anti-HIV drugs.

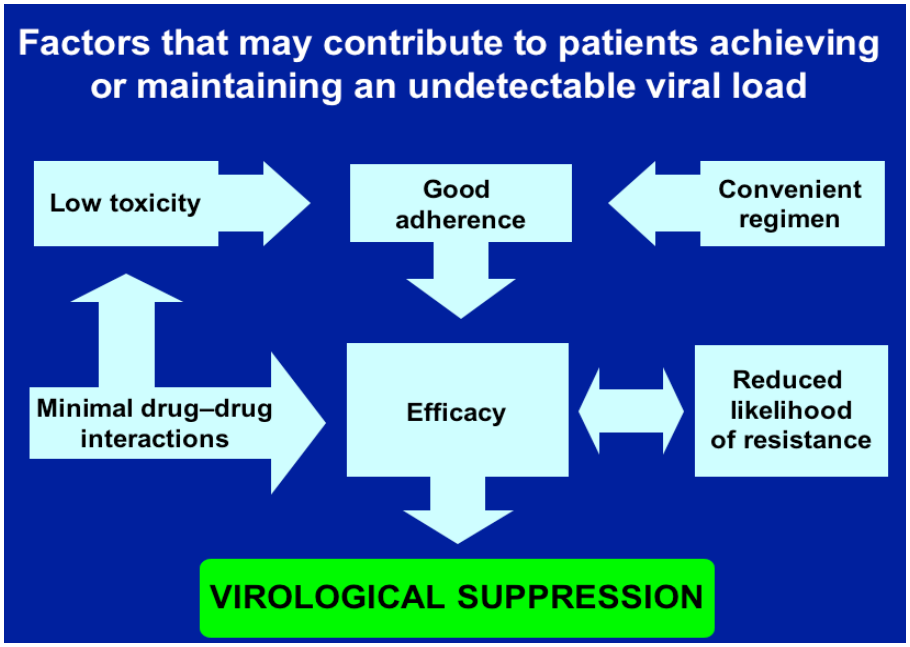
Right now (early 2007) there are expanded access programs for three new anti-HIV drugs in the United States, listed below. Which anti-HIV drugs you can get through expanded access changes regularly, as new drugs approach approval.

Maraviroc (a CCR5 inhibitor): Go to http://www.maravirocEAP.com.

Raltegravir (an integrase inhibitor): Call 1-877-EARMRK1 or go to http://www.earmrk.com.

Etravirine (TMC125) (a nonnucleoside): Call 1-866-889-2074 or e-mail TMC125EAP@i3research.com.

Figure 3. Several factors combine to make anti-HIV drug combinations work well and stop viral replication.



3. Get the drug after it is approved.

When the FDA approves a drug (Figure 3), anyone who can pay for the drug (including people in a government drug program or with health insurance) can get that drug with a doctor's prescription.

WARNING: Drugs You Take May Affect Each Other

Anti-HIV drugs may affect other drugs you take. And other drugs can affect your anti-HIV drugs. Taking certain drugs at the same time can make levels of one drug higher or lower in your body. Higher levels make side effects more likely (Figure 1). Lower levels raise the risk that a drug will not work. These problems are called "drug-drug interactions."

This is true of drugs that your doctor prescribes and (1) drugs you can buy yourself at the drug store or health food store, including acid-reducing drugs like Prilosec (omeprazole), (2) drugs like methadone and buprenorphine, and (3) illegal drugs.

It is very important to tell your doctor about ALL the drugs you are taking, including vitamins and natural remedies.

Do not start taking other drugs with your anti-HIV drugs without talking to your doctor first. And do not stop other drugs without talking to your doctor.

Anti-HIV Drugs in New Drug Groups

Integrase Inhibitors

• Raltegravir

Maker: Merck

For expanded access in US: Call 1-877-EARMRK1 or go to http://www.earmrk.com.

Study stage: Phase 3 studies (final stage before approval)

US approval outlook: Possibly 2007

Daily dose: Twice daily

Important findings: Raltegravir plus other anti-HIV drugs potently kept HIV under control much better than a dummy pill (placebo) plus other anti-HIV drugs in people with HIV resistant to drugs in three other anti-HIV drug groups [11]. More than 60% of people taking raltegravir got their viral load below 50 in 16 weeks, while 90% combining raltegravir with Prezista or Fuzeon had a viral load under 400 copies in 16 weeks. And 98% of individuals who combined raltegravir with both Prezista and Fuzeon achieved a viral load under 400 copies in 16 weeks.

In a study of people taking raltegravir alone for 10 days as their first antiretroviral, most reached a viral load under 400 [12]. When these people combined raltegravir with Viread (tenofovir) plus Epivir (lamivudine), they controlled HIV as well as people who combined Sustiva (efavirenz) with Viread and Epivir, and people taking raltegravir had no changes in blood fats (cholesterol or triglycerides) after 24 weeks of treatment [13].

Side effects: Serious side effects have been rare in studies done so far [11-13]. In addition, few or no effects on lipids (cholesterol, triglycerides) have been seen.

• Elvitegravir GS-9137

Maker: Gilead

Study stage: Phase 2 studies

US approval outlook: Possibly 2008

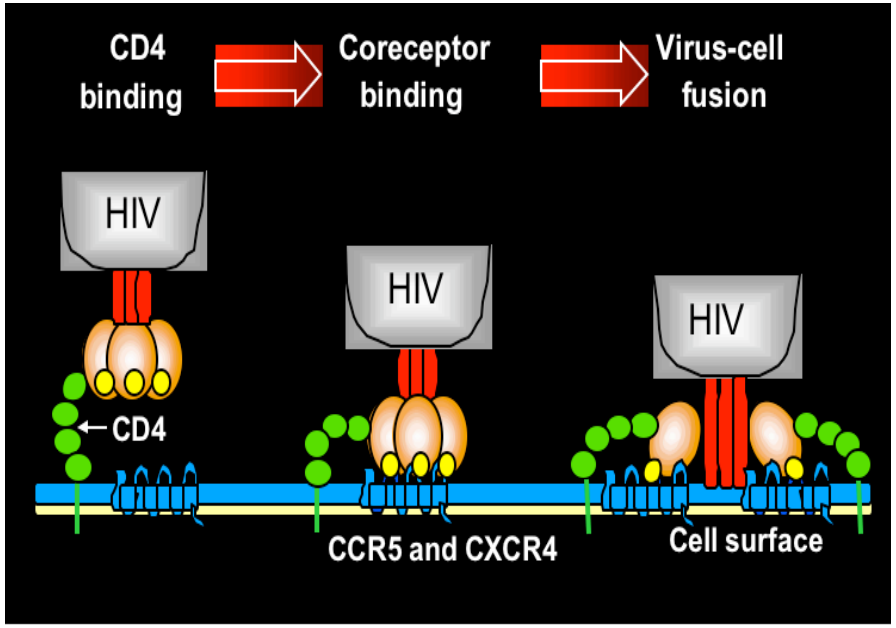
Daily dose: Once daily with Norvir (ritonavir)

Important findings: In early study, GS-9137 has been potent against HIV. Elvitegravir given once daily with 100 milligrams of Norvir (ritonavir) and other anti-HIV drugs controlled multidrug-resistant HIV better than some newer protease inhibitors in a 16-week study [14].

Side effects: People taking elvitegravir with other anti-HIV drugs had no more side effects than people taking protease inhibitors plus other drugs in this study [14]. Because elvitegravir will probably be given with a low dose of the protease inhibitor Norvir (ritonavir), people taking it will risk Norvir side effects.

Other concerns: Studies in cells suggest the two integrase inhibitors elvitegravir and raltegravir may have a degree of cross-resistance to each other.

Figure 4. To get inside CD4 cells, HIV first hooks onto CD4 itself. Then it hooks either CCR5 or CXCR4. Different types of anti-HIV drugs can block HIV at any of these three points.



CCR5 Inhibitors

• Maraviroc

Maker: Pfizer

For expanded access in US: Go to http://www.maravirocEAP.com.

Study stage: Phase 3 studies (final stage before approval)

US approval outlook: Possibly 2007

Daily dose: Twice daily

Important findings: Maraviroc plus other anti-HIV drugs potently lowered viral loads much more than a dummy pill plus other drugs in people with multidrug-resistant HIV that uses the CCR5 gateway to get inside CD4 cells (Figure 4) [16]. After 24 weeks of treatment 50% to 60% of people taking maraviroc had a viral load under 400 copies, *Side effects*: In studies done so far, side effects like headache, dizziness, and nausea have been mild.

Side effects: In studies done so far, side effects like headache, dizziness, and nausea have been mild.

Other concerns: (see below: *Other concerns for* ***Maraviroc*** *and* ***Vicriviroc)***

• Vicriviroc

Maker: Schering-Plough

Study stage: Phase 2 studies

US approval outlook: Possibly 2008

Daily dose: Once daily

Important findings: In people who have already taken anti-HIV drugs and whose HIV uses the CCR5 gateway to CD4 cells, vicriviroc plus other anti-HIV drugs kept HIV under control better than a dummy pill plus other anti-HIV drugs for 24 weeks [19]. After 24 weeks of treatment 43-53% of people taking vicriviroc had a viral load <400 copies. Everyone in this study was already taking anti-HIV drugs and had a viral load over 5000. People taking vicriviroc also gained more CD4 cells than people taking the dummy pill combination.

In people starting their first anti-HIV drugs, vicriviroc plus Combivir (Retrovir and Epivir) did not stop HIV as well as Sustiva (efavirenz) plus Combivir [20].

Side effects: Cancers developed in 5 of 83 people (6%) starting vicriviroc after virologic failure [19]. Researchers could not tell whether vicriviroc caused these cancers.

Other concerns for ***Maraviroc*** *and* ***Vicriviroc*** *:* HIV uses one main gateway to enter CD4 cells (CD4 receptor) and one of two secondary gateways (CCR5 or CXCR4 co-receptor) (Figure 4). A 'tropism assay' (test) is performed to see if patients might benefit from the CCR5 drug. CCR5 inhibitors are effective in blocking HIV from getting into cells for patients with 'R5' tropic virus. It is currently thought that CCR5 inhibitors should be used in patients with CCR5-tropic virus exclusively, those whose HIV use only CCR5 to enter CD4 cells. The tropism assay (test) should be performed to see if the patient has R5 tropic HIV-1. Approximately 85% of patients who are antiretroviral naive and 50-60% of patients who are highly treatment experienced have R5 tropic virus exclusively.

CD4 *Inhibitors*

• TNX-355

Maker: Tanox/Genentech

Study stage: Phase 2 studies

US approval outlook: Possibly 2008-2009

Dose: Once every 2 weeks, infused through a vein

Important findings: In a study of 82 people who had tried anti-HIV drugs from three drug groups, TNX-355 plus other anti-HIV drugs stopped HIV better than a dummy pill plus other anti-HIV drugs for 48 weeks [21]. But few people taking TNX-355 combined with other HIV drugs reached a viral load under 50. CD4 cell counts rose in people taking TNX-355.

Because TNX-355 acts against CD4, the main gateway on CD4 cells, it does not matter if the cell uses CCR5 or CXCR4 or both for a second gateway (Figure 4).

Side effects: People taking TNX-355 had no more side effects than people taking the dummy pill in this study [21].

Other concerns: Unlike all current anti-HIV drugs, TNX-355 must be given through a line put into a vein.

Maturation Inhibitors

• Bevirimat (PA-457)

Maker: Panacos

Study stage: Phase 2 studies; phase 3 studies beginning in 2007

*US approval outloo*k: Possibly 2008

Daily dose: Once daily

I*mportant findings:* In a 10-day study of people taking no other anti-HIV drugs, once-daily bevirimat lowered viral loads much better than a dummy pill [22]. The highest dose studied (200 milligrams daily) worked best in this 34-person study.

Bevirimat works differently from other anti-HIV drug groups. As a result, it can control HIV resistant to these other drug groups (nucleosides, nonnucleosides, protease inhibitors, and the entry inhibitor Fuzeon) [23].

Side effects: Few findings reported so far.

New Anti-HIV Drugs in Current Drug Groups

Nonnucleosides (NNRTIs)

• Etravirine (TMC125)

Maker: Tibotec

For expanded access in US: Call 1-866-889-2074 or e-mail TMC125EAP@i3research.com.

Study stage: Phase 3 studies (final stage before approval)

US approval outlook: Possibly 2007

Daily dose: Twice daily

Important findings: Etravirine worked well in a study of 16 people taking a failing nonnucleoside, Sustiva (efavirenz) or Viramune (nevirapine) [24]. The HIV in all these people was resistant to Sustiva and Viramune. Everyone replaced Sustiva or Viramune with etravirine and continued their other anti-HIV drugs. After taking etravirine for only 7 days, their viral loads fell sharply.

Etravirine also controlled HIV well for 48 weeks in 199 people with HIV resistant to other nonnucleosides and to protease inhibitors [25]. Viral loads fell 10-fold in people taking 800 mg of etravirine twice daily. After 48 weeks 30% of people taking etravirine had viral load under 400 copies.

A small study combined etravirine with Prezista (darunavir) in 10 people with HIV resistant to protease inhibitors, nonnucleosides, or both [26]. (See “Prezista” below.) Everyone also took nucleosides, and some people took Fuzeon (enfuvirtide). After 6 weeks 8 of 10 people reached a viral load below 400 and 5 of 10 had a load below 40. Other larger studies are also testing this combination.

Another study found that etravirine does not work well in people whose HIV has become too resistant to nonnucleosides and nucleosides [27].

A 7-day study compared etravirine with a dummy pill in 19 people who never took anti-HIV drugs before [28]. Viral loads dropped quickly in the etravirine group but not in the dummy pill group.

Side effects: Side effects seen so far with etravirine are usually mild and include headache and diarrhea [24]. In the 199-person study of etravirine, rash developed in 15% of people taking this drug [25].

Protease Inhibitors (PIs)

• Aptivus (tipranavir)

Maker: Boehringer Ingelheim

Web site: http://www.aptivus.com

Study stage: Approved for use in the United States

Daily dose: Twice daily with 200 milligrams of Norvir (ritonavir)

Important findings: Important findings: Two studies of almost 1500 people with multi-drug resistant HIV found that Aptivus plus Norvir (ritonavir) and other anti-HIV drugs control HIV better than Lopinavir plus Norvir (Kaletra), Crixivan plus Norvir (indinavir), Invirase plus Norvir (saquinavir), or Agenerase plus Norvir (amprenavir) along with other anti-HIV drugs [29]. CD4 cell counts also rose more with Aptivus plus Norvir than with other protease inhibitors in this 48-week study. Continued study of these people for another 48 weeks showed that Aptivus/Norvir kept controlling HIV better than the other protease inhibitors tested in this trial [30]. But Aptivus plus Norvir caused more side effects than the other anti-HIV drug combinations. (See “Side effects” below.)

In these two studies, people who could start Fuzeon (enfuvirtide) for the first time did better than those who could not [29]. This was true for people taking Aptivus and for those taking other protease inhibitors. Combining a new anti-HIV drug with one or two drugs to which HIV is not resistant (“active drugs”) is the best way to fight resistant HIV.

Two studies show that Aptivus plus Norvir works best if HIV has not developed certain resistance mutations that can greatly affect how well Aptivus works [31,32] Resistance testing is necessary for anyone who may start Aptivus plus Norvir to make sure these are the best protease inhibitors to use.

Side effects: Compared with people who took other protease inhibitors in two big studies, those who took Aptivus plus Norvir had higher rates of blood fats (which raise the risk of heart disease) and liver enzymes (elevated liver enzymes may or may not indicate liver damage). [29].

Nausea, vomiting, diarrhea, and stomach pain are other side effects of Aptivus plus Norvir.

A few people taking Aptivus plus Norvir have had bleeding in the brain, which can cause death. It remains uncertain if this was related to Aptivus since these were individuals with advanced HIV.

The FDA warns that people with liver damage (such as people with hepatitis) need special attention if they start Aptivus plus Norvir. Anyone who starts these anti-HIV drugs should have regular liver tests.

Other concerns: Aptivus plus Norvir should not be part of a person’s first anti-HIV drug combination.

• Prezista (darunavir, TMC114)

Maker: Tibotec

Web site: http://www.prezista.com

Study stage: Approved for use in United States

Daily dose: Twice daily with 100 milligrams of Norvir (ritonavir)

Important findings: Two studies compared Prezista plus Norvir (ritonavir) (and other anti-HIV drugs) with another protease inhibitor plus Norvir (and other anti-HIV drugs) in 255 people who had already taken protease inhibitors, nucleosides, and nonnucleosides [33]. After 48 weeks, HIV control was much better in people taking Prezista than in those taking other protease inhibitors.

Almost half of the people taking Prezista reached a viral load below 50. More than half of the people who took Fuzeon (enfuvirtide) for the first time with Prezista reached a viral load below 50. Combining a new anti-HIV drug with one or two active drugs is the best way to fight resistant HIV.

Side effects: Mild to serious rashes have developed in some people taking Prezista. The most common side effects are diarrhea, nausea, headache, and the common cold.

Other concerns: People with less resistance to protease inhibitors do better when they start Prezista plus Norvir than people with more resistance [33]. Resistance testing is necessary for anyone who may start Prezista plus Norvir to make sure these are the best protease inhibitors to use.

Entry Inhibitors

• **Fuzeon (enfuvirtide)**

Maker: Roche, Trimeris

Web site: http://www.fuzeon.com

Study stage: Approved for use in the United States

Daily dose: Twice daily by injection

Important findings: Two worldwide studies compared Fuzeon (plus other anti-HIV drugs) and other anti-HIV drugs without Fuzeon in people who had multidrug-resistant HIV [34,35]. Viral loads fell much farther in people taking Fuzeon than in people taking only other anti-HIV drugs. And CD4 cell counts rose more in people taking Fuzeon.

These studies also showed that people who started Fuzeon and other drugs with a CD4 count above 100 did better than those who started with a lower CD4 count [36]. And people who started with a viral load below 100,000 did better than people who started with a higher viral load.

Studies of other new drugs like raltegravir, Aptivus, and Prezista (above) compared people who also took Fuzeon with people who did not [11,29,33]. Taking Fuzeon with another new anti-HIV drug worked better than not taking Fuzeon. These findings make an important point: anti-HIV drug combinations for people with multidrug-resistant HIV should contain at least two active drugs.

Side effects: Almost everyone who takes Fuzeon gets swelling, soreness, redness, or itching in spots where they inject the drug. These problems are usually mild to moderate but can be severe. Your doctor or nurse can give you pointers on relieving these problems. A “drug gun” (“Biojector”) that shoots Fuzeon into the skin without a needle should be available soon in the United States. It may prevent quite a bit of this swelling and soreness [37,38]. But some people using Biojector had nerve pain lasting up to 6 months. Such pain may be prevented by avoiding certain body sites when using Biojector

People taking Fuzeon may get bacterial pneumonia more often than people not taking Fuzeon. Contact your doctor right away if you have a cough, fever, or trouble breathing while taking Fuzeon.

A few people starting Fuzeon may have rash, fever, chills, shaking, nausea, or vomiting—or a combination of these problems. If you do, contact your doctor immediately.

Do’s and Dont's for People With Extensive Anti-HIV Drug Experience

People with multidrug-resistant HIV now have a better chance than ever of reaching a viral load below 50. HIV experts recommend that this should be the goal for people who can combine two or three active drugs (drugs to which HIV has not become resistant) [1,2].

The goal of reaching a viral load under 50 is now possible for more people because several new anti-HIV drugs are available. Some of these drugs are in new anti-HIV drug groups, so they can fight resistant virus well.

Studies show that more and more people can build combinations including new anti-HIV drugs and get their viral loads under 50 [13,19,25,29,33,36].

Much of the advice in this book can be summed up as a list of do’s and dont's for people with multidrug resistance (Table 4).

Table 4. Do’s and dont's for people with multidrug-resistant HIV

Do's	*Don'ts*
• Do: Wait until you can combine at least two or three active anti-HIV drugs before starting a new combination.	• Don’t: Add only one active drug to a failing combination. Don’t use a drug combination that may not be potent enough.
• Do: Get a resistance test to help pick the best anti-HIV drugs for a new combination.	• Don’t: Get a resistance test weeks after stopping a failing combination. The test is more accurate if it is done while a person is still taking the failing drugs or shortly thereafter.
• Do: Give your doctor a list of all drugs you’re taking—including vitamins and natural products.	• Don’t: Start a new drug, vitamin, or natural product without first talking to your doctor.
• Do: Take all your anti-HIV drugs every day in the way your doctor or nurse instructs.	• Don’t: Skip anti-HIV drugs at any time.
• Do: Consider taking Epivir (lamivudine) or Emtriva (emtricitabine) if continuing a partly effective combination while waiting for new anti-HIV drugs.	• Don’t: Stop taking anti-HIV drugs unless your doctor tells you to.
	• Don’t: Take Sustiva (efavirenz) or Viramune (nevirapine) in a partly effective combination while waiting for new anti-HIV drugs.

References

1. Hammer SM, Saag MS, Schechter M, et al. Treatment for adult HIV infection: 2006 recommendations of the International AIDS Society-USA panel. JAMA. 2006;296:827-843.

2. DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. October 10, 2006

3. Lawrence J, Mayers DL, Hullsiek KH, et al. Structured treatment interruption in patients with multidrug-resistant human immunodeficiency virus. N Engl J Med. 2003;349:837-846.

4. Ruiz L, Ribera E, Bonjoch A, et al. Role of structured treatment interruption before a 5-drug salvage antiretroviral regimen: the Retrogene Study. J Infect Dis. 2003;188:977-985.

5. Ghosn J, Wirden M, Ktorza N, et al. No benefit of a structured treatment interruption based on genotypic resistance in heavily pretreated HIV-infected patients. AIDS. 2005;19:1643-1647.

6. Benson CA, Vaida F, Havlir DV, et al. A randomized trial of treatment interruption before optimized antiretroviral therapy for persons with drug-resistant HIV: 48-week virologic results of ACTG A5086. J Infect Dis. 2006;194:1309-1318.

7. Kaufmann D, Pantaleo G, Sudre P, et al. CD4-cell count in HIV-1-infected individuals remaining viraemic with highly active antiretroviral therapy (HAART): Swiss HIV Cohort Study. Lancet. 1998;351:723-724.

8. Miller V, Phillips AN, Clotet B, et al. Association of virus load, CD4 cell count, and treatment with clinical progression in human immunodeficiency virus-infected patients with very low CD4 cell counts. J Infect Dis. 2002;186:189-197.

9. Deeks SG, Wrin T, Liegler T, et al. Virologic and immunologic consequences of discontinuing combination antiretroviral-drug therapy in HIV-infected patients with detectable viremia. N Engl J Med. 2001;344:472-480.

10. Eron JJ Jr, Bartlett JA, Santana JL, et al. Persistent antiretroviral activity of nucleoside analogues after prolonged zidovudine and lamivudine therapy as demonstrated by rapid loss of activity after discontinuation. J Acquir Immune Defic Syndr. 2004;37:1581-1583.

11. 11. Cooper D, Gatell J, Rockstrok J, et al. Results of BENCHMRK-1, a phase III study evaluating the efficacy and safety of MK-0518, a novel HIV-1 integrase inhibitor, in patients with triple-class resistant virus. 14th Conference on Retroviruses and Opportunistic Infections. February 25-28, 2007. Los Angeles. Abstract 105aLB. Steigbigel R, Kumar P, Eron J, et al. Results of BENCHMRK-2, a phase III study
evaluating the efficacy and safety of MK-0518, a novel HIV-1 integrase inhibitor, in patients with triple-class resistant virus. 14th Conference on Retroviruses and Opportunistic Infections. February 25-28, 2007. Los Angeles. Abstract 105bLB.

12. Markowitz M, Morales-Ramirez JO, Nguyen BY, et al. Antiretroviral activity, pharmacokinetics, and tolerability of MK-0518, a novel inhibitor of HIV-1 integrase, dosed as monotherapy for 10 days in treatment-naive HIV-1-infected individuals. J Acquir Immune Defic Syndr. 2006;43:509-515.

13. Markowitz M, Nguyen B-Y, Gotuzzo F, et al. Potent antiretroviral effect of MK-0518, a novel HIV-1 integrase inhibitor, as part of combination ART in treatment-naive HIV-1 infected patients. XVI International AIDS Conference. August 13-18, 2006. Toronto. Abstract THLB0214.Teppler H, Azrolan N, Chen J, et al. Differential effects of MK-0518 and efavirenz on serum lipids and lipoproteins in antiretroviral therapy (ART)-naive patients (24 week results). 46th ICAAC. September 27-30, 2006, San Francisco. Poster H-0256a.

14. Zolopa A, Mullen M, Berger D, et al. The HIV integrase inhibitor GS-9137 demonstrates potent ARV activity in treatment-experienced patients. 14th Conference on Retroviruses and Opportunistic Infections. February 25-28, 2007. Los Angeles. Abstract 143LB.

15. Jones G, Ledford RM, Yu F, et al. In vitro resistance profile of HIV-1 mutants selected by the HIV-1 integrase inhibitor, GS-9137 (JTK-303). 14th Conference on Retroviruses and Opportunistic Infections. February 25-28, 2007. Los Angeles. Abstract 627.

16. Nelson M, Fatkenheur G, Konourina I, et al. Efficacy and safety of maraviroc plus optimized background therapy in viremic, ART-experienced patients infected with CCR5-tropic HIV-1 in Europe, Australia, and North America: 24-Week Results. 14th Conference on Retroviruses and Opportunistic Infections. February 25-28, 2007. Los Angeles. Abstract 104aLB. Lalezari J, Goodrich J, DeJesus E, et al. Efficacy and safety of maraviroc plus optimized background therapy in viremic ART-experienced patients infected with CCR5-tropic HIV-1: 24-week results of a phase 2b/3 study in the US and Canada. 14th Conference on Retroviruses and Opportunistic Infections. February 25-28, 2007. Los Angeles. Abstract 104bLB.

17. Westby M, Lewis M, Whitcomb J, et al. Emergence of CXCR4-using human immunodeficiency virus type 1 (HIV-1) variants in a minority of HIV-1-infected patients following treatment with the CCR5 antagonist maraviroc is from a pretreatment CXCR4-using virus reservoir. J Virol. 2006;80:4909-4920.

18. Mayer H, van der Ryst E, Saag M, et al. Safety and efficacy of maraviroc, a novel CCR5 antagonist, when used in combination with optimized background therapy for the treatment of antiretroviral-experienced subjects infected with dual/mixed-tropic HIV-1: 24-week results of a phase 2b exploratory trial. XVI International AIDS Conference. August 13-18, 2006. Toronto. Abstract THLB0215.

19. Gulick R, Su Z, Flexner C, et al. ACTG 5211: phase II study of the safety and efficacy of vicriviroc in HIV-infected treatment-experienced subjects. XVI International AIDS Conference. August 13-18, 2006. Toronto. Abstract THLB0217.

20. Greaves W, Landovitz R, Fatkenheuer G, et al. Late virologic breakthrough in treatment-naive patients on a regimen of Combivir + vicriviroc. 13th Conference on Retroviruses and Opportunistic Infections. February 5-8, 2006. Denver. Abstract 161LB.

21. Norris D, Morales J, Godofsky E, et al. TNX-355, in combination with optimized background regimen (OBR), achieves statistically significant viral load reduction and CD4 cell count increase when compared with OBR alone in phase II study at 48 weeks. XVI International AIDS Conference. August 13-18, 2006. Toronto. Abstract THLB0218.

22. Smith P, Forrest A, Beatty G, et al. Pharmacokinetics/pharmacodynamics of PA-457 in a 10-day multiple dose monotherapy trial in HIV-infected patients. 13th Conference on Retroviruses and Opportunistic Infections. February 5-8, 2006. Denver. Abstract 52.

23. Kilgore N, Reddick M, Zuiderhof M, et al. The first-in-class maturation inhibitor, PA-457, is a potent inhibitor of HIV-1 drug-resistant isolates and acts synergistically with approved HIV drugs in vitro. 13th Conference on Retroviruses and Opportunistic Infections. February 5-8, 2006. Denver. Abstract 509.

24. Gazzard BG, Pozniak AL, Rosenbaum W, et al. An open-label assessment of TMC 125--a new, next-generation NNRTI, for 7 days in HIV-1 infected individuals with NNRTI resistance. AIDS. 2003;17:F49-F54.

25. Cohen C, Steinhart C, Ward D, et al. Efficacy and safety results at 48 weeks with the novel NNRTI, TMC125, and impact of baseline resistance on the virologic response in study TMC125-C223. XVI International AIDS Conference. August 13-18, 2006. Toronto. Abstract TUPE0061.

26. Boffito M, Winston A, Fletcher C, et al. Pharmacokinetics and ART response to TMC114/r and TMC125 combination in patients with high-level viral resistance. 13th Conference on Retroviruses and Opportunistic Infections. February 5-8, 2006. Denver. Abstract 575c.

27. Woodfall B, Vingerhoets J, Peeters M, et al. Impact of NNRTI and NRTI resistance on the response to the regimen of TMC125 plus two NRTIs in study TMC125-C227. 8th International Congress on Drug Therapy in HIV Infection. November 12-16, 2006. Glasgow. Abstract PL5.6.

28. Gruzdev B, Rakhmanova A, Doubovskaya E, et al. A randomized, double-blind, placebo-controlled trial of TMC125 as 7-day monotherapy in antiretroviral naive, HIV-1 infected subjects. AIDS. 2003;17:2487-2494.

29. Hicks CB, Cahn P, Cooper DA, et al. Durable efficacy of tipranavir-ritonavir in combination with an optimised background regimen of antiretroviral drugs for treatment-experienced HIV-1-infected patients at 48 weeks in the Randomized Evaluation of Strategic Intervention in multi-drug reSistant patients with Tipranavir (RESIST) studies: an analysis of combined data from two randomised open-label trials. Lancet. 2006;368:466-475.

30. Gazzard B, Antinori A, Cheli C, et al. Combined analysis of RESIST 96 week data: durability and efficacy of tipranavir/r in treatment-experienced patients. 8th International Congress on Drug Therapy in HIV Infection. November 12-16, 2006. Glasgow. Abstract P23.

31. Baxter JD, Schapiro JM, Boucher CA, et al. Genotypic changes in human immunodeficiency virus type 1 protease associated with reduced susceptibility and virologic response to the protease inhibitor tipranavir. J Virol. 2006;80:10794-10801.

32. Naeger LK, Struble KA. Food and Drug Administration analysis of tipranavir clinical resistance in HIV-1-infected treatment-experienced patients. AIDS. 2007;21:179-185.

33. Lazzarin A, Queiroz-Telles F, Frank I, et al. TMC114 provides durable viral load suppression in treatment-experienced patients: POWER 1 and 2 combined week 48 analysis. XVI International AIDS Conference. August 13-18, 2006. Toronto. Abstract TUAB0104.

34. Lalezari JP, Henry K, O'Hearn M, et al. Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. N Engl J Med. 2003;348:2175-2185. Erratum in: N Engl J Med. 2003;349:1100.

35. Lazzarin A, Clotet B, Cooper D, et al. Efficacy of enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia. N Engl J Med. 2003;348:2186-2195.

36. Nelson M, Arasteh K, Clotet B, et al. Durable efficacy of enfuvirtide over 48 weeks in heavily treatment-experienced HIV-1-infected patients in the T-20 versus optimized background regimen only 1 and 2 clinical trials. J Acquir Immune Defic Syndr. 2005;40:404-412.

37. Harris M, Joy R, Larsen G, et al. Enfuvirtide plasma levels and injection site reactions using a needle-free gas-powered injection system (Biojector). AIDS. 2006;20:719-723.

38. True AL, Chiu YY, Demasi RA, et al. Pharmacokinetic bioequivalence of enfuvirtide using a needle-free device versus standard needle administration. Pharmacotherapy. 2006;26:1679-1686.

www.natap.org

NATAP
NATIONAL AIDS TREATMENT ADVOCACY PROJECT
EDUCATING COMMUNITIES ABOUT HIV AND HEPATITIS