

aids treatment update

HIV and cancer

In this month's lead article, Michael Carter talks to cancer specialist Dr. Mark Bower about the interaction between HIV, HAART and cancer. It's not an easy subject to think about, and some readers may find the article particularly sobering.

But there is some good news, particularly for women and HIV, and not just because it appears that cervical cancer is now being seen less often in HIV-positive women in the UK who are on successful anti-HIV therapy. It also seems to be the case that being infected with HIV appears to make the incidence of breast cancer in women less likely; news that is both surprising and welcome.

For men, however, the increased incidence of anal cancer is a concern. It is currently one of the three most common non-AIDS defining illnesses amongst HIV-positive gay and bisexual men, but when caught early enough, like cervical cancer, it is completely preventable.

Until recently, it was assumed that human papilloma virus (HPV) – the virus associated with both vaginal and anal cancer – was acquired in men sexually through receptive anal intercourse. But last year French investigators found that almost half of the HIV-positive heterosexual men in their study were also infected anally with HPV.

The researchers conclude that "anal HPV infection...may be acquired in the absence of anal intercourse in HIV-positive men" and suggest that "all HIV-positive men with CD4 cell counts less than 500 cells/mm³, regardless of history of anal intercourse, should be considered" for anal pap smears.

Currently, HIV clinics in the UK rarely carry out routine anal pap smears. Perhaps it's time for a rethink.

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cancer and hiv

2 Is cancer occurring more or less often in people on HAART? by Michael Carter

It is generally agreed that the incidence of the AIDS-defining cancer Kaposi's sarcoma (KS) in people on HAART has declined dramatically. It is also likely that the incidence of cervical cancer has fallen among women on HAART. And although non-Hodgkin's lymphoma (NHL) diagnoses have risen sharply since 1996, doing well on HAART appears to be a very important factor when it comes to surviving NHL.¹

However, the incidence of non-AIDS-defining cancers – such as Hodgkin's lymphoma, anal, liver, lung, and testicular cancer – has been the subject of some debate since the US National Cancer Institute published a study last year which found that such cancers have not become much more common as HIV-positive people in resource-rich countries live longer, despite other studies suggesting that non-AIDS-defining cancers have become more common. Additionally, they argued that non-AIDS-defining cancers were unrelated to CD4 counts².

The Chicago-HOPS Study

Adding to the debate was a presentation in February from The Chicago-HOPS Study at the Eleventh Conference on Retroviruses and Opportunistic Infections (CROI) in San Francisco, which asserted not only that non-AIDS-defining cancers were more common nowadays in HIV-positive people, but that they were related to lowest, or nadir, CD4 counts³.

The researchers looked at the five most common non-AIDS-defining cancers in two major cohorts – 6700 patients at the two largest Chicago HIV clinics and a further 5400 members of the multi-centre HIV Outpatient Study (HOPS) cohort – and compared them with the general population to determine the incidence and relative risk of these

cancers in people with HIV for the years 1992 to 2002.

The five non-AIDS-defining cancers were lung cancer, head/neck cancer, Hodgkin's lymphoma, anorectal cancer, and melanoma (skin cancer). Among the HOPS cohort, in analyses adjusted for age, race, smoking, and gender, incidence of four cancers was significantly greater than expected compared with the general population. These were, in order of risk, anorectal, Hodgkin's disease, melanoma and lung cancer. Among Chicago clinic patients, however, the risk for all five cancers was significantly increased, although the relative risk appeared to be much higher for Hodgkin's lymphoma than it did for head/neck, anorectal, melanoma and lung cancer.

When looking at factors associated with these cancers, the researchers found that those who had developed cancer had a significantly lower mean nadir CD4 count – strongly suggesting that immune suppression plays an important role in the pathogenesis of these cancers. Additionally, both lung and head/neck cancers were significantly associated with being a current or past smoker, as in the general population. There was also a trend to older age in those with cancer, which is similar to the general population.

Q & A with Dr. Mark Bower

To help explain what this all means, ATU spoke with Dr. Mark Bower, Consultant Medical Oncologist, at the Chelsea and Westminster Hospital, London.

ATU: Let's start with the AIDS-defining cancers. What can you say about Kaposi's sarcoma and non-Hodgkin's lymphoma in the HAART era?

Mark Bower (MB): There has been a dramatic decline in the incidence of KS since the introduction of HAART, and we now see about a third of the number of cases we saw in the pre-HAART era.

Of the people we see who develop KS, about three-quarters are not on HAART at the time, either because they are unaware that they have HIV, or because they are from areas where HAART is not available.

However, there is a small minority of patients who present with KS whilst on HAART. Of these, about three-quarters are failing HAART, have a detectable viral load and are probably resistant to some anti-HIV drugs.

Then you get down to a very small number of patients - five to ten patients a year, here at the Chelsea and Westminster - who really shouldn't be getting KS. Their viral loads are undetectable and they have a good CD4 cell count, about 300 – 400 cells/mm³. The jury is out as to why this might be happening. It could well be that they've only experienced partial restoration of their immune systems and still have 'holes' in it that allow the virus that causes KS (HHV-8) to cause disease. An interesting factor that might be worth investigating is what these patients' lowest-ever CD4 count was – I just don't know.

ATU: How do you treat KS?

MB: If you have the odd KS lesion on your skin that isn't troublesome, either in terms of symptoms or looks, then in treatment-naïve individuals we'll use HAART as the first-line treatment. The trouble is that it can take up to six months for the KS to improve. Indeed, for the first couple of months, it can even get worse, and it can take up to two years for the colour to come out of lesions. Nevertheless, for about two-thirds of patients started on HAART alone as KS treatment, that's enough.

For patients with more extensive KS, or systemic KS, then chemotherapy is needed.

Although treatments for KS have improved dramatically, when KS affects internal organs – particularly the lungs – it causes a significant amount of mortality in patients, even in the era of HAART.

ATU: Has non-Hodgkin's lymphoma become any less of a problem with HAART?

MB: Primary cerebral (brain) lymphoma is all but disappearing. In the pre-HAART era we used to see ten or 15 patients a year with primary cerebral lymphoma. We now see one or two patients a year, and this diagnosis can often be questionable.

The prognosis is still terrible, however.

That's only part of the picture. There are also systemic lymphomas. There's evidence from a number of studies that there has been a modest reduction in incidence since the introduction of HAART, and it's been shown that being on HAART reduces your risk of developing systemic lymphoma.

On the reverse side though, with the increase in the number of patients with HIV, and the reduction in the number of other opportunistic infections since HAART, and greater life-expectancy, the small reduction in risk has translated, if anything, into us seeing an increase in the number of patients with HIV lymphomas.

ATU: How do you treat systemic lymphoma?

MB: Aggressively, with chemotherapy. Survival is much better than it used to be. But to have the best chance of your treatment working, it's important to receive treatment in a centre, like the Chelsea and Westminster, that has experience of managing and treating lymphoma.

There's clear evidence that where there is a working relationship between HIV specialists and cancer specialists, the outcome for patients with systemic lymphoma is much better. If you're diagnosed with a systemic lymphoma, my message to your readers would be to get yourself to a major HIV treatment centre as soon as possible.

ATU: Are there any characteristics which predict an increased risk of developing lymphoma?

MB: The risk factors for developing systemic lymphomas include some complex genetic factors, such as cytokine and chemokine receptor polymorphisms.

Glossary

anorectal relating to the anus and/or rectum.

chemokine a substance manufactured by cells and tissues, that stimulates movement and activation of immune system cells to the area where the chemokine is produced.

chemotherapy the use of drugs to treat an illness, often denotes drugs used to treat cancer.

cohort a group of people who share at least one common factor (e.g. being HIV-positive) and who are studied over a period of time.

cytokine a natural chemical used to pass signals between cells.

HAART Highly Active Antiretroviral Therapy, a term used to describe anti-HIV combination therapy with three or more drugs.

Hodgkin's lymphoma a cancer that develops in Reed-Sternberg cells, a specific kind of white blood cell, or lymphocyte.

invasive in medical terms, going inside the body.

Kaposi's sarcoma lesions on the skin and/or internal organs caused by abnormal growth of blood vessels.

lymphatic system a bodily system that drains away excess fluids from tissues and plays an important role in maintaining the body's immune defences.

Lymph nodes (also known as glands) lie along the lymph vessels and filter the lymph fluid to remove bacteria or any dead or abnormal cells.

Non-Hodgkin's lymphoma a group of several closely related cancers that affect the lymphatic system, broadly divided into two major groups: B-cell lymphomas and T-cell lymphomas.

pathogenesis the ways in which disease is caused by a pathogen.

But most important are immunological issues. The older you are, the lower your lowest-ever CD4 cell count (and, to a lesser extent, your nadir CD8 cell count), then the greater your risk of developing systemic lymphoma.

NNRTI- or PI- based HAART, is equally effective at protecting against lymphomas, and it's very uncommon to see lymphomas in patients with a CD4 cell count above about 350.

ATU: What are your chances of survival with lymphoma?

MB: The two-year overall survival for patients with systemic lymphoma at the Chelsea and Westminster is about 55% with chemotherapy. We don't see relapse and death from lymphoma more than a year after the end of treatment. Basically, if you get to more than a year after the end of your chemotherapy, you're probably cured of your lymphoma. I'll stress again the importance of receiving your treatment at a hospital with integrated HIV and cancer specialities.

ATU: During chemotherapy for lymphoma, do patients remain on HAART?

MB: Remaining on HAART during chemotherapy can protect your immune system. We've seen that during chemotherapy your CD4 cell count drops by about 50%, but recovers within a couple of months after the end of chemotherapy.

There is a potential, however, for drug interactions between the chemotherapy and HAART – particularly protease inhibitors – that can lead to rather high levels of the chemotherapeutic drugs and, therefore, more side-effects from the chemotherapy.

However, if you stop HAART during chemotherapy, it can take up to twelve months after your anti-cancer treatment finishes and you restart your HIV medication for your CD4 cell count to recover.

ATU: Since 1993 cervical cancer has been an AIDS-defining condition. Have you noticed any changes in patterns of this disease since HAART?

MB: As you say, cervical cancer is an AIDS-defining condition, but it was always debatable in the pre-HAART era how increased the risk actually was in women with HIV. However, since HAART, very clear evidence has emerged of increased incidence of invasive cervical cancer in HIV-positive women not on HAART.

Other centres in the UK have seen that HAART has reduced the incidence of cervical cancer, but given the patient population at the Chelsea and Westminster, we don't really see much cervical cancer.

ATU: What about cancers that aren't traditionally associated with HIV? There's been a lot of interest in these since the introduction of HAART. Which ones are you chiefly concerned about?

MB: The biggest issue at this treatment centre, where most of the patients are gay men, is invasive and pre-invasive anal cancer. In addition, lung cancer and testicular cancer seem to be occurring more often in HIV-positive individuals. We'll deal with them one by one.

ATU: What causes anal cancer and how many cases are you seeing?

MB: As I'm sure many of your readers know, human papilloma virus (HPV), the cause of anal and genital warts, is the underlying reason for anal cancer, and HAART doesn't work against it. If anything, there's been a modest increase in the number of cases of anal cancer since HAART was introduced. This could be because people are living longer due to HAART and/or because HAART doesn't affect the pre-cancerous lesions – AIN (anal intraepithelial neoplasia).

intraepithelial neoplasia). There's a slow rate of disease progression from infection with HPV through the three stages of AIN (AIN I, AIN II and AIN III), and the development of cancer, perhaps ten years or more.

There are high-risk genotypes of HPV for anal cancer. Women with cervical cancer tend to have only a few genotypes of HPV in their cervix. However, in gay men we tend to find infection with multiple genotypes of HPV, some of which are

high-risk. However, in a study at the Chelsea and Westminster, we were unable to find any association between high-risk HPV genotypes and the stage of disease progression.

ATU: How do you treat anal cancer?

MB: Treatment for invasive anal cancer is aggressive, involving a combination of chemotherapy and radiotherapy. It's pretty horrible, but the cure rate is about 60%, although some patients may also need surgery.

ATU: Can you screen for anal cancer?

MB: Yes, we're starting to get the ability to screen for AIN, using a test very similar to the PAP smear for pre-cancerous cervical cells in women. It involves smearing the anal mucosa, and in San Francisco men are being trained to do this for themselves.

We have yet to establish how we can prevent pre-invasive anal cancer progressing to invasive anal cancer, and if we had an effective therapy to stop that – and let's be clear, it isn't HAART – we would have made a major breakthrough in preventing this illness. There are a number of studies looking at potential treatments.

ATU: Is screening worthwhile?

It's clear that if you catch anal cancer early, there's a much better chance of curing it. Further, you can determine who's at risk of anal cancer by looking at their AIN status. If there's a small area of AIN, even high-grade AIN, then localised treatment seems effective. If you have an extensive area of AIN, then there are roles for frequent monitoring (to see if aggressive treatment should be started) or surgical resection. A large, carefully designed study is needed to look at the utility of screening.

ATU: What about lung cancer?

MB: If anything, the risk of lung cancer is rising in patients with HIV. It used to be said that this was because people with HIV were more likely to be smokers. The data for this are pretty poor actually, and it does seem that people with HIV have a two or threefold increased risk of developing lung cancer compared to similar people without HIV.

The prognosis is awful, as it is for all lung cancer, but it's no worse in people with HIV. We really don't know why the incidence of lung cancer should be elevated in people with HIV.

ATU: And testicular cancer?

MB: Again, this seems to occur more often in men with HIV, but it's uncommon. The treatment and outcomes for men with HIV are similar to those for HIV-negative men. Data from the UK and Denmark suggest that HIV-positive men with testicular cancer are at no greater risk of dying of the condition than are HIV-negative men.

If you notice a lump in your testicle, get it looked at. If the tumour is localised to the testicle, then treatment will consist of its removal. If the disease has spread elsewhere, chemotherapy will also be used.

ATU: What about liver cancer?

MB: There are very few data on liver cancer in people with HIV. But there does seem to be an increased incidence of liver cancer in people with HIV, particularly in association with hepatitis C and hepatitis B. I think this is going to be a developing issue, though, given the rates of HIV and hepatitis C and hepatitis B co-infection.

ATU: Any good news?

MB: Yes there is! A number of studies have shown that HIV reduces the risk of breast cancer. One possible theory for this is because a functioning immune system contributes to this malignancy, which is more common in well-fed, affluent, immuno-competent women — like Samantha Jones in *Sex and the City*.

ATU: What about HAART - is there any evidence that the increased incidence of non-AIDS defining cancers could be side-effect of HAART?

MB: Another optimistic point is that there's no evidence that HAART causes tumours. If there is an increased risk of some malignancies since HAART, it's because people just aren't dying of other things.

polymorphisms natural variations in a gene, DNA sequence, or chromosome that have no adverse effects on the individual and occur with fairly high frequency in the general population.
resection the surgical removal of part of a bodily structure, in this case, the anus.
systemic a disease or process that affects a larger part of the body, as opposed to a localised disease, which just affects one part of the body.

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Boosting alternatives

6 Can PIs be boosted without ritonavir? by Megan Nicholson

Understanding PI boosting

Protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are extensively metabolised by the cytochrome P450 system, as are many other drugs.

Cytochrome P450 is a group of enzymes found in the liver and the gut which have a number of functions in the human body. One function is the breakdown and clearance of medications and other chemicals.

Taking two or more drugs which are metabolised by cytochrome P450 may produce a drug interaction affecting concentrations of one or both drugs, and causing side-effects or undermining the clinical efficacy of the medication(s).

The activity of cytochrome P450 differs between individuals and between populations. Small genetic variations can affect how much particular enzymes are expressed, and thus

The ritonavir (*Norvir*) US price hike announced by Abbott Laboratories in December last year was a PR disaster. Outraged HIV clinicians, researchers and non-government organisations called for a global boycott of Abbott products and Abbott was forced to review its initial price increase in order to protect treatment access for low-income Americans.

However, US price increase aside, there has been growing concern from both clinicians and people living with HIV regarding the increasing reliance of low-dose ritonavir to boost PI therapy. This is because the DAD study – a large international trial set up to monitor the risk of heart disease in people taking anti-HIV therapy – has shown that people receiving ritonavir and ritonavir-boosted PIs are significantly more likely to have elevated cholesterol and triglyceride levels than those taking other PIs.¹ This is an important risk factor in the increasing incidence of heart disease and stroke now seen in HIV-positive people on HAART.

These elevated blood fats don't take long to reach worrying levels, either. A Canadian study found that HIV-negative adults given a 100mg

booster dose of ritonavir twice a day for just 14 days had significant increases in total cholesterol, triglycerides and LDL ("bad") cholesterol, and a reduction in HDL ("good") cholesterol.²

The search for PI boosting agents

Ritonavir-boosted PIs are now the preferred standard of care for PI therapy in Europe and the US, and a lot of effort has gone into identifying safe and effective ritonavir-boosted dosages. In some circumstance, PIs are only recommended when boosted by ritonavir.

Given the current importance of ritonavir to PI therapy, can it easily be replaced by other drugs?

Several drugs have been used to boost PI levels, but at present no drug is a serious rival to ritonavir. According to Britain's leading HIV pharmacologist, Professor David Back of the University of Liverpool, "There's nothing, in terms of potency or being able to boost in same the way, that is equivalent to ritonavir".

Ideally what is required is a drug which causes few side-effects but is a powerful PI booster.

When looking for alternatives to ritonavir for PI boosting, several other drugs are known to inhibit the same liver enzyme. These include: other HIV protease inhibitors; the NNRTI, delavirdine; -azole antifungals (e.g. ketoconazole, fluconazole); calcium channel blockers used to treat heart conditions; certain types of antibiotics (e.g. troleandomycin, Erythromycin); SSRI antidepressants (e.g. *Prozac*); the antacid, cimetidine; and concentrated grapefruit juice.

However, the search for PI-boosting agents needs to weigh the benefit of increased PI exposure against potential short- and long-term side-effects as well as dosing considerations.

How drugs interact also needs consideration. Generally, PI boosting increases total drug exposure and trough levels and extends drug half-life. A less desirable effect of boosting may be too much drug exposure or very high peak levels. These can cause or worsen adverse effects.

Given the risks attached to PI boosting, the British HIV Association guidelines recommend monitoring drug levels when boosting PIs with alternatives to ritonavir (e.g. with delavirdine), or when using ritonavir to boost two or more PIs (e.g. *Kaletra* and amprenavir).

Indinavir

Co-administration of indinavir and nelfinavir can modestly boost exposure to both drugs.³

The AIDS Clinical Trials Group ACTG 388 Study compared standard indinavir three times daily with either 1000mg or 1200mg indinavir plus nelfinavir twice daily. The study found that nelfinavir slowed clearance of indinavir.⁴

However, only the 1200mg indinavir/nelfinavir combination produced adequate trough concentrations of indinavir. The average trough concentration of indinavir in the 1200mg group was 146ng/ml (none of seven people had less than 10ng/ml) compared to an average that was below 10ng/ml in the 1000mg group.

Another study found that 1200mg indinavir and 1250mg nelfinavir twice daily were required to achieve adequate trough levels of both drugs.⁵

The danger with indinavir boosting is the risk of increasing kidney toxicities. When peak indinavir concentrations are boosted, there is greater risk of kidney stones or high bilirubin. This has been a key problem with ritonavir-boosted indinavir. Combining indinavir with other drugs which are associated with kidney toxicities, such as the new PI atazanavir, is also not recommended.

Nelfinavir/saquinavir

Nelfinavir/saquinavir is another mutually enhancing dual PI combination. Saquinavir exposure is boosted 3-5 fold³, and trough levels of both drugs are substantially increased.⁶

However, several randomised studies have used this combination and failed to find a clear-cut clinical benefit. In a long-term study, nelfinavir/saquinavir produced lower rates of viral suppression than soft-gel saquinavir after 48 weeks.⁷ In the SPICE study, four-drug therapy including nelfinavir/saquinavir was equivalent to triple therapy with saquinavir or nelfinavir, although it did extend the average time to viral rebound.⁸

The failure of the saquinavir/nelfinavir drug interaction to produce a clinical benefit may be due to the prevalence or severity of gastrointestinal side-effects associated with this combination.

Amprenavir

Pharmacokinetic studies of amprenavir plus protease inhibitors other than ritonavir have used mainly the original formulation of amprenavir. Co-administration of standard amprenavir with nelfinavir or indinavir can slow clearance and increase drug exposure and trough levels to some extent.^{9,10,11} However, this formulation has been superseded by fosamprenavir – a pro-drug of amprenavir which achieves higher blood levels than the original formulation – and a new set of pharmacokinetic studies are required.

Atazanavir

In contrast to the mediocre PI boosting described above, more promising results have been reported using atazanavir. For instance, atazanavir and saquinavir interact to slow drug

how quickly the drug is metabolised.

Cytochrome P450 enzymes which derive from a particular gene are called isoforms. Based on the similarity of their chemical make-up, isoforms are divided into families, subfamilies and individual genes. Enzyme variants are described through a numbering and lettering system which reflects their chemical and genetic structure.

CYP3A4 is one particular metabolic pathway which is very important to many medications and other substances.

Protease inhibitors are metabolised through the cytochrome P450 system and CYP3A4 in particular. Drugs which induce (speed up) the activity of CYP3A4, such as the TB drug rifampicin, can reduce exposure to the PIs.

CYP3A4 has a complex interrelationship with PIs. It binds well with PIs and starts to break them down. But as this occurs, the drug 'damages' and inhibits the activity of CYP3A4.

This means that PIs can slow the processing of other medications which are metabolised through CYP3A4. Ritonavir is a particularly potent inhibitor of CYP3A4, hence its role in PI boosting.

Drug metabolism is also affected by p-glycoprotein – a transport protein which protects cells from poisons. P-glycoprotein is important in PI metabolism because it treats PIs as if they were poisons and pumps them out of cells.

Ritonavir inhibits the activity of p-glycoprotein, as do, to a lesser extent, saquinavir, nelfinavir and indinavir.²⁶ When taken with another PI, ritonavir can increase cellular exposure to the other PIs.

An ideal alternative agent to ritonavir for PI boosting would also slow the activity of p-glycoprotein.

Glossary

adverse effects an unwanted side-effect of a treatment.

cholesterol a waxy substance, mostly made by the body and used to produce steroid hormones. High levels can be associated with atherosclerosis.

cryptococcosis a type of fungal infection usually affecting the membrane around the brain, causing meningitis. It can also affect the lungs and chest.

HAART Highly Active Antiretroviral Therapy, a term used to describe anti-HIV combination therapy with three or more drugs.

pharmacokinetics the study of how a drug is absorbed and distributed throughout the body.

resistant virus a drug-resistant HIV strain is one which is less susceptible to the effects of one or more anti-HIV drugs.

thrush a fungal infection of the mouth, throat or genitals, marked by white patches. Also called candidiasis.

triglycerides the basic 'building blocks' from which fats are formed.

wild-type virus HIV that has not been previously exposed to anti-HIV drugs.

clearance, allowing once-daily dosing at a dose of 400/1200mg.¹²

Atazanavir and amprenavir also have a useful interaction which increases amprenavir exposure. A small dosing study found that 400mg atazanavir once daily combined with 600mg amprenavir twice daily produced amprenavir trough levels equivalent to those seen with ritonavir/amprenavir. Total exposure to amprenavir compared favourably with concentrations produced by ritonavir boosting.¹³

Unfortunately, atazanavir levels were not measured in this study, so it is not known whether participants were being exposed to adequate levels of atazanavir. Another limitation of this study was the use of tenofovir, which is known to lower atazanavir levels.

Studies are ongoing to assess atazanavir's boosting potential with other PIs, which could be promising, although atazanavir itself is currently only approved in the EU when boosted with 100mg ritonavir.

The good news is that studies have found that atazanavir appears to counteract ritonavir's lipid-raising effects, which means that ritonavir-boosted atazanavir appears to be the only boosted PI combination not associated with increased cholesterol and triglycerides.^{14,15}

Delavirdine

Delavirdine was the first NNRTI to be developed, and although approved in the US, it is only available to individuals in the UK if their HIV clinician requests it. Delavirdine is a weaker inhibitor of CYP3A4 than ritonavir but it is a more potent inhibitor of another enzyme (CYP2C19) which plays an important part in the metabolism of nelfinavir.

Several studies have combined delavirdine with PIs but it seems to be less effective in slowing the breakdown and clearance of PIs than ritonavir. Unlike ritonavir, delavirdine does not act on p-glycoprotein to maintain cellular PI concentrations. Other downsides to delavirdine are its weakness relative to the other NNRTIs and, at three pills twice daily, a relatively high pill count. Nevertheless, it has been suggested as a potential boosting agent in people with

NNRTI resistance, and, in Brighton, for example, delavirdine is being used for this purpose in at least two individuals.

Pharmacokinetic studies with some PIs have been somewhat favourable, indicating that drug exposure to indinavir and amprenavir is increased when each is dosed with delavirdine.^{16,17}

Several salvage studies have also used delavirdine in combination with PIs. For instance, the ACTG 359 study randomised 277 people with indinavir resistance to one of six treatment arms including saquinavir/nelfinavir (800mg and 750mg three times a day) plus delavirdine. At 16 weeks, 46% of people in this arm had a viral load below 500 copies/ml.¹⁸

Cimetidine

Cimetidine is an antacid which has been tested as a potential PI-boosting agent in twelve HIV-negative people. Participants took saquinavir soft gel 1200mg three times a day for 13 days and then switched to saquinavir soft gel 1200mg twice a day, with cimetidine 400mg twice a day from day 14 to 26.

Cimetidine boosted saquinavir exposure by an average of 120%. However, although it doubled saquinavir peak levels, trough concentrations did not differ significantly.¹⁹ Professor Back comments that this increase of 120% is inferior to the 1000% rise in saquinavir levels seen when saquinavir is boosted with ritonavir.

Azole Antifungals

The class of drugs known as -azoles – fluconazole, itraconazole, ketoconazole – are antifungal agents commonly used to treat HIV-associated conditions such as thrush and cryptococcosis. They are known to inhibit the P450 enzymes and several have been tested as PI boosting agents.

A small pharmacokinetic study of fluconazole and saquinavir found that, when saquinavir was taken at the standard dose of 1200mg three times daily over eight days, and fluconazole was taken at 400mg on day 2 and 200mg on days 3 to 8, total exposure to saquinavir was doubled.²⁰

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Ketoconazole is also known to boost blood plasma concentrations of saquinavir and amprenavir. However, the increases are generally modest and do not approach the levels of boosting produced by ritonavir.^{21, 22}

However, side-effects are a concern with the - azoles – they can cause severe liver toxicity and lower testosterone levels. This makes them a poor option for PI boosting, according to David Back.

Grapefruit juice

A boosting strategy from the early days of saquinavir was the use of concentrated grapefruit juice. David Back and his colleagues at Liverpool University tested five components of grapefruit juice, and found that naringin, 6', 7'-dihydroxybergamottin and bergamottin inhibit and downregulate CYP3A4 and modulate P-glycoprotein, producing higher levels of saquinavir as well as slower clearance by the liver.²³

However, according to Professor Back, five years on it is clear that grapefruit juice is neither a viable nor a reliable method of boosting saquinavir. "It works," Prof. Back says, "but there's a lot of variability between brands of grapefruit juice."

Unless a concentrated grapefruit juice pill were formulated to exacting standards, it would be very difficult to ensure that one is consuming appropriate levels of the active constituents. Additionally, simply eating half a grapefruit at breakfast or drinking a small amount of regular strength juice will not adequately boost saquinavir levels because the active chemicals are mainly found in the skin of the grapefruit.

Another downside with grapefruit juice is that it does not appear to boost concentrations of other PIs,²⁴ although it does affect the metabolism of many other medicines.²⁵

A new drug?

Ritonavir is not simply an imperfect boosting drug due to its association with higher lipids. The current formulation of ritonavir is not heat-stable, which means that, once dispensed, it can only be stored out of the fridge for up to a month as long as the room temperature is

below 25 degrees C. This has major implications in resource-limited nations. Although the NNRTI class is currently the major component of HAART in these nations, there will soon be a demand for second-line and salvage regimens as first-line NNRTI therapies fail. Since boosted PIs are the gold standard in these cases, finding an alternative to ritonavir that does not require refrigeration appears to be rather urgent.

Although one of Abbott's justifications for its ritonavir price increase is to fund research into a heat-stable formulation, this is likely to be several years away, and still does not address ritonavir's lipid-raising issues. Furthermore, it is likely that even at greatly reduced cost, ritonavir will be too expensive for many resource-limited nations.

It might be considered, then, that the best long-term option would be to develop a new drug aimed at inhibiting cytochrome P450 and P-glycoprotein. Professor Back believes that any such drug development is likely to come out of a research centre. However, funding such a project may be difficult.

Another key issue is the need to investigate the long-term adverse effects of any new agent. This would require the lengthy and costly procedure of drug development. Additionally, any new drug which inhibits P450 and P-glycoprotein may have unwanted effects on other bodily processes. For instance, P450 has a role in the production of steroids and thus a drug which inhibits P450 may cause unwanted effects related to steroid activity.

Nevertheless, Professor Back notes that scientists do have the ability to develop a new drug "Funding and motivation have got in the way until now," Professor Back concludes. "However, I think that we're at a situation where if there was enough will, a programme could be developed. In the meantime, ritonavir is with us for the foreseeable future. There is absolutely no doubt."

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Adherence to HAART means more CD4s

People who take 95% or more of their anti-HIV therapy exactly as prescribed experience the best improvements in their CD4 cell counts, irrespective of their CD4 numbers when they began treatment, according to a Canadian study.

"We found that substantial and sustained gains in CD4 cell count were observed among adherent patients, regardless of baseline CD4 cell count," commented the investigators, adding, "in addition, the time to CD4 cell response was most strongly predicted by patient adherence... even among patients who initiated HAART with CD4 cell counts below 200 cells/mm³."

NAM produces a booklet on the importance of taking your anti-HIV therapy as prescribed, and on time. The new 2004 edition is available free of charge to people living with HIV by e-mailing: info@nam.org.uk.

Reference

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Atazanavir now widely available in UK

Atazanavir (*Reyataz*), the new protease inhibitor from Bristol Myers Squibb (BMS), is now available on prescription in the United Kingdom.

Atazanavir is the first once-daily protease inhibitor to be licensed and is dosed as two capsules once a day with food, together with a single ritonavir capsule (300/100mg).

Atazanavir is most likely to be used after the failure of first-line treatment that includes a non-nucleoside reverse transcriptase inhibitor, either nevirapine or efavirenz.

A European license for atazanavir unboosted by ritonavir in patients new to treatment has not yet been granted, although this formulation is already approved in the US. The European Agency for the Evaluation of Medicinal Products want to see more follow-up information before they give approval for atazanavir to be dosed without ritonavir.

In treatment-experienced patients, they decided that atazanavir should be given with a boosting dose of ritonavir because of fears that people with a degree of resistance either to protease inhibitors or to other drugs in their regimen might be at risk of treatment failure due to the possibility of variations in blood levels of atazanavir between individuals. People with low blood levels of atazanavir would be at higher risk of treatment failure, and the European medicines regulators decided that the margin of

error was too small with atazanavir for it to be used in treatment-experienced patients without boosting by ritonavir.

Whilst atazanavir seems to cause less diarrhoea than *Kaletra*, patients in BMS' 045 study (which compared boosted atazanavir with *Kaletra*) were not altogether free of diarrhoea if they received atazanavir: 17% of atazanavir-treated patients reported diarrhoea, compared with 44% of the *Kaletra* treated patients.

Atazanavir's advantages in terms of lipids are clear-cut, however. Triglyceride levels that become elevated as HIV disease progresses tend to fall in atazanavir-treated patients. Also, when compared with people receiving other protease inhibitors, their cholesterol levels do not rise, and they don't need lipid-lowering medication as often as people receiving *kaletra* in the 045 study.

The chief side-effect noted with atazanavir is elevated levels of bilirubin, a waste product from the breakdown of old red blood cells. High and persistent levels of bilirubin caused by atazanavir (known as unconjugated hyperbilirubinemia) are not clinically harmful to the liver but can lead to the development of jaundice (yellowing of the skin and whites of the eyes). Although trials have shown that up to 45% of people who take atazanavir may develop elevated bilirubin levels, few people have needed to discontinue the drug as a result. Trials have typically shown that less than 1% of people who take atazanavir will decide to discontinue treatment as a result of jaundice.

Combination abacavir/3TC pill available

A fixed-dose combination pill of the nucleoside analogues (NRTIs) abacavir and 3TC is now available in the UK on a named-patient basis. This means that anyone over 12 who weighs more than 40kg for whom their doctor considers this drug to be "the best therapeutic option" as part of their anti-HIV combination should be able to obtain it from the manufacturers, GlaxoSmithKline (GSK).

The tablet contains 600mg of abacavir and 300mg of 3TC and is taken once daily as part of a HAART regimen. This combines what is currently four pills (two abacavir 300mg tablets and two 3TC 150mg tablets) into one, which may help people for whom pill burden or twice-daily dosing is a problem. As with the existing twice-daily separate doses of abacavir and 3TC, the once-daily combined pill can be taken with or without food.

Last year, data from the ZODIAC study presented at the ICAAC conference in Chicago showed that once-daily dosing of abacavir and 3TC was just as safe and effective as the twice-daily separate doses. Although there were no new safety concerns about once-daily abacavir dosing, and comparable numbers of patients in both arms of the study experienced a hypersensitivity reaction to abacavir (9% once daily versus 7% twice daily), the level of hypersensitivity seen in the ZODIAC study was significantly higher than the 3-5% incidence suggested by earlier studies.

Patients who believe that the combined abacavir/3TC pill would be suitable for them should discuss this with their regular HIV doctor. Any doctor who wishes to prescribe the pill should contact the GSK medical information line on 0800 085 8747. The medical information line cannot deal with enquiries from individual patients.

TB/HIV draft BHIVA guidelines published

The British HIV Association (BHIVA) has issued draft guidelines for the treatment of tuberculosis (TB) in patients with HIV. The draft guidelines cover TB diagnosis, treatment and prevention, and also offer recommendations for the sequencing of TB and anti-HIV therapy.

A four-drug TB regimen is recommended by the guidelines for the first two months of treatment, followed by a continuation phase involving therapy with two drugs for four months for most patients, or seven months for certain groups.

In addition to routine HIV monitoring, patients with TB should have, as a minimum, liver function tests, a sputum test and a chest x-ray, both at the commencement of treatment and at the conclusion of TB therapy.

Information on how to manage potential interactions between some anti-TB drugs and antiretroviral medicines is included, as is advice on the overlapping toxicities which some TB and HIV drugs can have, including liver toxicity and peripheral neuropathy.

Patients with TB whose CD4 cell count is below 100 cells/mm³ are recommended by the guidelines to start anti-HIV therapy as soon as possible. Individuals whose CD4 cell count is between 100 – 200 cells/mm³ are recommended to start HAART after two months of TB therapy, and individuals with a CD4 cell count above 200 cells/mm³ are recommended to begin HAART after completing six months of TB treatment.

Advice on treating multidrug-resistant TB, treatment during pregnancy and the management of TB reactivated by immune reconstitution is also included in the draft guidelines.

The guidelines can be downloaded as an Adobe Acrobat file from the BHIVA website at: www.bhiva.org/pdf/2004/TB-DRAFT-Feb04.pdf

Comments are welcomed, and should be addressed to the guidelines' author, Dr Anton Pozniak. E-mail: anton.pozniak@chelwest.nhs.uk

news from nam thank you

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nam forum

New HIV vaccine approaches - thinking outside the box: the next forum will take place on Monday 26th April and will feature Dr Barry Peters, who will be explaining what the latest information about HIV immunity and vaccines means to you. The forum will take place at the usual time (7-9pm), usual place: University of London Union, Palms Room, 4th Floor, Malet Street, London, WC1. See www.aidsmap.com for a map and more details.

in next month's issue

The May issue of AIDS Treatment Update will include a feature on the latest treatments for the management of peripheral neuropathy, as reported at CROI, as well as an investigation into the connection between the development of HIV-related dementia and ageing.

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For more information, and details of our other publications and services, please contact us, or visit our website, www.aidsmap.com.

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NAM recommends that you discuss all your treatment decisions with your doctor.