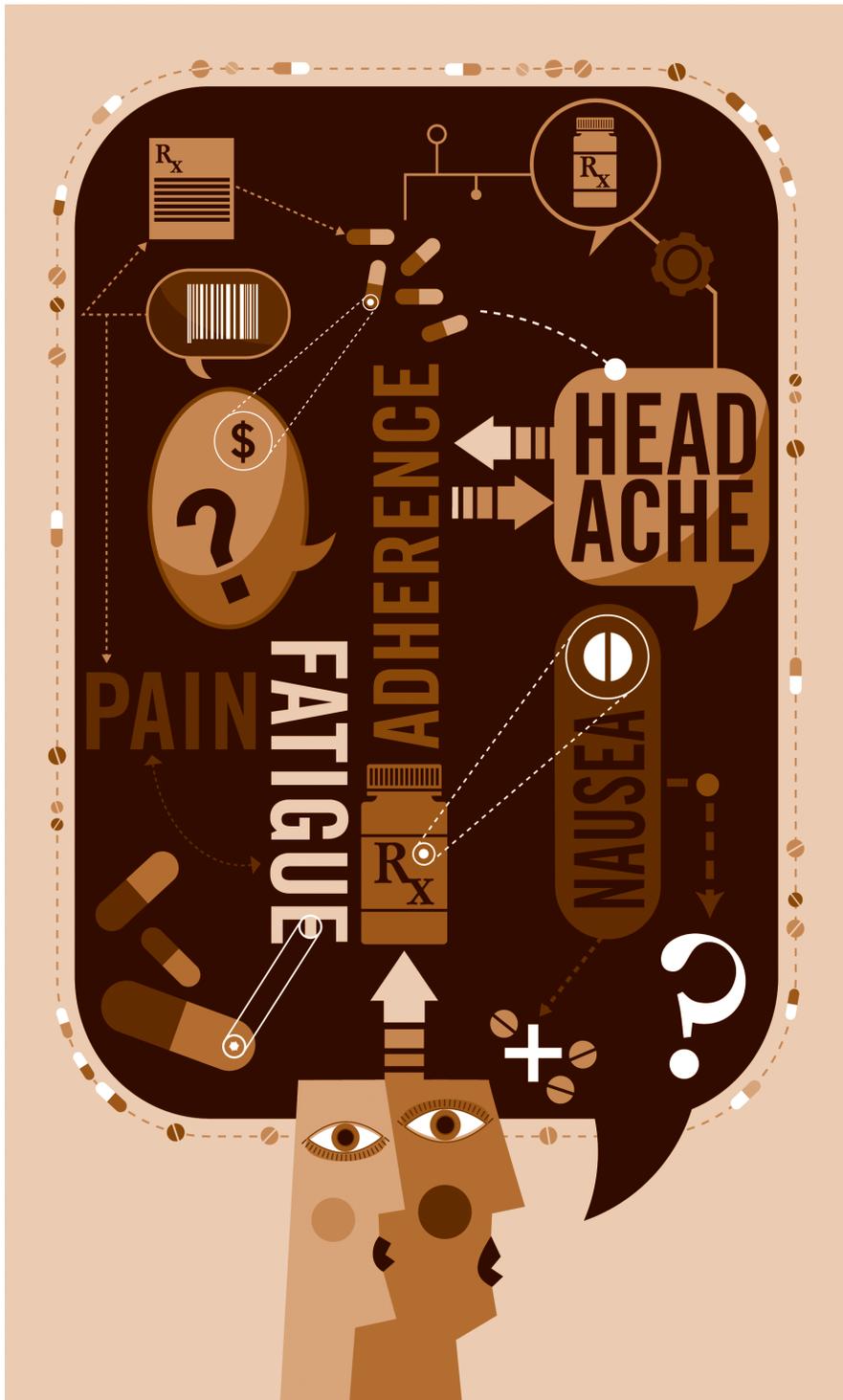


Making Sense of Side Effects

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The advent of potent combination antiretroviral therapy (ART) in the 1990s allowed people with HIV to live longer, healthier lives. Current United States treatment guidelines recommend that all HIV positive people start antiretroviral therapy if their CD4 count (a key marker of immune health) drops below 350 cells/mm³, and suggest those with a CD4 count between 350 and 500 cells/mm³ consider starting ART.

Despite the lifesaving benefits of ART, many people still struggle with the decision to start taking antiretroviral drugs. For some, the prospect of committing to lifelong drug therapy is daunting. Others hesitate because medications remind them of their disease. For many, the biggest factor in deciding whether to start ART or change their current regimen is the fear of medication side effects.



Geri (who asked that her last name be withheld for privacy) is HIV positive and currently on ART. “Thinking about HIV medicine side effects is very scary,” she said in an interview. When Geri switched to a new antiretroviral regimen, she experienced nightmares—one of which was particularly vivid: “It felt so real, and I just couldn’t wake up. I didn’t even know it was a dream until I *did* wake up.” She also experienced pain and weakness in her legs after starting the new regimen.

Side effects like these can occur with any drug—even common medicines like aspirin—and the vast majority stop or reverse when people work with their doctors to manage symptoms or change treatments. Geri’s medical team was able to identify her drug-related side effects and stop the medications responsible for them. This article will discuss antiretroviral drug side effects, including risk factors, preventive approaches, and steps to take when you are experiencing side effects yourself.

SIDE EFFECTS 101

The accepted definition of “side effect” is any effect of a medication that is in *addition* to its intended effect, especially an effect that is harmful or unpleasant. Side effects can also be referred to as “adverse events” or “adverse drug reactions.” Side effects are categorized according to their frequency (how commonly they occur), severity (how intensely they are experienced), and timing (when they occur and how long they last). If a side effect occurred in greater than 1 out of every 10 persons in clinical trials (10%), it could be considered common. Very rare side effects occur in less than 1 out of every 100 persons taking a drug (less than 1%).

In clinical studies, the severity of antiretroviral side effects reported by trial participants is often classified according to a grading system. Grade I side effects are considered mild, while

Grade II, III, and IV side effects are considered moderate to severe. Timing, when known, also helps to describe side effects. Most antiretrovirals have short-term side effects (such as nausea and diarrhea) which typically occur soon after starting and subside within weeks to months, as well as long-term side effects which may develop more slowly and persist for longer periods (such as lipodystrophy, or body fat redistribution).

Many factors contribute to the development of side effects. They can be the result of a drug’s direct effect on the body, sometimes referred to as the drug’s pharmacodynamic effect. Some (but not all) are related to the dose of the medication used. The way a person’s body chemistry reacts with the medication (also known as the drug’s pharmacokinetics) can contribute to side effect development. For example, some people lack important enzymes that process certain medications, leading to higher levels of the drug in the blood and possibly contributing to the development of side effects. Other people have enzymes that change the drug into an active metabolite (or byproduct) that in turn causes side effects. These differences in our physiology explain why some patients experience certain side effects and others do not.

WHO IS AT RISK FOR SIDE EFFECTS?

Though many people tolerate antiretrovirals without significant problems, everyone is at risk of experiencing a medication side effect at least once in their life. It is difficult for scientists and clinicians to predict who might experience side effects while on ART. Factors such as sex, race or ethnic background, age, and genetic makeup influence whether an individual will react poorly to a medication.

A growing body of scientific research suggests that antiretroviral side effects impact women more often or more severely. “Women seem to

experience side effects more frequently or more intensely than men do on ART, which can lead to higher rates of discontinuation in the clinical setting,” said Monica Gandhi of the University of California, San Francisco (UCSF), who conducts research in the national Women’s Interagency HIV Study. “One reason for this could be that women have higher concentrations of antiretrovirals in their bloodstream than men do with the same dose of drug. Investigators are still researching differences in drug exposure between men and women to determine whether this is the reason why women may experience more side effects on therapy.”

A classic example of these sex differences is the occurrence of rash and liver toxicity with the antiretroviral medication nevirapine (Viramune). Various studies have found that women may be anywhere from 4 to 12 times more likely to develop a nevirapine-related rash compared with men. Women are also 12 times more likely to develop severe hepatotoxicity, or liver inflammation, from using nevirapine.

Other studies have found that women are at higher risk of experiencing diarrhea, fat accumulation, changes in their blood lipids (fats in the bloodstream), and other side effects from various antiretroviral medications. Some of these may be manageable, but the heavy burden of side effects may drive women to stop their regimen completely. For example, an Italian study with 826 participants found that women were more likely than men to stop taking their antiretroviral drugs due to side effects.

Gandhi encourages women to communicate with their health care provider before deciding to stop following their treatment regimen. “The best thing a woman on ART can do is to stay in very close touch with her treating clinician and pharmacist about how she is feeling on her medications,” said Gandhi. “Right

from the beginning, she should try to get help with side effects. If they do not get better with time, it is also very important for a woman taking ART to know that she does not need to live with side effects that are too difficult for her.” Gandhi suggested exploring other, less challenging treatment options: “There are a number of HIV medications now available, and she may be able to try other regimens until she finds one that is tolerable for her and that works well.”

Race and ethnic background, which are linked to a person’s genetics, may also play an important role in the development of side effects. One example of this interplay is illustrated by the central nervous system side effects associated with the non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz (Sustiva), a drug contained in the widely used Atripla combination pill.

People taking efavirenz may experience grogginess, dizziness, and “fuzzy thinking.” A study by the AIDS Clinical Trials Group found that African Americans experienced more of these side effects than other people and had higher levels of efavirenz in their blood. Other studies have reported similar findings. Researchers suggest that these higher levels and more common side effects may be due to differences in the functioning of a metabolic enzyme, CYP2B6 (cytochrome P450, family 2B6), that helps rid the body of efavirenz through the urine. These enzymes are genetically encoded: A specific arrangement in the CYP2B6 gene is more common in African Americans and Latinos and can cause CYP2B6 to work more slowly or not at all. This in turn can lead to an excess build-up of efavirenz in the blood and an increased risk of side effects.

In the future, clinicians using the science of pharmacogenomics (also known as personalized medicine) will be able to take a drop of blood, analyze a person’s genes, and figure out which side effects their body is

prone to. With these types of tests, HIV positive individuals will be able to make better-informed choices regarding which antiretrovirals they want to take. Clinicians are already using pharmacogenomics for this purpose: A special blood test called the HLA-B5701 can help determine whether someone is hypersensitive (severely allergic) to the nucleoside reverse transcriptase inhibitor (NRTI) drug abacavir (Ziagen).

To understand side effects in specific populations, better information must be gleaned from clinical trials involving a broader, more representative sample of participants. As Monica Gandhi explained, “a number of drugs available on the market today—including antiretrovirals—have been studied in homogeneous populations, predominantly Caucasian men. Therefore, we are unable to tell whether women or patients of other ethnic backgrounds will tolerate a drug’s side effects.”

Gandhi stressed the importance of increasing gender balance and ethnic diversity among clinical trial participants: “The only way to know whether a drug will work well in a specific population (like women) is for those people to be well represented in clinical studies. Because of this, it is extremely important for all types of HIV positive persons to participate in clinical trials of new ART drug formulations.”

WHAT TO EXPECT WHEN STARTING NEW ANTIRETROVIRAL DRUGS

It is important to weigh many pieces of information when choosing an antiretroviral regimen. HIV positive individuals should discuss convenience, number of pills, how potent the regi-

men will be against their virus, and potential side effects with their doctor and pharmacist.

The U.S. Department of Health and Human Services’ current antiretroviral treatment guidelines list four “preferred” regimens—based on NNRTIs, PIs, and an integrase strand transfer inhibitor (INSTI)—for people first starting antiretroviral therapy (Table 1). Side effects for the ART medications recommended for initial therapy are discussed on page 22.

TENOFOVIR (VIREAD) PLUS EMTRICITABINE (EMTRIVA)

These two NRTIs (part of the combination pills Truvada, Atripla, and Complera) are recommended for inclusion in every new antiretroviral regimen, unless there is a condition that prohibits their use.

Common side effects include weakness or fatigue, headaches, diarrhea, nausea, and gas. Other possible side effects include kidney injury, Fanconi’s syndrome (in which the kidneys spill glucose, magnesium, and other essential electrolytes into the urine instead of reabsorbing them), osteopenia and osteomalacia (decreased bone density and other bone abnormalities), and darkening of the skin on the palms and soles of the feet.

People with hepatitis B virus who start this medication are advised to talk with their health care provider before discontinuing it, as the liver disease may flare up when tenofovir is stopped. The treating clinician can monitor the kidneys and liver through blood and urine tests and the bones through bone density tests before and during treatment.

Table 1. Preferred Initial Antiretroviral Therapy Regimens

NNRTI-Based Regimen	tenofovir + emtricitabine + efavirenz
PI-Based Regimens	tenofovir + emtricitabine + atazanavir + ritonavir <i>or</i> tenofovir + emtricitabine + darunavir + ritonavir
INSTI-Based Regimen	tenofovir + emtricitabine + raltegravir

EFAVIRENZ (SUSTIVA)

The NNRTI efavirenz is also part of the combination pill Atripla. Common side effects seen with efavirenz include skin rash, dizziness, grogginess, vivid dreams or nightmares, liver inflammation, and increases in cholesterol. Pregnant women should avoid taking this medication during their first trimester, as it has been linked to brain and spinal cord defects in the developing fetus.

In addition, a small minority of people may experience severe depression, angry outbursts, and disturbing or even suicidal thoughts while taking efavirenz. These psychiatric issues tend to emerge more frequently in people with pre-existing mental health problems. For this reason, it is especially important to discuss your current mental health state and any past mental health issues with your clinician before considering a regimen that includes efavirenz.

ATAZANAVIR (REYATAZ) BOOSTED WITH RITONAVIR (NORVIR)

Atazanavir and ritonavir belong to the protease inhibitor class. Ritonavir is a “pharmacoenhancer” or “booster” drug: Low doses of ritonavir are used to raise levels of atazanavir (and other PIs) in the blood.

Common side effects experienced with atazanavir include hyperbilirubinemia (an increase in the body’s level of bilirubin, a byproduct of red blood cells), jaundice (yellowing of the skin and eyes due to increased levels of bilirubin in the blood), skin rash, and liver inflammation. The jaundice and hyperbilirubinemia caused by atazanavir may cause self-consciousness, but they are not dangerous and go away when the medication is discontinued.

Ritonavir may cause stomach upset, nausea, vomiting, diarrhea, taste disturbances, and numbness and tingling around the mouth. Other possible side effects include increases in cholesterol, weakness, fainting, liver

toxicity, decreased insulin sensitivity, changes in body shape, and increased bleeding in hemophiliacs. Individuals and their physicians can monitor drug-related changes in liver health, cholesterol, and blood sugar through regular blood tests.

DARUNAVIR (PREZISTA) BOOSTED WITH RITONAVIR

Darunavir also belongs to the PI drug class. Common side effects from darunavir use include skin rash, liver toxicity or liver inflammation, nausea, diarrhea, and headaches. The low dose of ritonavir used with darunavir may cause stomach upset, nausea, vomiting, diarrhea, taste disturbances, and numbness and tingling around the mouth. Other possible side effects include high cholesterol, body shape changes, and increased bleeding in hemophiliacs. Darunavir contains a sulfonamide structure in its chemical makeup, so some (though not all) people with a sulfa allergy may also be allergic to darunavir.

RALTEGRAVIR (ISENTRESS)

Raltegravir belongs to the integrase strand transfer inhibitor (or simply integrase inhibitor) class. HIV positive individuals starting raltegravir may experience headaches, stomach upset, nausea, and diarrhea. Other possible side effects include drug-induced fevers, muscle pain and weakness, and rhabdomyolysis (breakdown of muscle fibers). Physicians can monitor muscle health via blood tests.

OTHER DRUGS

Table 2 lists side effects typically associated with currently available antiretroviral drugs. While it is important for people with HIV to be aware of potential drug side effects, it is also essential to remember all the benefits associated with treatment. The goal of antiretroviral therapy is to build and maintain the immune system’s strength to avoid contracting debilitating or life-threatening opportunistic infections such as

Pneumocystis pneumonia, *Mycobacterium avium* complex, and cytomegalovirus retinitis (a viral eye disease)—and ultimately to ensure a longer and healthier life with HIV.

INSIDE THE BLACK BOX

The U.S. Food and Drug Administration (FDA) requires drug manufacturers to highlight any very severe medication side effects in a special “black-box warning” in the product package insert. Boxed warnings are surrounded by a border or a box (hence the name) to bring special attention to them.

As explained by Christine Cheng, who studies black box warnings at the UCSF School of Pharmacy, “the purpose of a boxed warning is to alert prescribers to a serious, potentially life-threatening side effect that may be associated with use of a medication.” These warnings describe the serious side effect and outline ways to minimize the risk. “For example, Accutane (isotretinoin) is an acne medication that has a boxed warning about the potential for birth defects, and the warning includes specific information about a program that ensures that women who take the medication do not become pregnant,” said Cheng.

Black-box warnings may be assigned to individual medications or to a whole drug class. For example, a black-box warning about lactic acidosis (severe build-up of lactate, one’s of the body’s toxic waste products, in the blood) is placed in every NRTI’s product package insert. Black-box warnings associated with antiretrovirals are listed in Table 2.

Should people avoid taking medications with black-box warnings? Not necessarily, according to Cheng. “Whether you should avoid taking a drug due to a boxed warning depends on...what the boxed warning is, whether it is clinically applicable to you, and whether an alternate therapy is available. There are hundreds of medications with boxed warnings, and

many people take them without serious side effects.” Cheng emphasized the importance of good patient-provider communication about the potential for serious side effects from drugs with black-box warnings: “As with any medication, you and your clinician need to discuss the risks and benefits.”

DEALING WITH SIDE EFFECTS

Although the side effects that most people experience are not the serious, potentially life-threatening ones described in black-box warnings, they can still be challenging to handle. Common side effects such as nausea, diarrhea, rash, and fatigue can weaken your resolve to continue treatment. Below are some tips to combat these common side effects and help you stick to your regimen.

NAUSEA

Many antiretrovirals can cause nausea, especially during the first four weeks of treatment. Intractable nausea (severe nausea that continues for long periods of time and does not get better with supportive treatment) can occur and may require a switch in therapy. However, for most people, ART-associated nausea does get better with time.

HIV positive persons taking abacavir should pay special attention to nausea symptoms; nausea that is persistent or worsens over time may be an indicator of abacavir hypersensitivity and warrants a call to the treating clinician.

Prescription medications are available to help reduce nausea. A common medication prescribed for nausea is prochlorperazine (Compazine). Prochlorperazine works to block certain neurotransmitters in the brain; this slows the release of brain hormones that trigger nausea and vomiting. For nausea that is not controlled by prochlorperazine, some clinicians may prescribe a stronger anti-nausea medication such as ondansetron (Zofran), which is mostly

used to prevent chemotherapy-induced nausea and vomiting. Ondansetron blocks the uptake of the chemical serotonin in both the brain and peripherally in the body, which helps to reduce nausea. Ondansetron is typically not covered by prescription drug insurance companies unless the patient is undergoing treatment for cancer, however, so it may be preferable to start with prochlorperazine.

In addition to medications to help control nausea and vomiting, there are several non-pharmacologic (non-drug) ways to soothe a queasy stomach—most of which involve changing eating habits.

Consuming smaller meals more frequently (rather than eating two or three large meals per day), eating lukewarm meals instead of piping hot food, and avoiding fatty, fried, spicy, or dairy-containing foods may help avoid or relieve nausea. Bland foods such as bread, rice, toast, bananas, and crackers can also help quell queasiness, as may ginger (fresh or in the form of capsules, sodas, or teas) or teas made from mint leaves.

DIARRHEA

As with nausea, diarrhea is usually a transient side effect that can occur with antiretrovirals, predominantly protease inhibitors. It tends to be worst during the first few weeks of treatment.

If diarrhea occurs, non-antiretroviral causes should be ruled out; lactose intolerance, unfamiliar foods, and food-borne illnesses can also cause diarrhea. Unusual symptoms such as bloody or very foul-smelling stools should be reported to a clinician so that other diarrhea causes can be explored.

Various medications are available to control diarrhea associated with ART. Loperamide, available over the counter as Immodium AD, slows the muscles of the intestines and allows more water to be absorbed from the stool. If loperamide does not control

diarrhea sufficiently, a treating clinician may consider prescribing medications such as diphenoxylate/atropine (Lomotil) or tincture of opium.

Calcium supplements (200–500 mg) have been shown to help control loose stools, especially for those taking the protease inhibitor nelfinavir. Maintaining a healthy amount of fiber in the diet by eating whole grains, apples, and other fruits and vegetables can also help reduce diarrhea.

Lastly, drinking plenty of fluids and staying well hydrated is crucial, as diarrhea can result in significant water loss to the body. Drinks to replace electrolytes (such as Gatorade) are not necessary but can be used.

RASH

Several antiretrovirals can cause rashes. Medications in the NNRTI class of antiretrovirals have been found to cause rashes in as many as one out of every five persons taking them!

Antiretroviral-related rashes typically occur within the first two weeks of therapy. A common drug-related rash may look like tiny pimples spread over the arms, legs, and trunk. The skin may be erythematous (red and irritated) and the rash may appear to be worse where the skin is exposed to sunlight.

Rashes in people on ART should be reported to the treating clinician immediately. Most drug-related rashes are not dangerous and go away on their own over two to four weeks, but some can be dangerous. Watch for severe peeling of the skin, rashes in unusual places (such as the mouth, nose, eyes, and genitals), painful rash, fevers, or abdominal pain. These symptoms suggest that there may be a dangerous rash developing which requires immediate medical attention.

If your rash is not threatening and your treating clinician recommends you continue your treatment regimen, you can take extra steps to pamper your skin. Take lukewarm (not hot) showers and use mild, fragrance-

Table 2. Side Effects Commonly Associated with Antiretroviral Drugs

Drug Class	Drug Name	Side Effects	Black Box Warnings
NRTI	Abacavir (Ziagen; in Trizivir and Epzicom)	Nausea, rash, drug hypersensitivity reaction	Drug hypersensitivity reaction or allergy (especially during the first 8 weeks of treatment), lactic acidosis, liver enlargement with fatty liver
	Didanosine (Videx)	Nausea, vomiting, pancreatitis, peripheral neuropathy, lactic acidosis with fatty liver	Pancreatitis, lactic acidosis (especially in pregnant women also using didanosine and stavudine), and liver enlargement with fatty liver
	Emtricitabine (Emtriva; in Truvada, Atripla, and Complera)	Discoloration (spotting) of the palms and soles of feet, flare-up of hepatitis B disease when treatment is stopped	Lactic acidosis, liver enlargement with fatty liver, and flare-up of hepatitis B disease when treatment is stopped
	Lamivudine (EpiVir; in Combivir, Trizivir, and Epzicom)	Flare-up of hepatitis B disease when treatment is stopped	Lactic acidosis, liver enlargement with fatty liver, flare-up of hepatitis B disease when treatment is stopped
	Stavudine (Zerit)	Nausea, pancreatitis, peripheral neuropathy, lipoatrophy (loss of fat in arms and legs, cheeks, and buttocks), lactic acidosis with fatty liver, increased cholesterol, changes in the way the body handles sugars	Pancreatitis (especially when combined with didanosine), lactic acidosis (especially in pregnant women using the combination of didanosine and stavudine), and liver enlargement with fatty liver
	Tenofovir (Viread; in Truvada, Atripla, and Complera)	Nausea, gas, diarrhea, kidney damage, Fanconi syndrome, changes in bone tissue and bone density, flare-up of hepatitis B disease when treatment is stopped	Lactic acidosis, liver enlargement with fatty liver, and flare-up of hepatitis B disease when treatment is stopped
	Zidovudine (Retrovir; in Combivir and Trizivir)	Nausea, vomiting, headaches, muscle aches, lipoatrophy, anemia (low red blood cell count), neutropenia (low white blood cell count), lactic acidosis with fatty liver, increased cholesterol, changes in the way the body handles sugars	Neutropenia, severe anemia, muscle inflammation, lactic acidosis, and liver enlargement with fatty liver
NNRTI	Delavirdine (Rescriptor)	Nausea, headaches, rash, liver inflammation	None
	Efavirenz (Sustiva; in Atripla)	Grogginess, dizziness, vivid dreams/nightmares, depression, rash, liver inflammation, increased cholesterol, birth defects if used during pregnancy	None
	Etravirine (Intelence)	Nausea, rash, drug hypersensitivity reaction, Stevens-Johnson syndrome (a life-threatening skin reaction)	None
	Nevirapine (Viramune)	Rash, liver toxicity, drug hypersensitivity reaction, Stevens-Johnson syndrome	Severe liver toxicity and rashes/skin reactions (especially during the first 6 weeks of treatment)
	Rilpivirine (Edurant)	Headache, nausea, rash, liver inflammation, depressive disorders	

Table 2, continued

Drug Class	Drug Name	Side Effects	Black Box Warnings
PI	Atazanavir (Reyataz)	Rash, diarrhea, nausea, increases in bilirubin in the blood, yellowing of the skin and eyes, liver inflammation, abnormal electrical patterns in the heart, changes in the way the body handles sugars, increased cholesterol, changes in body fat distribution, kidney stones, increased bleeding in hemophiliacs	None
	Darunavir (Prezista)	Rash, diarrhea, nausea, liver inflammation and liver toxicity, changes in the way the body handles sugars, increased cholesterol, changes in body fat distribution, increased bleeding in hemophiliacs	None
	Fosamprenavir (Lexiva)	Rash, diarrhea, nausea, liver inflammation and liver toxicity, changes in the way the body handles sugars, increased cholesterol, changes in body fat distribution, kidney stones, increased bleeding in hemophiliacs	None
	Indinavir (Crixivan)	Rash, diarrhea, nausea, weakness, dizziness, hair loss, kidney stones, increases in bilirubin in the blood, yellowing of the skin and eyes, liver inflammation, changes in the way the body handles sugars, increased cholesterol, changes in body fat distribution, increased bleeding in hemophiliacs	None
	Lopinavir/ritonavir (Kaletra)	Nausea, vomiting, diarrhea, weakness, changes in the way the body handles sugars, increased cholesterol, liver inflammation, pancreatitis, changes in body fat distribution, abnormal electrical patterns in the heart, increased bleeding in hemophiliacs	None
	Nelfinavir (Viracept)	Diarrhea, increased cholesterol, liver inflammation, pancreatitis, changes in body fat distribution, increased bleeding in hemophiliacs	None
	Ritonavir (Norvir; also in Kaletra)	Nausea, vomiting, diarrhea, weakness, increased cholesterol, changes in the way the body handles sugars, liver toxicity, taste disturbances, numbness and tingling around the mouth, changes in body fat distribution, abnormal electrical patterns in the heart, increased bleeding in hemophiliacs	Do not combine with some sedative hypnotics (e.g., midazolam), antiarrhythmic cardiac drugs, and ergot alkaloids (often used for migraines) due to dangerous drug interactions
	Saquinavir (Invirase)	Nausea, headaches, diarrhea, liver inflammation, abnormal electrical patterns in the heart, changes in the way the body handles sugars, increased cholesterol, changes in body fat distribution, abnormal electrical patterns in the heart, increased bleeding in hemophiliacs	None
	Tipranavir (Aptivus)	Rash, liver toxicity, nausea, diarrhea, changes in the way the body handles sugars, increased cholesterol, changes in body fat distribution, rare increased intracranial bleeding episodes, increased bleeding in hemophiliacs	Severe liver toxicity and intracranial bleeding
Fusion Inhibitor	Enfuvirtide (Fuzeon)	Pain, redness, bruising, bumps/nodules at the injection site, drug hypersensitivity reaction, increased episodes of bacterial pneumonia	None
CCR5 Antagonist	Maraviroc (Selzentry)	Dizziness, abdominal pain, rash, fevers, liver toxicity, low blood pressure upon standing	None
Integrase Inhibitor	Raltegravir (Isentress)	Headache, nausea, diarrhea, muscle weakness, muscle breakdown, fevers, rash	Severe liver toxicity and drug hypersensitivity reaction

free soaps (such as glycerin soaps or brands like Dove or Cetaphil) that are marketed for sensitive skin. Keep your skin moisturized with a fragrance-free lotion (brands such as Keri and Eucerin may be useful). Wear loose clothing and avoid excessive sun exposure on rashy areas. Monitor your skin every day to ensure that the rash is improving.

FATIGUE

Many people feel tired when they start new antiretroviral medications. While some of this is normal—remember, not only is the body adapting to the treatment, it may also be trying to process dead HIV particles as the regimen starts working—everyone should pay attention to the severity of the fatigue and monitor how long it seems to be lasting.

Very severe fatigue—sometimes described as the “worst fatigue of your life”—may be a sign of a more serious side effect such as anemia (loss of red blood cells) and is a hallmark of lactic acidosis from NRTI medications. Simple blood tests can rule out these conditions.

Fatigue due to starting new ART medications has no prescription or over-the-counter remedy other than rest and time. If you are starting new medications, you might consider waiting until you have a few days off from work or school so you can rest and have some extra time to deal with side effects. As the initial fatigue passes and the medications control viral replication, many people feel they gain more energy than they had before they started ART.

AVOIDING LONG-TERM SIDE EFFECTS

Are there ways to lower your risk of developing long-term side effects? “Preventing long-term side effects from HIV medicines is one of the most challenging aspects of treating HIV,” according to Eddy Machtinger, director of the UCSF Women’s HIV Program.

ONLINE RESOURCES

AIDSinfo, an informational resource offered by the Department of Health and Human Services, includes a searchable database of HIV meds, with comprehensive descriptions of side effects and potential risk factors for adverse events for each drug.

<http://aidsinfo.nih.gov/DrugsNew/Default.aspx>

AIDSmeds.com provides a full-color chart of approved and experimental antiretroviral drugs; click the drug name to see side effect details.

www.aidsmeds.com/list.shtml

TheBody.com offers the online “Resource Center on Keeping Up with Your HIV Meds,” with videos, personal stories, and tips and tricks for adhering to your ART regimen despite side effects.

www.thebody.com/content/63615/keeping-up-with-your-hiv-meds-home.html

Clinicians can try to lower the risk of long-term side effects by considering a person’s current health status and family risk factors before selecting antiretroviral medications. For example, “for patients with pre-existing conditions such as heart disease or diabetes, a discussion should be had about the risks and benefits of protease inhibitors,” said Machtinger.

However, for people with few risk factors, or for those with limited antiretroviral choices, “knowing exactly which regimen will avoid all long-term complications is nearly impossible. Usually, the data are not robust enough to significantly affect our treatment decisions.”

When side effects such as increased cholesterol, pre-diabetes or diabetes, and bone changes do occur, they are treated in the same way as they would be in HIV negative persons: with medications and therapeutic lifestyle changes. In Machtinger’s view, “being HIV positive and taking ART are two more excuses to seize every opportunity to prevent long-term illnesses by staying on top of your health care maintenance,” including minimizing cardiovascular risk with

regular exercise, a healthy diet, and quitting smoking.

Regular medical visits can help track any side effect symptoms and provide opportunities for your clinician to perform non-invasive bone scans and check laboratory values. “This can help you to be vigilant about the development of any long-term side effects, and can help you treat them early,” said Machtinger.

HEY, THAT’S NOT IN THE PACKAGE INSERT!

It is unusual but still possible to have a side effect that is not normally associated with a particular regimen or medication.

Maizie (who asked that her last name be withheld for privacy) had taken abacavir/lamivudine (Epzicom) as part of her antiretroviral regimen many years ago. When she changed doctors, she started a new regimen that worked well for a while, until her kidneys began to show signs of impairment. Her doctor recommended she switch back to abacavir/lamivudine to lower the risk of further kidney injury. Soon after she switched, Maizie began to have occasional palpitations (rapid,

strong heartbeats). It was then that she remembered why she had stopped taking abacavir years before: She had experienced heart palpitations the last time she used the drug.

Maizie's doctor searched the product package insert and the available medical literature and could find no mention of heart palpitations occurring with abacavir use, but her unusual side effect was added to her medical chart to help ensure Maizie would not use the drug again unless absolutely necessary.

ART medications are studied in large clinical trials, but there is still the potential for emergence of "new" or previously unknown side effects during postmarketing studies. There is also the possibility, if only a small one, for someone to experience a unique individual reaction to a medication.

Anyone experiencing an unusual symptom that may be related to their HIV treatment should inform the treating clinician, who will consider factors such as whether the side effect has been reported in others, the timing of the drug dose and the appearance of the side effect, and whether the side effect is dangerous or merely bothersome.

If the side effect is not dangerous, the clinician may try "discontinuing and rechallenging." If the drug is stopped and symptoms resolve or improve, evidence is in favor of a drug-related effect. (If the side effect continues despite the medication being stopped, the symptom is likely due to other causes.) After stopping the medication, the clinician may suggest trying the drug again. If the symptom reappears after restarting the drug, as in Maizie's case, there is even stronger evidence that it is related to the medication.

STARTING OFF RIGHT

Side effects can be unpredictable—some people experience only mild nuisances from new antiretroviral drugs, whereas others struggle with more

challenging adverse events—and fear of the unknown may get in the way of starting or changing ART. Preparing yourself well to begin new antiretrovirals (and face any side effects) will give you the best possible start.

BEFORE YOU START ART

The following strategies can prepare you for any side effects you might experience after starting or changing treatment, and help you stick to your new or altered treatment regimen.

Inform yourself—and your doctor. The descriptions of side effects provided in this article can help prepare you to talk frankly with your clinician about what to expect after starting antiretroviral therapy or switching regimens. You can also find information about drug side effects—and how to keep them from interfering with adherence to your regimen—from reliable online sources (see sidebar on page 26).

As you educate yourself about potential side effects from your new medicines, it may be helpful to jot down any questions you want to ask your clinician and take them with you to your medical visit. Also, be sure to inform your clinician about any past or present medical issues of your own or in your family; for example, current depression may mean that efavirenz is not the right drug for you, and a family history of diabetes may warrant close monitoring for metabolic side effects after starting ART.

Create an adherence plan. Adhering to a treatment regimen may not be as straightforward as it seems. "The underlying causes of missing your ART medication are so much more complex than 'just forgetting,'" said Mallory Johnson of the UCSF Center for AIDS Prevention Studies, who conducts research on ways to improve ART adherence. "The things we forget the most tend to be things that are negative to us or things that feel unpleasant. For example, you're probably not going to forget that you have a trip to Hawaii

planned for next Thursday, but you are more likely to forget to take a medication that is giving you side effects."

Because having side effects can make it that much harder to adhere to your regimen, he explained, it may be necessary to plan ahead about "ways to remember [your medicines] that take into account any personal barriers you have to taking medication, and using adherence strategies that motivate you to take your medication."

Your adherence strategies may include following some of the tips outlined below. You might also think about your daily routines and consider where taking your medicines will fit. For example, you probably rarely forget to brush your teeth in the morning, so you might plan to take your medicines right before brushing your teeth.

Also think about what motivates you in other areas of your life. Do you reward yourself after cleaning the kitchen or hitting the gym? Can you promise yourself the same (healthy!) rewards after a week of no missed or late doses?

Finally, it may be helpful to examine your mindset about taking ART. The pills or injections may at first seem like an unwelcome reminder of your virus, but those medicines also show that you are working to beat that virus and manage your own health. These approaches can help keep you motivated and on track with your regimen even if side effects emerge.

Ready your adherence devices. Part of your adherence plan may include using medication reminder devices such as cell phone alarms or daily text messages. Personalizing the alarm or text with a small motivating message may help. ART medication packaging can also make a difference; some people prefer to keep their medicines in pillboxes marked with the days of the week so they can easily see if they've already taken that day's doses. Some HIV-specialized pharmacies can package ART in pillboxes or in special daily "bubble" packaging.

If getting to the pharmacy to pick up your medications is problematic, you may want to talk to the pharmacist about getting medications delivered or mail-ordered. You may also wish to set up automatic refills and reminder calls when your prescriptions are ready.

Assemble your support team.

Your adherence plan can also include sharing your situation with other people. For example, you might assemble a team of “medication cheerleaders.” These can be friends, family members, or other people living with HIV—anyone who might provide support as you start on your new medications.

You might ask this team to check in on you via in-person visits, phone calls, texts, or online. If you are taking a drug that may cause depression or other psychiatric side effects, you may want to ask your support team to watch out for these symptoms and be prepared to help you seek assistance. Sometimes just knowing that people are watching out for you and are available to talk to if you’re feeling bad (or good) can be comforting and motivating.

You can also ask for extra support from your medical provider when starting or switching ART regimens. For example, if you get care at a busy clinic or are not always able to get appointments on short notice, you might arrange follow-up appointments in advance, in case you need to discuss any side effects with your clinician.

Ready your anti-side effect

arsenal. Prior to starting or changing ART, gather any supportive therapies you might want to use. For example, if you are worried about having nausea, you might ask your doctor about anti-nausea medications. (Make sure you pick up any anti-nausea medicines *before* you start your new regimen; if you do end up having nausea, the last thing you will want to do is go back to the pharmacy!) You might also want to stock up on soothing or

plain foods from the grocery store (such as bread, bananas, rice, toast, soups, mint tea, and ginger or ginger ale) so you already have these on hand if you do experience nausea or diarrhea.

Other things you may want to have handy are “distractors”—things that can help keep your mind off of side effects. Books, DVDs, and other hobbies can help take your mind off your symptoms.

Finally, extra time to rest is not always easy to obtain but can be extremely helpful. Try to plan ahead for some time off work or school.

IF YOU HAVE SIDE EFFECTS

The “Dealing with Side Effects” section on page 23 has a wealth of tips on relieving side effect symptoms. In addition, keeping track of your symptoms and talking about them with your medical team are crucial to managing side effects and getting the most from your ART.

Keep track of your symptoms.

If you are experiencing a side effect which seems pretty common (nausea, diarrhea, or fatigue) and is not very severe, the supportive therapies mentioned above may help. It may also be useful to keep a “side effect diary.” This can be as simple as a piece of paper on which you write down the date, note what time you took your medicines, and describe your side effect symptoms (and when you first noticed them).

This type of diary can help you keep track of side effects and whether they are improving, getting worse, or staying the same. For example, if you’re monitoring nausea, you may want to write down how many times you vomited that day, or how many

hours the nausea seemed to last. If you’re having diarrhea, you may want to tally how many times you had to rush to the bathroom. If you’re having a rash, you may want to describe what it looks like and where it is.

You might also describe the severity of your side effect using a 1 to 10 numerical scale: “1” would describe a very minimal, non-bothersome side effect; “5” would describe a moderately bothersome side effect; and “10” would describe a very bothersome side effect.

Talk to your medical team. Descriptions in a side effect diary can help you take the most important step: talking to your clinician and pharmacist about your side effects. This is especially important if you’re unsure whether the side effect you are experiencing is normal or unusual, mild or serious. If it is not dangerous, your medical team might encourage you to treat the side effect symptoms with supportive therapies and “wait it out.” Many common ART side effects appear quickly after starting (within days), are at their worst over the first two weeks of therapy, and get better over the next few weeks.

However, an honest conversation with your health-care providers is extremely important. If your side effects feel unbearable or are keeping you from working or taking care of yourself, staying with the regimen for a month or two may not be the right choice for you.

Keeping an open dialogue about side effects is key to maintaining a trusting partnership with your medical team so you can make the best decisions about your treatment strategy and your health.

For more strategies for communicating with your clinician and getting the best possible treatment wherever you access care, see “Making the Most of Your Medical Visits” in the Winter/Spring 2009 issue of *BETA*.

CONCLUSION

According to Geri, fear of side effects shouldn't stop anyone from taking HIV medicines. "I would tell people living with HIV to talk to other people living with HIV," she said. "You can ask them if they are on medications and ask about their side effects. If you can't ask an HIV positive person, ask an HIV social worker if it would be OK to ask questions about the medicines. Most of the time people are going to say 'yes' because they are willing to help."

Although medication side effects can be distressing or downright scary, those associated with today's more tolerable antiretrovirals are mostly mild, manageable, and transient—and are far outweighed by the longer-term benefits of ART. Even after her own frightening experiences with side effects, Geri still manages to take her medications every day. "That's the thing about taking the HIV medicines," she said. "Even if they might cause side effects, they are helping me *live* with the virus."

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HIV Testing and HIV Health Resources

Knowing your HIV status is the first step toward staying healthy with HIV or remaining negative. As a *BETA* reader, chances are you already know your HIV status—but do your friends and family members know theirs? Not everyone knows they may be at risk for HIV, or where and how to get tested and what to do if they test positive.

Please take advantage of these resources to help keep yourself and those you care about safe and healthy.

The following hotlines offer information and anonymous counseling about HIV testing, prevention, transmission, and health.

National AIDS Hotline

1-800-CDC-INFO (1-800-232-4636)
1-888-232-6348 (TTY)
Hours: 24 hours a day, 7 days a week

California HIV/AIDS Hotline

www.aidshotline.org
1-800-367-AIDS (Toll-free within California)
Hours: Monday through Friday, 9 am to 4 pm PT

GMHC Helpline

www.gmhc.org
1-800-AIDS-NYC (1-800-243-7692)
Hours: Tuesday, 2 pm to 5 pm ET; Wednesday, 10 am to 2 pm ET; Friday, 2 pm to 5 pm ET

Project Inform HIV Health InfoLine

1-800-822-7422
Hours: Monday through Friday, 10 am to 4 pm PT

The National Prevention Information Network, part of the U.S. Centers for Disease Control and Prevention (CDC), can help you or someone close to you find an HIV testing site, and can help answer questions about HIV testing and HIV prevention.

CDC National Prevention Information Network

www.hivtest.org/contact
1-800-458-5231 (U.S.)
1-404-679-3860 (International)
Hours: Monday through Friday, 9 am to 6 pm ET