

3rd International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV

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Cause & effect

Every conference must have its buzzword, and the favoured theme for this workshop was “multifactorial”. As in: “The causes of HIV drug-related metabolic disorders are likely to be multifactorial.” There was as much time at the workshop spent debating and discussing the causes of some common adverse drug reactions as there was considering their clinical management and significance, though happily, there was due recognition from all present – including the basic scientists — of the importance of exploring clinical implications.

In the several years since the emergence of metabolic problems as a result of anti-HIV therapy, basic scientists have been working to unravel the mystery of why these drugs should cause a range of problems ranging from fat accumulation on the breasts, belly or neck, to severe fat wasting of face and limbs; elevated triglycerides and cholesterol levels; insulin resistance sometimes leading to diabetes; and some rarer but potentially life-threatening conditions such as lactic acidosis.

A number of theories have been proposed which may explain some of these problems. It was Kees Brinkman, at the first of these workshops, who identified mitochondrial toxicity (damage to the crucial ‘energy centres’ of cells) as a likely candidate for setting off a train of metabolic anomalies which might lead, eventually, to wasting, myopathies (muscle damage), neuropathies (nerve damage), and lactic acidaemia.

Research presented at this workshop did confirm that anti-HIV drugs — in particular, the nucleoside analogues — certainly do damage mitochondrial DNA (both alone but particularly in combination). But it is the way of grand explanatory narratives in all disciplines (cosmology, philosophy, politics, biochemistry ...) that they do not account for all aspects of a puzzle. In this the mitox theory is no different. While there’s broad (though not unilateral) agreement that the decrease in mitochondrial DNA is related to the development of fat wasting, the relationship is far from one of uncomplicated cause-and-effect. Further, mitochondrial damage or depletion does not necessarily account for a series of other HIV treatment adverse effects, such as raised blood fats, hypersensitivity reactions, or insulin sensitivity and glucose intolerance. Blood fat and sugar changes are in any case associated with the use of protease inhibitors, and much of the conference was dedicated to an exploration of how and why these phenomenon occur, and usefully, how might they be avoided. It was stressed that metabolic changes associated with

HIV drugs are likely to be “multifactorial”, a shorthand (if a slightly inelegant one) signaling there may be a range of biochemical triggers and changes which lead to these problems. No one cause is likely to be responsible (which makes finding a ‘solution’ harder – apart from developing less toxic drugs), and it is apparent that, when drugs are used in combination and across classes, some of these effects may be worsened.

Following is an exploration of some of the adverse effects which were discussed, with a comment on drugs, causes and possible ways to ameliorate these problems.

Insulin sensitivity & glucose intolerance

One of the most curious and worrying effects of protease inhibitors has been the emergence of glucose intolerance, which can, in some cases, lead to or put people at risk of developing diabetes.

Background:

Glucose is a simple sugar found in the blood, and is the body’s main source of energy. Insulin is a hormone produced by cells in the pancreas, called beta cells, which allow the body’s cells to use glucose as a source of energy.

However, sometimes, the body is unable to handle glucose properly, because either the body is not producing enough insulin (as happens with childhood onset diabetes), or the body is not responding to the action of the insulin — a situation called insulin resistance. Insulin resistance can lead to diabetes, a situation where there are elevated levels of glucose in the blood or urine (hyperglycaemia), as the body is not metabolising it properly. If low insulin levels or insulin resistance prevent the body from using glucose as a fuel, the body – its cells effectively starved of energy — will attempt to find alternative sources of fuel, such as stored fats. Effects of long-term high blood glucose levels can include damage to the kidneys, nerves and heart and leave individuals open to a higher risk of cardiovascular disease.

Sometimes, people have a condition called impaired glucose tolerance, where blood glucose levels may be higher than normal, but are not high enough to be classified as diabetes. Insulin resistance therefore does not mean a person has diabetes — but it can be an important marker of a person being at risk of developing this condition. One of the problems identified in some HIV positive people using combination antiviral treatments includes high blood sugar levels and impairment of glucose tolerance. This may put some people at real risk of developing diabetes, especially when other risk factors are present (such as weight gain or ageing). Some cases of diabetes have been identified, associated with combination therapy.

Effect of PIs on glucose tolerance

- The effects of **indinavir** on insulin resistance may be acute. (MA Noor et al, Abstract 3). In this study, a standard dose of indinavir versus a

placebo was administered to six HIV negative men, and their glucose tolerance was measured. Compared to placebo, the men receiving indinavir had rapid rises in blood insulin. This also correlated with another study (Hruz et al, Abstract 2), which looked at glucose tolerance in rats. In rats, the effect of indinavir on glucose tolerance was acute, but reversible: as indinavir levels dropped and the drug passed from the rats' bodies, normal glucose disposal resumed. Both of these studies theorised that indinavir may "blockade" a key glucose transporter in some way, interfering with normal glucose metabolism.

- Michael Dube et al (Abstract 14) found that unlike indinavir, **amprenavir** did not cause similar, short-term insulin resistance and high blood sugar. However, amprenavir did appear to cause morphological changes, including weight gain in the stomach and other areas. Insulin resistance did appear later in some of the amprenavir-treated patients, following weight gain, and about six months into therapy. Amprenavir, Dube told the conference, behaves more like ritonavir than indinavir in this regard.

Clinical implications

- You may not have to take indinavir for a long time to get insulin resistance/blood sugar problems. Though the effect of indinavir appeared short-term and reversible, in that glucose tolerance normalised when drug was out of the body, the cumulative effects over time could explain sustained blood sugar changes & onset of diabetes associated with PI use?
- If insulin resistance is associated with the peak levels of indinavir in the blood, but appears normal when indinavir is at trough levels, is all insulin resistance being identified in clinical practice? Some questions were raised from the floor about what this meant for the best time to measure glucose tolerance in people using PIs, to get a true picture of how PI treatment may be affecting glucose tolerance.
- As the effects of indinavir on blood sugar may be dose-dependent effect (the higher the dose of indinavir the greater the effect), testing drug levels in individuals (therapeutic drug monitoring) may have a role, to ensure people are getting the maximum level of indinavir exposure with the minimum risk of acute insulin resistance.
- What is the overall impact of PIs in combination?

Other drugs or causes?

- People with lipodystrophy may have insulin resistance in the **liver (hepatic insulin resistance)**. (SB Haugaard et al, Abstract 5). This may correlate with increased visceral fat (fat accumulation on the belly etc), but in this study – which only looked at men – wasting did not have the same relationship. Since protease inhibitors are associated with accumulated fat and nucleosides with fat wasting, it also suggests that the mechanisms of each class of drug might be

operating differently on the metabolism. This study could not associate hepatic insulin resistance with any particular drug or time of treatment, however. Kevin Yarasheski (Abstract 6) also noted that in his work, they found impaired hepatic glucose tolerance in people with HIV even when they did not have insulin resistance in standard blood glucose tests, or diabetes.

- Could problems with **fat metabolism** be a cause of insulin resistance in people with lipodystrophy? Hadigan et al (Abstracts 7 and 8) found that HIV positive people have increased rates of lipolysis, and increased levels of free fatty acids in the blood. Lipolysis is the process by which fats in tissue are split up and broken down into their constituent fatty acids, and released into the blood. High levels of free fatty acids in the blood can be dangerous, especially in people who already have heart disease. The researchers thought that unusually increased rates of lipolysis/fat breakdown and release in HIV-associated lipodystrophy might also signal broader metabolic disturbances, and could also contribute to insulin resistance. They theorised: if you could slow down or inhibit the process of lipolysis and the release of fatty acids, you could also improve insulin sensitivity. They compared insulin resistance (in HIV positive people with lipodystrophy) where people were given either placebo, or a drug called acipimox, and anti-cholesterol agent, which inhibits lipolysis. The acipimox led to a reduction in lipolysis and free fatty acid levels, and subsequently improved insulin sensitivity. The authors thought long-term strategies to reduce FFA concentrations could therefore improve metabolic disturbances associated with HIV lipodystrophy.

A combination of factors?

- At least one study found the causes of impaired glucose tolerance were probably several (KA Yarasheski et al, Abstract 6). Glucose intolerance in HIV positive people was associated with: a) insulin resistance; b) insufficient secretion of insulin from an important kind of pancreas cell called a beta-cell; c) a longer time on antivirals, and d) insulin resistance in the liver.

Blood fats: cholesterol, triglycerides & heart disease risks

Is the much-talked about potential epidemic of HIV drug-related heart disease necessarily a time-bomb waiting to go off?

Heart disease: are HIV treatments a risk?

There's been much speculation recently about whether we are on the verge of an epidemic of cardiovascular disease among HIV positive men on treatments. Vincent Mooser (Lausanne), explored this question.

According to Mooser:

The major risk factors for heart disease are still the major risk factors, even in HIV. These are:

- Smoking
- Age
- Hypertension and hardening of the arteries

HIV and its treatment does pose an additional risk, due to the presence of chronic inflammation, and also due to the ways in which some treatments interfere with blood fats and cholesterol.

Mooser's epidemiological modeling showed, however, that while HIV and its treatment *per se* were not sufficient in themselves to drive an epidemic of heart disease, if you were to add in additional risk factors: smoking (of which there are high levels among pos people), and age, the risk of a cardiovascular "event" is dramatically increased. In HIV negative populations, risk of cardiovascular disease rises threefold with increased age, and smoking can push this up to an almost 1 in 2 risk. The average number of risk factors which a person has when they develop heart disease is two.

Mooser concluded with the following observations:

- clinicians should consider "general" risk factors – smoking, hypertension, family history, in pos people as well, and manage these risk factors as a priority;
- there is limited evidence that switching treatments is of benefit;
- there is limited data on use of diet and exercise;
- consider use of statins (cholesterol lowering medications), particularly in people with a higher number of risk factors.

Clinical implications:

- Smoking is bad news, especially where there are other risks.
- Lipid lowering medications may have a role.
- Diet and exercise may not be the answer alone, but they may reduce overall risk.
- Age needs also to be thought of as a risk factor.

Is it a particular risk for women?

In general, due to the protective effect of certain hormones, women are considered at lower risk of heart disease, at least until post-menopause. However, there was one particular poster (Grinspoon et al, Neuroendocrine Unit, Massachusetts General Hospital, Abstract 125), which did suggest that women with HIV lipodystrophy may be at increased risk of developing some markers for cardiovascular disease. The authors theorised this could be so in part because fat accumulation around the belly, common among women with HIV who have lipodystrophy, is precisely one of a number of factors ordinarily associated with risk of problems such as heart disease and diabetes. This poster found positive women with lipodystrophy are at increased carotid intima-media thickness (the carotid artery is an artery in the neck and thickness of the wall can be used as a marker of cardiovascular disease risk). In the positive women with lipodystrophy, their carotid IM thickness was

comparable at the age of 45 with that of HIV negative women at 55. Relationships were found between this thickening, and age, blood pressure and insulin levels. However, the authors said further research would be needed to conclude “more definitively” whether women with HIV and lipodystrophy are at increased risk of stroke or heart attack. No relationship with any particular treatments could be identified, but the poster did imply that women with lipodystrophy may at least wish to be aware of the potential increased risk, and discuss with their clinicians any other risk factors which may exacerbate this.

What about the lipid-lowering drugs?

A couple of researchers (Martinez et al, Abstract 29; Visnegarwala et al, Abstract 30) looked at the effects of standard lipid-lowering drugs to see if they were of any benefit with HIV-associated lipodystrophy, or elevated blood fat levels in HIV.

- Martinez found that neither metformin nor gemfibrozil (two common lipid-lowering drugs) had any real effect on the reduction of fat-accumulation lipodystrophy, particularly in women. The study argued on the basis of this “negligible” effect, their study did not support the use of either gemfibrozil or metformin as a treatment for HIV lipodystrophy. There was some discussion following this presentation as to whether the study was sufficiently powerful to support the rather emphatic conclusions, given the study’s limitations. In addition, some people felt that there were questions from the floor about the tools which the study had used to define lipodystrophy, and how valid they truly are.
- The Visnegarwala study looked at a different question. Using observational data collected from a database, and a referral clinic specialising in metabolic treatment, they retrospectively evaluated the effects of lipid medications on controlling high blood fat and cholesterol levels in people with HIV. There are two main kinds of drugs used to lower lipids: statins (which include common drugs like atorvastatin); and fibrates (which include gemfibrozil). In this analysis, people with HIV had mixed responses to these drugs, both separately and in combination. There was a variety of responses, with some people managing only to lower their triglycerides, and others managing only to lower cholesterol. In the end, the researchers suggested:
 - the effects of lipid-lowering medications in the context of HIV are modest;
 - fibrates, used with or without statins, did appear to have better results, and “may be an appropriate first-line management strategy”;
 - statins, used alone, may have little effect;
 - although it is unclear whether standard lipid management guidelines alone are useful for management of HIV blood-fat problems, dietary

interventions may be especially important for patients with very high baseline cholesterol and triglycerides;

- having high baseline cholesterol/triglycerides suggested less likelihood of a good response to these drugs.

Perhaps most arrestingly, when a number of factors were considered to see if they predicted a good response, ONLY **stopping PI treatment** was a statistically significant predictor.

Once again, there were some comments about this study — mainly to the effect that future studies should standardise and evaluate the effects of non-pharmaco interventions (diet, exercise), to more clearly distinguish their effects from those of the drugs. It should also be noted that the beneficial effects of statins on cardiovascular risk cannot be explained by their lipid lowering effect alone – therefore even though they don't normalise lipids, they may still be of benefit.

Blood lactates; lactic acidaemia/acidosis

Should people with HIV be worried about the risk of lactic acidosis?

Background:

Lactic acidosis is caused by very high levels of lactic acid in the blood. Lactic acid is produced in the body as a by-product of the processing of sugars, and at very high levels, can be dangerous. Lactic acid forms in the cells when the body's cells can't keep up with the demand for energy (eg. if you're exercising really vigorously, or in shock). It is high lactic acid levels in the blood which can make you vomit when doing vigorous exercise.

Elevated blood lactates are certainly seen in HIV positive people, but its manifestation as lactic acidosis is generally considered rare. It is thought lactic acidosis is one of several conditions caused by damage to mitochondria, and it has been broadly associated with the use of the nucleoside reverse transcriptase inhibitors (AZT, d4T, 3TC, ddI, ddC, abacavir).

You can test for elevated blood lactates, but there is really a great deal of debate about what this tells us about a person's risk of lactic acidosis.

Symptoms of lactic acidosis are also non-specific, which may make identifying the condition acutely difficult. Symptoms can include:

- gastrointestinal pain;
- bloating;
- vomiting;
- shortness of breath;
- malaise (feeling extremely lethargic).

What does lactate testing tell us? Which drugs are a problem?

In what was certainly one of the most interesting presentations at the workshop, Graeme Moyle (Moyle at el. Chelsea-Westminster Hospital;

Abstract 98), explored the relevance of lactate testing in clinical practice, and attempted to identify risk factors for lactic acidosis. They drew on the large database from one of the main HIV treating centres in England. A total of 1,239 patients treated for more than four months for whom lactate levels were available were analysed.

Much has been made of the potential for lactic acidosis as a result of HIV treatment, but Moyle's presentation was perhaps a useful reminder that we need not get carried away by fear of the latest high-profile symptom or toxicity. Here are some of the things they found.

- In general, these HIV patients didn't have high lactates. Having one elevated lactate level did not predict further rises or elevations. Most of the (modest) number of people who had elevated lactates at any one reading had normal lactates the next time they were tested.
- People taking abacavir were 60 percent *less likely* to have elevated lactates.
- Out of the whole 1239, there were nine individuals identified with severe hyperlactataemia and/or lactic acidosis, and one death from lactic acidosis.
- Women were over-represented in the group of people reporting any raised lactates.
- ddI and d4T were also over-represented in the group reporting any raised lactates although interestingly, 3TC was not. (3TC has been in some other studies considered a particular culprit for raised lactates).
- Elevated lactate levels manifest as lactic acidosis only rarely, and acute lactic acidosis remains rare.
- Of all risk factors, only ddI was statistically associated with an increased risk of elevated lactates.
- Women may be at slightly increased risk.

On this basis, Moyle suggested that where risks are absent, ongoing screening of all patients may be of limited value. The screening of lactate is not usually clinically predictive. He told the conference: "The [routine] screening of lactate has most of the time produced more neurosis than clinical benefit".

Fat accumulation

What causes fat accumulation, what does it mean, and what can be done?

The body fat changes which we call "lipodystrophy" are often lumped together as if they are one phenomenon. But it is important to distinguish between changes which cause accumulation of fat (eg. fattening belly, breasts etc), and those which cause fat loss, because:

- the drugs which are associated with these two effects appear to be different;

- the mechanisms which cause them are probably different (but probably linked); and — last but not least,
- managing these changes may require some separate approaches (although fixing one may have a beneficial effect on the other).

Fat accumulation is much more strongly associated with protease inhibitor use, and is of importance on its own because increased belly fat (called central adiposity) is also more strongly associated in the HIV negative population with the development of heart disease, and diabetes.

However, fat accumulation is also an obvious issue for personal esteem reasons. So: can the physical manifestations be improved and can you also improve blood lipids (triglycerides, cholesterol)?

Kathleen Mulligan (Schwarz et al, Abstract 26) looked at human growth hormone to improve fat metabolism and insulin sensitivity in people with HIV-related fat accumulation. Previously, this group had reported that using recombinant human growth hormone did ameliorating this particular manifestation of lipodystrophy.

In this study, they found:

- use of human growth hormone did improve blood lipid profiles, lowering cholesterol and triglycerides, and raising high density lipoprotein, so-called “good cholesterol”;
- frustratingly however, growth hormone worsened, rather than improved, insulin resistance, including insulin resistance in the liver, such that it could increase the risk of hyperglycaemia or diabetes;
- the researchers argued patients wanting to use growth hormone to help fat accumulation and blood lipid changes should first be tested for glucose tolerance, with people with impaired glucose tolerance excluded;
- they argued growth hormone should not be used if people have insulin resistance, but that lower doses should be tested for this group.

Children get lipodystrophy too

Vigano et al (Abstract 13) presented evidence that children treated with antivirals including PIs can also show signs of clinical lipodystrophy. Increased central fat and peripheral lipoatrophy (fat loss from face & limbs), were, they found, distinctive features of the 34 HIV positive children whom they compared to age-matched negative children.

These changes in body fat composition were, they said, present if you did a DXA scan (a scan for looking at fat distribution), even when the children didn't have clinical signs of lipodystrophy (such as belly fat). Drugs the children had used included AZT, ddI, d4T plus protease inhibitors.

Mitochondrial toxicity

Is mitox the cause of many HIV drug problems? Which drugs damage mitochondria?

Background

Mitochondria are structures which occur in various numbers in every living cell. They are the “energy centres” of cells, supplying more than 90 percent of cells’ energy needs. They contain the enzymes, or substances, responsible for the metabolic activities of the cell.

Metabolism refers to the many ways in which the cells of the body convert materials into the energy required to function, form tissues and organs and so forth. All the time, the millions of cells in our bodies and organs are transforming different foods, drugs, chemical substances etc. into forms which allow the body to break them down, and allow the body’s functions and processes to go on: eliminating waste, building muscle, transporting fat, glucose etc.

There are lots of mitochondria in fat cells.

Each of these mitochondria contain DNA, the ‘genetic blueprint’ which the mitochondria need to reproduce themselves, which they do by dividing and multiplying. Mitochondria produce their own DNA, but are also dependent on the cell they are in for DNA production. Because of this unusual and complex relationship, combined with their high energy turnover and replication rate, they are more prone to DNA damage. Mitochondrial DNA is easily damaged, difficult to repair, and can pass that damage on to new mitochondria.

Every cell contains mitochondria, and they help drive a range of complex bodily processes. However, if the mitochondria are destroyed, lost or damaged, they cannot function as effectively, and it is increasingly believed this may lead to a number of painful and common conditions reported by people with HIV, and especially taking HIV antivirals, which may include: neuropathy (nerve damage); myopathy (muscle damage); pancreatitis (inflammation of the pancreas, a gland associated with the metabolism of sugars); and lactic acidosis (described above).

- Ulrich Walker (Abstract 18) examined several antiviral drugs in combination and alone, to measure the extent to which they depleted mitochondrial DNA, in the cells of the liver and other tissues. To test this, they cultivated in the laboratory a particular human cell line found in the liver, and then exposed those cells in vitro (in the test tube) to ddC, ddI, 3TC, d4T and AZT, alone and in various combinations, to see what effect it would have on the mitochondrial DNA of these cells. (Interestingly, Glaxo refused to provide abacavir for this study, so it wasn’t included). Control cells were generated, which were not

exposed to drug, or were exposed only to efavirenz. Individually, the drugs which most rapidly depleted the DNA were (in descending order): ddC, ddI, d4T, and AZT equal to 3TC. In addition, AZT, and the combination of AZT/3TC behaved peculiarly, in that they increased lactate levels and caused cells to die without depleting the mitochondrial DNA. (Though it makes sense to remember here that AZT, originally pioneered as a cancer treatment, is a cytotoxic or cell-destroying drug). Other drugs in combination appeared to increase the rate of mitochondrial depletion, including 3TC/d4T and ddC/d4T, compared to any of these drugs used alone. There was some speculation as to the mechanisms for this increase in toxicity in combination compared to single drugs. The researchers concluded that there was indeed long-term mitochondrial toxicity from the nucleoside drugs, and this was possibly exacerbated in combination, due to a cumulative or a synergistic effect. Mitochondrial DNA depletion, using some combinations, was also shown to worsen after more than a month.

Clinical implications:

- Although this study did show that mitochondrial DNA was depleted by HIV nucleoside analogues, especially in combination, there were a number of unanswered questions. The researchers did not venture to suggest what the implications of this depletion might be at a clinical, rather than biochemical, level. They also noted that not all drugs appear to exert changes in the same way.

Liver toxicity

The liver is one of the main sites for adverse events from HIV treatment: both short term (eg. acute inflammation/hepatitis), to long-term problems such as hepatic steatosis (“fatty liver”, where the liver cells accumulate fat).

One of the eye-opening things about the European epidemic is the very high rates of hepatitis C co-infection: roughly 30 percent across Western Europe, and 50 percent in Spain. Indeed at one HIV treatment centre in Madrid, acute liver failure was the leading cause of death among patients in the year 2000.

Vincent Soriano (Instituto Salud Carlos III, Madrid), gave a plenary address on liver-related adverse events. These are some of the key points.

- There are a growing number of studies which identify hepatitis C as a predictor of liver toxicity following HIV treatments.

- There are separate mechanisms which may cause liver toxicity. Early or acute effects (eg. development of sudden inflammation or hypersensitivity on starting treatments) are primarily driven by the immune system and its responses. Starting treatment may add to this effect, especially in people with hepatitis C, because of the return of normal symptomatic inflammatory responses as the immune system is improved by the HIV treatments. The drugs most associated with these early hypersensitivity effects include nevirapine and abacavir.
- Late onset liver problems have a different cause: the cumulative toxic effect of the drugs over time, especially in people with hepatitis C. Drugs which can have a toxic effect on the liver over time are ddI, d4T and nevirapine. Toxicity of this kind generally appears at about 6 months after starting treatments.
- Nonetheless, elevated ALTs (liver enzymes) don't always predict drug-related liver toxicity, and in studies presented by Soriano, patients with elevated ALTs was greater than the number of people who went onto to develop what were classified as serious toxicities.
- Finally, there is some data to suggest that there might be a dose-dependent effect of nevirapine on the liver.

Bones

A brief word on bone density ...

Recently, some attention has focused on the question of whether HIV drugs can cause loss of bone mineral density (osteopenia). However, research in this area remains limited, and a number of important questions are yet to be answered, including:

- How common is the problem?
- What drugs might cause it and how?
- What is the relationship between osteopenia and osteoporosis?
- Are people with HIV and reduced bone mineral density necessarily at increased risk of fractures?

Mondy et al (Abstract 12) investigated bone mineral problems in HIV positive men taking antivirals. Although it was a small number of men and so a limited study, they noted that there are several diverse forms of osteoporosis in positive people on treatments. Again, it was stressed that "multiple mechanisms" may underlie the cause. They couldn't draw conclusions about which drugs caused this problem, nor how long it would take to develop, calling only for "longitudinal studies".

Clinical implications:

- Whether these bone changes would necessarily lead to increased risk of fracture, no one would speculate.
- Low calcium intake, smoking, and reduced Vitamin D may all be a factor in osteoporosis in HIV negative people. Discussion from the floor suggested there may be a role for calcium intake and vitamin D supplementation, as standard of care, for people with osteopenia or increased risk of osteoporosis.

Thyroid problems?

It is tempting, and not wholly flippant and inaccurate, to note at this point that it would hardly be a conference on HIV if it did not identify a new or emerging potential toxicity.

This time around, it was thyroid abnormalities which came under the spotlight. (Esnault et al, Abstract 16; Loignon et al Abstract 80).

Background:

The thyroid is a gland at the back of the neck which produces hormones which regulate the rate of metabolism. An underactive thyroid gland can result in a diverse array of problems, including severe tiredness and depression; some kinds of heart problems; musculoskeletal disorders; nerve problems like neuropathy and nerve entrapment; absence of menstrual periods; constipation; intolerance to cold. Thyroid problems occur commonly in people with autoimmune problems (eg. lupus), and diabetes.

This was a cross-sectional, rather than randomised control study, but it is worth noting nonetheless. The gist of the findings (221 people) were thus:

- Epidemiology in HIV negative populations (like the oft-quoted Framingham heart study) reckon hypothyroidism (underactive thyroid gland) occurs in roughly 0.1 percent of men, and 1 percent of women.
- The prevalence of hypothyroidism among the 221 HIV positive people in this analysis was roughly 7.9 percent for men, and 8.6 percent, with an increased incidence in people with AIDS. It should be noted that people who are sick have biochemical hypothyroidism but normal thyroid function – called ‘sick euthyroid’ – this may explain some of these findings.

Clinical implications:

- The authors raised the possibility that hypothyroidism in positive people might be treated with hormone therapy.

- Hypothyroidism can cause a range of metabolic disturbances, neurological and psychiatric problems, heart problems, nerve problems and skin problems (eg. extremely dry skin).

PS. Therapeutic drug monitoring

Although it was not specifically addressed, this conference added to an emerging theme in HIV: the relationships between drug dosages and the development of both acute and long-term toxicities. HIV treatment at its most ideal would include using those drugs which get into the blood at high enough levels and for long enough to effectively work against HIV, but ensuring that there is not so much extraneous drug in the blood as to cause increased risk of toxic effects for no additional benefit.

Enter Therapeutic Drug Monitoring (TDM), a technique still in its infancy in clinical practice, but which allows blood drug levels to be measured in individuals. How well a person absorbs a drug can vary for a variety of reasons, including:

- the drug has inherent design limitations which mean it is poorly absorbed into the body (eg. coating, fragility);
- individuals' metabolism;
- absorption problems for the person taking the drug (eg. diarrhoea, vomiting);
- body weight;
- presence of other drugs in the body, which can interfere or interact, causing lower or higher doses of a particular treatment (eg. ritonavir raises blood levels of lopinavir, and so a small amount of ritonavir is used to 'boost' the effects of lopinavir).

It's possible to get too little of a drug (leading to suboptimal or subtherapeutic treatment and the risk of resistance because virus is not being suppressed properly), but also to get too much, which can lead to toxicity. Indinavir in particular demonstrates a strong relationship between high peak levels of the drug, and the risk of side effects such as kidney problems.

The advantage of knowing how much drug an individual is getting is that you can adjust, reduce or boost the dose accordingly. TDM does have present limitations. There is still debate about its most appropriate applications, techniques are not standardised in pharmacological practice, and it gives information only about drug levels in blood, not other parts of the body (eg. tissue). And there is no indication that TDM is indicated for determining levels of the nucleoside reverse transcriptase inhibitors, because they are broken down and utilised inside the body's cells, so blood levels don't indicate therapeutic levels. But it is likely that TDM is going to become an

increasingly useful and utilised tool, and a technique which can help ensure anti-HIV drugs are being used in the safest and most effective way. Watch this space.