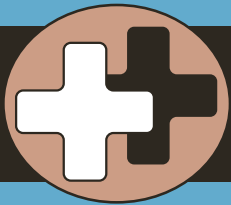


Special Issue Fall 2005



Positively Aware

The Journal of Test Positive Aware Network

How You Can Impact Treatment Outcomes!

Know More!

- PK Primer
- GI Problems
- Drug Interactions
- Navigating Healthcare
- Resources

GETTING THE MOST OUT OF TREATMENT



Editor's Note

describe the details of each individual interaction study would take up a huge amount of space and be of little or no value to most readers. We hope that we've presented the information about PPI interactions and similar information in a way that's accessible yet still accurate.

Finally, when providing information about various drugs or regimens, we try to be objective. Unless we're writing an opinion piece or describing data that clearly demonstrates the superiority of one drug over another, we do our best to discuss each HIV medication objectively. Since we're human and have personal biases, this isn't always easy. But we try to avoid bashing one drug or making another look better. This would actually be easy to do by selectively choosing which data to write about. Editors, colleagues, and medical reviewers are essential to the process. As much as possible, they help to ensure that bias doesn't creep into the final product.

These are just a few of the challenges we face when writing about treatment. Sometimes we get things right—sometimes we don't. That's one of the many reasons that hearing from readers is so important.

It has been a privilege to work on this special issue of *Positively Aware*. It's allowed me the opportunity to collaborate with thoughtful, dedicated writers and the terrific people at TPAN. I've contributed to *Positively Aware* often over the years and am always inspired by the editorial staff's professionalism and commitment to make sure that the content is relevant to the publication's diverse readership. I thank TPAN for inviting me to edit this issue. Above all, I hope that it provides information and tools to help you get the most benefit from your HIV treatment. ✚

Sincerely,
James Learned
James_Learned@prodigy.net

Being on HIV treatment isn't easy (let alone enjoyable) for anyone, despite recent improvements—once-a-day dosing, fewer food restrictions, and, in some cases, fewer side effects. This special issue of *Positively Aware* takes a look at factors that can help you benefit the most from therapy. If you're not on treatment, feel free to put the issue aside for now—it could come in handy should you decide to begin treatment in the future. And if you're in the process of considering treatment, the information included here might help clarify questions and concerns you want to discuss with your healthcare provider.

The goal of this issue is to help you take a more active role in your care, to have more control over your treatment decisions, and to get the most out of treatment. Many factors contribute to successful treatment. To varying degrees, some are beyond your control—genetics, lack of access to quality care, coexisting medical conditions, insufficient personal and community support, and needs like housing that take precedence over health concerns.

Other factors are more within your control—adherence (consistently taking the correct dose at the right time and following any food restrictions), scheduling and showing up for medical appointments, and getting answers to questions you have about your health and treatment.

This issue of *Positively Aware* focuses on some things that can happen inside your body that affect treatment.

Tim Horn's discussion of pharmacokinetics (PK)—a somewhat intimidating word that means how your body processes a drug from the time you take it until it's eliminated—describes how PK research has led to better treatment options for people with HIV and continues to do so.

Anne Monroe explains gastrointestinal conditions and the ways they can negatively affect treatment, while Joel Zive focuses on drug interactions and how interactions between HIV medications and other substances, including other drugs, herbs, and food, can impact treatment.

Jeannine Bookhardt-Murray's article about navigating the healthcare system includes practical tips for dealing effectively with members of your healthcare team. For many readers, hers may be the most directly useful piece in this issue.

We've also included a Personal Health Record that you can pull out and use to track your test results, vaccinations, and other important health information.

As HIV treatment becomes increasingly complex, writing about treatment issues becomes more challenging. All of science is complex, of course, and medicine is no exception. The potential for miscommunication is ever-present when we try to provide accessible treatment information. Reducing complicated issues into misleading, oversimplified, or incomplete information is always a danger. We faced many of the usual challenges as we put together this issue of *Positively Aware*.

One challenge was whether to include discussions of four HIV medications that are very rarely prescribed—Hivid, Rescriptor, Agenerase, and Fortovase. Since these drugs are approved by the Food and Drug Administration, on the market, and used by some people with HIV, we chose to include them. We felt it was important to discuss these medications since a few people who are on one of them might read this issue. If we were to omit them, a reader could well wonder why they're taking a medication that, according to *Positively Aware*, isn't used to treat HIV.

Another example of a challenge when presenting treatment information is in the discussion of potential interactions between proton-pump inhibitors (PPIs) and HIV medications. PPIs are used by many people with HIV to treat gastroesophageal reflux disease (GERD) and ulcers. Some PPIs are known to interact with certain HIV medications. But none of the PPIs have been studied with every HIV medication, so it would be inaccurate to write that each PPI interacts the same way with all of the HIV medications in a given class just because we know that one does. On the other hand, to

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A PK PRIMER

How your body
processes the drugs
you take

by Tim Horn

When it comes to developing new HIV medications—and understanding how best to use those we already have available—everyone is familiar with the importance of clinical trials. These studies provide us with important data about a drug's (or combination of drugs) side effects and its impact on viral load and CD4 counts, both in people new to HIV drug treatment and those with drug-resistant virus. But just as it's important to know how these drugs affect the body, it's also important to understand how the body affects these drugs. This is where the study of pharmacokinetics, or PK, comes in.

Knowledge about PK isn't only for pharmacologists (experts who study how chemical substances act in living systems, including the human body). Over the past several years, researchers, health-care providers, and people living with HIV have come to appreciate that a more detailed understanding of pharmacokinetics can dramatically improve the way we use available drugs, as well as drugs that are being developed. The details surrounding what happens to a drug, from the time it enters the body to the time it's eliminated, is both fascinating and complex, and the study of the various processes involved is continuing to help researchers figure out how to use HIV drugs with better effectiveness, less toxicity, and greater simplicity.

PHARMACOLOGY AND PK

As is true with virtually all medical terms, the word “pharmacology” is Greek in origin: *pharmacon* means drug and *logos* means science. The study of pharmaceuticals, or drugs, for medicinal use in people is called clinical pharmacology.

A drug has two central properties: its pharmacokinetics and its pharmacodynamics. Pharmacokinetics (PK) involves the relationship between the dose of the drug and the concentration (amount) of the drug in the body. Pharmacodynamics (PD) involves the relationship between the concentration of the drug in the body and the response it produces. In other words, PK describes what the body does to the drug, while PD describes what the drug does to the body.

In the past, PK studies of HIV drugs were simply an initial step in the development process. They were conducted in test tubes, animals, and a few people to help determine correct dosing, so that clinical trials evaluating a drug's effectiveness (for example, its effect on CD4 counts and viral load) and side effects could be conducted. Today, PK studies are much more involved. They are often conducted throughout the drug development process, and are sometimes required after the drug has been approved.

There are many reasons for the growing involvement of, and interest in, pharmacokinetics. For starters, HIV therapy involves combinations of drugs that sometimes must be used in conjunc-

tion with medications for AIDS-related complications and other diseases. This can lead to complex drug-drug interactions and it is very important for HIV-positive people and their healthcare providers to be aware of how drugs for HIV and other conditions affect each other.

Second, a drug's PK can vary considerably and depend on a number of biological factors. These include pregnancy, age, gender, race, body weight, genetics, and other illnesses (for example, liver or kidney disease). Knowing how drug concentrations vary under these circumstances is crucial, given that they can all apply to HIV-positive people.

Third, researchers now understand that HIV reproduces in many tissues throughout the body, including the brain. As a result, researchers need to determine the concentrations of HIV drugs not only in the blood, but also in the tissues where HIV replicates to ensure the drugs' effectiveness.

Fourth, understanding the PK of both new and older HIV drugs has allowed researchers to simplify treatment (for example, fewer pills or fewer doses), maximize the effectiveness of treatment, and reduce the risk or severity of side effects.

ALL ABOUT ADME

Every drug's PK profile depends on four factors: its absorption, distribution, metabolism, and elimination (ADME). This is a multi-step process that begins immediately after the drug, or combination of drugs, is swallowed and ends when the last trace of it leaves the body. Through all of these steps, a drug faces numerous challenges, underscoring the important role of PK research. Not only are PK studies helpful in figuring out what these challenges are, but they can help determine the best ways to avoid these challenges or use them to the patient's advantage.

ABSORPTION

In order for any drug to work, it needs to find its way into the body through a process known as absorption. This is actually a two-step process. First there is the release of the drug from its dosage form. Most HIV medications are taken orally (by mouth) in the form of a tablet, capsule, or liquid. The release of the drug from its dosage form usually takes place in the stomach. Capsules, for example, are made up of a gelatin outer coat, with the active ingredient contained inside. This allows for the drug to be swallowed and deposited in the gut, where the gelatin is dissolved by stomach acid, releasing the active ingredient.

Once the drug has been released from its dosage form, it must be moved from the gut into the portal vein, which carries the drug to the liver. With the help of stomach acid, a drug's active ingredient is made into a solution that can be absorbed by the membranes of the small intestine and then passed into the bloodstream.

The release of the drug from its dosage form, along with the movement of the drug from the gut into the portal vein, is a sensitive process. Some medications will break down too quickly—and won't be properly absorbed—if they come into contact with stomach acid. Videx, a nucleoside reverse transcriptase inhibitor (NRTI), is a prime example of this. Videx (didanosine) tablets contain an

antacid buffer to neutralize stomach acid. Videx EC capsules use an acid-resistant gelatin coat to prevent the active ingredient from being damaged by stomach acid before it has a chance to be absorbed.

The fusion inhibitor Fuzeon (enfuvirtide) is so sensitive to stomach acid that it can't be taken orally. It must be injected under the skin using either a hypodermic needle or the new needle-free device currently being evaluated in studies.

Some HIV medications, including most of the protease inhibitors (PIs)—especially Reyataz (atazanavir)—require acid in the stomach in order to be dissolved and absorbed properly. This is why HIV-positive people must be very careful if they also take medications that neutralize or decrease acid production in the stomach, such as those used for heartburn or acid reflux disease. (See Table 2 on page 12.)

Food can also affect the absorption of HIV drugs. Videx tablets, Videx EC capsules, and the protease inhibitor Crixivan (indinavir)—when it's used without Norvir (ritonavir)—should be taken on an empty stomach to ensure proper absorption, whereas the PIs Viracept (nelfinavir), Invirase (saquinavir), Kaletra (lopinavir/ritonavir), Aptivus (tipranavir), Reyataz, and the NRTI Viread (tenofovir) are best absorbed when taken *with* food. This is one of the many basic and important issues evaluated in PK studies. Your healthcare provider or pharmacist can tell you which medications should or shouldn't be taken with food.

DISTRIBUTION

After the drug has been absorbed and initially processed (metabolized)—an important step explained in the next section—the drug re-enters the bloodstream and is rapidly distributed throughout the body. The ultimate goal during the distribution phase is to get the HIV drug to where it's needed—inside CD4 cells. Once inside these cells, the drugs can go to work. However, there are a number of barriers that stand in the way of a drug being properly distributed throughout the body.

Protein binding is one such barrier. A drug that re-enters the bloodstream after leaving the liver will often attach to proteins in the blood, including albumin and alpha-1-acid glycoprotein. When bound to these proteins, the drug can't enter cells and is usually eliminated from the body. However, a percentage of the drug manages to evade protein binding and continues to circulate freely throughout the body. This free-circulating drug is sometimes referred to as the "free fraction."

A drug's free fraction remains constant in the circulation and is available to move into cells where it can act. Some drugs, such as PIs and the non-nucleoside reverse transcriptase inhibitor (NNRTI) Sustiva (efavirenz), are highly protein-bound, and only small fractions are protein-free. This can affect dosing; the more highly protein-bound a drug is, the higher the drug's concentration may need to be in the bloodstream to ensure that enough free fraction is available to do what it's supposed to do.

A drug's distribution also involves its concentration inside cells. With most HIV drugs, it's actually the intracellular concentration that matters most. In fact, PK studies evaluating intracellular con-

centrations have played a major role in simplifying treatment. For example, when the NRTIs Epivir (lamivudine) and Ziagen (abacavir) were first approved, they had to be taken twice a day, given that their levels in the blood were significantly reduced within 12 hours. Once researchers began looking at their intracellular concentrations, however, it was determined that enough drug was present inside cells over a 24-hour period to allow for once-daily dosing.

HIV doesn't only reproduce in CD4 cells in the bloodstream. It also reproduces in cells in the central nervous system (the brain), the genital tract, and the lymphoid tissues (the spleen, lymph nodes, and gut). In order for an HIV drug to stop the virus from reproducing in these compartments, it must be able to reach them. However, this can be a challenge for many drugs.

The central nervous system, for example, is protected by a network of blood vessels that make up the "blood-brain barrier." The blood-brain barrier (BBB) is semi-permeable—it only allows some materials to cross into the brain and spinal column. The smallest blood vessels, called capillaries, are lined with endothelial cells. Between these endothelial cells are small spaces that allow substances to move between the inside and the outside of the blood vessel. In the brain and spinal column, however, the endothelial cells fit tightly together, and substances can't filter out of the bloodstream. Small drug molecules do the best job of penetrating the blood brain barrier; large molecules—including those bound to protein—are kept out.

Transporter proteins, including P-glycoprotein, are yet another barrier. These proteins work like pumps, flushing potentially harmful chemicals out of cells and sensitive tissues in the body. They help keep toxins out of the brain (along with the BBB), as well as the testes and the lining of the gut. And while these proteins can be credited with keeping our cells healthy, they can also be blamed for keeping potentially useful medications—including the protease inhibitors and various chemotherapies for cancer—away from the cells and tissues where they are most needed.

PK studies have allowed us to determine which HIV drugs are able to pass the BBB and transporter proteins into the brain. This has been very useful, especially for people suffering from HIV-related dementia, a disease likely caused by HIV reproduction and cell destruction in the brain. The NRTIs Retrovir (zidovudine) and Ziagen, and the NNRTI Viramune (nevirapine), seem to maintain the best drug concentrations in the central nervous system. The PIs, unfortunately, are less likely to achieve adequate concentrations in the central nervous system because of the challenges they face with the BBB and transporter proteins.

METABOLISM

Pretty much everything we put into our bodies, including nutrients and medications, needs to be eliminated properly. While some HIV drugs, such as the NRTIs, are easily eliminated from the body, the NNRTIs and PIs need to be chemically broken down first. This process, known as metabolism, primarily takes place in the liver, but can also occur during the absorption stage in the gut. Because the gut and liver don't recognize drugs as serving a natural purpose in the body, their primary goal is to eliminate them. In turn, PK studies are necessary to determine how a drug is metabolized and how much active drug remains in the body after it has been prepared for elimination.

There are two types of chemical reactions, or phases, involved in drug metabolism—phase I reactions and phase II reactions. Dur-

ing phase I reactions, a drug is broken down in the gut and liver, most commonly through a process known as oxidation. During phase II reactions, the drug undergoes a process called conjugation, whereby it is made more water or fat soluble (dissolvable in water or fat). This allows the drug to be excreted from the body in either urine or feces.

Phase I reactions rely on a family of proteins known as the cytochrome P450 enzyme system. In people, there are approximately two dozen types of cytochrome enzymes, eight of which are responsible for metabolizing nearly all medications. Aside from their role in metabolizing drugs, these enzymes are also responsible for metabolizing nutrients, environmental toxins, and various other substances. To further complicate the issue, certain biological changes, such as hormonal changes during pregnancy, may contribute to changes in cytochrome enzyme activities. Genetics and other diseases, such as hepatitis C, can also alter the production and activities of these enzymes. In turn, they can affect drug metabolism.

The most notable enzyme is cytochrome P450 3A4 (CYP 3A4). This enzyme affects the metabolism of all of the PIs and NNRTIs on some level. The NRTIs are exempt from phase I reactions and, as a result, don't have to deal with these enzymes.

Almost all of the PIs and NNRTIs are substrates of CYP 3A4, meaning that they rely on this enzyme to be metabolized. A few of the HIV drugs are also inducers of CYP 3A4, meaning that they have the ability to *increase* the activity of this enzyme. This can increase the metabolism of drugs that are substrates of CYP 3A4, therefore decreasing their concentrations in the body. Many HIV drugs, including most of the PIs, are inhibitors of CYP 3A4, meaning that they can *decrease* activity of this enzyme. This can slow the metabolism of drugs that are substrates of CYP 3A4, therefore increasing their concentrations in the body.

Things only get more confusing when multiple drugs are taken at the same time, especially when so many of them interact with CYP 3A4. For example, the PI Norvir (ritonavir) is a very powerful CYP 3A4 inhibitor. Once it enters the liver, it drastically reduces the activity of CYP 3A4. In turn, the metabolism of drugs that depend on this enzyme slows down dramatically. With no place to go, these other drugs begin circulating through the bloodstream and into the tissues, waiting to be metabolized.

This can be a very serious issue and underscores the importance of PK studies, especially in HIV research. When a drug is first developed, the dose is based, in part, on how much drug reaches the bloodstream after being metabolized, with no other drugs interfering with the process. If it's combined with another substrate for the same CYP enzyme, or with a drug that inhibits (or induces) the CYP enzymes it uses, its concentration in the blood may increase (or decrease).

Sometimes, this decrease or increase isn't significant enough to cause problems. Other times, however, the decrease may be significant enough to make the drug ineffective, possibly leading to the development of resistance, or the increase may be significant enough to cause serious side effects. Because of this, PK studies—evaluating the effects one drug has on another drug's concentrations—are an absolute necessity.

Examples of potentially harmful drug-drug interactions abound, especially with Norvir. Many sedatives (Halcion and Versed, for example) are substrates for CYP 3A4, which is inhibited by Norvir. As a result, blood levels of these sedatives can become

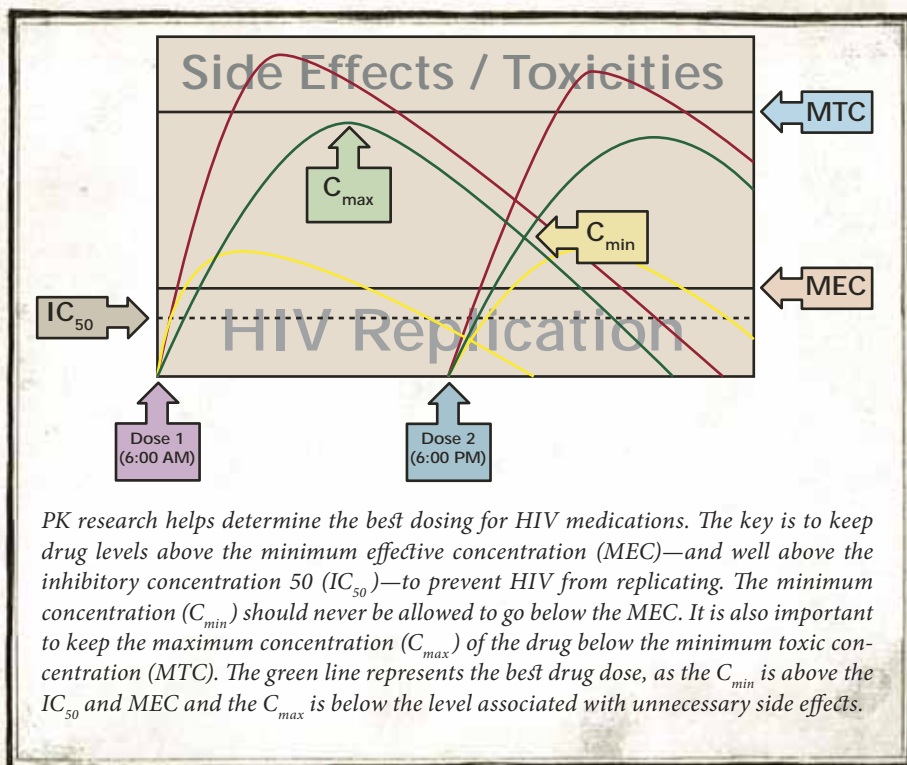
dangerously high, potentially resulting in coma or death if they're taken with Norvir. Similarly, Norvir's inhibitory effect on CYP 3A4 can result in high levels of many cholesterol-lowering drugs, most notably Zocor and Mevacor. This too can have serious consequences. While these sedatives and cholesterol-lowering drugs shouldn't be used with Norvir, PK studies have helped researchers to determine the best alternatives—and the best doses to use—to avoid problems.

PK studies have also allowed researchers to take advantage of drug-drug interactions. For example, the PIs Norvir and Crixivan are both substrates and inhibitors of CYP 3A4. Norvir is a more potent CYP 3A4 inhibitor than Crixivan and it causes Crixivan levels to increase in the bloodstream when the two are taken together. Without potent inhibition of CYP 3A4, two Crixivan capsules need to be taken three times a day on an empty stomach to ensure proper drug levels.

ELIMINATION

After drugs are metabolized and distributed, they must be eliminated. For some drugs, metabolism in the gut or liver takes care of this, either by making the drug water soluble (for elimination in urine) or fat soluble (for excretion in bile and elimination in feces). Some drugs, including the NRTIs, are eliminated by the kidneys.

Just as liver health is very important to the proper elimination of drugs via the liver, kidney health is very important to the proper elimination of drugs via the kidneys. Kidney problems or disease can impair the kidneys' ability to eliminate drugs in the urine. This can cause concentrations of the drug that depend on kidney elimination to increase in the blood. Similarly, certain drugs—such as Benemid (probenecid), a treatment for gout—can prevent other drugs, including Retrovir, from reaching kidney cells and slow down their elimination by the kidneys.



PUTTING IT ALL TOGETHER

Knowing that a drug faces many challenges during the absorption, distribution, metabolism, and elimination stages of its time in the body, researchers conduct PK studies to ensure two central factors:

- 1) That enough drug is administered to effectively treat the disease, and
- 2) That the drug dose is low enough to avoid or reduce the risk of side effects.

This, however, is easier said than done, and a great deal of research is often needed to make sure that the dose is just right for everyone taking the drug, especially when drug interactions are possible.

It all begins with the establishment of the IC_{50} —the inhibitory concentration (50). This represents the minimum amount of drug needed to reduce HIV replication by 50%. Research also sets out to determine a drug's minimum effective concentration (MEC), the drug concentration that must be maintained

in the blood to ensure effectiveness. The MEC is usually set much higher than the IC_{50} . Researchers can then make estimates as to how much drug needs to be maintained in the bloodstream—and inside cells—for HIV medications to remain active against the virus.

Researchers took what they knew about Norvir and Crixivan and conducted PK studies. As expected, a low dose of Norvir slowed down the metabolism of Crixivan and increased its concentration in the bloodstream significantly. In turn, a number of dosing improvements were possible. The total daily dose of Crixivan could be reduced from six capsules to four capsules; the number of times it needed to be taken each day was decreased from three to two times a day; and it did away with the need for Crixivan to be taken on an empty stomach.

Similar tactics have been used for almost all of the other PIs, including Reyataz and Invirase. In fact, Norvir is considered a necessity when taking Crixivan, Invirase, and the most recently approved PI, Aptivus.

In PK studies involving animals and both HIV-negative and positive people, researchers first set out to determine a drug's bioavailability. This refers to the amount of drug that reaches the blood after it has been administered and initially processed in the gut and the liver (this initial processing is known as *first-pass metabolism*). Bioavailability is usually expressed as a percentage. Drugs administered intravenously (through an IV line) are likely to have a bioavailability of 100%, whereas drugs administered by mouth—which must first be absorbed and undergo first-pass metabolism—are likely to have a lower percentage. If the percentage is too low, a higher dose may be necessary.

To increase a drug's bioavailability, researchers may also explore different formulations of their medications. For example, the PI Lexiva is an improved version of Agenerase. Both drugs contain the same active ingredient, amprenavir. Lexiva (fosamprenavir) is a prodrug of amprenavir, meaning that it is converted to the active ingredient once it has passed into the bloodstream. Studies have demonstrated that this improves the bioavailability of amprenavir, resulting in fewer gastrointestinal side effects and higher blood concentrations requiring many fewer pills a day.

After determining a drug's bioavailability, the drug enters more advanced PK studies, involving HIV-negative and/or HIV-positive people who check into a research unit for several days. Blood is collected from these study volunteers frequently—usually every hour—to monitor drug levels over time, either after a single dose or after several doses.

One PK characteristic researchers look for is the maximum concentration, the C_{max} for short. A drug's maximum concentration in the blood is achieved after absorption and first-pass metabolism. By comparing maximum concentrations and side effects that occur in these studies, researchers work to find the best tolerated maximum dose. The concentration at which unnecessary side effects start to occur is sometimes referred to as the minimum toxic concentration (MTC). The time it takes for an administered drug to achieve its maximum concentration is referred to as the T_{max} .

After the maximum concentration is achieved, the amount of drug begins to decrease. The lowest concentration in the bloodstream, before a second dose is taken and increases the concentration of the drug again, is known as the minimum concentration (C_{min}). The C_{min} must remain above the MEC and well above the IC_{50} to ensure the drug's effectiveness.

Another related term is the trough concentration (C_{trough}), the concentration of a drug in the blood immediately before the next dose is administered. ("Trough" is pronounced "troff.") The C_{trough} may be higher than the C_{min} to account for the fact that it can take some time for a second dose of the medication to halt and reverse the dropping concentration associated with the first dose of the medication. This helps to ensure that the drug concentration remains above the MEC.

The area-under-the-curve (AUC) is the total amount of drug maintained in the blood. Also of importance is the drug's half-life—the amount of time it takes the drug concentration to decrease by 50% in the blood or, even more importantly, inside cells (the intra-

cellular half-life). Knowing this helps researchers determine the number of doses needed in a 24-hour period, such as once, twice, or three times a day.

Evaluating these PK characteristics not only allows researchers to establish an initial dose for a drug, but also allows them to make new dosing recommendations when necessary. The development of resistance to an HIV drug is a prime example.

As HIV accumulates mutations that cause resistance to a particular HIV drug, its IC_{50} increases, meaning that more drug is needed to decrease HIV replication by 50%. In turn, its MEC increases as well. Higher concentrations of the drug need to be maintained in the body to control the mutated virus. This might be achieved by increasing the dose of the drug, but this can increase the drug's C_{max} , resulting in unacceptable side effects.

Another possibility might be to increase the number of times the drug is given each day, but this can be difficult for many people. A third solution, which has become very

common, is to use Norvir to decrease the metabolism of other PIs, resulting in blood concentrations that are high enough to maintain suppression of the virus without the need for more frequent dosing.

CONCLUSION

Aside from being a fascinating science, PK research has provided healthcare providers and people living with HIV with important information to help them decide how best to use medications safely and effectively. While PK research continues to play a significant role in the development of new HIV medications, it is also playing a major role in ongoing research of older medications.

Finding ways to simplify treatment and increase drug concentrations to effectively treat drug-resistant HIV without unnecessary side effects are just two examples of how this research helps to shape the various treatment options available to people living with HIV. In this sense, not only is PK research helping to create new HIV medications, it is also helping create important alternatives using the options we already have. ☒

Tim Horn is Executive Editor of The PRN Notebook and Senior Editor of AIDSmeds.com. He wishes to acknowledge the editorial support and guidance of John Gerber, MD, of the University of Colorado Health Sciences Center and David Back, PhD, and Laura Dickenson, BSc, of the Liverpool HIV Pharmacology Group.

Every drug's PK profile depends on four factors: its absorption, distribution, metabolism, and elimination (ADME).



Gastrointestinal Problems and HIV

The effect on treatment success

by Anne Monroe, MD

Gastrointestinal (GI) symptoms—diarrhea, nausea, and stomach pain—are among the most common problems that affect people with HIV. These symptoms can be challenging to sort out, as they can occur as side effects of HIV therapy and due to GI conditions related and unrelated to HIV. Try not to ignore GI symptoms—they could be signs of a more serious underlying problem or require treatment for symptom relief.

Make keeping the gut healthy a priority for you and your healthcare provider—successful HIV therapy depends on it! A healthy GI tract is necessary for proper absorption of medications. And controlling symptoms like nausea and diarrhea will improve your quality of life and help you adhere to your medications, causing better long-term treatment outcomes.

If GI symptoms persist and don't go away with standard therapy, it may be the sign of a more serious problem. Your provider may refer you to a gastroenterologist, a specialist in diseases of the digestive system, including the liver.

TABLE 1

Food Requirements and HIV Medications

Use this chart as a guide to determine how to time your HIV medications with meals and, in some cases, with other HIV medications. Talk with your healthcare provider or pharmacist about the correct way to take your medications. *Most HIV medications can now be taken with or without food, including Ziagen, Emtriva, Epivir, Zerit, Viread, Combivir, Epzicom, Trizivir, Truvada, Viramune, Rescriptor, and Lexiva.* But taking them with food may help avoid GI side effects like nausea that you might experience if you take the medication on an empty stomach.

MEDICATION	DIETARY RECOMMENDATIONS
NUCLEOSIDE/TIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)	
Videx buffered tablets or powder (buffered ddI, didanosine)	Take on an empty stomach (<i>at least</i> ½ hour before or 2 hours after eating). Buffered Videx shouldn't be taken at the same time as some protease inhibitors (especially Reyataz) or the NNRTI Rescriptor. If your combination includes buffered Videx and one of these drugs, check the amount of time required between taking the two drugs—it varies a lot.
Videx EC capsule (enteric coated ddI, didanosine)	Take on an empty stomach (<i>at least</i> ½ hour before or 2 hours after eating). Videx EC should be taken with water. It should not be taken with acidic juices, soda, or milk.
Hivid (ddC, zalcitabine)	Take with or without food. Taking Hivid with food may reduce stomach upset, but taking it on an empty stomach may improve absorption.
Retrovir (AZT, zidovudine)	Take with or without food, but not with a high-fat meal.
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)	
Sustiva (efavirenz)	Best to take on an empty stomach at bedtime (food raises drug levels and side effects).
PROTEASE INHIBITORS (PIs)	
Agenerase (amprenavir)	Take with or without food, but not with a high-fat meal.
Reyataz (atazanavir)	Take with a light meal or snack. Buffered Videx should not be taken at the same time as Reyataz. Take Reyataz (with food) 2 hours before or 1 hour after buffered Videx. Videx EC capsules aren't buffered and don't cause the same problem. But because Videx EC needs to be taken on an empty stomach, it should also be taken at a different time than Reyataz.
Crixivan (indinavir)	Take on an empty stomach if used without Norvir (unboosted), 1 hour before or 2 hours after a meal. A low-fat snack can be eaten during that time. Avoid taking it with grapefruit juice, 1%, 2% or whole milk. Take with or without food if used in combination with low-dose Norvir.
Kaletra (lopinavir/ritonavir)	Take with food (meal or light snack) to increase absorption.
Viracept (nelfinavir)	Take with a full meal, ideally one with high-fat content.
Norvir (ritonavir)	Low-dose Norvir (often used to boost other protease inhibitors) is best taken with food (meal or light snack) to reduce side effects and increase absorption.
Invirase (hard-gel saquinavir capsules)	Take within 2 hours after a meal—and only with low-dose Norvir.
Fortovase (soft-gel saquinavir capsules)	Take within 2 hours after a meal.
Aptivus (tipranavir)	Take with a full meal, ideally one with high-fat content.

Adapted from Johns Hopkins University Pocket Guide to Adult HIV/AIDS Treatment by John Bartlett, MD, aidsmeds.com, and other sources.

DISORDERS OF THE ESOPHAGUS

The GI tract is a long tube with one entrance (the mouth) and one exit (the anus), and problems can occur in any section on the way down. The esophagus is the part of the tube between the mouth and the stomach. The muscles of the esophagus contract and relax to propel food down. A muscular valve at the base of the esophagus closes off the stomach so that its acidic contents can't leak back up into the esophagus.

Heartburn—a burning sensation behind the center of the ribcage—occurs when stomach contents travel back up the esophagus. If you experience heartburn, it usually happens thirty to sixty minutes after eating and is sometimes accompanied by a sour taste in the mouth. Heartburn can be prevented by waiting at least three hours after meals to lie down, by elevating the head of the bed or using extra pillows in bed, and by avoiding spicy or acidic foods. Other lifestyle changes to help prevent heartburn include maintaining a healthy weight and avoiding tight belts or pants.

Frequent heartburn is a side effect of some HIV medications. It may also be a sign of gastroesophageal reflux disease, called GERD for short. GERD can damage the lining of the esophagus and lead to other complications. Frequent heartburn should be discussed with your healthcare provider, as inexpensive, over-the-counter treatments are available. Further testing by your provider, including looking down the esophagus with a camera (an upper endoscopy), may be necessary if the symptoms don't go away.

Another symptom related to the esophagus is pain when swallowing or difficulty swallowing. Those symptoms should raise a red flag, especially for people with low immune function (CD4 counts less than 200), as they may be signs of a yeast infection (esophageal candidiasis), cytomegalovirus (CMV), or herpes virus (HSV), each of which requires specific therapy. Left untreated, swallowing problems can have a significant negative impact on medication adherence, nutrition, and, of course, quality of life. Treating AIDS with highly active antiretroviral therapy (HAART) helps to cure esophageal infection and to prevent future infections.

Several medications—some used to treat HIV and opportunistic infections as well as some used to treat other illnesses and conditions—may cause direct injury to the lining of the esophagus if the pills get stuck in the esophagus as they travel down. They should always be taken with plenty of water while you're sitting up to make sure that the medications are appropriately washed down.

STOMACH DISORDERS

Gastritis (inflammation of the stomach lining) is a common problem regardless of HIV status. Symptoms of gastritis include stomach pain, nausea, vomiting, decreased appetite, and, in severe cases, vomiting blood. Common causes of gastritis are non-steroidal anti-inflammatory drugs (NSAIDs) like aspirin and ibuprofen, major health stress (patients who are sick enough to be in an Intensive Care Unit), heavy alcohol use, and infection with the bacteria *H pylori*. *H pylori* doesn't cause problems for most people who have it. And it is no more common in people with HIV than in those without HIV. But the presence of *H pylori* can negatively affect treatment success for people with HIV.

The breakdown of the stomach or intestinal lining causes an ulcer. Ulcers are extremely common—10% of adults have an ulcer at some point in their lives—and they cause dull or gnawing pain in the upper abdomen. Contrary to popular belief, ulcers occur more frequently in the small intestine than in the stomach, and they are more commonly caused by NSAIDs, excessive acid production, or *H pylori* infection than by stress or too much coffee. An upper endoscopy is performed to diagnose ulcers, often accompanied by specialized testing for *H pylori*.

HIV gastropathy, a condition caused by decreased stomach acid secretion, makes affected patients more susceptible to bacterial infections like salmonella and shigella. These bacteria would normally be destroyed by acidic stomach contents. HIV gastropathy also decreases absorption of medications that require an acidic environment, such as Nizoral (ketoconazole) and Sporanox (itraconazole), two commonly-used antifungal drugs. There is no specific test

for HIV gastropathy at this time, but your healthcare provider may make certain medication adjustments if he or she suspects this condition, such as switching to other drugs that don't depend on acid for absorption.

INTESTINAL DISORDERS

The churning action of the stomach breaks down food to help the absorption of nutrients in the small intestine. Malabsorption and diarrhea from intestinal problems are common in HIV and can result from both infectious and non-infectious causes.

Intestinal opportunistic infections are less frequent now than they were in the pre-HAART era, but people with advanced AIDS can develop *Mycobacterium avium* complex (MAC) or other bacterial infections of the small intestine. Cryptosporidium, a parasite which causes chronic diarrhea in people with AIDS, other parasites such as giardia and microsporidia, and some viruses can all infect the small intestine. Symptoms of small intestine infection often include upper abdominal cramping, bloating, and nausea, along with diarrhea. Stool and blood tests are necessary to check for infectious causes of diarrhea. When an infection can't be found, the diarrhea may be the result of small bowel bacterial overgrowth or HIV enteropathy—the direct infection of the intestine with HIV. HIV enteropathy alters the lining of the small intestine, decreasing the area available to absorb nutrients. This condition may also affect drug absorption, although it's difficult to test the effects directly.

Infection in the large intestine has a distinct set of symptoms—diarrhea with lower abdominal pain, defecating blood, or feeling the need to defecate but being unable to do so. The large intestine is a common site for infection with CMV, HSV, and bacteria like salmonella and shigella. Antibiotic therapy can alter the environment of the gut, allowing for overgrowth of the bacteria *clostridium difficile* in the large intestine, which causes diarrhea 3–4 times a day.

ANORECTAL INFECTIONS

Anorectal infections—infections in the anus or rectum—include gonorrhea, syphilis, and herpes. Unprotected anal sex also

TABLE 2

Interactions Between GI Drugs and HIV Medications

This table includes most prescription and over-the-counter medications used to treat common GI conditions. Known interactions between GI drugs and HIV medications (antiretrovirals) are listed. Some medications for GI conditions interact with many other medications used in HIV, including antibiotics and antifungals. Always tell your healthcare provider about all medications you're taking.

ANTACIDS—FOR HEARTBURN RELIEF

Examples	Interactions with Antiretrovirals	Notes
Alka-Seltzer* †	Some Protease Inhibitors Rescriptor (delavirdine) Hivid (ddC, zalcitabine) Videx buffered tablets (ddI, didanosine)	Antacids reduce stomach acid, which decreases absorption of some antiretrovirals. Don't take antacids at the same time as Rescriptor, Hivid, or the PIs Agenerase, Reyataz, or Aptivus. Don't take an antacid with buffered Videx—too much antacid can cause stomach problems.
Bromo-Seltzer* ‡		
Maalox*		
Mylanta*		
Tums*		

PROTON-PUMP INHIBITORS (PPIs)—FOR GASTROESOPHAGEAL REFLUX DISEASE (GERD) AND ULCERS

Examples	Interactions with Antiretrovirals	Notes
AcipHex (rabeprazole)	Reyataz (atazanavir) Rescriptor (delavirdine) Sustiva (efavirenz) Viramune (nevirapine)	PPIs reduce stomach acid, which decreases blood levels of some antiretrovirals—especially Reyataz and Rescriptor. The most serious interaction is between PPIs and Reyataz—PPIs significantly lower Reyataz levels. <i>Do not use a PPI if you're taking Reyataz.</i> A few studies have looked at interactions between PPIs and some protease inhibitors: <ul style="list-style-type: none"> Prilosec significantly reduces Crixivan levels, but adding low-dose Norvir increases Crixivan to effective levels. Crixivan hasn't been studied with the other PPIs. One study found that Nexium had no effect on Lexiva levels, but that may not be the case with the other PPIs. A study looking back at Kaletra levels in a few people who were also taking a PPI suggested that PPIs don't seem to affect Kaletra levels. More studies are needed to know whether this observation holds up. If you take a PPI and any protease inhibitor, monitor antiviral activity closely. Sustiva and Viramune speed up the metabolism of AcipHex and Prevacid, which may decrease their effectiveness against GERD/ulcers.
Nexium* (esomeprazole)	Reyataz (atazanavir) Rescriptor (delavirdine)	
Prevacid* (lansoprazole)	Reyataz (atazanavir) Rescriptor (delavirdine) Sustiva (efavirenz) Viramune (nevirapine)	
Prilosec* (omeprazole)	Reyataz (atazanavir) Rescriptor (delavirdine) Crixivan (indinavir)	
Protonix (pantoprazole)	Reyataz (atazanavir) Rescriptor (delavirdine)	

H2 BLOCKERS—FOR GASTROESOPHAGEAL REFLUX DISEASE (GERD) AND ULCERS

Examples	Interactions with Antiretrovirals	Notes
Axid* (nizatidine)	Reyataz (atazanavir) Rescriptor (delavirdine)	H2 blockers reduce stomach acid, which decreases absorption of some antiretrovirals. Unless you're also using low-dose Norvir, don't take Axid, Pepcid, or Zantac at the same time as Reyataz. <i>Take Reyataz as far apart from any of these drugs as possible—ideally 12 hours apart.</i> Tagamet raises levels of some PIs, so watch for increased side effects if you take Tagamet and a PI.
Pepcid* (famotidine)	Reyataz (atazanavir) Rescriptor (delavirdine)	
Tagamet* (cimetidine)	Some Protease Inhibitors Rescriptor (delavirdine)	
Zantac* (ranitidine)	Reyataz (atazanavir) Rescriptor (delavirdine)	

ANTI-DIARRHEALS		
Examples	Interactions with Antiretrovirals	Notes
Imodium* (loperamide)	No significant interactions	
Loperamide (prescription strength)	No significant interactions	
Lomotil (diphenoxylate/atropine)	No known interactions	
Kaopectate*	No known interactions	
Tincture of opium	No known interactions	
Pepto-Bismol*	No known interactions	
Metamucil* (psyllium)	No known interactions	Stool bulking agent
Ultras and Pancrease (pancreatic enzymes)	No known interactions	Take antacids and Pancrease or Ultras at least 2 hours apart.
ANTI-NAUSEA/VOMITING		
Examples	Interactions with Antiretrovirals	Notes
Compazine (prochlorperazine)	Kaletra (lopinavir/ritonavir) Norvir (ritonavir)	Certain medications used to treat nausea and vomiting interact with some antiretrovirals. Dose adjustments may be necessary to avoid drug interactions.
Emetrol* (cola syrup)	No known interactions	
Phenergan (promethazine)	Rescriptor (delavirdine) Kaletra (lopinavir/ritonavir) Viramune (nevirapine) Norvir (ritonavir)	
Reglan (metoclopramide)	No known interactions	
Thorazine (chlorpromazine)	Rescriptor (delavirdine) Kaletra (lopinavir/ritonavir) Norvir (ritonavir)	
Torecan (thiethylperzaine)	No known interactions	
Zofran (ondansetron)	Sustiva (efavirenz) Viramune (nevirapine)	Used for chemotherapy-associated nausea and vomiting; sometimes used in HIV. Dose adjustment may be necessary to avoid drug interactions.
PROMOTILITY AGENT—FOR SEVERE GERD, UNRESPONSIVE TO OTHER THERAPIES		
Examples	Interactions with Antiretrovirals	Notes
Propulsid (cisapride) <i>Limited availability in the U.S.</i>	Protease Inhibitors Non-Nucleoside Reverse Transcriptase Inhibitors	PIs and NNRTIs increase Propulsid levels, which can lead to fatal changes in heart rhythms. Do not use Propulsid with any PI or NNRTI.
APPETITE STIMULANT		
Examples	Interactions with Antiretrovirals	Notes
Marinol (dronabinol)	No known interactions	Marinol contains synthetic THC, the active ingredient in marijuana. Rescriptor and some protease inhibitors might increase Marinol levels, which would make you feel more stoned, but no information on such interactions is available.
Megace (megestrol acetate)	No significant interactions	

*Available over-the-counter; † Alka-Seltzer also contains aspirin; ‡ Bromo-Seltzer also contains Tylenol (acetaminophen)

transmits human papilloma virus (HPV), which causes anal warts and, in some cases, anorectal cancer. An anal Pap smear, similar to the Pap smear done to screen women for cervical cancer, is used to screen for anal cancer.

GASTROINTESTINAL CANCERS

Two gastrointestinal cancers are associated with HIV—Kaposi’s sarcoma (KS) and non-Hodgkin’s lymphoma. KS most often occurs in late-stage AIDS. Most people are familiar with the skin lesions of KS, but the disease can also affect the GI tract, the lungs, and other organs. KS may cause GI bleeding or malabsorption, but symptoms are rare, even though up to three-quarters of KS patients have it in their GI tract.

Non-Hodgkin’s lymphoma may occur at any stage of HIV disease and may be heralded by abdominal pain, weight loss, diarrhea, or a blockage of the intestine as well as enlarged lymph nodes. Lymphomas generally start in the lymph nodes when cancerous immune cells crowd out the healthy cells. The disease can start in the GI tract or spread there from lymph nodes. Treatment options include surgery, chemotherapy, or radiation.

Colon (large intestine) cancer is the second leading cause of cancer death in the United States, behind lung cancer. Most cases of colon cancer occur in people age 50 or older. As people with HIV live longer in the era of HAART, screening for colon cancer should be performed. After age 50, a test for blood in the stool (fecal occult blood testing) should be performed every year, with a colonoscopy (examination of the colon using a tiny camera in a long flexible tube) at least every 10 years.

MEDICATION SIDE EFFECTS

Overall, effective HIV treatment improves GI disease by improving immune function and decreasing opportunistic infections. However, GI symptoms are common side effects of antiretrovirals, especially early in treatment. The best way to handle

side effects is to know what to expect from each of the medications you’re prescribed and to have relief readily available before taking them.

► **Diarrhea**

If you have persistent diarrhea, your provider will run tests to rule out some of the infections described above. HIV medication may be the

to control the symptoms as much as possible.

► **Nausea**

Likewise, many HIV medications can cause nausea and vomiting. Nausea can get in the way of good adherence. Quite simply, if you don’t feel well enough to take your pills, you might skip them. Most

**Make keeping the
gut a priority
for you and
your healthcare
provider—**

only culprit, however. Some of the protease inhibitors, especially Viracept (nelfinavir), are notorious for causing diarrhea. The good news is that diarrhea often improves two to four weeks after starting the medication, and your provider can suggest anti-diarrheal treatment in the meantime to help you out. You can also try some non-pharmaceutical interventions to decrease diarrhea. The most basic is dietary modification—your provider may recommend that you leave out dairy, wheat products, and sugar. If you have long-term diarrhea and no infection or dietary intolerance is identified, work with your provider

protease inhibitors and nucleoside reverse transcriptase inhibitors, especially Retrovir (zidovudine), can cause these symptoms, but, again, they usually go away within a few weeks. Nausea from protease inhibitors can be relieved somewhat by boosting them with low-dose Norvir (ritonavir) to decrease the overall number of pills.

Another strategy to reduce nausea is to take your medications with food. Check with your provider or pharmacist to see which drugs can be taken with food. (See Table 1 on page 10.) Other tips to reduce nausea include eating small, frequent meals, eating bland food, sipping

ginger ale, and smelling a slice of lemon. If nausea causes you to lose your appetite or otherwise interferes with adherence or your quality of life, there are medications to help with your symptoms.

LISTENING TO THE GI TRACT: CLUES TO THREE DANGEROUS TOXICITIES OF HIV MEDICATIONS

The medication side effects described above can get in the way of good adherence and may disrupt your daily life. But there are some toxicities associated with HIV medications that can be life-threatening. Your first clue to these serious problems may be GI symptoms, so your best bet is to report any and all GI side effects to your provider.

► **Lactic Acidosis**

Lactic acidosis is a condition associated with NRTIs, especially Videx (didanosine) and Zerit (stavudine),

decreased appetite, nausea, vomiting, or abdominal pain, although many people who experience the condition may not experience or notice the symptoms right away. Your provider can run tests to check the level of lactate in your blood if he or she suspects lactic acidosis.

► **Pancreatitis**

Some HIV medications can cause pancreatitis, an inflammation of the pancreas that is life-threatening. This condition most frequently occurs with Videx (especially if it's used with Zerit, which it shouldn't be), Bactrim, and pentamidine (used to prevent *Pneumocystis pneumonia* [PCP]). Pancreatitis can cause abdominal pain which radiates to the back and is worst after eating, sometimes accompanied by nausea and vomiting.

► **Hepatic Necrosis**

Viramune (nevirapine) has caused cases of sudden liver failure (hepatic necrosis), particularly during the first four and a half months on the drug. Although this is a very rare occurrence, people most at risk include women starting their first combination with CD4 counts above 250, men starting their first combination with CD4 counts above 400, pregnant women, and

people with chronic hepatitis B or C infection. Early symptoms are often flu-like, including nausea, vomiting, muscle ache, and fatigue, followed by stomach pain, jaundice (skin turning yellow), and fever, with or without a rash.

BETTER TREATMENT OUTCOMES WITH A HEALTHY GI TRACT

GI symptoms in HIV are extremely common and can have a profound effect on treatment outcome. Symptoms like nausea and diarrhea affect quality of life and can make adherence a challenge, while changes in absorption can make some HIV drugs much less effective. Keep your healthcare providers informed of your symptoms and try different interventions to reduce them. Many over-the-counter and prescription drugs are available to relieve GI symptoms and treat infections of the GI tract. Some of these drugs interact with HIV medications, so be sure to talk with your provider and pharmacist about any drugs that you're taking or considering. (See Table 2 on page 12.) By minimizing the impact of symptoms—and investigating the possibility of GI infections—you have a better shot at long-term treatment success. 🏠

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Successful HIV therapy depends on it!

but Retrovir as well. NRTIs damage mitochondria, which are inside all human cells and use oxygen, fat, and sugar to produce energy for the cells. Mitochondrial damage leads to excess lactate production, which drives up the level of lactic acid in the blood. Lactic acidosis is more common in women, and it may be accompanied by liver abnormalities, including fatty liver. Symptoms of lactic acidosis may include



Creating a Friendly Environment for Your HIV Medications

The effect of interactions

by Joel L. Zive, R.Ph., Pharm.D.
with James Learned

The article on page 4, *A PK Primer*, describes how our bodies process drugs and our growing understanding of pharmacokinetics. Just as our bodies absorb and process HIV medications (antiretrovirals), they absorb and process other substances as well.

The way that one drug is absorbed, broken down (metabolized), or eliminated from the body can affect the way another drug or other substance is absorbed, metabolized, or eliminated. This is called a drug interaction. Most interactions are harmless, some require adjustments of the dose of one of the drugs to avoid harmful effects, some are dangerous, and a few are beneficial.

Effective HIV treatment requires having enough of each of your antiretrovirals in your system to effectively lower viral load and hopefully increase CD4 counts without causing severe side effects. If a drug (or drugs) that you're taking lowers the levels of an antiretroviral in your system, the effectiveness of your HIV treatment could be severely compromised. Similarly, some drugs can increase the levels of an antiretroviral in your system, which can increase the risk and severity of side effects. It can work the other way around as well—an antiretroviral can decrease or increase the levels of other drugs you take, possibly decreasing their effectiveness or increasing their side effects.

Interactions that might affect your health—and your HIV treatment—can occur between:

- ▶ Two or more HIV medications;
- ▶ An HIV medication and another prescription drug;
- ▶ An HIV medication and a recreational or illegal drug;

- An HIV medication and an over-the-counter (non-prescription) drug;
- An HIV medication and an herbal product or supplement;
- An HIV medication and food; or
- Two or more drugs not specific to HIV.

THE ROLE OF THE LIVER

Drugs are metabolized—chemically process them for elimination from the body—primarily in the liver, although your kidneys also play a role. The liver breaks down different drugs using specific systems of enzymes. Many drugs are broken down by the same enzymes, so this is where interactions usually occur.

If two drugs compete for the same enzymes to break them down, one might be metabolized too quickly, reducing drug levels in your blood and making it less effective. If it's an HIV drug, low drug levels could lead to an increase in viral load and the development of resistance to that drug (and perhaps to others in its class). Another interaction might cause a drug to be metabolized too slowly. You could end up with too high a concentration of the drug in your system because it's being metabolized too slowly. Depending on the drug, this could cause an overdose and even be fatal. If two drugs interact to make one or both drugs ineffective or dangerous, the combination is considered to be contraindicated—they should not be taken together.

Although the liver is able to break down many drugs at once, there's a limit as to how many drugs can be metabolized within a certain amount of time if the drugs require the same system of enzymes. Think of it as two or more trains approaching a railroad tunnel. Only one train can pass, while the other train (or trains) has to wait. This is something like what can happen in the liver, and drug interactions can be the result.

It might also be useful to think of the liver as a funnel—or many funnels, with funnels within funnels. The following are possibilities of taking two drugs at once, both competing for the same funnel or enzyme system to be properly metabolized:

- Levels of one or both drugs could *increase* in your system;
- Levels of one or both drugs could *decrease* in your system;
- Levels of one drug could *increase* in your system and levels of the other drug could *decrease*;
- Levels of one drug could *increase* in your system while the other drug could remain at effective levels;
- Levels of one drug could *decrease* in your system while the other drug could remain at effective levels; or
- Both drugs could remain at effective levels in your system.

The above example involves only two drugs. Some people with HIV take 10 or more different medications each day, for HIV and for other conditions. The more drugs or other substances you take, the more likely it is that drug interactions can occur. Break-

FDA-APPROVED ANTIRETROVIRALS FOR THE TREATMENT OF HIV
NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs, NUCLEOSIDE ANALOGS OR NUKES):
Ziagen (abacavir)
Videx (didanosine, ddI) – buffered tablets and enteric-coated capsules (Videx EC)
Emtriva (emtricitabine)
Epivir (lamivudine, 3TC)
Zerit (stavudine, d4T)
Hivid (zalcitabine, ddC)
Retrovir (zidovudine, AZT)
NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITOR
Viread (tenofovir)
COMBINATION FORMULATIONS:
Combivir (Retrovir & Epivir combined in one pill)
Epzicom (Epivir & Ziagen combined in one pill)
Trizivir (Retrovir, Epivir & Ziagen combined in one pill)
Truvada (Viread & Emtriva combined in one pill)
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs, NON-NUCLEOSIDES OR NON-NUKES):
Rescriptor (delavirdine)
Sustiva (efavirenz)
Viramune (nevirapine)
PROTEASE INHIBITORS
Agenerase (amprenavir)
Reyataz (atazanavir)
Lexiva (fosamprenavir)
Crixivan (indinavir)
Kaletra (lopinavir/ritonavir)
Viracept (nelfinavir)
Norvir (ritonavir)
Fortovase*/Invirase (saquinavir)
Aptivus (tipranavir)
ENTRY INHIBITOR
Fuzeon (enfuvirtide)

* Fortovase will no longer be available early in 2006.

ing down drugs properly gets trickier if your liver is damaged due to chronic hepatitis B or C, long-term alcohol use, or for any other reason. If you have liver or kidney damage, your provider may need to adjust the dose of some HIV drugs.

EXAMPLES OF INTERACTIONS BY HIV DRUG CLASS

The sidebar on page 17 lists the drugs approved to treat HIV by class. The drugs in each class have similarities, particularly in how they interfere with HIV reproduction. Most drugs in a class can cause some similar side effects, and some drug interactions are common within each class of antiretrovirals. But there are also significant differences between individual drugs in each class.

To list every possible interaction between HIV medications and other substances would require a book many times the length of this magazine. The following describes examples of specific interactions between HIV medications and other drugs or substances. *This is by no means a comprehensive list of interactions.*

NUCLEOSIDE/TIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)

Two NRTIs, combined with a protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI), make up what is often referred to as the backbone of combination therapy. Generally, the NRTIs work well together, although there are exceptions. Compared to the PIs and NNRTIs, the NRTIs have relatively few drug interactions because of the way our bodies process them. Select examples:

- ▶ Some NRTIs shouldn't be used together because they're antagonistic, meaning that they don't work well together in the body. Retrovir and Zerit should never be used together, for example.
- ▶ Some NRTIs shouldn't be used together because they can cause the same side effects. NRTIs that shouldn't be combined for this reason include Zerit and Hivid, Videx and Hivid, and, most significantly, Videx and Zerit.

Zerit, Videx, and Hivid can all cause peripheral neuropathy (painful tingling in the hands and/or feet that's sometimes irreversible). The risk of developing peripheral neuropathy and, with Videx plus Zerit, pancreatitis and high lactate levels in the blood as well, are greatly increased.

- ▶ Ribavirin, which is used as part of hepatitis C treatment, ideally shouldn't be used with Videx. Ribavirin significantly *increases* Videx levels, which can severely worsen

Videx side effects. If Videx needs to be part of your HIV regimen while you're on HCV treatment, be sure that you're monitored closely for any Videx-related toxicities (peripheral neuropathy, high lactate levels, and pancreatitis). If any signs or symptoms of these conditions develop, Videx should be stopped immediately.

- ▶ Methadone seems to significantly *decrease* the absorption of Videx buffered tablets. If you're on methadone, the amount of Videx getting into your system may not be enough to do its job, possibly leading to the development of resistance.

Rather than increasing the dose of Videx buffered tablets, it's probably best to switch to Videx EC, the more commonly used capsule version of the drug. Methadone doesn't seem to interact with Videx EC.

- ▶ Viread, the only nucleotide reverse transcriptase inhibitor approved to treat HIV, has some significant interactions with other HIV medications. Viread *increases* levels of Videx in the body, which can increase the risk of Videx side effects. Many providers avoid this combination completely. If the two drugs must be used together due to a lack of other options, the Videx dose should be reduced to 250 mg a day.

Viread also interacts significantly with the PI Reyataz. Combining these two drugs causes a significant *decrease* in Reyataz levels and a significant *increase* in Viread levels. If Reyataz is taken with Viread, low-dose Norvir (another PI) should be

used to boost the level of Reyataz in your bloodstream. Kidney damage is a possible side effect of Viread, so blood tests to monitor kidney function should be performed regularly due to the increased levels of Viread.

Viread can also interact with Kaletra, a PI that contains lopinavir and low-dose Norvir (ritonavir). If Viread and Kaletra are combined, Viread can significantly *decrease* lopinavir levels, and Viread levels can *increase*. As with the combination of Reyataz and Viread, kidney function should be monitored regularly.

- ▶ Only one NRTI, Videx, has a significant dietary restriction due to an interaction with food. Videx buffered tablets and Videx EC capsules need to be taken on an empty stomach for proper absorption. (See Table 1 on page 10.) And Videx buffered tablets shouldn't be taken at the same time as other medications.

▶ Combination formulations

Two or more NRTIs combined in one pill (Combivir, Epzicom, Trizivir, and Truvada) allow you to take fewer pills

Although the liver is able to break down many drugs at once, there's a limit as to how many drugs can be metabolized within a certain amount of time if the drugs require the same system of enzymes.

each day. If one of these combination formulations is part of your regimen, be aware of the drugs that it contains. They can cause the same interactions as if you were taking each drug the combination pills contain separately.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)

The three available NNRTIs have little in common except for the way that they block HIV replication, similar resistance profiles, and some shared side effects, notably rash. Otherwise, the potential side effects and drug interactions of the NNRTIs vary a lot. Of the three, Rescriptor is rarely prescribed. Rescriptor interactions are more like those of the protease inhibitors than those of the other NNRTIs. Select interaction examples:

- ▶ Sustiva and Viramune both interact with methadone, significantly decreasing methadone levels in your blood. This could make you feel as though your HIV meds are “eating” your methadone. The degree of the decrease varies from person to person. Some people experience as much as a 50% decrease in methadone levels, creating feelings of serious withdrawal. Other people experience no or very little decrease. To be effective, your methadone dose may need to be raised gradually 8 to 10 days after starting a combination that includes Sustiva or Viramune.
- ▶ Some drugs used to treat or prevent opportunistic infections interact with Sustiva, Viramune, or both. Using many of these drugs with Rescriptor can cause even more serious interactions.
- ▶ **Tuberculosis:** Rifampin decreases Sustiva levels enough in some people that a higher dose of Sustiva may be needed. Rifampin decreases Viramune levels so much that the two drugs should not be used together. Sustiva decreases Mycobutin (rifabutin) levels, requiring a higher dose of Mycobutin. Mycobutin can decrease Viramune levels, but not enough to require a dose change. Priftin (rifapentine) should not be used with either Sustiva or Viramune (or any protease inhibitor, for that matter).
- ▶ **MAC (*Mycobacterium avium* complex):** Both Sustiva and Viramune significantly decrease levels of Biaxin (clarithromycin) in the blood, and Biaxin can increase Viramune levels. Using an alternative to Biaxin, such as Zithromax (azithromycin), may be the best option.
- ▶ **Thrush:** Combining Viramune and Nizoral (ketoconazole) causes a two-way interaction: Nizoral levels *decrease* in the bloodstream, while Viramune levels *increase*. These drugs should not be used together. Vfend (voriconazole), another antifungal sometimes used to treat thrush, should not be used with Sustiva because of a two-way interaction

that’s even more pronounced than the one between Viramune and Nizoral.

- ▶ Some people are on multi-drug regimens that include an NNRTI and a PI. Sustiva and Viramune both significantly reduce levels of the PIs Reyataz, Agenerase, Lexiva, Crixivan, Kaletra, Fortovase, and Invirase. Viramune also reduces levels of Norvir and Aptivus. These interactions can lead to ineffective levels of the protease inhibitors in your bloodstream. To counter the interaction, the dose of the protease inhibitor may need to be increased or, when appropriate, low-dose Norvir may need to be added to boost levels of the PI. This latter strategy isn’t an option with PIs that are already taken with low-dose Norvir (Reyataz, Lexiva, Crixivan, Fortovase, Invirase, and Aptivus).

Rescriptor can increase blood levels of almost all of the PIs, so the PI dose may need to be decreased. An exception is Aptivus, which seems to reduce Rescriptor levels so significantly that the two drugs should never be used together.

PROTEASE INHIBITORS (PIs)

The PIs block a later stage in the HIV reproduction process than the NRTIs and NNRTIs. To varying degrees, they’re associated with certain long-term side effects, including increased blood sugar levels, insulin resistance, and high cholesterol and triglyceride levels. PIs come with a long list of drug interactions—between each other, with NNRTIs, and with many drugs used to treat other conditions. Select examples:

▶ Because of the way that Norvir is broken down by the liver, it can cause more interactions than any other antiretroviral. Although interactions between Norvir and many other drugs can be harmful, taking a low dose of Norvir with most of the PIs can increase—or boost—blood concentrations of the primary PI. Boosting another PI with low-dose Norvir can mean lower and less frequent dosing and better treatment outcomes. Kaletra capsules contain the active drug, lopinavir, and a small amount of Norvir. By itself, lopinavir is a relatively weak drug, but the Norvir boosts the lopinavir, making Kaletra an effective and commonly used PI. Every other approved PI except for Viracept can (or needs to) be taken with low-dose Norvir.

- ▶ Many people with HIV have high cholesterol, and the higher your cholesterol, the higher the likelihood of developing heart disease. Providers often prescribe drugs called statins to lower LDL (low density lipoprotein)—“bad” cholesterol—to offset this problem. Some statins interact considerably with PIs and some of the NNRTIs. Zocor (simvastatin) and Mevacor (lovastatin) should not be used if you’re on a PI or NNRTI because statin levels increase so much. If

Hopefully, the examples cited give you a better sense of the kinds of interactions that can occur.

Lipitor (atorvastatin) is used, careful monitoring is necessary because the PIs and NNRTIs can increase Lipitor levels. If you take Lipitor, start with a very low dose, have your cholesterol carefully monitored and, if necessary, slowly increase the dose. Of the statins, Pravachol (pravastatin) and Lescol (fluvastatin) seem least likely to interact with most of the PIs and NNRTIs.

- ▶ Kaletra reduces methadone levels significantly enough to require an increase in some people's methadone dose to avoid withdrawal. The reduced methadone levels seem to be caused by the lopinavir in Kaletra rather than by the small amount of Norvir the capsules contain.
- ▶ Proton-pump inhibitors (PPIs) are taken for the prevention and treatment of heartburn and other symptoms of gastroesophageal reflux disease (GERD). (See article on page 9.) PPIs can be helpful, but, by changing the acidity in the stomach, they can decrease levels of some protease inhibitors in the blood, making the PI less effective. A specific example is the interaction between Reyataz and the PPI Prilosec (omeprazole).

When a previously unknown, unappreciated or unexpected serious side effect or drug interaction is identified, the company that markets the drug is required to work with the Food and Drug Administration and send out a letter to doctors around the country informing them of the new or expanded information. In December 2004, Bristol-Myers Squibb, the manufacturer of Reyataz, had to do just that based on a study of the interaction between Reyataz and Prilosec. In the study of HIV-negative participants, Reyataz was taken with a light meal, two hours after Prilosec was taken on an empty stomach. Reyataz levels were decreased so much that if the two drugs were taken by people with HIV, Reyataz would be ineffective, increasing the chance of developing resistance. Even increasing the Reyataz dose or combining it with low-dose Norvir didn't help. As a result, the combination of Reyataz and Prilosec is contraindicated, and using any PPI while you're taking Reyataz isn't recommended.

As far as we know, most of the other PIs and the NNRTIs can safely be used with PPIs, but close monitoring of your anti-HIV response is strongly recommended if you're taking a PPI regularly.

Some PPIs, including Prilosec, Nexium (esomeprazole), and Prevacid (lansoprazole) are available over the counter. Be aware that some OTC medications can cause serious interactions just as some prescription drugs can.

- ▶ Two sedatives interact severely with all of the PIs and two of the NNRTIs—Halcion (triazolam), used for insomnia, and Versed (midazolam), an anesthetic. Taking either of these drugs with a PI or the NNRTIs Rescriptor or Sustiva could lead to a dangerous, life-threatening interaction. Halcion and Versed levels can increase so much that serious sedation could be the result, possibly leading to coma or death.

Using Halcion or Versed with any of these antiretrovirals is contraindicated.

- ▶ Viagra (sildenafil), Levitra (vardenafil), and Cialis (tadalafil) are used to help men get and keep an erection. The three medications have similar interactions with some other drugs. Protease inhibitors increase blood concentrations of Viagra, which raises the possibility of severe side effects—extremely low blood pressure, dizziness, fainting, vision changes, and prolonged erection (meaning hours, not a good thing).

Among the PIs, Norvir increases Viagra concentrations the most, while Fortovase and Invirase seem to have the least effect. The NNRTI Rescriptor also increases Viagra levels, as do many other drugs. Levitra and Cialis cause similar interactions with these drugs. Taking a lower dose of Viagra, Levitra or Cialis—and taking the drug less often—may help you avoid a possibly dangerous interaction.

- ▶ Very few studies have looked at interactions between herbal preparations and antiretrovirals. One study looked at potential interactions between St. John's wort (hypericum), an herb often used to treat depression, and Crixivan. St. John's wort significantly lowered Crixivan concentrations. Because of this study, taking St. John's wort with any PI or NNRTI is strongly discouraged. Combining the two may significantly lower blood levels of the antiretroviral, making it much less effective against HIV and could lead to the development of resistance to the antiretroviral.

Garlic supplements, sometimes used by people to try to lower their cholesterol, were studied with Fortovase to look for potential interactions. Study participants took high doses of garlic supplements, and their blood levels of Fortovase decreased significantly. High-dose garlic supplementation could be a problem if you're taking either Fortovase or Invirase, but the much lower amount of garlic used in cooking and as seasoning isn't likely to cause the same effect.

- ▶ Ethinyl estradiol, the main ingredient in most birth control pills, interacts with many antiretrovirals. The PIs Kaletra, Viracept, Norvir, and Aptivus and the NNRTI Viramune *decrease* the amount of ethinyl estradiol in the bloodstream to varying degrees. If you're taking one of these drugs, use at least one additional method of non-hormonal contraception to avoid pregnancy (condoms or an IUD, for example).

The PIs Reyataz, Crixivan, and Lexiva and the NNRTIs Rescriptor and Sustiva *increase* levels of ethinyl estradiol in the bloodstream to varying degrees. These increased levels could cause hormone-related side effects. Since antiretrovirals are taken in combination, it's safest to use alternative or additional methods of birth control if you're taking *any* PI or NNRTI.

Lexiva not only increases ethinyl estradiol levels, but ethinyl estradiol decreases levels of Lexiva, possibly leading to sub-therapeutic levels of the PI. To be safe, don't take

birth control pills that contain ethinyl estradiol or norethindrone with Lexiva.

ENTRY INHIBITORS

Fuzeon is the only drug approved in this class so far. Only a few Fuzeon interaction studies have been conducted to date—with Norvir, with Fortovase plus low-dose Norvir, and with rifampin, used to treat TB. No noteworthy interactions occurred in these studies. Because of the way that Fuzeon is administered (by injection) and metabolized, interactions between Fuzeon and other approved antiretrovirals, food, herbs or other drugs are unlikely.

HERBAL PRODUCTS

Many of us assume that if something's natural, it must be safe. That's often true, but herbs, like most substances, are metabolized in the liver. And many herbals use the same enzyme systems in the liver as HIV drugs do, which could result in harmful interactions. Unfortunately, there isn't a lot of research about interactions between herbals and HIV drugs. Before taking an herbal product, you might want to talk to your healthcare provider or pharmacist. They may have access to information about the product that you don't. But be prepared. Many healthcare providers are unfamiliar with herbal therapies and may dismiss the idea due to their lack of familiarity and a sense of discomfort. But don't give up!

If you choose to take an herbal product, a useful though time-consuming course of action is to try to evaluate the quality of the herbal product or supplement. If you're considering a supplement sold by a particular company, you could search the Internet to find the contact information for companies that manufacture and sell the product, ask the companies how it's made (including the complete contents), and how the quality of their product is assured (quality control). It may be a red flag if the manufacturer doesn't respond to your request, and it's probably a signal to move on.

PERSONAL EMPOWERMENT STRATEGIES

Information about drug interactions is constantly updated as new interactions are discovered thanks to further studies and anecdotal (word-of-mouth) reports. You may want to talk with your healthcare provider or pharmacist regularly about updated information and ask questions about interactions with the drugs you're taking.

Providers, pharmacists, and researchers may not be familiar with the interactions of a new drug at first. Aptivus, the protease inhibitor approved in June, is a case in point. Like other PIs, it can cause many drug interactions. Some of these interactions are

known—either due to studies that have been conducted or because of our understanding of how it's absorbed, distributed, and metabolized. But there's still much to be learned about potential interactions with Aptivus, and it will take time for further studies to be conducted and completed before we have more complete information.

Many over-the-counter (OTC) products contain drugs that you might not expect. For example, some Alka-Seltzer products contain Tylenol (acetaminophen). If you have a cold and take an Alka-Seltzer cold preparation along with Tylenol or other pain-relievers that contain acetaminophen, you'd have high levels of acetaminophen in your system. The maximum dose of acetaminophen (4 grams a day) is safe for people without liver problems, but high doses can cause serious liver disease and could affect the liver's ability to properly break down your HIV drugs. Be sure to read the list of ingredients listed on the packages of OTC products.

Finally, when you're prescribed a new medication, read all you can about it, including its possible interactions with other substances. A good place to start is the drug's package insert (the papers attached to the bottle the pharmacist uses to dispense your medications). You can read the package insert on the Internet or ask your pharmacist for a copy. The more you're aware of potential drug interactions, the better prepared you'll be to avoid or address them.

CONCLUSION

This article isn't intended as a description of every potential interaction between antiretrovirals and other substances—and it definitely isn't. Hopefully, the examples cited give you a better sense of the kinds of interactions that can occur. The resources listed on page 27 can help you take a more active role in your health and treatment by learning about interactions that might affect you. If you're going to endure treatment's ups and downs, why not make it work as well as it can for you? +

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James Learned is guest editor of this issue of Positively Aware. We thank Jerome Ernst, MD for his review.



Effectively Navigating the Healthcare System



You and your medical team at work

by L. Jeannine Bookhardt-Murray, MD, AAHIVS

Medical practice has drastically changed over the past 25 years. It used to be that you went to the doctor only if you became suddenly or acutely ill. The doctor would prescribe a treatment, and then the corner druggist would fill the prescription and instruct you how to take the medication.

Today, medical practice has evolved and is part of the larger healthcare delivery industry. At some point, you either have interacted or will interact with a spectrum of healthcare delivery systems, an array of services, and a variety of healthcare professionals. No wonder some people find the system to be such a confusing maze.

Patients are now referred to as clients, members, or consumers. These terms encourage individuals to be proactive in their care, and your role as a healthcare consumer has never been more important. You are more than a patient. You are your own best advocate, the person who can best inform your medical providers about your symptoms, problems, and details about other services you might be receiving.

Because of advances in technology, changing information, novel tests, and new medications, caring for people with chronic

illnesses is increasingly complex. As people age in this country, they are likely to develop at least one chronic illness and, with advancing age, additional chronic illnesses. HIV infection, heart disease, diabetes, kidney disease, lung disease, liver disease, and Alzheimer's disease are among the leading chronic conditions that require long-term management. It is not uncommon for older people with HIV to have an additional health condition. It is nearly impossible for one healthcare professional to treat all of the needs of an individual with a chronic condition. The team approach has become an accepted and necessary model of care.

In addition to the doctor, nurse, and pharmacist, other team members include nutritionists, social workers, case managers, medical specialists, and more, including home care nurses, physical therapists, massage therapists, and acupuncturists. Each healthcare professional on your team must focus on a particular part of your care. There has to be someone who understands how all parts of your care fit together in keeping you whole. That person is usually your primary care provider (PCP). But the most important member of your healthcare

team is you, the consumer, client, member and patient.

Understanding the role of healthcare professionals

Understanding the role of each team member and how to navigate the healthcare system while advocating for your needs will cut down on frustration, wasted time and energy, and delays in care. Family members, spouses, partners, friends, as well as case managers or home attendants can help you maneuver through your universe of healthcare so that you receive the best care possible. The importance of considering all of your healthcare providers as a team is vital to keeping your care connected. The more each provider on your team knows about where else you go for care and the kinds of services you receive, the better it is for you when it comes to prioritizing aspects of your health and care.

Your primary care provider may become your main focal point of care, depending on the state of your health. PCPs are responsible for providing health maintenance care and coordinating care. The PCP may be a Doctor (MD or DO), Nurse Practitioner (NP), or Physician's Assistant

(PA). PCPs are busier than ever these days because of the responsibility of caring for large numbers of patients and keeping up with the volumes of new medical information released every day.

Most PCPs spend the majority of their days going back and forth from one exam room to the other seeing patients. If you call your PCP's office, more than likely you'll be told, "Sorry, she's with a patient right now." PCPs create time to catch up on "behind the scenes" work. That behind the scenes work is just as important as seeing patients face-to-face; however, there is usually no time built into the day to complete those duties.

PCPs make the time to catch up during lunch, early in the morning, after hours, or on weekends. This work includes staying current with medical information, properly interpreting test results, researching information about puzzling cases, responding to phone calls and correspondence, completing paperwork, and coordinating care and interacting with all members of each individual patient's healthcare team.

This is why most PCPs ask patients to call for prescriptions or paperwork that you need several days in advance of needing them. The clinic or office staff is usually trained to handle the majority of calls and questions from patients during the day. When you phone your PCP's office, state the reason for your call. Chances are that someone in the office can help you. That will save you the frustration of waiting for a return call from the PCP.

All of the healthcare professionals on your team should have each other's contact information. There will be times when they need to speak with each other concerning your care. The better you understand the roles of your team members, the more familiar you will become with which ones need to communicate with each other at any given time.

Pharmacists handle prescriptions and double check that the consumer is not allergic to the medication and isn't taking other drugs that may interact with the newly-pre-

scribed medication. They offer advice and information about over-the-counter preparations and answer questions about your health. Some pharmacists provide home delivery services and extensive education about medications. Some pharmacists specialize in certain treatments like HIV therapy.

Nutritionists are knowledgeable about the specific dietary needs and requirements of diseases such as HIV. They offer guidance around meal planning, especially about weight concerns and medications.

Social workers can help you navigate the system and assist with everyday needs like housing, clothing, and food. Some social workers have special training and provide psychotherapy (talk therapy) for people who have depression or other emotional problems.

Psychologists (Ph.D. or Psy.D.) have doctorate degrees and specialize in counseling. They provide psychotherapy and, in some states, can write prescriptions for medications that help treat emotional and mental health problems.

Psychiatrists are medical doctors (MDs), have expertise in prescribing medications for mental health issues, and may also provide psychotherapy.

Many people today are enrolled in healthcare management organizations (HMOs) or managed care organizations (MCOs). These plans are designed to help streamline care and improve the efficiency and cost effectiveness of medical care. Some managed care companies have nurses available to answer questions, help coordinate appointments, and monitor your progress in care. HMOs credential doctors and Nurse Practitioners to work in their plan/network. The doctors and NPs who sign on with the plans are considered to be "in network," while others are "out of network" and, therefore, usually more expensive to see.

Helpful tips

The following tips may help you navigate and negotiate your way through healthcare systems, your appointments, and your relationships with healthcare professionals:

- *Prepare for your visit.* Write down your questions ahead of time. List your symptoms and concerns so you don't forget them. Your healthcare provider has a limited amount of time to spend with you, so make every minute count.
- *Know the names and doses of your medications.* Write the names and doses of your medications on a piece of paper and tuck it into your wallet or purse. Or take all of your medication bottles to your appointments. If another provider prescribes medications for you, be sure to inform the other healthcare professionals on your team. Inform your PCP if you use over-the-counter medications or natural remedies such as herbs and supplements.
- *Read all medication labels and instructions.* Ask your PCP or pharmacist about potential side effects or possible drug interactions of the medications you are taking. Let them know if you have side effects. Some side effects are serious, while others are not serious and are manageable.
- *Know how to contact your PCP if you have an emergency when the office is closed.* Most PCPs have systems in place to handle off hours emergency calls. Know whom to contact if your PCP is away and the hospital affiliation of your PCP in case you need to go for emergency care.
- *Know when you need refills on your medications.* Contact your PCP's

WHAT DO ALL THOSE LETTERS MEAN, ANYWAY?

Healthcare professionals and researchers often have many letters following their names. These titles indicate, to some degree, their training, experience, and qualifications. The following list isn't exhaustive, but explains what some of the abbreviations following professionals' names refer to.

AAHIVS – AMERICAN ACADEMY OF HIV MEDICINE (AAHIVM) HIV SPECIALIST

An MD, DO, PA, or NP who has completed 30 hours of continuing medical education (CME) credit in two years, has seen 20 or more patients with HIV within two years, and has passed a qualifications exam on HIV care. Two thousand providers are registered by the AAHIVM as HIV specialists. When choosing a healthcare provider, be aware that many providers may have equivalent experience in HIV care, but aren't certified by the AAHIVM. Visit www.aahivm.org for a referral.

ACRN – HIV/AIDS CERTIFIED REGISTERED NURSE

A registered nurse who has completed 70 hours of CME credits, has at least two years of experience in HIV/AIDS care, and has passed a certification exam for HIV/AIDS care.

DO – DOCTOR OF OSTEOPATHIC MEDICINE

A Doctor of Osteopathy has the same rights and privileges as a Medical Doctor (MD). They can prescribe medications and practice medicine in all fifty states. The training that a DO receives is comparable and, in some cases, identical to that of an MD but may have more of a “whole person/whole body” approach. DOs tend to consider the psychosocial as well as the physical well-being of a person, as well as how individual symptoms of certain parts of the body may affect others. DOs also receive additional training on the musculoskeletal system and Osteopathic Manipulative Treatment.

FAAN – FELLOW OF THE AMERICAN ACADEMY OF NURSING

A distinction given to nurses in recognition of their accomplishments in nursing. Many fellows have high levels of training (82% hold a doctorate in nursing), and most have leadership positions in academic, research, government, or community settings.

GI – GASTROENTEROLOGIST

An MD or DO who specializes in the care of the stomach, intestines and liver.

ID – INFECTIOUS DISEASE SPECIALIST

An MD or DO who specializes in treating a range of infectious diseases, including HIV.

LPN – LICENSED PRACTICAL NURSE

A nurse who has completed certification to administer certain treatments. Works under the supervision of a Registered Nurse (RN).

MSW – MASTERS IN SOCIAL WORK

Social work is a profession committed to helping individuals, families, and communities at multiple levels. Some social workers continue their training to become licensed or certified psychotherapists.

MD – MEDICAL DOCTOR

A physician who holds a medical degree and is licensed to practice medicine and surgery as well as prescribe medications and other treatments.

NP – NURSE PRACTITIONER

A registered nurse with advanced clinical and academic experience, including a master's degree. A Nurse Practitioner's abilities vary depending upon each state's regulations. In many states, a Nurse Practitioner can prescribe medications.

ANP – Nurse Practitioner (adult care)

FNP – Nurse Practitioner (family care)

GNP – Nurse Practitioner (geriatric care)

PNP – Nurse Practitioner (pediatric care)

PA – PHYSICIAN'S ASSISTANT

Clinicians who provide healthcare to individuals under the supervision of physicians (MDs or DOs). Their training is not as long as that of MDs and DOs, but their responsibilities are quite similar. They routinely take medical histories, examine and treat, order and interpret laboratory tests and X-rays, make diagnoses, and prescribe medications. They also treat minor

injuries by suturing, splinting, and casting. PAs also record progress notes, instruct and counsel patients, and order or carry out therapy. In rural and inner city areas, PAs may be the principal care providers when a physician is present only one or two days a week. They are able to practice in 47 states, all of which require PAs to pass a certification exam and are then designated as a PA-C (Certified Physician Assistant).

PH.D. – DOCTOR OF PHILOSOPHY

A doctorate (advanced) degree in any subject matter (not necessarily philosophy or medicine). Nurses, pharmacists, nutritionists, and social workers, among others, may continue their education to receive this doctorate degree.

PHARM.D. – DOCTOR OF PHARMACY

In addition to two years of pre-pharmacy study, a Pharm.D. has completed at least four years of graduate studies to earn a doctorate degree in pharmacy.

PSY.D. – DOCTOR OF CLINICAL PSYCHOLOGY

Psychologist with specialization in clinical psychology, including deep understanding of severe psychological disorders and psychotherapy.

RD – REGISTERED DIETICIAN

Many nutritionists are also registered dietitians. RDs are trained in the science of nutrition as well as dietetics, a discipline focused on relationships between dietary patterns and health, both in normal nutrition and in disease states.

RN – REGISTERED NURSE

A nurse who has completed a Bachelor of Nursing program.

R.PH – REGISTERED PHARMACIST

A Registered Pharmacist must be licensed in the state in which they practice and hold at least a bachelors degree in pharmacy.

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office about a week ahead of time to allow time for the prescriptions to be handled.

- ▶ *Leave clear messages when you call your PCP's office.* Chances are that if you leave a message for your PCP without stating the reason, the response will be delayed. PCPs must prioritize calls and respond accordingly. Tell the receptionist why you are calling. The receptionist is an important part of your healthcare team.
- ▶ *Update your address and phone number.* Your PCP's office should have your current contact information in case there is a need to contact you about test results, scheduling changes, and so on.
- ▶ *Know the reason you were referred to a medical consultant or for a special test.* That will help you stay focused on the reason for the appointment and provide accurate information to the consultant.
- ▶ *Carry your PCP's contact information with you at all times.* Whenever you see a specialist, go to the emergency department, or have a test performed, insist that the results be sent to your PCP. Ask whether there are any special forms you need to sign to make sure the information can be sent. Be sure to have your PCP's contact information with you when you travel.
- ▶ *Provide your PCP with names, addresses, and dates of specialists you have seen and tests that have been performed.* Your PCP may refer you but may not necessarily know the date of your test or where you were sent. Keep notes about who you saw, why you saw them, and what was recommended so that you can report that information back to your PCP so that he or she can follow up effectively.
- ▶ *Remind medical consultants to either call your PCP or send a report.* Take a note or referral from your PCP to the consultant. That will help make it clear as to exactly why you are there. The note also provides the consultant with your PCP's name, address, and phone number.
- ▶ *Know how to use your health insurance plan.* Understand your health plan. Your PCP may not know the details of all of the plans of all of his or her patients. For example, some plans require written referrals from your PCP to a specialist. Preapproval for equipment or special medications may be required. Each plan has its own formulary of medications that it covers.

► *Keep a notebook with dates and results of your test results.* Reviewing your results in private may allow you to learn more about what's happening with your health.

► *Call to cancel appointments you cannot keep.* Try not to miss appointments. It may be difficult to get another one in the near future depending on the availability of services in your community. Also, missed appointments send the message that you aren't interested or invested in your health. That may not be true, but that is the impression that is made.

► *Continue to educate yourself about HIV infection and other conditions that you may have.* Members of your healthcare team will be able to direct you to information sources that are accurate and credible. Ask questions and for explanations until you understand the answers. Inquire about options, expected results, and outcomes. If you don't ask questions, the members of your team may assume you know everything about what is going on.

► *Understand that waiting is an unfortunate norm in the world of healthcare.* Most healthcare professionals have very little control over their schedules. Because of the large numbers of people who need care, schedules are usually tightly packed. This can lead to backups and crowded waiting rooms. Computer problems, staff illnesses, staff turnover, misplaced medical records, or very complicated patients on any given day may result in even further

delays and increased waiting time. Many of these problems are beyond the control of the healthcare professional and are just as frustrating for the provider as they are for you. A crowded waiting room creates anxiety among the staff. The tension can lead to unproductive and dissatisfying visits, medical errors, and

Understanding the role of each team member and how to navigate the healthcare system while advocating for your needs will cut down on frustration, wasted time and energy, and delays in care.

staff resignations. This is ultimately detrimental to all involved. Look for someone to whom you can voice your complaints.

► *Complain in an effective manner.* Emotional outbursts in waiting areas make staff and other patients nervous and create even further delays. It is more effective to lodge a formal complaint. Most administrators take complaints seriously and use them to figure out systems so that problems can be fixed over time.

Continuity of care

Juggling medical appointments, taking medications on time, eating right, and exercising in order to keep your health together is a full-time job. Another part of keeping your health together is making sure that there is continuity in your care—no gaps, no missing information. Your medical record, lab and test results, and consultation reports must be available for your PCP or other healthcare professional on the day of your appointment.

A problem in many settings is the lack of systems for the exchange of information. Some patients believe that consultation reports are automatically sent to their

PCPs. While that is the way it *should* work, it doesn't happen on a consistent basis. A lot of time is wasted during the day tracking down missing information. Reports may arrive after you have already left the office.

Your PCP may be caring for thousands of people and so cannot possibly remember every detail about each individual. When you see a specialist, know the reason for

the appointment and any recommendations that the specialist suggests. That way, you can report back to your PCP and help to keep your care in

motion. The more healthcare professionals involved in the care of one individual, the more confusing things can become. Inaccurate information and confusion can diminish the effectiveness of your care.

Choosing a PCP

You can begin by making sure that the clinician you're seeing is experienced in the treatment of HIV/AIDS. Some PCPs provide HIV primary care in general medical settings, like private practices, health centers, or hospital-based clinics. PCPs who care for people with HIV/AIDS may have special credentials as an HIV Specialist. Special centers, like a Designated AIDS Center (DAC), may have both Infectious Disease (ID) specialists and PCPs.

ID specialists have extensive training in treating many kinds of infectious diseases, including HIV/AIDS. ID specialists may choose to provide only HIV care and not primary care. If you choose an ID specialist, you will likely also need to find a PCP. Take time to choose the type of medical setting that best suits you. Word of mouth, managed care plan listings, and trial and error are a few of the ways patients find a setting and a provider best suited for them.

As in any relationship, the course of care goes much more smoothly when a patient and the healthcare professional like

each other—call it the “click thing.” You can almost feel the click when it happens; it is the connection that blossoms in an instant or over time. “Clicking” requires mutual trust, honesty, and realistic expectations. The energy of healing then flows both ways.

Quality of care

Quality of care includes having a positive relationship with your PCP and other team members. While the quality of a relationship is difficult to measure, there are aspects of care that are measurable. Every single appointment should have a purpose. Most settings have quality check ups, and your record may be reviewed to make sure you are receiving quality care from your PCP. Your PCP may actually receive a report card from time to time. Work with your PCP and make sure you are up to date with all aspects of your healthcare maintenance. (Use the Personal Health Record on center pull-out chart.)

The more you learn about your health, your healthcare, and the healthcare system, the more empowered you will be to advocate for yourself and the more likely you will receive the quality of care necessary to keep you as healthy and happy as possible for as long as possible. +

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RESOURCES

PHARMACOKINETICS

Women & HIV: The Impact of Sex/Gender on Antiretroviral Therapy and Its Complications. *BETA (Bulletin of Experimental Treatments for AIDS*, from the San Francisco AIDS Foundation), Summer 2003: Article about the response to antiretroviral therapy in women and men, including pharmacokinetic differences that affect drug levels and side effects in women and men. See www.sfaf.org/treatment/beta/b53/b53_women.pdf.

GASTROINTESTINAL PROBLEMS

Gastrointestinal Manifestations of HIV. HIV InSite: Thorough clinical discussion of symptoms, diseases, and treatments.

Visit <http://hivinsite.ucsf.edu/InSite?page=kb-04&doc=kb-04-01-11>.

Managing Drug Side Effects. ACRIA (AIDS Community Research Initiative of America) booklet (also in Spanish). Describes common side effects and possible therapies. Includes a section about the digestive system. Contact ACRIA at 1-212-924-3934 for a hard copy, or write them at 230 W 38th Street, 17th Floor, New York NY 10018. Visit www.acria.org/treatment/treatment_edu_side_effects.html.

National Digestive Diseases Information Clearinghouse (NDDIC). Extensive information about various diseases of the digestive system (some material available in Spanish). Visit digestive.niddk.nih.gov/index.htm.

DRUG INTERACTIONS

AIDSmeds.com. Check My Meds: User-friendly interactive database. You enter the drugs you're taking to determine whether they interact with each other or with certain foods. Visit www.aidsmeds.com/cmm/DrugsNewContent.asp.

Drug Digest. Interactive database allows you to search for interactions between drugs for all conditions and diseases, herbals, food, and alcohol.

Visit www.drugdigest.org/DD/Interaction/ChooseDrugs/1,4109,,00.html.

Drug Interactions: HIV Medications, Street Drugs and Methadone. ACRIA Update, Spring 2005 (see above). Comprehensive discussion of interactions between HIV-related medications, street drugs, and methadone.

Visit www.acria.org/treatment/treatment_edu_springupdate2005.html.

HIV InSite. Interactive database allows you to search for interactions by antiretrovirals, other drugs, or types of drugs. Includes references and much more.

Visit www.hivinsite.com/arvdb?page=ar-00-02.

Project Inform. Anti-HIV Drug Interactions: Lists interactions by antiretroviral and other drugs commonly used in HIV.

See www.projectinform.org/fs/drugin.html.

Toronto General Hospital, University Health Network. This website includes tables in PDF format that describe detailed information about interactions between antiretrovirals, other HIV-related drugs, psychotropics, methadone, sedatives, recreational drugs, and other medications. References included.

See www.tthhivclinic.com/interact_tables.html.

University of Liverpool. Includes interactive database that allows you to determine antiretroviral drug interactions and PDF charts of interactions between antiretrovirals and other drugs. Visit www.hiv-druginteractions.org.

NAVIGATING THE HEALTHCARE SYSTEM

Building a Cooperative Doctor/Patient Relationship. Project Inform information sheet (also in Spanish). See www.projectinform.org/fs/dr-patie.html.

Working with Healthcare Providers. ACRIA Update (see above), Winter 2004/05: Issue focuses on the relationships between individuals and their healthcare providers. Includes personal stories.

See www.acria.org/treatment/treatment_edu_winterupdate2004_2005.html. +

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