Soon after taking medication, the maximum amount of that drug can be found in your blood. This maximum drug level is called Cmax; and the higher the level, the more likely you’ll experience side effects. Over time, the drug level decreases; and around the time you take your next dose, the lowest level can be found. This level is called Cmin, and the lower the level the more likely drug resistance will develop.

For certain antibiotics, the Cmax is the most important level to consider as it has been shown to correlate with a drug’s effectiveness. However, it has not been established which level shows a relationship with the activity of anti-HIV drugs, although most people believe that the Cmin is likely the most important.

There are many reasons why different aspects of pharmacology can help in managing your anti-HIV therapy. They include measuring drug levels in blood (Therapeutic Drug Monitoring or TDM); measuring drug levels inside cells (intracellular); drug interactions; and protein binding. Read on for more discussion of these areas.

Therapeutic Drug Monitoring
TDM is an area of intense interest as several small studies have shown that people with higher drug levels are more likely to have better and more sustained anti-HIV responses. Further, early results from a larger study known as ATHENA has also shown the benefits of TDM. Read the box on page 2 for more information.

TDM involves drawing a blood sample to measure the amount of a particular protease inhibitor and/or non-nucleoside reverse transcriptase inhibitor (NNRTI). Most experts believe that measuring the levels of nucleoside reverse transcriptase inhibitors (NRTIs) will be of little value as they block HIV inside the cell. Drug levels found in blood may not necessarily compare to those inside cells.

TDM may be particularly useful for protease inhibitors as their blood levels can vary greatly among individuals as there are differences in how people break down (metabolize) these drugs. Ensuring that people stay within a ‘therapeutic range’ may greatly improve the likelihood of a lasting anti-HIV response. TDM may also help determine the proper dose of a drug for a particular person.

Right now, most anti-HIV drugs are given in standard doses whether someone weighs 120 pounds or even 250 pounds. Many experts believe that this is one of the reasons why women experience more side effects as they generally weigh less than men.
As a result, TDM may not only help prolong anti-HIV response, but it may also help minimize side effects. Furthermore, standard doses are given to people regardless of their stage of disease. But since people with more advanced disease generally have liver and/or kidney dysfunction, different doses may actually be needed. People co-infected with hepatitis may also need a different dose.

The ‘therapeutic range’ may differ for someone just starting therapy than for someone who has already taken different drugs and has developed resistance to them. People with drug-resistant virus may need to achieve higher drug levels in order to “overcome” the resistant virus. This can be achieved by taking higher doses or using a boosting drug like ritonavir (Norvir). For more information, read the Drug Interactions section.

A few hurdles still have to be overcome before TDM can be used as part of routine medical care. One is about the tests themselves. When companies develop a new drug, they or a company they work with will develop a test to measure drug levels. More often than not, these companies do not publish how they developed these tests. So if university-based researchers want to measure levels of that particular drug, they develop their own tests, and there’s no way of knowing whether these new tests are as accurate as the original one. This is also true for most of the TDM tests now being offered by commercial laboratories.

Perhaps the bigger hurdle is determining the proper time to draw the blood sample. Different people taking the same drug will have a different pattern in how it gets absorbed by and eliminated from their bodies. In other words, everyone has a different drug level profile. This is especially true for children, as younger children eliminate drugs more rapidly than older children, and they in turn eliminate faster than adults.

For anti-HIV drugs, the Cmin is probably the most important level when looking at anti-HIV response. In this case, you would need to have your blood drawn right before you take your next scheduled dose. In practice, this would be very difficult to do. The more likely scenario is that people go for blood draws whenever they can get an appointment, and this may not be right before their next scheduled dose.

As a result, several groups are trying to map out drug levels over a 12- or 24-hour period, hoping they can use this information to predict what the Cmin might be for someone just starting therapy.
who took his or her drugs two hours before their blood draw. Furthermore, for someone more concerned about side effects, the Cmax will be more important and the same dilemma would exist around the time of the blood draw.

Some experts propose that TDM may be an effective way of measuring adherence. But others disagree, because a “nonadherent” person could take a dose of drug before going in for their blood draw and drug levels would then be detected. The assumption here is that he or she is taking meds as prescribed, even though in reality that may have been the only dose they took during the week.

Drug Levels Inside Cells (Intracellular)

Another possible complicating factor about TDM is the recent finding of protease inhibitor levels inside cells, similar to what has been seen with NRTIs. To date, nobody has shown a connection between protease inhibitor levels inside cells to anti-HIV response, but those studies are now being done. It is also not known if there’s a connection between protease inhibitor levels found in blood to those found inside cells.

Human cells have certain genes called P-glycoprotein (P-gp) and Multi-drug Resistance Proteins (MRPs). They control what substances, including drugs, can get into cells and how quickly they’re expelled in order to protect the cells from toxic substances.

It’s still not clear how these genes play a role in the overall effectiveness of anti-HIV therapy, although it is thought they factor in how well drugs are absorbed and how efficiently they get into certain parts of the body, like the brain. These genes already play a major role in the effectiveness of therapies for other diseases. For instance, a high expression of these genes has been shown to make cancer cells more resistant to traditional drugs.

Drug Interactions

Many anti-HIV drugs and therapies used to prevent or treat opportunistic infections are metabolized by the same enzyme in the body. This means that there are many possible drug interactions. As a result, it becomes more important to talk about this issue with your doctor or pharmacist about all the meds you’re taking, including over-the-counter herbs and vitamins. More information on drug interactions is available through Project Inform’s Hotline.

Women and Pharmacology

There are known and possible other considerations for women with regard to how drugs are processed in the body. Studies describing some of these considerations note sex differences in metabolism, drug levels and side effects.

One study that looked at differences in blood levels of the NNRTI drug, delavirdine (Rescriptor), in men and women showed that women who took delavirdine + AZT (Retrovir) had nearly twice the amount of delavirdine in their blood at trough levels than men, even though both took the same doses. Possible explanations for this difference include weight and body mass differences and hormones. Whatever the cause, the study suggests that women may absorb some drugs differently than men and that researchers should watch for this effect.

In addition to higher drug levels in blood, some studies report increased or varied side effects from anti-HIV drug use in women. A ritonavir study showed that women experienced more nausea, vomiting and malaise than men. Some women also experienced a unique and potentially dangerous side effect caused by ritonavir—excessive menstruation. While the cause of these differences remains unknown, it suggests that women and men might need different drug doses to lessen these effects.

Little research has taken place to evaluate different dosing schemes in women. It remains unknown if or how people might safely decrease their doses and maintain potency of a drug when faced with side effects. In the short-term, it’s probably unwise to simply decrease doses of anti-HIV drugs to manage side effects. Reduced dosing may result in fewer side effects, but it may also cause the drug to fail or HIV to develop resistance to it.

Drug interactions between anti-HIV therapy and other drugs commonly used by women are another important consideration. For instance, some protease inhibitors decrease estrogen among women on hormone replacement therapy (HRT) or oral contraceptives, while the protease inhibitor indinavir (Crixivan) and the NNRTI efavirenz (Sustiva) increase estrogen.

Practically speaking, women on protease inhibitors should be counseled on how to alter the dose of their oral contraceptives or HRT to maintain effectiveness and/or use other methods of birth control. Also, this suggests that some protease inhibitors might decrease the natural level of estrogen in women, leading to other health issues associated with low estrogen levels (like early menopause or loss of bone density).

As the field of HIV drug pharmacology becomes more complicated, many basic questions remain regarding differences in women. In order to answer them, it’s critical that sufficient numbers of women participate in studies of new therapies, as well as other studies that may reveal possible sex differences. Industry, government and community must work together to prioritize these research areas and to address the barriers that remain for women’s involvement in research.
Pharmacology: Drug Level Monitoring and Beyond

One of the most discussed issues on drug interactions in the past few years has been using ritonavir to boost the levels of other protease inhibitors. This approach can result in less frequent dosing and a reduced daily dose. This is achieved in one of two ways: A) ritonavir can greatly increase the Cmax of lopinavir and saquinavir without significantly changing the rate at which the other drug is eliminated from the body, or B) ritonavir can slow down the rate of indinavir, nelfinavir and amprenavir from being eliminated from the body without greatly changing the Cmax.

Early results suggest that ritonavir is able to boost the levels of two protease inhibitors at the same time, indicating that this may possibly be a useful strategy for third line therapy.

Boosting drug levels, however, may make interpreting resistance results more challenging because the higher drug levels may ‘overpower’ some of the drug-resistant viruses. Currently, most people consider a four-times decrease in sensitivity to a drug to mean low-level resistance while anything over a ten-times decrease means high-level resistance. This is generally considered acceptable because blood levels of a drug are usually only four to eight times higher than what is simply needed to block HIV from reproducing.

However, ritonavir boosts the drug levels of some protease inhibitors upward of 15 times or higher and so these standard 4-10 times changes for resistance tests may become irrelevant. In other words, you may “overpower” some of these resistant viruses by using ritonavir and another protease inhibitor even though your test results indicate you may be resistant to one or more of these drugs. As a result, it may be important to factor in drug levels when evaluating results from your tests. For more information on resistance tests, read Project Inform’s Genotypic and Phenotypic Resistance Tests.

Protein Binding

It is widely known that anti-HIV drugs get bound to certain proteins in the body, which results in decreased anti-HIV activity. In some cases, this has resulted in the drug being pulled from development because it lost almost all of its activity. The more a drug is bound to these proteins, the greater the loss in anti-HIV activity.

The amount of these proteins is:
- higher in HIV-positive than HIV-negative individuals,
- lower among people with cirrhosis (a liver disease caused by the loss of functioning liver cells) as the liver produces these proteins,
- higher during periods of inflammation, and
- different between genders and among ethnicities.

This has been an area of intense debate among the pharmaceutical companies developing drugs because you can get very different results on anti-HIV activity depending on the amount of protein used in their lab experiments. As a result, each company claims that its drugs, at least in their labs, are more active against HIV compared to their competitors.

Commentary

There’s a strong likelihood that advances in the field of pharmacology can result in greatly improving patient management by optimizing anti-HIV drugs as well as reducing the risk of side effects. TDM may provide another piece of useful information—along with CD4+ cell counts, viral load and resistance testing—that can help assess the effectiveness of an anti-HIV regimen. However, many issues still have to be worked out before TDM can be used as part of routine care.

Much research still has to be done to fully understand how drugs interact with certain genes in our bodies and what impact this has on anti-HIV activity. Also, there needs to be an agreed upon standard for lab tests to measure this activity. Ultimately, only head-to-head studies of these drugs involving large numbers of people can determine whether one is more effective than another.