

Winter 2005



Positively Aware

The Journal of Test Positive Aware Network

Special Issue

what's
PK
[Pharmacokinetics]
GOT TO DO
with it?

PK

IN THIS SPECIAL ISSUE: **ABC's of Pharmacokinetics (PK)** / The Nukes, Non-Nukes and Pls: Do They Play Well Together? / **Top 3 Websites**

Try new
TRUVADA™ as
part of your
combination
HIV therapy...

Just once

Make TRUVADA part of your daily routine.

Two well-known medications, VIREAD and EMTRIVA, have been combined into one convenient pill that you take only once a day. Plus, new TRUVADA can be taken with or without food. Ask your doctor if new TRUVADA is right for you as part of your combination HIV therapy.

TREATMENT FOR EVERYDAY LIVING


Truvada

emtricitabine - tenofovir disoproxil fumarate

INDICATION: TRUVADA is for use in combination with other anti-HIV agents to treat HIV infection in adults. TRUVADA contains two medicines, EMTRIVA® (emtricitabine) and VIREAD® (tenofovir disoproxil fumarate), combined in one tablet.

- EMTRIVA and VIREAD have been studied separately. Clinical studies with TRUVADA and EMTRIVA+VIREAD are ongoing
- Since EMTRIVA and Efavirenz® (3TC) are similar medicines, studies using VIREAD+3TC support the use of TRUVADA. Therefore, TRUVADA should be considered as an alternative to the combination of VIREAD+EMTRIVA or VIREAD+Efavirenz for someone who would benefit from a once-a-day regimen
- TRUVADA does not cure HIV infection. No studies show the effect of TRUVADA on the clinical progression of HIV. TRUVADA should not be used as part of a triple nucleoside regimen

IMPORTANT SAFETY INFORMATION:

- **Lactic acidosis** (a buildup of acid in the blood) can be a medical emergency and may need to be treated in the hospital. **Call your healthcare provider right away** if you have nausea, vomiting, unusual muscle pain, and/or weakness



- **Serious liver problems** (hepatotoxicity), with liver enlargement (hepatomegaly) and fat in the liver (steatosis), may occur. **Call your healthcare provider right away** if you have light colored stools, dark colored urine, and/or if your skin or the whites of your eyes turn yellow
- **Flare-ups of hepatitis B virus infection (HBV):** If you have HIV and HBV, your liver disease may suddenly get worse if you stop taking TRUVADA. Do not stop taking TRUVADA unless directed by your healthcare provider
- **Kidney problems:** If you have had kidney problems or take other medicines that can cause kidney problems, your healthcare provider should do regular blood tests to check your kidneys
- **Bone changes:** It is not known whether long-term use of TRUVADA causes damage to your bones. If you have had bone problems in the past, talk to your healthcare provider before taking TRUVADA

Changes in body fat have been seen in some people taking anti-HIV medicines. The most common side effects of TRUVADA when taken with other anti-HIV medicines are dizziness, diarrhea, nausea, vomiting, headache, rash, and gas. Skin discoloration (spots and freckles) may also occur.

Discuss all medicines you take with your healthcare provider and be aware:

- TRUVADA should not be used with Combivir®, Emtriva, Epivir, Epivir-HBV®, Epzicom™, Trizivir®, or Viread
- Your healthcare provider may need to follow you more closely or adjust your therapy if you are taking Videx®, Videx EC®, Reyataz™ or Kaletra® with TRUVADA

There is additional information about TRUVADA on the next page.

Patient Information

TRUVADA™ (tru-VAH-dah) Tablets

Generic name: emtricitabine and tenofovir disoproxil fumarate
(an NRTI with tenofovir) and tenofovir DF (PROVIRIL®/FOSAMVEX®)

Read the Patient Information that comes with TRUVADA before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment. You should stay under a healthcare provider's care when taking TRUVADA. Do not change or stop your medicine without first talking with your healthcare provider. Call your healthcare provider or pharmacist if you have any questions about TRUVADA.

What is the most important information I should know about TRUVADA?

- Some people who have taken medicine like TRUVADA (nucleoside analogs) have developed a serious condition called lactic acidosis (build up of an acid in the blood). Lactic acidosis can be a medical emergency and may need to be treated in the hospital. Call your healthcare provider right away if you get the following signs or symptoms of lactic acidosis:

- You feel very weak or tired.
- You have unusual (not normal) muscle pain.
- You have trouble breathing.
- You have stomach pain with nausea and vomiting.
- You feel cold, especially in your arms and legs.
- You feel dizzy or lightheaded.
- You have a fast or irregular heartbeat.

- Some people who have taken medicines like TRUVADA have developed serious liver problems called hepatotoxicity, with liver enlargement (hepatomegaly) and fat in the liver (steatosis). Call your healthcare provider right away if you get the following signs or symptoms of liver problems:

- Your skin or the white part of your eyes turns yellow (jaundice).
- Your urine turns dark.
- Your bowel movements (stools) turn light in color.
- You don't feel like eating food for several days or longer.
- You feel sick to your stomach (nausea).
- You have lower stomach area (abdominal) pain.

- You may be more likely to get lactic acidosis or liver problems if you are female, very overweight (obese), or have been taking nucleoside analog medicines, like TRUVADA, for a long time.

- TRUVADA is not for the treatment of Hepatitis B Virus infection. Patients infected with both HIV and human immunodeficiency virus (HIV) who take TRUVADA need close medical follow-up for several months after stopping treatment with TRUVADA. Follow-up includes medical exams and blood tests to check for HIV that could be getting worse. Patients with Hepatitis B Virus infection, who take TRUVADA and then stop it, may get a "flare-up" of their hepatitis. A "flare-up" is when the disease suddenly returns in a worse way than before.

What is TRUVADA?

TRUVADA is a type of medicine called an HIV (human immunodeficiency virus) nucleoside analog reverse transcriptase inhibitor (NRTI). TRUVADA contains 2 medicines, EMTRIVA® (emtricitabine) and VIREAD® (tenofovir disoproxil fumarate, or tenofovir DF) combined in one pill. TRUVADA is always used with other anti-HIV medicines to treat people with HIV infection. TRUVADA is for adults age 18 and older. TRUVADA has not been studied in children under age 18 or adults over age 65.

HIV infection destroys CD4 (T) cells, which are important to the immune system. The immune system helps fight infection. After a large number of T cells are destroyed, acquired immune deficiency syndrome (AIDS) develops.

TRUVADA helps block HIV reverse transcriptase, a chemical in your body (enzyme) that is needed for HIV to multiply. TRUVADA lowers the amount of HIV in the blood (viral load). TRUVADA may also help to increase the number of T cells (CD4 cells). Lowering the amount of HIV in the blood lowers the chance of death or infections that happen when your immune system is weak (opportunistic infections).

TRUVADA does not cure HIV infection or AIDS. The long-term effects of TRUVADA are not known at this time. People taking TRUVADA may still get opportunistic infections or other conditions that happen with HIV infection. Opportunistic infections are infections that develop because the immune system is weak. Some of these conditions are pneumonia, herpes virus infections, and *Mycobacterium avium* complex (MAC) infection. It is very important that you see your healthcare provider regularly while taking TRUVADA.

TRUVADA does not lower your chance of passing HIV to other people through sexual contact, sharing needles, or being exposed to your blood. For your health and the health of others, it is important to always practice safer sex by using a latex or polyurethane condom or other barrier to lower the chance of sexual contact with semen, vaginal secretions, or blood. Never use or share dirty needles.

Who should not take TRUVADA?

Do not take TRUVADA if you are allergic to TRUVADA or any of its ingredients. The active ingredients of TRUVADA are emtricitabine and tenofovir DF. See the end of this leaflet for a complete list of ingredients.

What should I tell my healthcare provider before taking TRUVADA?

Tell your healthcare provider if you:

- are pregnant or planning to become pregnant. We do not know if TRUVADA can harm your unborn child. You and your healthcare provider will need to decide if TRUVADA is right for you. If you use TRUVADA while you are pregnant, talk to your healthcare provider about how you can be on the TRUVADA Antinatal Pregnancy Registry.
- are breast-feeding. You should not breast feed if you are HIV-positive because of the chance of passing the HIV virus to your baby. Also, it is not known if TRUVADA can pass into your breast milk and if it can harm your baby. If you are a woman who has or will have a baby, talk with your healthcare provider about the best way to feed your baby.
- have kidney problems or are undergoing kidney dialysis treatment.
- have bone problems.
- have liver problems including Hepatitis B Virus infection.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Especially tell your healthcare provider if you take:

- COMBIVIR®, EMTRIVA®, EPIVIR®, EPIVIR-HBV®, EPIDOCIM™, TRIZIVIR®, or VIREAD®. TRUVADA should not be used with these medicines.
- Drugs that contain didanosine (VIDEX®, VIDE XEC™), tenofovir DF (a component of TRUVADA) may increase the amount of VIDE in your blood. You may need to be followed more carefully if you are taking TRUVADA and VIDE together.
- REBETAZ™ (zalcitabine sulfate) or KALETRA™ (zidovudine/zalcitabine). These medicines may increase the amount of tenofovir DF (a component of TRUVADA) in your blood, which could result in more side effects. You may need to be followed more carefully if you are taking TRUVADA and REBETAZ or KALETRA together.

Keep a complete list of all the medicines that you take. Make a new list when medicines are added or stopped. Give copies of this list to all of your healthcare providers and pharmacist every time you visit your healthcare provider or fill a prescription.

How should I take TRUVADA?

- Take TRUVADA exactly as your healthcare provider prescribed it. Follow the directions from your healthcare provider, exactly as written on the label.
- The usual dose of TRUVADA is 1 tablet once a day. TRUVADA is always used with other anti-HIV medicines. If you have kidney problems, you may need to take TRUVADA less often.
- TRUVADA may be taken with or without a meal. Food does not affect how TRUVADA works. Take TRUVADA at the same time each day.
- If you forget to take TRUVADA, take it as soon as you remember that day. Do not take more than 1 dose of TRUVADA in a day. Do not take 2 doses at the same time. Call your healthcare provider or pharmacist if you are not sure what to do. It is important that you do not miss any doses of TRUVADA or your anti-HIV medicines.
- When your TRUVADA supply starts to run low, get more from your healthcare provider or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to TRUVADA and become harder to treat.
- Do not change your dose or stop taking TRUVADA without first talking with your healthcare provider. Stay under a healthcare provider's care when taking TRUVADA.
- If you take too much TRUVADA, call your local poison control center or emergency room right away.

What should I avoid while taking TRUVADA?

- Do not breast-feed. See "What should I tell my healthcare provider before taking TRUVADA?"
- Avoid doing things that can spread HIV infection since TRUVADA doesn't stop you from passing the HIV infection to others.
 - Do not share needles or other injection equipment.
 - Do not share personal items that can have blood or body fluids on them, like toothbrushes or razor blades.
 - Do not have any kind of sex without protection. Always practice safer sex by using a latex or polyurethane condom or other barrier to reduce the chance of sexual contact with semen, vaginal secretions, or blood.
- COMBIVIR®, EMTRIVA®, EPIVIR®, EPIVIR-HBV®, EPIDOCIM®, TRIZIVIR®, or VIREAD®. TRUVADA should not be used with these medicines.

What are the possible side effects of TRUVADA?

TRUVADA may cause the following serious side effects (see "What is the most important information I should know about TRUVADA?").

- Lactic acidosis** (buildup of an acid in the blood). Lactic acidosis can be a medical emergency and may need to be treated in the hospital. Call your doctor right away if you get signs of lactic acidosis. (See "What is the most important information I should know about TRUVADA?")
- Serious liver problems** (hepatotoxicity), with liver enlargement (hepatomegaly) and fat in the liver (steatosis). Call your healthcare provider right away if you get any signs of liver problems. (See "What is the most important information I should know about TRUVADA?")
- "Flare-up"** of Hepatitis B Virus infection, in which the disease suddenly returns in a worse way than before, can occur if you stop taking TRUVADA. Your healthcare provider will monitor your condition for several months after stopping TRUVADA if you have both HIV and HBV infection. TRUVADA is not for the treatment of Hepatitis B Virus infection.

- Kidney problems.** If you have had kidney problems in the past or take other medicines that can cause kidney problems, your healthcare provider should do regular blood tests to check your kidneys.

- Changes in bone mineral density (thinning bones).** It is not known whether long-term use of TRUVADA will cause damage to your bones. If you have had bone problems in the past, your healthcare provider may need to do tests to check your bone mineral density or may prescribe medicines to help your bone mineral density.

Other side effects with TRUVADA when used with other anti-HIV medicines include:

- Changes in body fat have been seen in some patients taking TRUVADA and other anti-HIV medicines. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the waist part of your body (trunk). Loss of fat from the legs, arms and face may also happen. The cause and long-term health effects of these conditions are not known at this time.

The most common side effects of EMTRIVA or VIREAD when used with other anti-HIV medicines are dizziness, diarrhea, nausea, vomiting, headache, rash, and gas. Skin discoloration (small spots or freckles) may also happen with TRUVADA.

There are not all the side effects of TRUVADA. This list of side effects with TRUVADA is not complete at this time because TRUVADA is still being studied. If you have questions about side effects, ask your healthcare provider. Report any new or continuing symptoms to your healthcare provider right away. Your healthcare provider may be able to help you manage these side effects.

How do I store TRUVADA?

- Keep TRUVADA and all other medicines out of reach of children.
- Store at room temperature up to 77 °F (25 °C).
- Keep TRUVADA in its original container and keep the container tightly closed.
- Do not keep medicine that is out of date or that you no longer need. If you throw any medicines away, make sure that children will not find them.

General Information about TRUVADA:

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use TRUVADA for a condition for which it was not prescribed. Do not give TRUVADA to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about TRUVADA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about TRUVADA that is written for health professionals. For more information, you may also call 1-800-GILEAD-5 or access the TRUVADA website at www.TRUVADA.com. Do not use TRUVADA if seal over bottle opening is broken or missing.

What are the ingredients of TRUVADA?

Active ingredients: emtricitabine and tenofovir DF

Inactive ingredients: Croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch (gluten free). The tablets are coated with Opadly II Blue 1-30-10701 containing FD&C Blue #2 aluminum lake, hypromellose, lactose monohydrate, titanium dioxide, and triacetin.

Rx Only

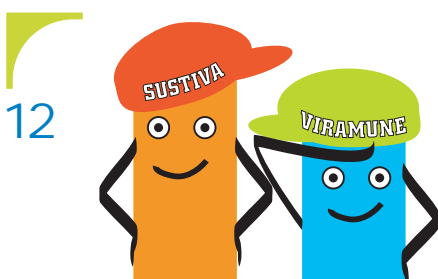
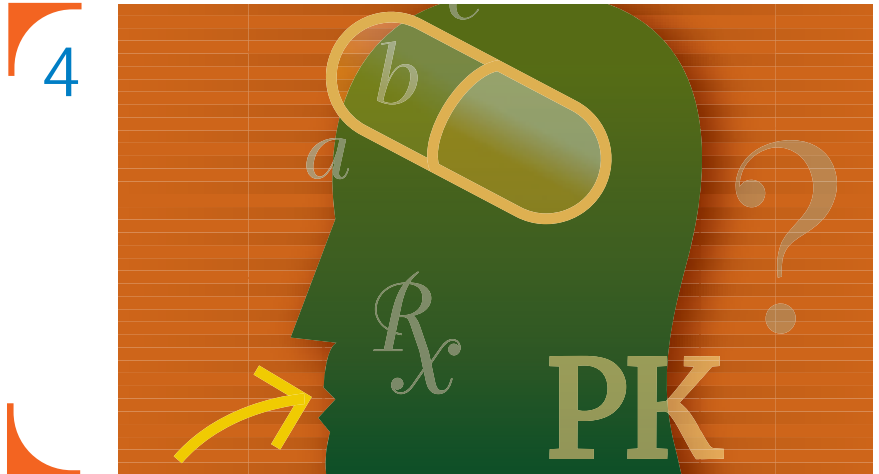
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The ABC's of Pharmacokinetics 4

What's PK got to do with it? Recent data from PK, the study of what the human body does to drugs to eliminate them from the body, provides us with information which can show us the life of a drug through absorption, distribution, metabolism and elimination.



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The most complicated of the HIV drugs. These block the ability of HIV to infect more cells.

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PATRICK G. CLAY, GUEST EDITOR

Supplement Introduction

This supplement was the brainchild of the late editor of *Positively Aware*, Charles Clifton. Charles and I met in (appropriately enough) San Francisco, during the Retrovirus conference in 2004 to discuss ways to educate patients about how their body breaks down medicines. The intent of this supplement is to provide foundational general knowledge about the pharmacokinetics and pharmacodynamics (*see ABC's of Antiretrovirals*) of antiretroviral medications. It also gives specific recommendations on currently available medicines. Why does your doctor prescribe Lexiva once a day for you and twice a day for your partner? Why do you have to eat with Reyataz and cannot eat with Crixivan? Why is Videx EC given sometimes at 250 mg and sometimes at 400 mg daily? These were just some of the questions Charles and I hoped to be able to answer with this supplement.

How much (milligrams) of a drug should be taken at one time? The answer most often times is: enough to work, but not too much to cause significant side effects. Most antiretrovirals are dosed to achieve in the body a level of drug that falls into what is called a “therapeutic range” (*see Figure 1: Therapeutic Range*). Taking enough of the medicine (having drug concentrations somewhere on the graph) will, in most cases, give you an effect. These effects can be good (therapeutic) or bad (toxic).

If the drug level is appropriate for the virus in your body, you could see a lowering of the viral load and/or increasing of the CD4 count. These would obviously be good therapeutic effects. Taking too much or not having

enough of the medicine in your body (incorrect dosing or poor adherence) could result in either toxic effects or no effect. Neither of these are desired outcomes — for you or your doctor! The paragraph below provides a more detailed explanation of the graph. It is important to understand these concepts, as they are pivotal to the information provided in this supplement.

The drug concentration in the blood rises as you go from left to right along the x-axis or bottom of the graph. The actual amount (milligrams per mil-

YOU AND YOUR DOCTOR SHOULD HAVE TALKED ABOUT WHAT THE GOALS FOR YOUR DRUGS ARE BEFORE YOU STARTED TAKING THEM

liliter of blood, *see ABC's of Pharmacokinetics*) varies depending on several factors including: the drug, prescribed dose, how long you have been taking the medicine and how long it has been since you took your last dose. The chance of the drug having an effect increases up to a maximal amount as you go from bottom to top or up the y-axis. As stated previously, for antiretrovirals this effect is measured by changes in T-cell count and viral load. You probably know that the most you can reduce your viral load is down to less than 50 copies per milliliter — so there is a maximal effect the drug can have on your virus. Same with T-cells — your body can only make so many over time and at some point you will have T-cells in the “normal” or non-HIV infected range. These two levels (undetectable viral load and normal CD4 count) represent a maximal effect of the

anti-HIV medicines. What your maximal effect may be, however, is also dependent on your history of taking HIV medicines and how much damage the virus has already done to your body. You and your doctor should have talked about what the goals for your drugs are before you started taking them. Not everyone can or should use an undetectable viral load and “normal” T-cell count as goals.

If the drug you take is not in sufficient quantity, you can get sub-optimal levels. At this drug concentration, you would likely not see a therapeutic (good) benefit from taking the medicine. Even though you don't get a positive effect, you can still see a negative one. For instance, taking low doses of Retrovir will not change your viral load or T-cells, but may still cause you to have anemia.

If too much medicine is taken, then the chance that you will have a toxic effect becomes more likely. An example of this is taking too much Crixivan. Very high levels of Crixivan can cause you to develop stones in your kidneys (very painful!). Not only is this drug's recommended doses (from the company and in this supplement — *see Protease Inhibitors*) at levels that usually don't allow this to happen, drinking plenty of water immediately after the dose and during the day help minimize this risk.

The challenge with HIV medicines is that the “therapeutic range” in many instances is still being discovered. What is the maximum level of drug that should be in the body daily to provide long term therapeutic effects? Sadly, this is not known for every drug. What

doctors and researchers understand more clearly for most anti-HIV drugs is what dose of a drug is associated with toxicity. Manufacturers' and doctors' recommended and prescribed doses reflect this knowledge. This does not mean side effects cannot happen from having therapeutic levels of the drug in the body. As you are probably aware, long-term side effects of some of these medicines (lipodystrophy and diabetes, for example) may result from taking the proper amount of medicine and having therapeutic levels of the drugs. Unfortunately, long-term side effects from medicines, even when

dosed appropriately, are not unique to anti-HIV drugs. Diabetics can develop resistance to their insulin and those with asthma who have to take steroids are all too familiar with long-term side effects of medicines. However, many side effects are related to the amount of drug in the body. Having the optimal amount of drug in your body and keeping it that way consistently over time may offer the most effective way to minimize side effects.

Though this supplement presents the most appropriate doses, levels and combinations of antiretrovirals, long-term therapeutic success is still only achievable with continual maximal

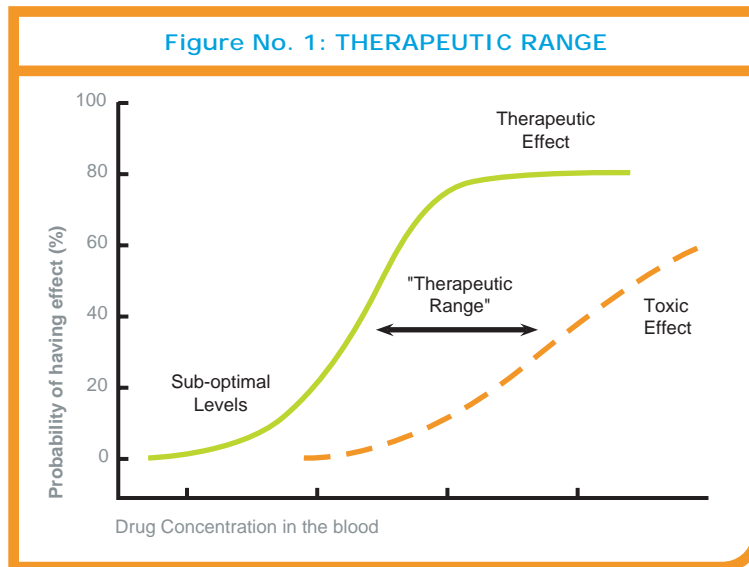
adherence. The emphasis on honest communication with your doctor, pharmacist and nurse about your HIV medicines, other medicines you might be taking (especially ones available over the counter!) and how these medicines make you feel cannot be strong enough. This supplement is meant to help you understand more about what happens to the drugs after they are inside your body. It should be used as a reference when you are talking to your doctor about current or new medicines. It is the intent of the authors that by providing this educational material, we are able to increase your understanding of the medicines used to treat HIV. If by

dose, frequency or diet instructions for your anti-HIV medicines without first talking with and getting approval from your doctor. What we try to emphasize in this supplement are that these medicines are different in everyone and your doses are likely to reflect this. Only you and your doctor know what is best for you — that is how your medicines are best managed. ✚

Sincerely,



Patrick G. Clay, PharmD
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Sub-optimal levels: These are drug concentrations that are associated with a low chance of a therapeutic effect.

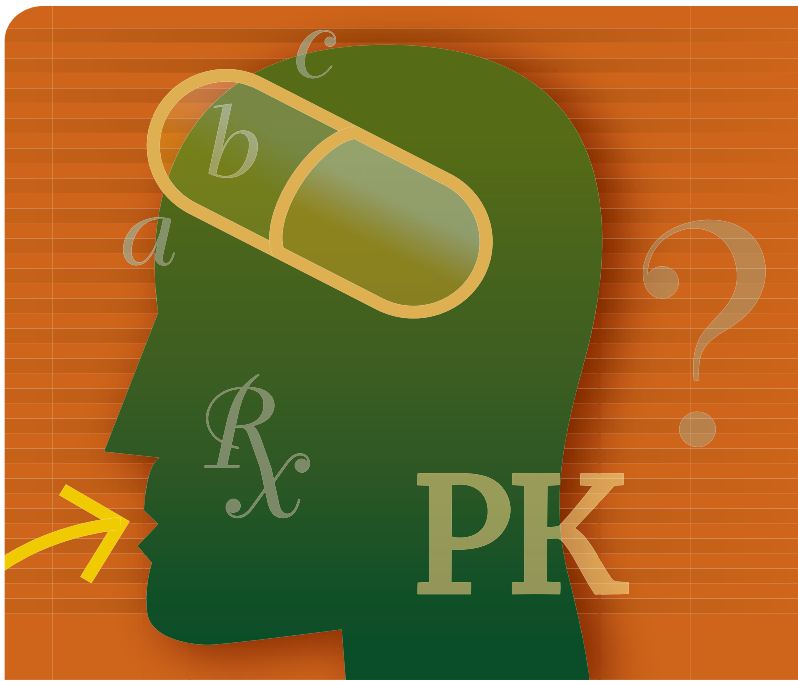
Therapeutic effect: In the case of antiretroviral drugs, it is the reduction of HIV-RNA, the increase in CD4 cells, and the prevention of opportunistic infections.

Therapeutic range: The size of the difference between doses or drug levels that cause a therapeutic effect versus a toxic effect.

Toxic effect: Toxicity from the drug

accomplishing a higher knowledge level about antiretrovirals in persons affected by this virus, we are able to improve one person's outcome or prevent one virus from becoming resistant — then we will say this supplement was successful.

Lastly, this supplement provides many recommendations that are not found within the package inserts of medicines. Many of the recommendations made within are based on the authors', editor's and TPAN's current understanding of the currently approved anti-HIV medicines. This supplement in no way should supplant what your doctor has prescribed for you. At no time should you consider altering the



What's PK got to do with it?

BY PETER L. ANDERSON, PharmD

THE ABC'S OF Pharmacokinetics

Parmacokinetics (PK) is talked about a lot in the HIV community. PK is the study of what the human body does to drugs to get the drug out of the body. The main ways the human body handles drugs are listed below. These are all a part of PK.

Step 1. Drug absorption: This is how the drug enters the blood — usually from tablets or capsules in the stomach and intestines. For some drugs, the amount of acid in the stomach, or the amount of food in the stomach, really changes the amount of drug that is absorbed. This is the reason that some drugs have “food requirements”, or why some drugs have warnings not to take antacids along with the drug. (see *Figure 1: Drug Metabolism Pathways*):

Step 2. Drug distribution: This is how the drug travels in the bloodstream and how it goes into and comes out of other areas of the body. Did you

know that some areas of the body, like the brain and reproductive organs, are specially protected from chemicals (including drugs)? It is hard to measure drug levels in the brain and reproductive organs in people.

One way that drug distribution is studied in people is by finding out what percentage of the drug in the blood is stuck to proteins (called protein binding). This is important

PHARMACOKINETICS IS
WHAT THE BODY DOES TO THE DRUG —
PHARMACODYNAMICS IS
WHAT THE DRUG DOES TO THE BODY

because only drug that is free of proteins can travel in and out of other areas of the body to be effective. Protein binding is often studied when a drug is being developed by a drug company. However, protein binding is not routinely studied after that because knowing the total blood concentration (both protein-bound plus protein-free)

is generally good enough.

Step 3. Drug metabolism: This is how the body chemically changes a drug — usually in the intestines and liver. Metabolism involves breaking a drug down or adding a chemical that makes it easier to pass it into urine or stool. A lot of drug-drug interactions happen because one drug interferes with the metabolism of another drug (called inhibition). Inhibition causes higher drug levels. On the other hand, a drug can also speed up the metabolism of another drug (called induction). Induction causes lower drug levels.

The CYP-450 (pronounced “sip”) enzyme system is a well-known group of human enzymes that metabolize drugs and chemicals in the body. CYP-450 enzymes are mostly in the intestines and liver.

The CYP-450 enzymes are broken into three families (CYP1, CYP2 and CYP3) (see *Figure 2: Antiretrovirals and CYP450 Isoenzymes*). When doctors and pharmacists talk about the

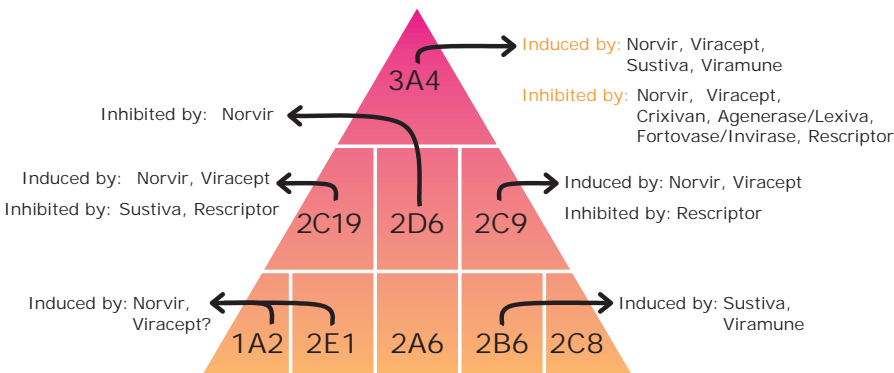
CYP-450 system, they often just refer to the system as CYP and drop the 450 part. Within the CYP-450 system, though, there are different enzyme families. To distinguish one family from another, a letter and number are added to CYP (again, dropping the 450 numbering). Some examples of this are CYP1A2, CYP2D6, CYP3A4, etc. (Note how the 450 is dropped, but the CYP remains.)

Each CYP has a different ability to metabolize a given chemical or drug. For example, CYP3A4 is probably the most important drug metabolizing enzyme because it metabolizes the most drugs, including protease inhibitors.

Norvir strongly inhibits CYP3A4 and causes most of the other protease inhibitors to build up in the blood. This is called Norvir boosting. For the protease inhibitors that are boosted by Norvir, the higher blood levels may help the “boosted” drug work better. But, for other drugs that are metabolized by CYP3A4, like cholesterol drugs or erectile dysfunction drugs, Norvir and protease inhibitors may cause undesirable increases in blood concentrations (see Protease Inhibitor article on page 16).

Step 4. Drug elimination: This is how the body gets the drug out — usually by passing the drug into the urine (via the kidneys) or stool (via the liver). Sometimes people have some kidney or liver illness. In these people, the blood level of some drugs may build to very high levels if the drug

Figure No. 2: ANTIRETROVIRALS and CYP450 ISOENZYMES



Pyramid depicts the various CYP 450 enzymes in the body and the drug interactions with antiretrovirals. CYP3A4, shown at the top of the pyramid and largest single part of the pyramid, is very important. Arrows point to the various antiretrovirals and the general affect(s) that medicine has on that enzyme. Note that drugs can be listed as both an inducer and inhibitor and with multiple enzymes.

dose is not reduced (see Figure 1: Drug Metabolism Pathways).

PK DEFINITIONS

There are certain terms and tests that researchers or doctors use when they study PK. The following is a summary of these PK measurements and what they mean. Please refer to Figures 3 and 4 for a picture of what all these PK measurements represent.

AUC (area-under-the-curve): This is the overall amount of drug in the bloodstream after a dose. AUC studies are often used when researchers are looking for drug-drug or drug-food interactions. The way to get an AUC

involves collecting many blood samples (usually every one or two hours) right after a person takes a dose up until the next dose is due. In each blood sample, the concentration of the drug is measured with a machine (discussed later). Then all the drug concentrations are put onto a graph based on the time after the dose that they were collected. A curve is made by

connecting the points on the graph. The AUC for that drug is then calculated as the area under this drug concentration curve. An AUC study contains a lot of information about PK. It is probably the best way to understand how people handle a drug (PK).

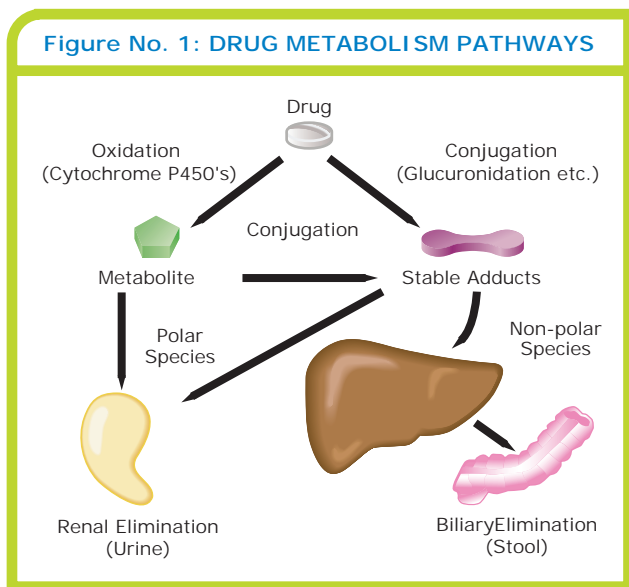
C_{max} (maximum concentration): This is the highest concentration of drug in the blood that is measured after a dose. C_{max} usually happens within a few hours after the dose is taken. The time that C_{max} happens is referred to as T_{max}. For some antiretroviral drugs, a high C_{max} is thought to increase the risk of side effects from the drug.

C_{min} or trough (pronounced “troff”) (minimum concentration): This is the lowest concentration of the drug in the blood that is measured after a dose. It happens right before a patient takes the next usual dose. It is not known for certain, but many people in the HIV community believe that keeping the trough concentration (C_{min}) above a certain level is especially important for anti-HIV activity.

Half-life (t_{1/2}): This is the amount of time it takes for the drug concentration in the blood to decline by half. The half-life is among the most important PK measurements for how often a drug has to be dosed (once-a-day or twice-a-day, etc).

Steady-state: This means that a person has been on a drug for enough

Figure No. 1: DRUG METABOLISM PATHWAYS



time (usually one to two weeks) so that the drug concentration is not building up in the bloodstream anymore. The time it takes to get to steady-state depends on the half-life of the drug. A drug gets to steady state in

about five half-lives.

As an illustration, before a patient reaches steady-state, each additional dose may be building the drug up in the body so each dose would be giving a higher C_{max} , C_{min} ,

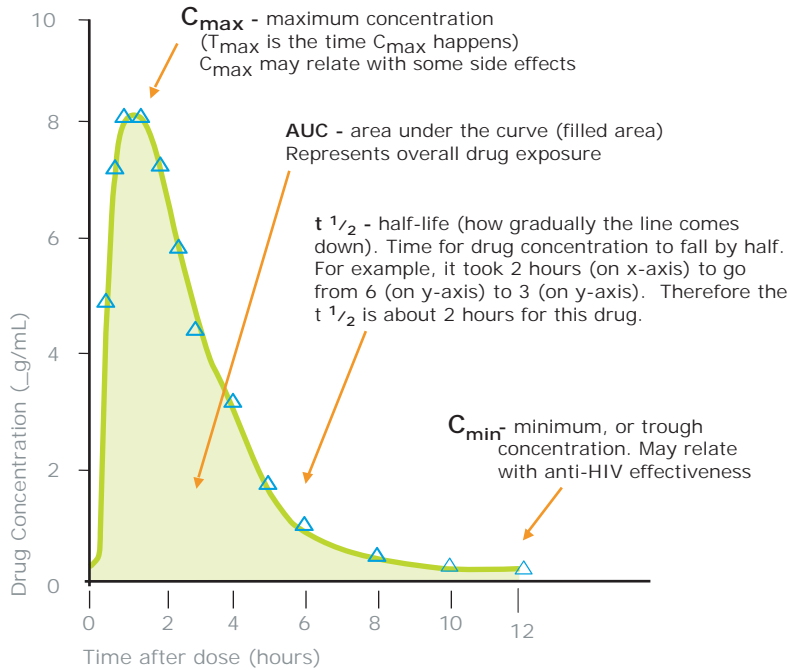
and AUC. But, at steady-state, every dose would give the same C_{max} , C_{min} , and AUC in the patient because it is not building up any more.

Adherence: Remarkably, anti-retroviral regimens lose effectiveness even with a small drop from perfect (or near-perfect) adherence. For example, going from 95–100% adherence down to 90–95% adherence with protease inhibitors resulted in a drop in effectiveness (viral load below 400) from 81% to 64%. It seems that the usual drug levels are not much higher than what's needed for sustained efficacy. Additionally, the half-lives of the agents must have been relatively fast, such that the drug exposure fell below a level associated with a high probability of efficacy after the missed dose. Obviously, taking as close to 100% of antiretroviral doses is critically important.

Once-a-day dosing: Once daily combination antiretroviral therapies is a newer concept that is targeted to improve adherence. Several once-daily regimens are now available where all drugs have similar dietary requirements so that the whole regimen can be taken at the same time (see Figure 7: *Options for Once-daily Dosing*). It should be noted that only approved once-daily combinations should be used at this time (such as Truvada plus Sustiva as initial therapy). Some other antiretrovirals are currently approved for twice-a-day dosing, but they are being studied as once-a-day drugs. These “investigational” regimens should only be used in very controlled settings (like in a study). This is because it is not yet known if “investigational” drugs provide the right amount of drug exposure for effective and safe once-daily dosing (especially if a dose is missed). Which is better — once a day or twice a day dosing? The conservative answer is: both. In studies done to date comparing once to twice a day dosing, they come out equal at the end.

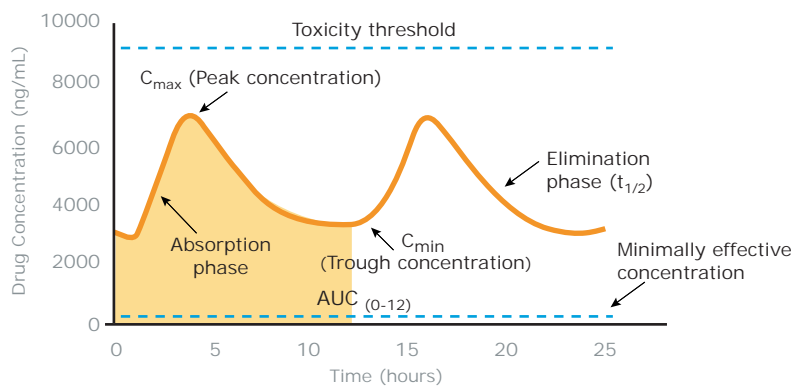
Pharmacodynamics (PD): PD is just a fancy term for drug efficacy and toxicity. PD refers to what the drugs do to the human body. For example, HIV drugs cause HIV viral

Figure No. 3: BLOOD LEVELS of A DRUG OVER TIME



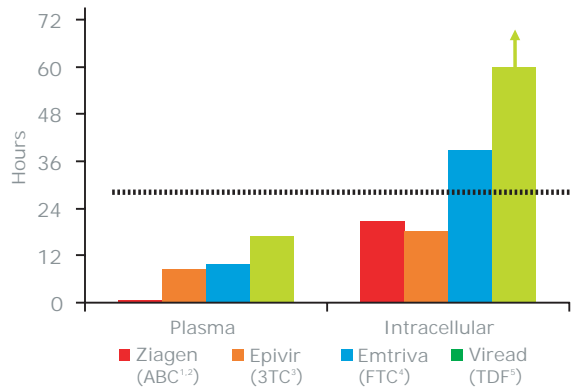
Above are blood levels (Y-axis) of a drug over time (X-axis) after a patient takes a single dose. In this representation, the patient took the dose at time 0 and would be due for another dose at time 12 (hours). Since the time 0 level is about equal to the time 12 level, the patient is at steady state. For AUC measurements, blood levels are usually collected every hour or so. Figure No. 4 below is another way of looking at these same concepts.

Figure No. 4: CONCENTRATION-TIME CURVE at STEADY-STATE



See Figure No. 3 above for explanation

Figure No. 5: PLASMA and INTRACELLULAR HALF-LIVES of SELECT NRTI's



1 Weller, et al. Antimicrob. Agents Chemother. 2000 Aug;44(8):2052-60
 2 Pillero, et al. 43rd ICAAC, Chicago, A-1797
 3 Yuen et al. Antimicrob. Agents and Chemother. 2004 Jan;48(1):176-82
 4 Wang et al. 14th IAC. 2002. Poster #4546
 5 Hawkins T, et al. 5th International Workshop of Clinical Pharmacology of HIV Therapy, Rome, Italy. 2004 #2.4

This figure depicts the half-lives of select nukes. Note how the half-life in the plasma is always much shorter than the half-life within the cell. Two examples of this are shown with Viread and Emtriva.

Figure No. 6: SUGGESTED MINIMUM TARGET TROUGH CONCENTRATIONS for PERSONS with WILD-TYPE HIV-1

DRUG	CONCENTRATION (NG/ML)
amprenavir (Agenerase, Lexiva)	400
indinavir (Crixivan)	100
lopinavir/ritonavir (Kaletra)	1000
nelfinavir (Viracept) ^a	800
ritonavir (Norvir) ^b	2100
saquinavir (Fortovase, Invirase)	100-250
efavirenz (Sustiva)	1000
nevirapine (Viramune)	3400

a. Measurable active (M8) metabolite. b. Ritonavir given as a single PI.

Sources:

- Acosta EP, and Gerber JG. Position paper on therapeutic drug monitoring of antiretroviral agents. *AIDS Research Human Retroviruses* 2002; 18(12):825-34.
- Back D, Gatti G, Fletcher CV, et al. Therapeutic drug monitoring in HIV infection: current status and future directions. *AIDS* 2002;16 (suppl 1) S50S37.
- Burger DM, Armoutse RE, Hugen PWH. Pros and cons of therapeutic drug monitoring of antiretroviral agents. *Curr Opin Infect Dis* 2002;15(1):17-22.
- Optimizing TDM in HIV clinical care. (May 20, 2003. <http://pharmacology.com>)

This table provides suggested trough (C_{min}) concentrations for people taking these drugs who do not have a resistant virus.

load to decline and CD4 cells to increase. Also, drugs sometimes cause certain side effects and toxicity in the human body.

WHAT'S PK GOT TO DO WITH IT?

PK is studied a lot in HIV and it is important for many reasons.

First of all, the PK of many HIV drugs is really changed by certain things. For example, the blood levels of HIV drugs can be increased or lowered by not following the food requirements with dosing, taking antacids with the drugs, or taking certain other drugs or herbals that cause big inhibition or induction interactions (see metabolism above). It is important to find the dose requirements out so that patients know how best to take the drugs.

Secondly, every person who takes HIV drugs is a bit different in the way their body handles these drugs (absorption, distribution, metabolism, and/or elimination). This means that a patient

can have high or low blood levels after taking the same dose just because of the way they handle the drug.

Finally, all of this matters because the levels of drugs in your body affect how well the drug works against the virus or whether the drug might cause side effects. In the case of high levels there could be more side effects. Poor efficacy against HIV

This is called “therapeutic drug monitoring” (TDM).

MEASURING DRUG LEVELS

Determining your drug levels from blood samples is usually only done in specialty labs. These labs use machine tests called “high performance liquid chromatography (HPLC or LC)” and sometimes “mass spectrometry (MS)”.

This is generally how it works: Your blood is collected in a tube. The tube is spun very fast in a centrifuge to get the red blood cells to sink to the bottom of the tube leaving the plasma on the top. This is done because the drug level is actually measured in the plasma.

Once at the lab, the drug needs to be purified from the plasma because the plasma is also full of a lot of other things besides the drug (sort of like filtering the drug out). This “filtering” step usually leaves a liquid with the purified drug in it. This purified drug portion is then put into an HPLC machine that filters the drug to make it even more purified and

Continued on page 19

Figure No. 7: OPTIONS for ONCE-DAILY THERAPY

Options currently available or with evidence of QD efficacy

Viread + Emtriva
 Viread + Epivir
 Ziagen + Epivir
 Viread + Videx
 Videx + Emtriva
 Videx + Epivir

+

Sustiva
 Reyataz or Reyataz/Norvir
 Agenerase/Norvir
 Invirase/Norvir
 or Fortovase/Norvir

could result from low levels. In some special cases, your doctor may think that it might be a good idea to measure the blood levels of your drugs. Based on the result, your doctor may adjust your doses and then re-check your blood levels of drug to try and get them right where they want them.

from the plasma because the plasma is also full of a lot of other things besides the drug (sort of like filtering the drug out). This “filtering” step usually leaves a liquid with the purified drug in it. This purified drug portion is then put into an HPLC machine that filters the drug to make it even more purified and

the Nukes

EACH ONE WORKS A LITTLE DIFFERENTLY

The backbone of antiretroviral therapy remains two nucleoside reverse transcriptase inhibitors (also called **nucleosides** or “**nukes**”), whether you are taking a non-nucleoside or protease inhibitor (*Table 2: Antiretroviral Regimens Recommended for Treatment of HIV-1 infection in Antiretroviral Naïve Patients*).

HOW THESE DRUGS WORK

Upon entering the cell, all but Viread (also part of Truvada) have to be activated via a three-step process by enzymes within the cells (three phosphate groups are added by enzymes called kinases). Viread only needs two steps for activation. Once activated, these drugs can then bind to an enzyme (reverse transcriptase) within the cell that prevents the virus from making copies. RTIs (nukes) bind to a different site on this enzyme than the non-nucleoside reverse transcriptase inhibitors (non-nukes). Also, except as noted below, each nuke works slightly differently on this enzyme, allowing most of them to be used together safely and effectively.

METABOLISM

The “nukes” are mostly metabolized by pathways not used by PIs or NNRTIs. Some of the nukes are metabolized in the liver but by different methods than the PIs or NNRTIs (Retrovir and Emtriva for example). Ziagen has a unique metabolism. It is broken down by the

same enzyme that breaks down alcohol. Though no interaction occurs if they are given together, this is *not* a recommendation to enjoy an adult beverage when you take your Ziagen or Ziagen containing-products! Some nukes are not metabolized to any great extent and are eliminated mostly through the urine (Epivir and Viread for example). For this reason, the doses of many nukes should be decreased if you have kidney disease. Exactly how some of these drugs are broken down by the body is still unknown (Zerit for

pete for the same activating kinase enzymes (see introductory paragraph above for explanation). When these two drugs are given at the same time, Retrovir prevents Zerit from being activated, giving you no benefit from taking Zerit.

Zerit: Other than mentioned above, Zerit has no significant drug-drug interactions with any of the other “nukes”. Your doctor may be able to discuss other possible reasons why Zerit is not combined with other “nukes”, but these are not for pharmacokinetic reasons.

Viread: When Viread and Videx EC are given together, increases in Videx blood levels are seen. An increase in the Videx AUC (area under the curve, see page 5) varied from 48% to 60% when these two drugs were given together without and with food, respectively. Studies were done with lower doses of Videx EC and food. The best combination (250 mg of Videx EC and 300 mg Viread) resulted in no change in the AUC of Videx compared to when 400 mg of

Videx EC was taken by itself. No meaningful changes were seen in Viread’s pharmacokinetics. Therefore, the drug-drug interaction can be addressed by adjusting the dose of Videx EC. When they are used together, you should be on a lower dose of Videx (250 mg daily in persons weighing greater than 60 kgs) and taking these agents with food at the same time. Long-term safety data are



example). This is why research and TDM (therapeutic drug monitoring) continue to be conducted on drugs that have even been in use for 10 years. *Table 1* shows the pharmacokinetic parameters for the nucleosides.

DRUG INTERACTIONS WITH DUAL RTIs

Retrovir: Retrovir and Zerit cannot be used together. These two drugs com-

Table No.1: CHARACTERISTICS of NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTI'S)

Generic Name (abbreviation) Trade Name	Formulation	Dosing Recommendations	Food Effect	Serum half-life	Intra-cellular half-life	Elimination	Adverse Events
Abacavir (ABC) Ziagen Trizivir w/ZDV+3TC Epzicom w/3TC	Ziagen 300 mg tablets or 20 mg/mL oral solution Trizivir ABC 300 mg + ZDV 300 mg + 3TC 150 mg Epzicom ABC 600 mg + 3TC 300 mg	300 mg two times/day; or 600 mg once daily; or as Trizivir 1 tablet two times/day Epzicom 1 tablet once daily	Take without regard to meals; Alcohol increases abacavir levels 41%; abacavir has no effect on alcohol	1.5 hours	12-26 hours	Metabolized by alcohol dehydrogenase and glu- curonyl transferase. Renal excretion of metabo- lites 82% Trizivir & Epzicom not for patients with CrCl < 50 mL/min	Hypersensitivity reaction which can be fatal, symptoms may include fever, rash, nausea, vomit- ing, malaise or fatigue, loss of appetite, respiratory symptoms such as sore throat, cough, short- ness of breath
Didanosine (ddI) Videx, Videx EC	Videx EC 125, 200, 250, or 400 mg Videx buffered tabs 25, 50, 100, 150, 200 mg Videx buffered powders: 100, 167, 250 mg	Body weight > 60 kg: 400 mg once daily (buffered tablets or EC capsule); or 200 mg two times/day (buffered tablets); with TDF: 250 mg/day < 60 kg; 250 mg daily (buffered tablets or EC capsule); or 125 mg two times/day (buffered tablets) with TDF; appropriate dose not estab- lished; probably < 250 mg/day	Levels decrease 55%; Take 1/2 hour before or 2 hours after meal	1.5 hours	> 20 hours	Renal excretion 50% Dosage adjustment in renal insufficiency	Pancreatitis; peripheral neuropathy; nausea; diarrhea. Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity associated with use of NRTIs.
Emtricitabine (FTC) Emtriva Truvada w/ TDF	Emtriva 200 mg hard gelatin capsule Truvada FTC 200 mg + TDF 300 mg	Emtriva 200 mg once daily Truvada One tablet once daily	Take without regard to meals	10 hours	> 20 hours	Renal excretion Dosage adjustment in renal insufficiency Truvada - not for patients with CrCl < 30 mL/min	Minimal toxicity; lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with use of NRTIs.)
Lamivudine (3TC) EpiVir Combivir w/ ZDV Epzicom w/ABC Trizivir w/ZDV+ABC	EpiVir 150 mg and 300 mg tablets or 10 mg/mL oral solution Combivir 3TC 150 mg + ZDV 300 mg Epzicom 3TC 300 mg + ABC 600 mg Trizivir 3TC 150 mg + ZDV 300 mg + ABC 300 mg	EpiVir 150 mg two times/day; or 300 mg daily Combivir 1 tablet two times/day Epzicom 1 tablet once daily Trizivir 1 tablet two times/day	Take without regard to meals	5-7 hours	18 -22 hours	Renal excretion Dosage adjustment in renal insufficiency Combivir, Trizivir & Epzicom not for patients with CrCl < 50 mL/min	Minimal toxicity; lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with use of NRTIs)
Stavudine (d4T) Zerit	Zerit 15, 20, 30, 40 mg capsules or 1mg/mL for oral solution	Body weight >60 kg: 40 mg two times/day; Body weight <60 kg: 30 mg two times/day	Take without regard to meals	1.0 hour	7.5 hours	Renal excretion 50% Dosage adjustment in renal insufficiency	<ul style="list-style-type: none"> Peripheral neuropathy; Lipodystrophy Rapidly progressive ascending neuromuscular weakness (rare) Pancreatitis Lactic acidosis with hepatic steatosis (higher incidence with d4T than with other NRTIs Hyperlipidemia
Tenofovir Disoproxil Fumarate (TDF) Viread Truvada w/FTC	Viread 300 mg tablet Truvada TDF 300 mg + FTC 200 mg	Viread 1 tablet once daily Truvada 1 tablet once daily	Take without regard to meals	17 hours	>60 hours	Renal excretion Dosage adjustment in renal insufficiency Truvada - not for patients with CrCl < 30 mL/min	Asthenia, headache, diarrhea, nausea, vomiting, and flatulence; renal insufficiency; lac- tic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with use of NRTIs)
Zalcitabine (ddC)	Hivid 0.375, 0.75 mg tablets	0.75 mg three times/day	Take without regard to meals	1.2 hours	N/A	Renal excretion 70% Dosage adjustment in renal insufficiency	<ul style="list-style-type: none"> Peripheral neuropathy; Stomatitis; Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with use of NRTIs); Pancreatitis
Zidovudine (AZT, ZDV) Retrovir Combivir w/3TC Trizivir w/3TC+ABC	Retrovir 100 mg capsules, 300 mg tablets, 10 mg/mL intravenous solution, 10 mg/mL oral solution Combivir 3TC 150 mg + ZDV 300 mg Trizivir 3TC 150 mg + ZDV 300 mg + ABC 300 mg	Retrovir 300 mg two times/day or 200 mg three times/ day Combivir or Trizivir 1 tablet two times/day	Take without regard to meals	1.1 hours	7 hours	Metabolized to AZT glucuronide (GAZT). Renal excretion of GAZT. Dosage adjustment in renal insufficiency. Combivir & Trizivir - not for patients with CrCl < 50 mL/min	<ul style="list-style-type: none"> Bone marrow suppression: macrocytic anemia or neu- tropenia; Gastrointestinal intolerance, headache, insomnia, asthe- nia; Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity asso- ciated with use of NRTIs).

Source: Guidelines for the use of Antiretroviral Agents in HIV-Infected Adults and Adolescents, U.S. Department of Health and Human Services, www.hivatis.org

not available on this recommendation however, so be sure to discuss this with your doctor or pharmacist.

Emtriva: Emtriva and EpiVir do not have a “drug interaction” per se, but since they have very similar chem-

ical structures, antiviral activities and can select for the same resistance mutation, they should not be taken together (see “How these Drugs Work” above for more detailed explanation). No formal drug interaction

studies have been conducted, but it would be wise to avoid using these two agents as the RTIs of your regimen until more information is available (studies suggested to be done in non-infected persons!).

Table No. 2: ANTIRETROVIRAL REGIMENS RECOMMENDED for TREATMENT of HIV-1 INFECTION in ANTIRETROVIRAL NAÏVE PATIENTS

	REGIMENS	NO. OF PILLS
Preferred Regimens NNRTI-based	Sustiva + (Efavirenz or Emtriva) + (Retrovir or Viread) (AII) – [Note: Sustiva is not recommended for use in first trimester of pregnancy or in women with high pregnancy potential*]	2-3
PI-based	Kaletra (lopinavir/ritonavir co-formulation) + (Efavirenz or Emtriva) + Retrovir (AII)	8-9
Alternative Regimens NNRTI-based	Sustiva + (Efavirenz or Emtriva) + (Ziagen or Videx or Zerit) (BII) – [Note: Sustiva is not recommended for use in first trimester of pregnancy or in women with high pregnancy potential*]	2-4
PI-based	Viramune + (Efavirenz or Emtriva) + (Retrovir or Zerit or Videx or Ziagen or Viread) (BII) - [Note: High incidence (11%) of symptomatic hepatic events observed in women with pre-Viramune CD4 + T cell count more than 250 cells/mm ³ and men with CD4 more than 400 cells/mm ³ (6.3%). Use with caution in these patients, with close clinical laboratory monitoring, especially for the first 18 weeks of therapy]	3-6
	Reyataz + (Efavirenz or Emtriva) + (Retrovir or Zerit or Ziagen or Videx) or (Viread + Norvir 100 mg/d) (BII)	3-6
	Lexiva + (Efavirenz or Emtriva) + (Retrovir or Zerit or Ziagen or Viread or Videx) (BII)	5-8
	Lexiva/Norvir + (Efavirenz or Emtriva) + (Retrovir or Zerit or Ziagen or Viread or Videx) (BII)	5-8
	Crixivan/Norvir + (Efavirenz or Emtriva) + (Retrovir or Zerit or Ziagen or Viread or Videx) (BII)	7-12
	Kaletra + (Efavirenz or Emtriva) + (Zerit or Ziagen or Viread or Videx) (BII)	7-10
3NRTI-based	Viracept + (Efavirenz or Emtriva) + (Retrovir or Zerit or Ziagen or Viread or Videx) (CII)	5-8
	Fortovase (SGC) or Invirase (HCG) / Norvir + (Efavirenz or Emtriva) + (Retrovir or Zerit or Ziagen or Viread or Videx) (BII)	13-16
	Ziagen + Retrovir + Efavirenz – only when a preferred or an alternative NNRTI- or a PI-based regimen cannot or should not be used (CII)	2

* Women with child-bearing potential implies women who want to conceive or those who are not using effective contraception. Source: www.hivatis.org, see page 9.

DRUG INTERACTIONS WITH TRIPLE RTIs

Viread and Efavirenz, when given with either Videx or Ziagen once a day, resulted in poor rates of efficacy. The exact mechanism of this has not been determined, but it is not believed to be one related to plasma pharmacokinetics. Regardless, these medicines should not be used as a once-daily antiretroviral regimen.

DRUG INTERACTIONS WITH RTIs AND NNRTIs

None of the RTIs have any known impact on the pharmacokinetics of the

NNRTIs. One potential interaction is that Rescriptor (which needs acid in the stomach for absorption) would need to be separated from Videx buffered tablets (which reduces acid in the stomach).

DRUG INTERACTIONS WITH RTIs AND PIs

As detailed above in the metabolism paragraph, most of the RTIs are metabolized by pathways other than those used by PIs. Therefore, drug interactions resulting from inhibition or induction of CYP metabolism are not usually seen between the nukes and PIs. There are a few noteworthy exceptions to

this. They are provided below.

Viread and Reyataz: When Reyataz is administered with Viread, decreased Reyataz AUCs of 30% and C_{min} of 40% were seen. To counter this, 300 mg of Reyataz was given with 100 mg of Norvir and 300 mg Viread — all given simultaneously once daily. This is done to raise the Reyataz trough concentration to about the level it usually is when you are not taking Viread. When these three were given together to HIV-positive persons, Reyataz's AUC and C_{min} were actually higher compared to Reyataz alone. However, longer clinical studies of these three would be welcome.

In the meanwhile, TDM may be prudent to use to ensure the Reyataz level is high enough

Viread levels are increased by Reyataz by about 30%. But, Viread (and Truvada) dose adjustments are not recommended. So far controlled clinical trials extending beyond 96 weeks have not shown evidence of toxicity. Patients and doctors should just be aware of the increase so they can be on the watch for a potential increase in Viread side effects.

Viread and Kaletra: Kaletra is not significantly impacted by Viread. Kaletra does impact Viread though. When given together, increases in Viread AUC and C_{\min} were observed to be about 30% and 51%, respectively. As noted above, dose adjustments are not necessary, but being extra vigilant for any potential increase in Viread side effects is probably warranted.

It is not known why these interactions between Viread and these two PIs happen. Formal clinical studies using pharmacokinetic or TDM-based dosing of Reyataz and Kaletra have not been conducted to date. These types of

studies may provide a better understanding of why these interactions occur, and hopefully this will be forthcoming. Importantly, Viread has been shown not to interact with Crixivan, Viracept, or Fortavase or Invirase boosted with Norvir.

Retrovir: Retrovir does have some minor interaction with both Viracept and Norvir. With Norvir and Viracept, Retrovir's AUC can be decreased by 25% to 35%, respectively. No dosing changes are recommended.

Videx: The remaining drug interactions possible are the result of absorption or dietary issues. Most of the protease inhibitors have dietary restrictions (food requirements, see Protease Inhibitors). The exceptions are Lexiva and Crixivan/Norvir. As Videx should be taken on an empty stomach and the protease inhibitors are to be given with food, these medicines should be separated by a minimum of one hour when prescribed in combination. As described earlier, if Videx is being given with Viread simultaneously with food, then taking the protease inhibitors at the same time is accept-

able. If you have any questions, please check with your doctor or pharmacist.

STARTING AND STOPPING THE MEDICINES

The plasma and intracellular half-lives of these drugs vary considerably (from 7 hours for Retrovir and Zerit to about 39 to more than 60 hours for Emtriva and Viread) (see Table 1 on page 9 and Figure 5 on page 7). While there are recommendations for how to deal with the long half-lives of the non-nukes when stopping a regimen, there are no similar recommendations for how to deal with the nukes' long half-lives. This is an area where more studies are needed. ☚

Patrick G. Clay, PharmD, is an Associate Professor of Medicine and Director of Clinical Research for the Kansas City University of Medicine and Biosciences. He is primarily involved in investigations of antiretrovirals in infected and non-infected persons and has been working in HIV since 1995.

Editor's TOP 3 Websites

RECOMMENDED DRUG INTERACTION WEBSITES (AND THEY'RE FREE!)

1 = University of Liverpool:

www.hiv-druginteractions.org. This informative and educational HIV pharmacology resource is valuable for healthcare professionals, scientific researchers or anyone with an interest in HIV therapy. You can find reports on recent news and hot topics in HIV, discover comprehensive information and advice on drug interactions, read about advances in therapeutic drug monitoring (TDM), and much more!

2 = Toronto General Hospital:

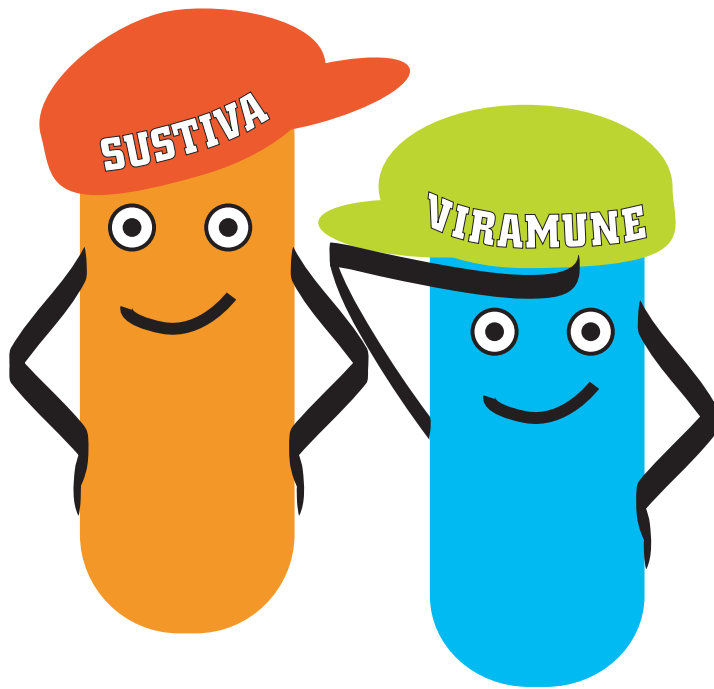
www.tthivclinic.com/interact_tables.html. This website is primarily for health professionals, but is an excellent site for up-to-date information on anti-HIV medicine drug interactions as well as herbal medicine interaction data. The information in these charts is intended for use by experienced physicians and pharmacists. The tables are

not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Due to the rapidly changing nature of information about HIV treatment and therapies, users are advised to re-check the information contained herein with the original source before applying it to patient care. Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about HIV-related illness and the treatments in question.

3 = UCSF: <http://hivinsite.ucsf.edu/>.

HIV InSite is developed by the Center for HIV Information (CHI) at the University of California/San Francisco (UCSF), one of the world's leading health sciences institutions. Within UCSF, HIV InSite is produced in col-

laboration with the San Francisco Veterans Affairs Medical Center, the Positive Health Program at San Francisco General Hospital and the Center for AIDS Prevention Studies, components of the University's AIDS Research Institute. Launched in March 1997, HIV InSite's mission is to be a source for comprehensive, in-depth HIV/AIDS information and knowledge. The site has an extensive collection of original material, including the HIV InSite Knowledge Base, a complete textbook with extensive references and related links organized by topic. Unlike many commercially oriented sites, HIV InSite's policy is to link to the best of the Web, and thousands of links to external websites are incorporated into the site's original content. It is the policy of HIV InSite to allow free, anonymous access to all of the site's content.



THE TWO MAJOR PLAYERS

BY JEAN LEE, PharmD

the Non-Nukes

How do they work against the virus?

The non-nucleoside reverse transcriptase inhibitors (NNRTIs, also known as “**non-nukes**”) are drugs that attach to the reverse transcriptase enzyme. They bind in a site that is somewhat different than the “nukes”, but essentially do the same thing. Although they bind on the same enzyme as the nukes, because they bind on a different site, they are safely (and recommended to be) combined with the nukes. Once bound, the virus can no longer convert its genetic makeup into your T-cells, thus preventing the virus from replicating.

There are three drugs in this class: Sustiva (efavirenz, EFV), Viramune (nevirapine, NVP) and less used Rescriptor (delavirdine, DLV). These drugs have differences but also similarities. *Table 1* shows some unique factors. The similarities of the NNRTI class will also be reviewed.

DO THEY PLAY WELL TOGETHER?

This part of the article will focus more on Sustiva and Viramune since they are prescribed more often than Rescriptor. The following are drug interactions between the NNRTIs and PIs and NRTIs, indicating the various PK changes and what should be done with dosing.

NNRTIs AND PIs Sustiva

Remember: Sustiva is an inducer, mostly of CYP3A4, so it generally tends to decrease the concentration of the other drug!

Sustiva and Reyataz – Because Sustiva may decrease the AUC of Reyataz by 74% and C_{min} by 93% (see *ABC's of Pharmacokinetics on Page 4*), it is recommended that 100 mg of Norvir is given once daily with the Reyataz and Sustiva combination. Also, Reyataz will need to be decreased from the usual 400 mg daily to 300 mg daily when Norvir is added (see Protease Inhibitors). Because you

need to take Reyataz with food, you may want to separate your dose of Reyataz/Norvir and Sustiva. If you cannot or you simply want to take them all together, make sure you don't have a high fat snack when you take these medicines, as this may increase the concentrations of Sustiva in your body and the chance for side effects (see *Table No. 1*).

Sustiva and Lexiva – Sustiva will decrease Lexiva's C_{min} by 36%. If you are taking Lexiva once daily, it is recommended to take 300 mg (3 capsules) of Norvir with the Lexiva (2 tablets). This is more Norvir than is recommended to be taken with Lexiva without Sustiva (see Protease Inhibitors). Total dose will be Lexiva 1400 mg + Norvir 300 mg once daily with or without food. Remember that if you decide to eat when taking this combination, eat a low-fat or no-fat snack. This only applies to once-daily dosing of this combination. No additional Norvir dosing is needed if you are taking boosted Lexiva twice daily (see Protease Inhibitors).

Sustiva and Kaletra – Sustiva will lower the C_{min} of Kaletra by 39%. Thus you need to add an extra capsule of Kaletra for a total of 4 pills twice daily with food. Since Sustiva should be taken on an empty stomach, it is best to separate these medications by at least 2 hours. Remember that if you decide to eat when taking this combination, eat a low-fat or no-fat snack.

Sustiva and Crixivan – Sustiva lowers the AUC of Crixivan ranging from 33-46%, and C_{min} ranging from 39-57%. You have to either increase the Crixivan dose to 1,000 mg every 8 hours or, more recommended, use 100 mg–200 mg of Norvir twice daily (Crixivan 800 mg + Norvir 100 mg–200 mg twice daily). The latter regimen allows you to go from three times daily to twice daily dosing (by adding Norvir). Your doctor will let you know if you should take the 100 mg or 200 mg dose. If you take Crixivan/Norvir and Sustiva at the same time, make sure you take it on an empty stomach, to avoid high Sustiva concentrations. If you want to take your Crixivan/Norvir with some food, it is best to separate it from the Sustiva by at least 2 hours. Remember that if you decide to eat when taking this combination, eat a low-fat or no-fat snack.

Sustiva and Invi- rase and Fortovase – When you take Sustiva with this drug, it will decrease the AUC by 62%, thus you cannot use this without boosting it! For both Invi- rase and Fortovase, there are two dosing regimens: Invi- rase/Fortovase 400 mg + Norvir 400 mg given twice daily with food or Invi- rase/Fortovase 1,000 mg + Norvir 100 mg given twice daily with food. Your doctor may have you take more Norvir to make sure you have adequate Invi- rase/Fortovase in your

body. Since Sustiva should be taken on an empty stomach, it is best to separate the Invi- rase or Fortovase with Norvir from Sustiva by at least 2 hours. Remember that if you decide to eat when taking this combination, eat a low-fat or no-fat snack.

Viramune

Remember: Viramune is an inducer of CYP3A4, so it may decrease the con-

ONCE BOUND, THE VIRUS CAN NO LONGER CONVERT ITS GENETIC MAKEUP INTO YOUR T-CELLS

centration of the other drug!

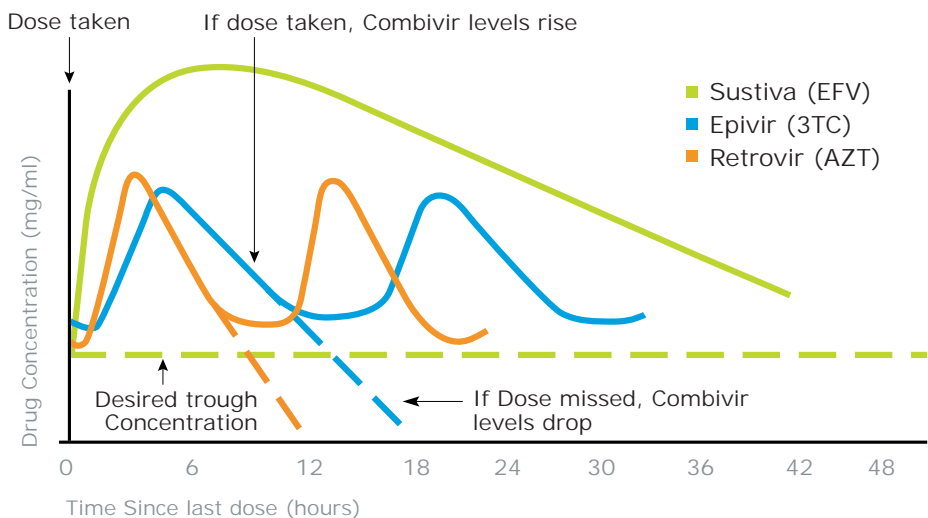
Viramune and Reyataz – There are no conclusive data with this combination, but the drug concentration of Reyataz is expected to decrease due to the inducing effects of Viramune. Thus, at this time, it is recommended to boost 300 mg of Reyataz with 100 mg of Norvir (see Pro- tease Inhibitors).

Viramune and Lexiva – There are no data with this combination, but the drug concentration of Lexiva is expected to decrease due to the inducing effects of Viramune. Thus you will likely need to use a boosted regimen. While 700 mg Lexiva + 100 mg Norvir is commonly used, it is unknown if this will be sufficient to offset the interaction. This may be one of the times where TDM would be useful (see Pro- tease Inhibitors).

Viramune and Kaletra – Like the interaction with Sustiva, if you take Viramune and Kaletra, we can see a decrease in the Kaletra AUC by 27% and C_{min} by 51-55%. Thus, you need more Kaletra! For this interaction, you should be taking Kaletra 4 capsules twice daily with food (533 mg/133 mg).

Viramune and Crixivan – When you take these two drugs together, the C_{min} of Crixivan is decreased by 44%, so you need a different dose. You either have to increase Crixivan to 1000 mg every 8 hours or add 100 mg–200 mg of Norvir

Figure No. 1:
THEORETICAL PHARMACOKINETICS of SUSTIVA + COMBIVIR (AZT + 3TC)



This figure shows the drug concentration (solid lines) of zidovudine (AZT), lamivudine (3TC) taken twice daily, and efavirenz (EFV) when taken once daily. If the medications are stopped, the concentration of AZT and 3TC will fall (dashed lines), but the concentration EFV will still be present hours later. This graph, however, does not predict how the drug behaves inside the cell. This represents what happens in the blood only. See ABC's of PK for more information about levels of drugs inside the cells.

twice daily (Crixivan 800 mg + Norvir 100 mg–200 mg twice daily). If you add Norvir, this interaction allows you to go from three times daily to twice-daily dosing, taken with or without food. Your doctor will decide which dose of Norvir you should be taking.

Viramune and Inivrase or Fortovase – With this interaction, the AUC of Inivrase/Fortovase is decreased by 38%, thus boosting is needed with Norvir. The amount of Norvir depends on the drug (Inivrase or Fortovase) and amount of drug used as listed below.

- Inivrase 1,000 mg + Norvir 100 mg given twice daily with food
- Fortovase 400 mg + Norvir 400 mg given twice daily with food
- Fortovase 1,000 mg + Norvir 100 mg given twice daily with food

Your doctor may have you take more Inivrase, Fortovase and/or Norvir to make sure you have adequate Inivrase/Fortovase in your body. Your doctor may also decide to use TDM to make sure you are getting adequate drug in your body.

Rescriptor AND PIs

Concentrations of PIs may be increased due to the inhibitory effect of Rescriptor. A PI dose reduction may be required. Talk to your pharmacist or doctor about these interactions.

NNRTIs AND RTIs

No clinically significant interactions with either Sustiva, Viramune or Rescriptor.

Stopping or switching medications

Stopping medications: Because Sustiva and Viramune have a long half-life, it will take longer for it to clear from your body. If you were to stop all your antiretrovirals at the same time, some of the nukes with shorter half-lives will be cleared sooner than the non-nukes (See *Figure 1: Theoretical Pharmacokinetics of Sustiva + Combivir*). For a period of time, you may only have the non-nukes in your blood. Conversely, if you have a nuke backbone that has longer half-lives (See *Figure 2: Theoretical Pharmacokinetics of Truvada + Sustiva*) extension of nucleoside dosing may not be necessary. Depending on the nuke backbone, there is some information that if you stop the non-nuke, you might need to continue the nukes to avoid the development of mutations — but you should discuss this with your doctor first. There may also be drug interactions if you quickly switch from a non-nuke regimen to a PI regimen. For example, if you switch from Sustiva to Kaletra, you need to make sure there isn't any Sustiva around to

interact and lower Kaletra levels. Ask your clinical pharmacist or physician on how to plan your switch!

Switching between non-nukes

Switching from Sustiva to Viramune: Some recent information may change how you take your Viramune if you are switching to it from taking Sustiva. You may be able to take the full dose of Viramune from day one (200 mg twice daily). This would mean you may not have to go through the lead-in dosing of 200 mg once daily for 2 weeks. You might be able to do this because the remaining Sustiva in the body may lower concentration of Viramune in the body. By taking the full dose of Viramune from day 1 on, drug levels may be higher and closer to normal. This is very different than what you find in the package insert for either drug, so be sure to talk to your doctor or pharmacist about this first! Taking too much Viramune too soon may increase the risk for side effects (liver problems for example).

Switching from Viramune to Sustiva: Take the full dose of Sustiva on the first day of the switch.

Again, talk to your clinical pharmacist or doctor on how to plan this switch.

The metabolism of NNRTIs makes it very important when it comes to the potential drug interactions. The last thing you'd want is to lower the concentration of your HIV meds and risk developing resistance. Always check with your doctor or pharmacist whenever you are prescribed a new medication. ☒

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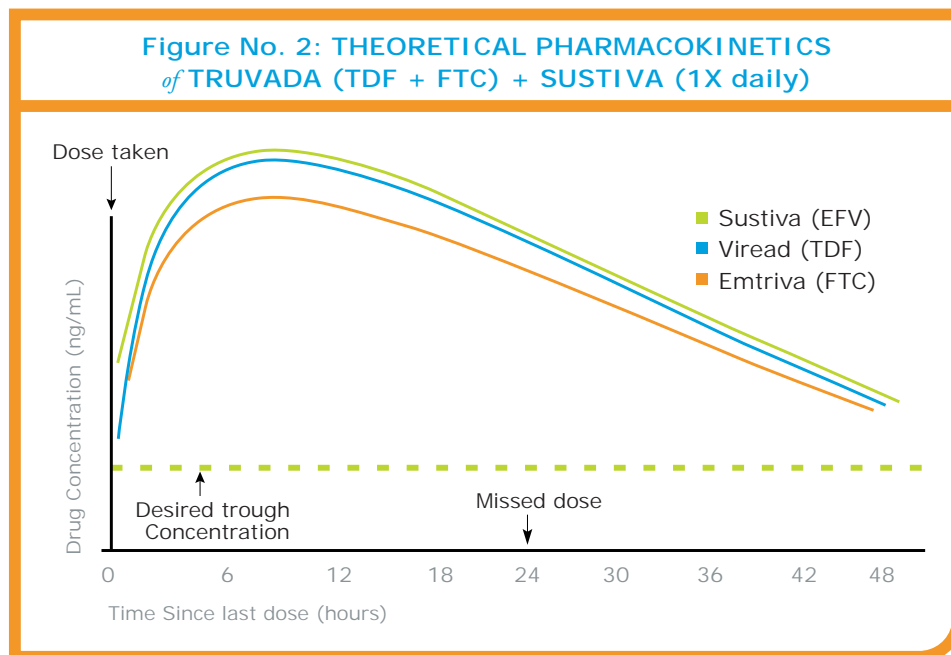


Table No. 1: REGIMEN and PHARMACOKINETIC PROPERTIES of the NNRTI CLASS

Drug	SUSTIVA (efavirenz)	VIRAMUNE (nevirapine)	RESCRIPTOR (delavirdine)
Care	Store at room temperature and avoid high humidity.	Store at room temperature.	Store at room temperature.
Dose	600 mg at bedtime (1 pill/day)	200 mg once daily x 14 days— to decrease the chance of rash, then 200 mg twice daily (2 pills/day)	400 mg three times daily (ideally every 8 hours for best drug levels) 100 mg tabs: (12 pills/day) 200 mg tabs: (6 pills /day) With or without food
Administration	Empty stomach or low-fat snack Food, especially high fat food, will increase absorption, causing higher drug levels. This may cause more frequent and intense side effects.	400 mg once daily outside US With or without food	Only 100 mg tabs can be dissolved in liquid.
Primary side effects	Neurological side effects: (dizziness, drowsiness, altered dreams) Rash: within the first 6 weeks	Rash within first 6 weeks. Increased liver enzymes within first 18 weeks. Should be monitored closely by your provider.	Rash within 1-3 weeks of therapy. Nausea, diarrhea, headache, fatigue, increased liver enzymes
Absorption	Higher levels seen if taken with fatty meal with both capsules and tablets. Recommended to take on an empty stomach	Quick with >90% absorption after a dose. Dosing is the same with oral solution and tablets, thus similar PKs.	Needs acid for best absorption. You can take drug with acidic beverage (OJ, cranberry juice). If you need antacids you should take them at least 1 hour apart from this medication.
Metabolism	Metabolized by liver: CYP3A4, CYP2B6 Inducer of: CYP3A4, CYP2B6 Inhibitor of: CYP2C9, CYP2C19, CYP3A4	Metabolized by liver: CYP3A4, CYP2B6 Inducer of: CYP3A4, CYP2B6 Inhibitor of: None	Metabolized by liver: CYP3A4, CYP2D6 Inhibitor of: CYP3A4, CYP2C9, CYP2C19, CYP2D6

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The Protease Inhibitor Drugs

BY JAMES D. SCOTT, PharmD

Currently, there are eight approved compounds for the treatment of HIV infections that are in the class known as protease inhibitors. Of all classes of HIV medications, the protease inhibitors are the most complex in terms of pharmacokinetics, drug interactions and dosing changes based on those interactions.

MECHANISM OF ACTION

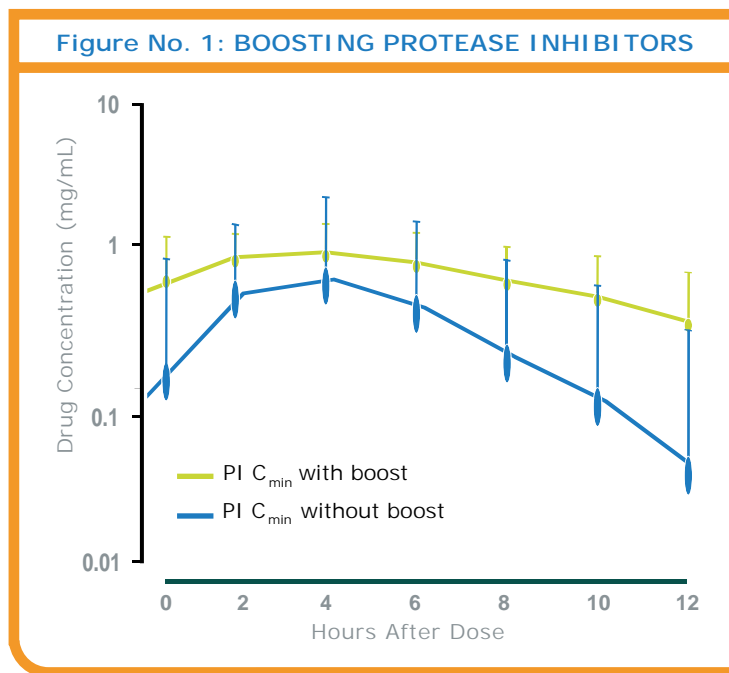
All protease inhibitors work in the same manner. They block the activity of the protease enzyme within human cells or new virus particles. This enzyme is what allows a virus to undergo final maturation for producing new viruses that can go out and infect other cells. When the PIs bind to the enzyme, the new viruses still leave the cell, but they are unable to infect other cells.

GENERAL CONCEPTS IN THE PK OF PROTEASE INHIBITORS

All current protease inhibitors are administered by mouth. They are all absorbed in the gastrointestinal (GI) tract (stomach and intestines). Metabolism, occurring after absorption, is typically performed by the CYP enzymes found in the liver and some in the intestines as

well (mainly CYP3A4) (see ABC's of PK). Sometimes, multiple enzymes may affect the same PI (see *Figure 2 page 5*). The PI, in turn, may also affect how these enzymes function. This is why PIs can affect the metabolism of other protease inhibitors and other drugs for different illnesses. The protease inhibitor that has the strongest effect on these enzymes is Norvir. Most

Norvir to see if boosting is optional (Reyataz, Lexiva), recommended (Crixivan, Fortovase) or required (tipranavir [experimental], Invirase, Kaletra). The pharmacokinetics of the available protease inhibitors are summarized in *Table 1*, with and without Norvir boosting. Currently, the only approved protease inhibitor for which boosting is not recommended is Viracept.



These are representative drug concentration-time curves for “boosted” and “unboosted” PI regimen dosing schemes. The “boosted” regimen usually provides for higher C_{min} than “unboosted”. This generally allows for fewer pills to be given per day compared to “unboosted” regimens. Also, there are error bars around each point plotted on this graph. These error bars reflect potentially how different the levels may be from one person to the next or within the same person. Regimens that are “boosted” generally tend to have less variability compared to “unboosted” (smaller error bars).

of the time, Norvir will slow down how fast the other protease inhibitors are eliminated (see *Figure 1: Boosting Protease Inhibitors*). This is called PI boosting. As such, the newer and some older PIs are studied with and without

There are few drug interactions between PIs and the nucleoside/nucleotide reverse transcriptase inhibitors.

Fortovase and Invirase (both are referred to as saquinavir)

It would be best to take Fortovase and Invirase at the same time as the Norvir. This is because saquinavir is broken down both by enzymes in the intestines and the liver. Norvir decreases the activity of these enzymes and allows more drug to enter the blood stream and to stay in the blood longer. If one were to separate these medications, the blood level of Fortovase or Invirase may be too low to allow the medication to do its job, and may increase the risk of developing resistance.

Norvir is not the only protease inhibitor that can affect the other protease inhibitors. Many studies have been done on this topic. These interactions are summarized in *Table 2*. The protease inhibitors also have effects on the pharmacokinetics of

some of the other antiretrovirals. See *The Non-Nukes* on page 12 for details of the interactions there.

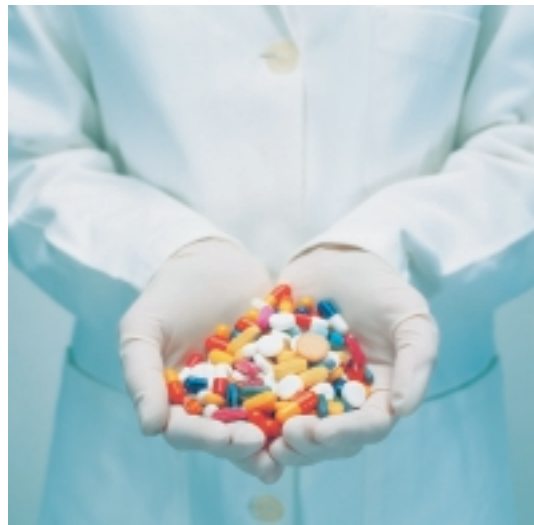
PIs and Viread

Viread decreases the blood levels of Reyataz. The cause of this is not yet known. When a clinician decides to start a patient on both Viread and Reyataz, the Reyataz must be boosted (see Table 1). Additionally, Reyataz and also the combination product of Kaletra have been shown to increase levels of Viread. The clinical implications of this are not yet known. No dose adjustments are recommended at this time (see The Nukes).

DAY-TO-DAY PHARMACOKINETICS

Food restrictions

Most protease inhibitors do not require food to in order to maintain normal,



therapeutic drug levels but, and perhaps as important, it may make them more tolerable. The two exceptions to this rule are Reyataz and Viracept. Reyataz requires an acidic stomach environment to be absorbed, and food stimulates the production of acid. The amount of food that should be eaten is not specified by the manufacturer, and

is not likely to be of importance. However, certain amounts of food intake have been shown to increase how much Viracept is absorbed with each dose. A meal of at least 500 calories (20% of calories from fat) should be eaten with each dose of Viracept in order to achieve normal therapeutic levels. Increasing the amount of food to 1,000 calories will increase Viracept levels even further. Crixivan, when not given with Norvir, requires little to no food for optimal absorption but food (a low-fat snack only) may make the pills more tolerable.

Missed doses

Missing doses of most protease inhibitors has been shown to increase the likelihood of a person's virus changing (resistance developing). This makes it less likely that the protease inhibitor will work against the virus. Occasionally, everyone who takes medications for a long period of time

Table No. 1: PHARMACOKINETICS of PROTEASE INHIBITORS

BRAND NAME	GENERIC NAME	DRUG PER TAB/CAPSULE	UNBOOSTED DOSES ¹	BOOSTED	
				DOSE ¹	NORVIR 100 MG CAPS
CRIXIVAN	indinavir	200 mg ⁵ 333 mg ⁵ 400 mg	XXXXXX XXXXXX 2 caps TID ⁴	XXXXXX 3 caps BID ^{2*} 2 caps BID	XXXXXX 1-2 caps BID* 1-2 caps BID*
FORTOBASE	saquinavir	200 mg	6 caps TID	5 caps BID	1 cap BID
INVIRASE	saquinavir	200 mg 500 mg	Not recommended Not recommended	5 caps BID 2 tabs BID	1 cap BID 1 cap BID
KALETRA	lopinavir/ ritonavir	133 mg/33 mg	3 caps BID	4 caps BID*	XXXXXX
LEXIVA	fosamprenavir	700 mg	2 tabs BID	1 tab BID 2 tabs QD ^{3,6}	1 cap BID 2 caps QD
NORVIR	ritonavir	100 mg	6 caps BID	XXXXXX	XXXXXX
REYATAZ	atazanavir	150 mg 200 mg	XXXXXX 2 caps QD	2 caps QD ⁷ XXXXXX	1 cap QD XXXXXX
VIRACEPT	nelfinavir	250 mg 625 mg	5 tabs BID 3 tabs TID 2 tabs BID	Cannot be boosted with Norvir	Cannot be boosted with Norvir

* These doses are supported by clinical trials or experience, but are not FDA approved
 1. All doses assume that the product is being used in combination with at least two other active antiretroviral agents
 2. BID = twice a day
 3. QD = once a day
 4. TID = three times a day
 5. These strengths are typically used to complete doses needed to compensate for various drug interactions requiring dose adjustments
 6. Once daily dosing of Lexiva with Norvir is not recommended in patients who are protease inhibitor experienced
 7. Reyataz with Norvir has not been studied in patients receiving HIV treatment for the first time

Table No. 2: DRUG INTERACTIONS *between* PROTEASE INHIBITORS, *with* CLINICAL COMMENTS *when* AVAILABLE

DRUG AFFECTED	RITONAVIR (RTV)	SAQUINAVIR (SQV)	NELFINAVIR (NFV)	LOPINAVIR/RITONAVIR (LPV/r)	ATAZANAVIR (ATV)
INDINAVIR (IDV)	IDV levels ↑, combo is used clinically (see Table 1 for dosing)	SQV levels ↑, no change in indinavir (no dose recommendations)	Levels of both ↑, some data supported this combo (IDV 1200 mg/NFV 1250 mg BID)	IDV levels ↑, some data supported this combo (use IDV 600 mg BID)	Not rec'd to give these two together due to side effects
RITONAVIR (RTV)	X	SQV levels ↑, combo is used clinically (see Table 1 for dosing)	Variable effects of NFV, this combo is not rec'd	RTV ↑'s LPV, additional RTV has been used with LPV/r (LPV 3 caps/RTV 100 mg BID)	ATV levels ↑, combo is used clinically (see Table 1 for dosing)
SAQUINAVIR (SQV)	SQV levels ↑, combo is used clinically (see Table 1 for dosing)	X	Levels of both ↑, some data support this combo (NFV 1250 mg BID, SQV 800 TID or 1200 mg BID)	SQV levels ↑, some data support this combo (LPV 3 caps/SQV 1000 mg BID)	SQV levels ↑, no clinical rec's yet ¹
NELFINAVIR (NFV)	Variable effects of NFV, this combo is not rec'd	Levels of both ↑, some data support this combo (NFV 1250 mg BID, SQV 800 TID or 1200 mg BID)	X	LPV levels ↓, NFV levels ↑, this combo is not supported	No data
FOSAMPRENAVIR (FPV)	APV levels ↑, combo is used clinically (see Table 1 for dosing)	APV levels ↓ (no dose rec's)	No data with FPV, expect APV levels ↑	APV levels ↓, LPV levels ↓, combo is not rec'd at this time	Limited data, no rec's yet
LOPINAVIR/RITONAVIR (LPV)	RTV ↑'s LPV, additional RTV has been used with LPV/r (LPV 3 caps/RTV 100 mg BID)	SQV levels ↑, some data support this combo (LPV 3 caps/SQV 1000 mg BID)	LPV levels ↓, NFV levels ↑, this combo is not supported	X	No data

1. While one clinical trial using the combination of ATV and SQV results in poor clinical results, the doses of this combination may not have been optimal. Additional studies are underway to identify the optimal dose for this combination.

will find that they have missed a dose of their medication. When it comes to taking protease inhibitors, it is best to take the missed dose as soon as possible. If the missed dose is not realized until the next dose is due, it is not recommended to take a double dose. If more than one dose has been missed, it is best to consider those doses missed, and start anew with the next dose that is due. Protease inhibitors should not be taken without the other antiretrovirals that are prescribed, and vice versa. So, if doses of any HIV medication are missed due to the lack of availability of any of the components of the regimen, the entire regimen should be stopped until all components are available. Be sure to speak with your doctor's office or pharmacist as soon as you realize you do not have all of your medicines!

DRUG LEVEL TESTING

Drug level testing (also called therapeutic drug monitoring, or TDM, also see ABC's of PK) is available to most clinicians. There are recommended trough concentrations for several PIs for patients who do not have drug resistant virus (see Figure 6 on page 7). However, TDM for PIs is not yet routinely recommended. It might be useful in certain circumstances (see ABC's of PK). In patients who have had many antiretrovirals in the past (treatment experienced), what may ultimately guide targets for drug concentrations is the amount of resistance that the person's virus has. Unfortunately, the resistance test that shows the amount of drug needed to decrease the growth of the virus (a phenotype) has many limitations of its own. These limits, in

turn, limit the usefulness of TDM for protease inhibitors. Currently, TDM is best done using trough levels (C_{min}).

SPECIAL CIRCUMSTANCES

There are two of the protease inhibitors to which special discussion should be given. Amprenavir is the active drug that makes up both Lexiva and Agenerase. Lexiva, which was approved in October 2003, is a "prodrug" of Agenerase. A special chemical group was added to the Agenerase molecule. This molecule allows it to be made into a tablet formulation that is more compact, as well as allowing for better absorption from the GI tract. Once Lexiva is absorbed, the extra chemical group is removed in the blood, releasing the active drug, amprenavir. As such, once the drug is absorbed, it has

the same pharmacokinetics as amprenavir. The pro-drug formula greatly reduces the number of pills taken.

The second product is saquinavir. It is available under two brand names, manufactured by the same pharmaceutical company. Invirase, which resembles a typical capsule formulation containing a powder, was first approved in late 1995 (in fact, it was the first protease inhibitor approved in the U.S.). This formulation is referred to as a

hard-gel capsule. Though Invirase was effective at killing the virus, very little of it was actually absorbed into the blood stream. To improve this aspect, Fortovase was developed. Fortovase offers significantly improved absorption compared to Invirase, and quickly became the preferred formulation. When Fortovase and Invirase are boosted by Norvir, the blood levels of saquinavir are similar. As such, Invirase and Fortovase come close to being equal over the

past few years with perhaps greater tolerability of the boosted Invirase compared to boosted Fortovase. ☚

Jim Scott, PharmD, is an Assistant Professor of Pharmacy Practice at the Western University of Health Sciences, and Director of the Adherence Improvement Program at the Jeffrey Goodman Special Care Clinic, in Los Angeles, CA. He has been working with HIV patients for over 10 years.

ABC's of PK from page 7

then pumps the drug to a detector.

There are a lot of different kinds of detectors. The common ones for HIV drugs are a mass spectrometer (MS) and an ultraviolet light absorbance detector (UV). A MS detects drugs according to how heavy it is (and also the positive and negative charge of the drug). The detector gives a signal based on how much drug is there. The signal is compared with signals that the detector gives for known amounts of drug that are also put onto the machine (called a standard curve). This gives the drug level in the patient.

IMPORTANT THINGS ABOUT PK AND TDM

One important point is that TDM is not really useful for nukes in most cases. This is because nukes have three phosphate groups attached while inside cells in order to become active against HIV (called triphosphates). Therefore, the best way to do TDM for nukes would be to measure the nuke-triphosphates that are in cells, not the plasma level of the nuke. But, this is very hard to do, so TDM for nukes is not usually done.

Since nuke-triphosphates inside cells are really important for anti-HIV activity, it is important for researchers to measure the half-life of the triphosphate in patients to understand whether the nuke can be given once a day, twice a day, and so on. For many nukes, the half-life of the triphosphate in cells is quite a bit longer than the half-life in plasma, so the nuke can be given once or twice a day (see Figure 5: *Plasma and Intracellular Half-lives of Select NRTIs*).

As an example, Ziagen (abacavir)

has a fast half-life (about 1.5 hours) in plasma, but the half-life of the triphosphate in cells is about 20 hours. So, abacavir can be given once a day.

On the other hand, PIs and NNR-TIs are not chemically changed in cells to become active, so the plasma levels can be used for TDM. But, TDM is not routinely used in the U.S. for several reasons. First, TDM has not really been studied much in patients, so doctors are not yet sure about TDM in all their patients.

Secondly, it is not yet clear exactly how to use the information TDM provides. There are some questions that are still unanswered regarding TDM, including:

- 1.) What are the target levels for efficacy in patients with resistant viruses? Right now, levels that are recommended in treatment guidelines are only for viruses that are not resistant. If a person has a resistant virus, precisely how much of the drug should they have in their body is unknown.
- 2.) How is it best to adjust doses to meet targets — for example, should Norvir boosting be the main way to increase levels for PIs?
- 3.) Are C_{max} levels useful for reducing toxicity?
- 4.) Is an expert needed to do TDM?
- 5.) And, should laboratories be required to pass the same quality-assurance test to get official approval to do the levels?

Although TDM may not be used routinely in all patients, there are some situations where TDM may be useful. These include: childhood, obesity, very

small body size, elderly, pregnancy, liver or kidney diseases, and drug-drug interactions. Also, TDM may be used in patients with an unexpected adverse effect or poor efficacy. For these occasions, as mentioned above, there are suggested target levels for PIs and NNR-TIs in situations where there is no drug resistance (see Figure 6: *Suggested Minimum Target Trough Concentrations for Persons with Wild-type HIV-1*).

Finally, if TDM is to be undertaken, there are some very important things to do. First, if the level is for efficacy, it is very important to get the level as close to the trough as possible. This is the best way to interpret the level.

If the level is for toxicity, and a C_{max} is desired, it would be best to watch the dose being taken and to obtain the level thereafter. In general, it is very important to realize that the TDM test completely depends on accurately recording when the patient last took their dose and accurately recording when the blood was collected. Other drugs that might have been taken with the dose should also be recorded. Since the current state of TDM for HIV is in the development phase, it would be best to obtain expert advice if undertaking TDM. ☚

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