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in this issue

The first of this year's major scientific conferences - the Conference on Retroviruses and Opportunistic Infections (CROI) held in Los Angeles in February - suggests that the more we learn about HIV and the drugs used to treat it, the more we need to know.

For example, we used to think that anti-HIV drugs were the 'cause' of the increased numbers of heart attacks that some HIV-positive people have been experiencing in the past few years. Last year's SMART study, however, suggests that it's not just the drugs, but HIV (or at least stopping anti-HIV drugs) that increases the risk.

Until CROI, we assumed that lipoatrophy (fat loss in the face and limbs) was due to nucleoside analogues, notably d4T and, to a lesser extent, AZT. Now we discover that efavirenz (*Sustiva*) may play a role, since the risk of lipoatrophy doubled in those taking it no matter which nucleoside they also took.

It's important not to panic when new information comes in about drug side-effects because they may be contradicted by the next study. After all, if we've learned one thing in a quarter of a century of HIV disease, it's this: in the end, HIV is much more harmful than any anti-HIV drug.

page 3 In this month's *Upfront*, we highlight recent studies examining the links between HIV and some cancers, and suggest some things you can do to reduce the risks.

page 4 Do your anti-HIV drugs 'play well with others'? asks Derek Thaczuk in our main article on *Drug interactions*. He talks to Heather Leake Date, Principal Pharmacist for HIV and Sexual Health at Brighton and Sussex University Hospitals, about the challenges of drug interactions and how best to deal with them.

page 9 In *Measuring drug levels*, Heather Leake Date explains about therapeutic drug monitoring (TDM), and who might benefit. There are also some real-life examples to illustrate that although TDM isn't a routine test, it can help in certain situations.

page 12 In a special four-page *News in Brief*, we focus on some of the most important studies presented at the recent CROI. Promising new data were presented on several new drugs, including those for people who have HIV that is resistant to some or all currently approved drugs. Also featured is a report on a study that found a surprising link between efavirenz (*Sustiva*) and lipoatrophy.

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aids treatment update

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staying well with hiv

by Edwin J Bernard

In the UK and other rich countries, we're now expected to live more or less a normal lifespan - as long as we are diagnosed with HIV early enough to benefit from anti-HIV drugs, and can take them regularly and on-time for the rest of our lives. And when we do eventually die, it's not likely to be of AIDS - we're more likely to succumb to liver or heart diseases or to cancers that have not been associated with HIV in the past. Several new studies presented at the Fourteenth Conference on Retroviruses and Opportunistic Infections (CROI) held in Los Angeles in February provide us with some explanations as to why this is so - and what we can do about it.

Smokers triple their cancer risk

Last year, an *ATU* cover story (*ATU* 159, Sept/Oct 2006) explained that HIV-positive smokers were much more likely to die sooner than HIV-positive non-smokers. Now two more studies suggest that there are compelling reasons why people with HIV should stop smoking.

The D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study team reported that deaths from non-AIDS-defining cancers were now more common than deaths from AIDS-defining cancers. The four most frequently reported fatal non-AIDS cancers were lung cancer (20% of cases); cancer of the gastrointestinal tract, such as stomach or liver cancer (13%); cancers of the blood and lymphatic system, such as Hodgkin's lymphoma (7%); and anal cancer (7%).

When they investigated the factors that put people at risk for these cancers they found that current tobacco smokers were three-times more likely to die of cancer, notably of the lungs.

A second study, undertaken amongst gay men in Germany, found that smoking increases the rate of human papilloma virus (HPV) reproduction. The association between smoking and HPV viral load was particularly strong in men who had been infected with anal cancer-associated HPV (types 16 and 18) but had not yet developed precancerous changes, suggesting that smoking may possibly speed the development of anal cancer.

In addition, the D:A:D study found that people with active hepatitis B virus infection doubled their risk of liver cancer-related death.

CD4 counts matter

We've known for a long time that an HIV-positive person was more likely to develop an AIDS-defining illness when they had low CD4 counts. That's why anti-HIV therapy is effective in preventing AIDS: it raises CD4 counts.

The D:A:D study is the largest study so far to show that this is also the case for the cancers that haven't traditionally been linked to AIDS. It found that the relative risk of dying from either AIDS-defining or non-AIDS-defining cancers increased gradually as CD4 cell counts fell.

These results agree with data from another study presented at CROI. The FIRST study found that lower CD4 cell counts in people on anti-HIV

therapy were associated with an increased risk of developing non-AIDS-defining cancers.

Is it ageing?

In the D:A:D study, the overall risk of both types of cancer was higher amongst older individuals, but the risk of non-AIDS-defining cancer increased more steeply than that of AIDS-defining malignancies with every additional five years of age.

However, Jason Baker, lead author of the FIRST study, told the conference that becoming ill even when HIV is well controlled by anti-HIV drugs isn't just about ageing. "The fact that it's associated with CD4 level starts to build the case that these people aren't just getting these illnesses because they're living longer."

Dr Baker suggests that starting treatment at higher CD4 counts - which would reduce the risk of ever having low CD4 cell counts - might be the solution for people who haven't yet begun anti-HIV treatment.

Three basic things

However, for those of us already on anti-HIV treatment, these studies (and the SMART heart disease study reported on page 2) suggest there are also three basic things we can do to reduce the risk of becoming seriously ill.

- Stop smoking.
- Get treated for, or vaccinated against, hepatitis B.
- Don't interrupt anti-HIV treatment. ■

drug interactions

do your anti-hiv drugs
'play well with others'?

by Derek Thaczuk



As the number of approved antiretrovirals (anti-HIV drugs, or ARVs) increase, so do our HIV treatment options. However, as the number of possible drug combinations multiplies, so do the potential complications - not just from the individual drugs themselves, but in the ways that they combine with other drugs.

For example, one drug can often have a direct effect over the way another drug works, and this has to be taken into account when planning a treatment regimen. Consequently, along with all the other considerations for choosing the right treatment for you - such as potential side-effects, dosing frequency and pill count - a drug's ability to 'play well with others' is also a crucial factor.

In this expert interview, we speak to Heather Leake Date (HLD), Principal Pharmacist for HIV and Sexual Health at Brighton and Sussex University Hospitals, about the challenges of drug interactions and how best to deal with them.

ATU: Let's start with some background on drug dosing. Why is getting it right so crucial?

HLD: In order to keep HIV under control, it's very important to take the correct doses of each antiretroviral medication, all of the time. People who take antiretrovirals are generally quite well aware of that; it's certainly something we stress a lot. The reason is to constantly keep drug levels within the right range within the body - neither too high nor too low.

Each of your medications has what's called a 'minimum effective concentration' - the absolute minimum you always need to have circulating to keep the virus under control. Dosages and schedules are based on keeping levels above that minimum amount. That's why we stress adherence - taking meds at the right dose in the right way at the right time.

However, you also have to avoid getting too high a concentration of drug in your bloodstream. That's usually not a good thing either - it can increase the toxicity and side-effects of the drug, sometimes dangerously so.

ATU: How can drug interactions complicate that picture?

HLD: The term 'drug interaction' refers to anything that interferes with how a drug works. That might be another medicine you're also taking, or a herbal medicine, or a recreational drug. In some cases interactions can even happen with food. Interactions can make the bodily levels of drugs go up or down, neither of which is desirable.

Let's say you're taking lopinavir/ritonavir (*Kaletra*), for example, plus another treatment such as efavirenz (*Sustiva*) that could potentially reduce the levels of lopinavir. If this were to happen, you'd be taking the doses correctly but your body would process the lopinavir more quickly, and you could end up with lower levels. If the lopinavir levels in your body were lower than the 'minimum effective concentration', you could end up with HIV becoming resistant to the medication, even though you've been taking it right, unless you correct for the difference (for example, by increasing the dose of *Kaletra*). This is a situation where therapeutic drug monitoring (TDM) can be useful. (For more on this see *Measuring drug levels* on page 9)



Another example is taking the herbal product, St. John's wort, alongside protease inhibitors (PIs) - such as *Kaletra*, atazanavir (*Reyataz*), fosamprenavir (*Telzir*), or saquinavir (*Invirase*) - or non-nucleosides (NNRTIs) - such as efavirenz or nevirapine (*Viramune*). St. John's wort can potentially reduce the levels of PIs and NNRTIs, which could lead to them no longer working effectively.¹

The other scenario is drug interactions that can increase drug levels. That's really only a concern if the drug has what's called a 'narrow therapeutic window' - in other words, only a small difference between an effective level and a toxic level. With many medications, there's a wider 'window' than that - you can get higher levels without that necessarily being a problem. It may even be desirable for some drugs that may not be absorbed very well, in order to get more effective levels at lower doses and reduce the number of tablets that you need to take.

Concern over interactions causing increased drug levels is frequently a consideration with PIs that use a mini boosting dose of ritonavir. Ritonavir slows down a key chemical process in the human liver, responsible for clearing many drugs out of the body. Taking any drug that relies on this pathway with ritonavir results in much higher levels of that drug in the body. So, if it is taken with a lipid-lowering medication called simvastatin (*Zocor*), ritonavir increases the simvastatin to much higher levels, which greatly increases the risks of potentially serious side-effects occurring.

ATU: Which drugs are the most likely to cause interactions?

HLD: In HIV care, interactions are most likely with PIs and NNRTIs. Those drugs are metabolised (i.e. processed) by certain liver enzymes, and are particularly susceptible to the effects of other drugs. They can also affect how efficiently those liver enzyme systems work, affecting the levels of other drugs.

One particular liver enzyme, called cytochrome P450 3A4 (CYP3A4 for short), is responsible for the processing of most of the PIs and some of the NNRTIs. Some drugs increase the action of the enzyme and therefore increase the speed at which the drug is broken down and so reduce the drug levels, whereas others do exactly the opposite by inhibiting the enzymes, leading to increases in the drug levels. So anything that affects how that enzyme functions - which quite a few medications do - can cause interactions. All of the examples of interactions that I've mentioned so far involve CYP3A4.

ATU: How do you account for drug interactions when managing someone's treatment?

HLD: If a drug has problematic interactions, there may be alternatives - other medications that do the same job, but don't have the same interactions. Ideally you'd use the alternative that's least likely to cause problems. For example, if someone on a PI needs a lipid-lowering medication we will avoid simvastatin and choose another medicine from the same family that does not interact so significantly with ritonavir.

But sometimes that's not possible. In many cases we'll have studied the interaction enough to know how to adjust the doses - you may simply be able to take a different dosage, whether higher or lower, to get the same effect.

Now, in some cases, we may not have enough information to be sure what's going to happen. Sometimes, we can then actually measure drug levels in your bloodstream to see what's happening and make sure that we're getting enough of the medication on board.

(For more on this see *Measuring drug levels* on page 9)

However, there are two different kinds of interactions: pharmacokinetic (PK) and pharmacodynamic. PK is the way medications are handled by the body: how they get absorbed, processed, and eliminated. PK interactions, then, are anything that influences those things.

Those are the kinds of interactions that can be measured (and are what we've talked about so far).

On the other hand, pharmacodynamic interactions are not about drug levels *per se*, but about similar or overlapping medication effects. For example, sildenafil (*Viagra*) causes a blood pressure drop. Therefore, any other drug with a similar effect, such as poppers (inhaled nitrates) - can cause a profound drop in blood pressure if used at the same time as *Viagra*. That's why combining the two can be dangerous and is not recommended. Another example of where we generally avoid combining two different drugs with similar toxicities is with ddI (*Videx EC*) and d4T (*Zerit*), both of which can cause peripheral neuropathy - nerve pain in the feet, legs or hands.

ATU: Not taking drugs 'at the same time' can mean different things to different people. Can you explain whether this means that you can take them at different times of the day or not at all?

HLD: Actually, it can mean either: some drugs should not be taken close together in time; others should not be taken at all if you are taking an interacting drug. It depends on the drugs.

For example, take atazanavir (*Reyataz*) - a drug which needs stomach acid to be absorbed. There are two kinds of medicines that work to reduce stomach acid. There are short-acting antacids, like *Gaviscon*, which should not be taken within two hours of atazanavir. In other words, it's okay to take *Gaviscon* if you are on atazanavir as long as you take them at separate times.

Then there are other kinds of stomach acid suppressors - H2 antagonists such as ranitidine (*Zantac*) and proton pump inhibitors, such as omeprazole (*Losec*). These have 24-hour action and should not be taken at all if you are taking atazanavir (unless your HIV doctor/pharmacist has advised you otherwise). Atazanavir levels can be

reduced by 75% if you are taking a proton pump inhibitor.

ATU: You've mentioned a few specific examples like simvastatin and St John's wort. How widespread is the potential for drug interactions with ARVs?

HLD: First of all, there are the potential interactions between prescription drugs. We can keep a closer eye on that when we're actually dispensing all the drugs at the same pharmacy. But sometimes drugs like *Viagra* can be obtained via the internet or bought in a club. Ritonavir also boosts the levels of these drugs, so you end up with a higher level that stays in the body longer. That may sound like a good thing, but it can be dangerous to have such high levels of *Viagra* in the body for so long - it can cause side-effects relating to the heart and blood pressure. In fact there's been a case report of a 47 year-old man who died of a heart attack taking *Viagra* alongside ritonavir.²

If we know you're taking the two drugs together we can make dose adjustment recommendations, for example starting off with a very low dose - no more than 25mg of *Viagra* within a 48 hour period - and being particularly vigilant for side-effects.

There are also non-prescription 'over-the-counter' medications - which includes things you may not think of as 'medicines'. A classic example is a steroid called fluticasone. It's found in some nasal sprays and inhalers used to treat asthma and hay fever (the three most common brands are *Flixonase* nasal spray, *Flixotide* inhaler, and *Seretide* inhaler). People don't often think of these as likely to interact with their ARVs, but in fact they are metabolised by the same CYP3A4 enzyme. So if you're also taking ritonavir (or *Kaletra*, which includes ritonavir) you can end up with worryingly high fluticasone levels, which can adversely affect your body's production of certain hormones.

Even food and nutritional supplements have the potential to cause

interactions. Fortunately, most of today's HIV treatments don't generally interact with food. However, there are certain drugs, such as tipranavir (*Aptivus*) or nelfinavir (*Viracept*), that still need to be taken with food and ddI (*Videx EC*) should be taken on an empty stomach. Years ago, there was a fashion for using grapefruit juice to help boost the levels of saquinavir, but nowadays there's no particular need for someone on HIV treatment to either seek out or avoid grapefruit juice (because low dose ritonavir is a more reliable 'booster').

However, when it comes to nutritional supplements and herbal preparations, those can be more significant. For example, we don't think that eating garlic in food is a big issue, but a study showed that high dose garlic capsules had an effect on saquinavir levels³, so we advise people not to take those. There's also St. John's wort, as we mentioned, and there are others we know may be of concern.

ATU: That covers quite a bit of territory. If there's potential for so many problems, how can people avoid these problems in a practical way, without constantly worrying?

HLD: First of all, your pharmacy will only be aware of the medicines that they themselves supply, unless you tell them otherwise. So, if you're getting medicines from more than one place, it's important to inform your doctor or your HIV pharmacist. The kind of things they'd like to know about include not just the things that your GP or dentist might have prescribed, but also medicines or supplements that you buy from the supermarket, high street chemist, or health food store, as well as





recreational drugs. And don't forget to tell them about inhalers and other things that you might use occasionally or at certain times of the year!

ATU: In North America people are often recommended to have a 'brown bag' check-up, where you periodically scoop the contents of your medicine cabinet - prescription, over-the-counter and any other drugs - into a bag, and show it to your HIV pharmacist. Is that a good idea?

HLD: Yes, I think there are different situations where that makes sense. You certainly don't have to do it every month, but if you are just about to start a new medication of some sort, and you're going to the clinic, it would be useful to bring along your medications or to make a list. Some people might find an annual 'medicines MOT' would be useful. Talk to your HIV pharmacist to find out if they can offer this service.

ATU: Many patients may be reluctant to talk about their use of recreational drugs, not only because they're illegal but also because they might be unwilling to admit to doing "bad things" to someone they think will judge them. Do you have any advice?

HLD: Healthcare providers certainly won't recommend or encourage you to take any illegal or potentially harmful drugs - both because of the illegality, but also because you don't know exactly what's in them (you could easily end up taking a drug that contains something unexpected, so we

might not be able to predict the outcome). We can certainly tell you what we know or don't know about any given recreational drugs. We're not going to advise you to go ahead and take them, but we could have suggestions on how to reduce the risk that might be associated with them. We're not there to police you or to pass judgment; the idea is to give you information so you can make an informed decision. And we can only do that if we know what it is that you are taking or planning to take - so I would definitely say that honesty is the best policy!

ATU: What 'take home' messages can you provide? What should concern us, and what should we do about it?

Ordinary vitamins and minerals are generally fine to take with anti-HIV drugs. Most everyday drugs, such as paracetamol or ibuprofen, are also absolutely safe. However, if in doubt, it's always best to check.

Remember, though, most 'one-off' drug interactions are generally not going to be too significant. Although they can occasionally be serious, generally if you just take something once it's not a reason to worry too much.

However, if you're taking anything regularly alongside your anti-HIV drugs, it's sensible to check with your HIV pharmacist - even if, like the inhalers we discussed earlier, it's something you might not generally think of as a 'medication'. And if you notice any new or changed symptoms that you think could be due to combining medications, do let your HIV doctor or pharmacist know.

Further information

You can search www.aidsmap.com to learn more about the specific drugs, herbs and other medicines mentioned in this article.

The University of Liverpool produces an excellent drug interaction website, with customised drug interaction charts: www.hiv-druginteractions.org

The site can be difficult to interpret, however, so ask someone on your HIV clinic team if you're not sure what the results mean.

measuring drug levels



In *Drug interactions*, HIV pharmacist Heather Leake Date explained that it is possible to measure drug levels in the blood in order to assess whether interactions between different anti-HIV drugs are resulting in unusually high or low levels. This is known as therapeutic drug monitoring, or TDM.

However, drug interactions aren't the only reason that drug levels may be unusually low or high.

Once swallowed, anti-HIV drugs pass through the digestive system where they are absorbed into the blood stream and distributed throughout the body. The rate at which they are absorbed varies between individuals. This means that if two people take identical treatments at the same doses and with the same foods, the amount of drug that will reach their blood streams can be very different.

To a certain degree, this variability is unimportant. In order to be effective against HIV, antiretrovirals must reach a level in the blood that falls within a range that is established when new drugs are first developed. A blood level which is higher than this 'therapeutic range' can lead to more side-effects. A lower level will allow ongoing HIV replication, which provides the circumstances for drug resistance to develop, causing the treatment to fail.

Drug levels reach their peak soon after they are taken, and then taper off over the subsequent hours to a lower 'trough level' before the next dose. It is this trough level which is likely to be pivotal in determining a drug's potency and effectiveness.

On the other hand, high concentrations of certain drugs in the blood may worsen the severity of side-effects. Consequently, TDM may be able to check that lower dosages with improved tolerability are still effective against HIV.

TDM has been available in UK clinics for several years. Although it is not a routine test it can be an extremely useful tool to guide treatment choices in certain circumstances. The latest British HIV Association (BHIVA) guidelines note that TDM can be beneficial in situations where drug levels are difficult to predict.¹

These include:

- People experiencing unusual toxicity or side-effects on standard anti-HIV drug doses.
- People taking unusual anti-HIV drug combinations.
- People on 'salvage' therapy (in combination with resistance test results).
- Women during pregnancy.
- Children.
- People with kidney or liver impairment, or following transplants.

ATU: What does therapeutic drug monitoring actually measure and how useful is it?

Heather Leake Date (HLD): Therapeutic drug monitoring (TDM) can measure the levels of protease inhibitors (PIs) and non-nucleosides (NNRTIs) in a person's blood. We don't measure levels of nucleoside 'backbone' drugs (NRTIs) in clinical practice as it is a more complex procedure. This is because it is NRTI levels in the cells of the body, rather than the blood, that are important, and they are much more difficult to measure.

Although it can be useful in certain circumstances, the exact role of TDM in the HIV clinic has not really been fully established. A few studies from several years ago demonstrated its value in certain circumstances – decreasing indinavir (*Crixivan*) toxicity, or ensuring adequate levels of nelfinavir (*Viracept*) – but neither of those particular drugs are widely used today.

ATU: Is TDM available at every HIV clinic in the UK?

HLD: Most TDM analysis in the UK is done in Liverpool. It is overseen by the Liverpool HIV Pharmacology Group (LHPG), based within the Department of Pharmacology & Therapeutics at the University of Liverpool, but since October 2005 the routine TDM service has been under the direction of a private company, Delphic Diagnostics, with LHPG having an advisory role in the running and development of the service.

Although TDM is available to any clinician who wants it, I suspect most clinicians don't regularly use it as part of their routine practice. At our own centre in Brighton we use it when we think it might be useful (as per the BHIVA guidelines). For example, when the new *Kaletra* tablet formulation became available last year, there weren't really any recommendations for dose adjustments with NNRTIs, so we routinely did TDM on patients who were taking *Kaletra* tablets in combination with NNRTIs. We routinely perform TDM if someone is on two drugs we think are likely to interact.

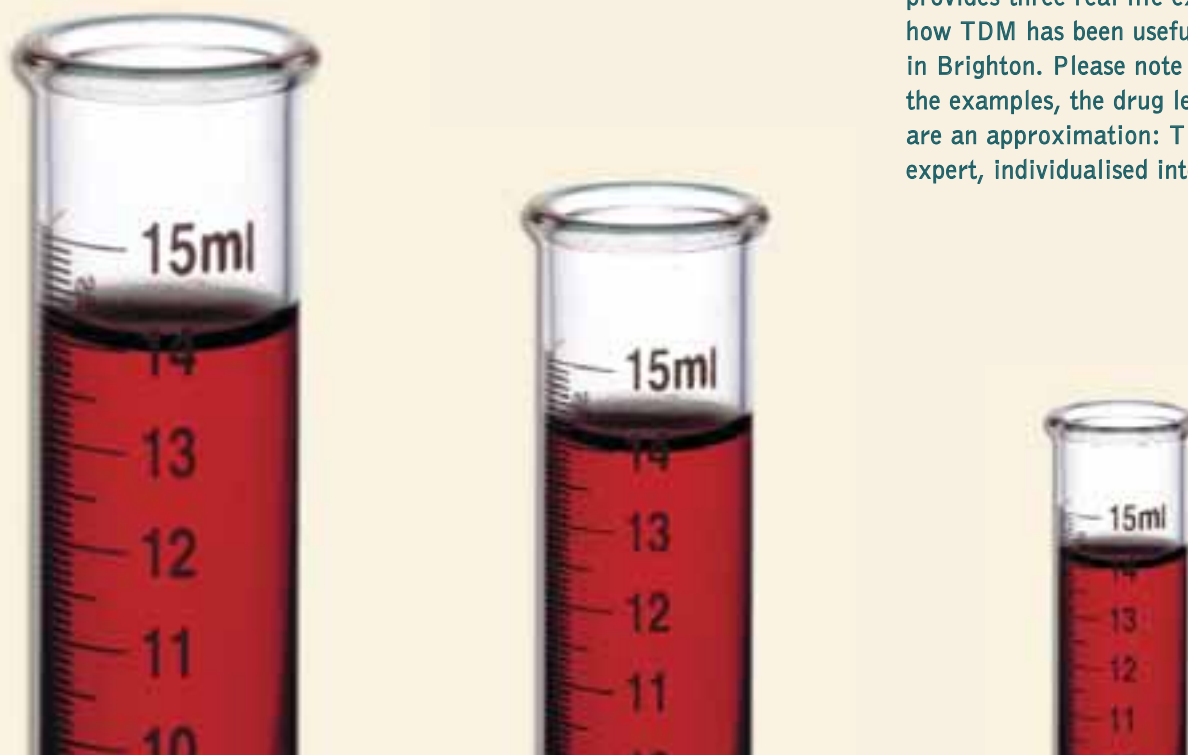
ATU: When is the best time to take blood for TDM?

That's a very good question, and the answer isn't straightforward. We know that drug levels vary, both from patient to patient, and within any one given patient over time. How do we know that a TDM result is accurate and consistent? How do we know we'll get the exact same result at the same time the next day? Actually, we don't: variations in the results are one of the reasons that TDM is not more widely used.

However, when we think TDM will be useful, generally we will take two measurements. One will be immediately before someone is due to take the next dose of the drug(s) being tested, and another will be two hours after the dose. The pre-dose measurement will correspond approximately to the minimum drug concentration in the blood, and the post-dose measurement will correspond approximately to the maximum drug concentration in the blood.

If you are having TDM done, then, it's important to tell the person drawing the blood exactly when your last doses were taken. Even if you usually take a dose at 9am, we'd need to know whether you took your previous dose actually at 9am, or 15 minutes before or after.

On the next page Heather Leake Date provides three real life examples of how TDM has been useful for patients in Brighton. Please note that in all the examples, the drug levels quoted are an approximation: TDM requires expert, individualised interpretation.



using TDM to enable interacting drugs to be used together safely

A patient on ritonavir-boosted atazanavir also required a more powerful acid suppressing medication for symptoms of acid reflux (severe heartburn) because regular antacids (taken at separate times from atazanavir) were not sufficient to resolve the symptoms. Before an H2 blocker (ranitidine) was prescribed (to be taken once daily, two hours after atazanavir, to minimise any interaction), atazanavir TDM was performed. Results showed that the patient had a trough (lowest) atazanavir level of 1500ng/ml (about ten times higher than the minimum required to suppress wild type virus). After a four-week trial of ranitidine the patient's acid reflux symptoms were no better, suggesting that a

proton pump inhibitor (PPI) may be useful. Although combining a PPI and atazanavir is officially contra-indicated (due to a 75% reduction in atazanavir levels), since the patient had such high trough atazanavir levels it was decided to increase the atazanavir dose from the usual 300mg once daily to 400mg (still with 100mg ritonavir) and to prescribe a PPI (omeprazole 20mg once daily, taken two hours after atazanavir). Atazanavir TDM was repeated a week later and the trough level was 1000ng/ml (i.e. still therapeutic) so the patient was able to remain on the PPI for a six-week course, which helped resolve the acid reflux symptoms.

A patient on ritonavir-boosted lopinavir (*Kaletra*) who had been experiencing diarrhoea for several years – which was thought to be related to *Kaletra* capsules – wanted to switch to the new formulation of *Kaletra* tablets, since these may be associated with less diarrhoea. However, the patient was taking *Kaletra* with efavirenz and tenofovir and was on four *Kaletra* capsules twice daily (a higher than usual dose because efavirenz reduces levels of lopinavir). The standard dose of *Kaletra* tablets is two tablets twice daily, but for this previously PI-experienced patient higher lopinavir levels may be required

(above 4000ng/ml, rather than above 1000ng/ml for PI-naive) and so it was thought that a higher dose (e.g. three tablets, twice daily) may be required. Two weeks after the patient started on three *Kaletra* tablets twice daily, lopinavir TDM was performed. The lopinavir trough level was found to be much higher than necessary (8365 ng/ml), so the dose was reduced to two tablets twice daily. A repeat TDM two weeks later showed a still satisfactory trough lopinavir level (5425ng/ml), and the patient found that although the diarrhoea had not completely resolved, it was more manageable.

using TDM to help manage toxicity

using TDM to optimise efficacy

A pregnant woman was taking her first-ever ARV combination – which included *Kaletra* – in order to prevent mother-to-child transmission. Lopinavir TDM was performed at 29 weeks because as pregnancy progresses lopinavir levels in the blood can decrease, due

to an increased volume of blood circulation. Since it was found to be just over the minimum-required trough level (1020ng/ml) it was decided to increase the *Kaletra* dose until the baby was born to ensure levels remained therapeutic for the remainder of the pregnancy.

News from 14th CROI, Los Angeles

February's Conference on Retroviruses and Opportunistic Infections (CROI), held this year in Los Angeles, provided a wealth of information regarding some very promising new drugs, increased our knowledge of how to use current drugs better, and explained more about the causes, of and treatment for lipodystrophy and other drug side-effects. For more details of all these studies - and more - visit NAM's website, www.aidsmap.com.



HIV and illness

Treatment interruptions slightly increase risk of heart disease

Further analysis of the SMART treatment interruption study has found that the participants who were randomised to take CD4-guided treatment interruptions had a slightly increased risk of cardiovascular disease compared with those who remained on anti-HIV treatment.

The SMART study was the largest HIV clinical trial ever, involving close to 6,000 participants in several countries. The study was stopped early after it was found that participants who interrupted their treatment not only had a higher risk of progression to AIDS, but also of serious illnesses including liver, kidney and heart disease.

Researchers from the study have now compared the risk of heart disease between the two arms of the study. A total of 79 cardiovascular events, such as fatal and non-fatal heart attacks, coronary artery disease, and stroke, occurred. There were 48 events in the treatment interruption arm and 31 amongst participants who took anti-HIV treatment continuously. The investigators calculated that the participants who interrupted treatment had a risk of cardiovascular events that was 50% higher than those who did not interrupt. The analysis also found that, of the participants who were on anti-HIV therapy at the start of the study, those taking a regimen that included an NNRTI were over twice as likely as those taking a protease inhibitor to experience a cardiovascular event. But the researchers also found that each additional year of treatment with a protease inhibitor also increased the risk of a cardiovascular event slightly.

Because the number of cardiovascular events in the study was small, the difference between the two arms was of only slight statistical significance. The study's authors noted that while there was "no evidence that interruption immediately increases risk of cardiovascular disease," longer-term consequences remain to be determined. In the meantime, they said, the data suggest that anti-HIV therapy should not be stopped or avoided due to concerns about perceived cardiovascular risk.

new drugs

New NNRTI may compete with efavirenz

Tibotec's investigational NNRTI, TMC278, appears to have the potency of efavirenz (*Sustiva*), but with significantly fewer side-effects, according to 48-week results of a 96-week study of the drug in people new to anti-HIV treatment.

In this study, participants were randomised to receive efavirenz or one of three doses of TMC278, all taken once daily. These were taken alongside AZT/3TC (*Combivir*) or tenofovir/FTC (*Truvada*).

After 48 weeks, there was no significant difference between any of three doses of TMC278 or efavirenz in the proportion of participants whose viral load fell to below 50 copies/ml (between 77 - 81% on TMC278

and 81% on efavirenz). Increases in CD4 cell counts were also broadly similar.

Although there was no difference in the frequency of serious side-effects between the two drugs, participants taking TMC278 were less likely to experience central nervous system or psychiatric side-effects than those taking efavirenz, and the incidence of rash was also lower amongst the TMC278-treated participants. Blood fats (total cholesterol and triglycerides) were also lower in the participants on TMC278.

Slightly higher discontinuation rates for the highest dose (150mg) of TMC278 resulted in the investigators selecting the 75mg dose for further phase III study. If successful, Tibotec is likely to market TMC278 as a direct competitor to efavirenz for first-line anti-HIV treatment.

drug-dosing strategies

Caution over once-daily *Kaletra* or nevirapine

In the UK, it is not recommended to take lopinavir/ritonavir (*Kaletra*) or nevirapine (*Viramune*) once daily, even though some people do take these drugs this way in clinical practice. Two studies at CROI suggest that some people are more likely to have their treatment fail them using these drugs in this way.

A large open-label study sponsored by the US government (rather than Abbott, *Kaletra's* manufacturer) found that taking *Kaletra* (using the old, soft-gel formulation) once daily appeared to be less effective than taking the drug twice a day in participants with viral loads above 100,000 copies/ml when they started anti-HIV therapy for the first time.

And a small study from France that compared once-daily nevirapine with once-daily tenofovir (*Viread*) and once-daily 3TC (*Epivir*) to twice-daily nevirapine with twice-daily *Combivir* (AZT/3TC) was stopped early due to high rates of early virological failure in people taking the once-daily treatments. It's not clear why this was the case, but the study's authors suggest that once-daily nevirapine should not be taken with the combination of tenofovir and 3TC.

side-effects

New treatment safe and effective for bone loss

Bone problems, such as osteopenia, osteoporosis and osteonecrosis, are increasingly being recognised as potential side-effects of anti-HIV therapy. New research presented at CROI suggests that alendronate (*Fosamax*) is a safe and effective treatment for HIV-positive individuals with loss of bone mineral density. This drug is already approved for the treatment of osteoporosis in HIV-negative people in the United States and Europe. No-one taking alendronate reported any significant side-effects, and the drug appeared to work equally well in men and women.



new drugs

Four new drugs show promise for treatment-experienced



Data on three new drugs aimed at people with drug-resistant HIV were presented at this year's CROI, and details of a fourth were released just as *ATU* went to press.

Of the two integrase inhibitors currently in clinical trials, Merck's raltegravir (formerly known as MK-0518) is furthest along. This drug is taken twice a day and cannot be boosted by a 'mini' dose of ritonavir.

Interim results (some from 16 weeks and some from 24 weeks) from the 48-week BENCHMRK 1 and 2 studies showed that twice as many participants who were randomised to receive treatment with raltegravir plus optimised background therapy achieved a viral load below 50 copies/ml compared to those who received a placebo plus optimised background therapy. Participants taking raltegravir also gained between two and three times more CD4 cells than those on placebo.

Considering that the participants were highly treatment-experienced (all had extensive resistance to drugs from the main three classes of antiretrovirals, about 90% had received an AIDS diagnosis, and they had taking antiretroviral therapy for an average of ten years) these data are very promising indeed. Results from the study also showed that the drug was well tolerated, with very few people leaving the study early. Particularly good results were seen for the participants who were able to combine raltegravir with T-20 (*Fuzeon*) and the newest protease inhibitor, darunavir (*Prezista*) - 98% achieved a viral load below 400 copies/ml. However, even 61% of those participants who were taking no other active drugs achieved a viral load below 400 copies/ml.

The conference also heard interim results from a smaller, less advanced study of a second integrase inhibitor, Gilead's elvitegravir (formerly GS-9137 or JTK-303) that can be taken once daily because it is ritonavir-boosted. This study suggests elvitegravir is potent, but only when used in higher doses (three doses were tested and the lowest dose arm of the study was stopped early due to too many people 'failing' treatment) and

lasting, but only when it is combined with at least one other active drug.

"The story here [is that] we have a potent drug, but it is only good if there are other companion drugs available to use with it," the study's lead author, Andrew Zolopa, told the conference.

One of the problems seen with elvitegravir was the emergence of resistance if other drugs weren't used to back it up, similar to what is seen with NNRTIs like efavirenz (*Sustiva*) or nevirapine (*Viramune*). In fact, test tube studies hint that there may be some cross resistance with raltegravir, suggesting that resistance to one drug may mean the whole class will not work, just like NNRTIs.

Interim, 24 week results were also presented on the only chemokine antagonist (also known as CCR5 inhibitors) to reach advanced clinical trials. In these studies, Pfizer's maraviroc was dosed either once daily or twice daily, depending on the other drugs that participants took in the Motivate-1 and -2 studies.

Up to 48% highly treatment-experienced participants who received maraviroc achieved a viral load below 50 copies/ml when the drug was added to an optimised background regimen (compared with 25% or fewer taking a placebo). Participants taking maraviroc also gained almost twice as many CD4 cells as those taking the placebo. Data so far suggest that maraviroc appears to be safe, since treatment discontinuation and disease progression rates were broadly similar between the placebo and treatment arms of both studies.

Finally, promising early results were announced in March by Australian biotechnology company, Avexa. A 21-day study of their new nucleoside backbone drug (NRTI), apricitabine (formerly AVX754), suggests that even in people with high level 3TC- or FTC- resistance, significant viral load reductions are possible. The drug, which is taken twice a day, also appeared to be well tolerated. More details will be presented later this year at the next major HIV conference, the fourth IAS Conference on HIV Pathogenesis, Treatment and Prevention in Sydney, Australia.

side-effects

Efavirenz twice as likely to lead to fat loss as *Kaletra*

The most surprising data to be presented at CROI came from the (non-drug company-funded) ACTG 5142 study, which last year suggested that efavirenz was more durable than lopinavir/ritonavir (*Kaletra*) over two years. This time, it was *Kaletra*'s chance to shine: people taking *Kaletra* with two nucleoside backbone drugs were significantly less likely to experience fat loss (lipoatrophy) than those taking efavirenz with two nucleoside backbone drugs. In fact, participants who took efavirenz were almost twice as likely to experience fat loss in the face or limbs compared to those who took *Kaletra*. Until now, it was thought that fat loss was primarily caused by the thymidine nucleoside analogues (primarily d4T and, to a lesser extent, AZT).

ACTG 5142 was a large, randomised study that compared a nucleoside-sparing regimen of *Kaletra* and efavirenz against *Kaletra* or efavirenz paired with 3TC plus either d4T, AZT or tenofovir. The study was designed to test whether avoidance of nucleoside analogue drugs was effective and safe.

Lipoatrophy (defined as a 20% loss of limb fat at week 96), was experienced by 32% of the efavirenz + two nucleoside group, 17% of the *Kaletra* + two nucleoside group, and 9% of the *Kaletra*/efavirenz group.

Even though participants who received tenofovir were less likely to experience lipoatrophy compared to those receiving d4T or AZT, when

lipoatrophy incidence was analysed according to pairings of drugs, participants on tenofovir who also took efavirenz were twice as likely to develop lipoatrophy (12%) than those who received *Kaletra* (6%).

Similarly, AZT recipients who took efavirenz were also at greater risk of lipoatrophy (40% versus 16% for *Kaletra* recipients). The difference was less pronounced for d4T recipients (51% for efavirenz, 33% for *Kaletra*).

The study's authors concluded that efavirenz recipients had, on average, a 2.7-fold higher risk of lipoatrophy compared to *Kaletra* recipients when both were taken with two nucleoside backbone drugs.

Lead author, Richard Haubrich of the University of California, San Diego, told the conference that treatment guidelines would now need to take into account the effects of different regimens on body fat distribution.

However, Judith Aberg, of the ACTG told US HIV information website, 'The Body', that it was too early to come to any firm conclusions regarding efavirenz's link with lipoatrophy. "I don't want people to think because they see this that they shouldn't be using efavirenz," she said. "That's the wrong message. People need to take a step back. We need to figure out what's going on...before we make any further comments about it."

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