

aids treatment update

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in this issue

The biggest treatment-related news from Toronto is that ten years after the confirmation that potent anti-HIV therapy works well at keeping HIV at bay, new drugs and new treatment strategies promise to improve both quantity and quality of life - for those who have access to them.

Yet it's hard not to feel incredibly angry/guilty/privileged at the increasing chasm between what is available to us in the UK - where those of us who can access treatment on the NHS have some of the best care in the world - and what is not available to most people in poorer countries.

Denying people access to treatment is primarily a political issue. That's why there was so much focus on world politics at the conference. But there are problems in our own backyard, too.

Some people who cannot access treatment in their home country are denied treatment when they come here in search of asylum. Some still get cared for by compassionate doctors; others are sent home to an uncertain future.

Whilst the UK government's Department for International Development (DfID) provides help for people with HIV overseas, the Home Office and the Department of Health do little to help the same people on our own soil.

Isn't it time for some serious joined-up thinking?

page 3 This month's *Upfront* examines the implications for future prosecutions of HIV transmission in England & Wales of the recent 'not guilty' verdict in the trial of a gay man accused of 'recklessly' infecting his ex-partner with HIV.

page 4 Over the following eight pages, *Understanding Toronto* provides an overview of the most important scientific papers presented at the 16th International AIDS Conference.

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aids treatment update

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not guilty

by Edwin J Bernard

In August, a young gay man was cleared of 'reckless' HIV transmission after the judge directed the jury to find him 'not guilty'. The most important difference between this case and the two previous cases that went to trial - those of Mohammed Dica and Feston Konzani - is that this case was fought and won on scientific evidence, rather than arguments about the disclosure of HIV status and the informed consent of the complainant(s) to have unprotected sex.

In this case, although the complainant believed that the defendant had infected him with HIV, and had done so without disclosing his HIV-positive status before they both agreed to have unprotected sex during their short-lived, on-off relationship, the defence argued that it could not be proven "beyond reasonable doubt" that the defendant had actually infected his former partner.

Key evidence

The key evidence came from expert witness, Dr Anna Maria Geretti, a virologist from London's Royal Free Hospital. Using a technique known as phylogenetic analysis she closely examined the structure of both men's HIV, and then compared it with HIV from other gay men in London. Although previous prosecutions had used the same technique, experts used in those court cases had said that the genetic similarities between the HIV of the complainant(s) and defendant were too similar for there to be any other conclusion drawn other than that the defendant had infected the complainant(s).

However, Dr Geretti said that although the two men's viruses were genetically

important new developments on prosecuting HIV transmission in england & wales

similar, there was no way that she could be certain that the defendant infected the complainant and stressed that it was possible that a third party was involved.

The defence then successfully argued that since the complainant had engaged in high-risk sexual activities with other men during this period, and had acquired a variety of sexually transmitted infections placing him at high risk of HIV infection, he may have been infected by someone else.

What this means

This case has two important implications. In future, the Crown Prosecution Service (CPS) - who decide on which cases to prosecute - may no longer be able to rely on phylogenetic testing to prove that one person infected another, as they have in all previous cases, including those that did not go to trial. Dr Geretti says that this evidence alone should not lead to a conviction. "Virological evidence should be seen in the context of other facts," she said after the trial. "You should not build a case around this type of evidence alone. There could be a chain of transmission, where four or five people are infected with a similar virus, so it is impossible to tell whether transmission has occurred between two people with a related virus."

Much of the "reasonable doubt" that led the judge to tell the jury that he was "duty bound to direct [them] to acquit" was raised because the complainant had a sexual history (documented in his sexual health clinic notes) that suggested he could have

acquired HIV at any time - and from a variety of other men - between his HIV-negative test in 1999 and his HIV-positive test in 2004.

Consequently, anyone who is considering making a police complaint needs to be prepared for an intrusive investigation into their own sexual history. This may result in a prosecution being more likely to go ahead when the alleged HIV transmission is between long-term monogamous couples rather than people who have short-lived relationships, many sexual partners and/or a history of sexually transmitted infections. ■

See news in brief on page 13 for more important criminalisation news.



understanding

The Sixteenth International AIDS Conference, held between August 13th and 18th in Canada's largest city, Toronto, was considered by some to be long on spectacle but short on science.

Once relatively small, science-focused meetings, international AIDS conferences are now rather overwhelming, overblown affairs that have become much more focused on the link between politics, prevention and treatment for the millions who live with HIV in low- and middle-income nations.

The conference will mainly be remembered for the 'double Bill' of former US President Bill Clinton and Microsoft billionaire Bill Gates, both of whom ensured that HIV prevention became the conference's main agenda and whose appearances - and those of entertainer/activists like Richard Gere and Alicia Keys - ensured huge media coverage in celebrity-obsessed nations like the United States (US) and the United Kingdom (UK).

It will also be remembered for the refreshingly honest and angry outbursts of outgoing UN special envoy for AIDS in Africa, Stephen Lewis, against the "obtuse, dilatory and negligent" South African government's "lunatic fringe" policies towards HIV/AIDS, which drew much-needed attention to the fact that South

Africa's HIV treatment 'scale-up' is overseen by people who do not believe that HIV causes AIDS.

However, these high-profile attendees also meant that the voices of people living with HIV/AIDS were less evident, even if they made up the majority of the record-breaking 24,000 conference attendees. Interrupting a lacklustre press conference held to discuss 25 years of AIDS, an angry South African woman pointedly asked, "Is this an AIDS conference or is this a Hollywood conference?"

Nevertheless, many important new scientific data were presented in Toronto, providing a great deal of insight into how we might approach HIV treatment in the UK, both now and in the near future. Of the more than 10,000 scientific papers from 145 countries submitted for presentation at the conference, a mind-boggling 4,500 were actually presented during the week long meeting.

Subjects covered included:

- new information on how best to use currently approved anti-HIV drugs;
- good news about some promising new drugs in the pipeline;
- experimental treatment strategies, such as treatment simplification and structured treatment interruption.





toronto

what the science means for hiv treatment today and tomorrow
by Edwin J Bernard

New treatment guidelines

The US branch of the International AIDS Society (IAS-USA) launched their new treatment guidelines at the conference¹.

The guidelines' authors are world-class experts in HIV treatment - Professor Brian Gazzard of London's Chelsea & Westminster Hospital represents the UK - and the new guidelines, last updated two years ago, are aimed at well-resourced nations, although they note that the principles of the guidelines are "pertinent" to resource-limited settings, too.

The IAS guidelines are based on drugs that are currently approved in the US. Some of these drugs - notably the new protease inhibitor (PI) darunavir (also known as TMC114, and marketed as *Prezista* in the US) and the triple drug once-daily pill marketed as *Atripla* in the US that contains the non-nucleoside (NNRTI) efavirenz (*Sustiva*) with the nucleotide/nucleoside 'backbone' of tenofovir/FTC (*Truvada*) - are not yet approved in the European Union (EU). In addition, some drugs are approved at different doses or are approved for people at different stages of treatment in the US compared with the EU.

For example, once-daily ritonavir-boosted lopinavir (*Kaletra*) is

approved in the US for people new to treatment, whereas in the EU, only twice-daily *Kaletra* currently has approval. Another PI, atazanavir (*Reyataz*), is approved in the US for anyone, with or without ritonavir boosting, whereas in the EU only ritonavir-boosted atazanavir (*Reyataz*) currently has approval, and this is only for treatment-experienced individuals.

The reasons for these differences in drug approvals are complex, and relate to different approaches between the US Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMA) and will be explored in detail in a future issue of *ATU*.

Nevertheless, the IAS recommendations are broadly similar to the draft version of the updated British HIV Association (BHIVA) treatment guidelines, which were published on BHIVA's website² for consultation just before the Toronto conference.

The final version is due to be published in December, and it is possible that some of BHIVA's draft recommendations may have changed - based on feedback from the consultation as well as some of the new data that was presented in Toronto - after this issue of *ATU*

went to press. We'll let you know if they have.

Guarded optimism

"Today, I can tell my patients with HIV that they can have a normal life expectancy, if they stay on their medicines," IAS guidelines co-author and former IAS president, Italy's Dr Stefano Vella said at a press conference to launch the new guidelines.

"We have so many medicines now, and they are so good that we know we can keep the virus suppressed for years," he continued. "We now have drugs that allow us to construct second, third and even fourth lines of treatment that are all capable of suppressing the virus.

"What's more," he added, "we are going to see even better drugs in just a couple of years."

Although his optimism is encouraging, there exists the very real possibility that some of the most promising new drugs discussed in this article may not be approved due to unexpected issues with potency and toxicity not yet seen in clinical trials.

This suggests that any optimism regarding future treatment choices should remain guarded. In other words, we should hope for the best, but expect the unexpected!

understanding starting treatment

When to start treatment?

Both the IAS and BHIVA guidelines continue to agree that anti-HIV treatment should be started in all people with symptoms of HIV/AIDS regardless of CD4 cell count, and in asymptomatic individuals once the CD4 cell count has fallen below 350 cells/mm³ but before it drops below 200 cells/mm³.

In addition, both guidelines also suggest that since the decision to start treatment is based on patient choice, as well as on finely balancing the risks of HIV disease progression with anti-HIV treatment's toxicity and tolerability (and the risk of running out of options due to resistance), it is now feasible to start treatment closer to 350 cells/mm³ for those who want to. This, they say, is because newer anti-HIV drugs appear to be less toxic and easier to take than earlier drugs, and new versions of current drugs as well as brand new classes, such as integrase inhibitors, promise to provide more options even in the face of resistance.

The BHIVA guidelines also note that in certain groups of people with a higher risk of HIV disease progression - such as older people (e.g. aged 50 and above), those with extremely high viral loads, and those coinfecting with hepatitis B and/or C - "it will increasingly become reasonable to

consider starting therapy earlier than previously", at CD4 cell counts above 350 cells/mm³.

What to start with?

Both guidelines stress that there is no one-size-fits-all approach to choosing the right combination of drugs. The choice will come down to (real and perceived) concerns about short-, medium- and long-term side-effects; how well a combination fits into an individual's lifestyle and the results of a battery of tests that should be done when first diagnosed, and again before starting treatment.

These ought to include:

- checking for resistance (about 9% of people starting treatment for the first time in the UK will have picked up a strain of HIV that is resistant to at least a couple of drugs);
- finding out if you are coinfecting with hepatitis B or C, or both;
- finding out whether you are at risk of cardiovascular disease;
- making sure your heart, liver and kidneys are working well;
- finding out if you are pregnant, planning to become pregnant and if not, what contraception you are using;

- and taking into consideration other medications that may interact or have overlapping toxicities.

All of these factors will narrow down the choice from the array of drugs on offer.

NNRTI or boosted PI?

One of the most important - and surprising - treatment-related findings to come out of Toronto was presented at the conference by the US-government funded AIDS Clinical Trial Group (ACTG)³. Their data suggest that the NNRTI efavirenz (*Sustiva*) may be more durable - and therefore more effective - than the boosted PI, *Kaletra*, for people starting treatment for the first time.

Until now, there had been no large-scale randomised clinical trials comparing the two regimens, although there had been a perception amongst some experts that *Kaletra* was more potent for people starting therapy with viral loads greater than 100,000 copies/ml, and that it was possibly more durable than efavirenz, based on longer clinical experience as well as four-year follow-up data from the drug's manufacturer, Abbott, in a small group of individuals.

Both the IAS guidelines and the draft BHIVA guidelines currently recommend that first-line therapy

merck's new
integrase
inhibitor
a future third option?

The battle for first-line supremacy between boosted PIs - and between PIs and NNRTIs - may turn out to be relatively short-lived. There is already a perception amongst some experts that the whole class is beginning to appear outdated, since they require a boosting dose of ritonavir (*Norvir*), which is strongly associated with increased blood fats, as well as the inconvenience of diarrhoea.

Enter Merck's integrase inhibitor, MK-0518. Preliminary findings presented in Toronto⁵ - six months into a small-ish one-year study - suggest that it may be as effective as efavirenz when taken with a dual nucleotide/nucleoside 'backbone' of tenofovir/3TC.

Integrase is an HIV enzyme that allows the virus to insert its genetic material into the DNA of human CD4 T-cells. By blocking this step in the viral lifecycle,

toronto



should contain one of several choices of dual nucleoside/nucleotide 'backbone' drugs plus either one NNRTI or a boosted protease inhibitor (PI). Efavirenz and *Kaletra* are among the most favoured choices, and these two drugs are currently the most frequently prescribed in their respective classes.

However, the first head-to-head comparison of these two drugs by the ACTG found that the group of people randomised to take *Kaletra*-based triple therapy had a significantly shorter time to 'virological failure' (a viral load measurement above 200 copies/ml) than those taking efavirenz-based triple therapy.

Notably, 89% of the participants receiving efavirenz-based triple therapy had viral loads below 50 copies/ml after two years, compared with 77% receiving *Kaletra*-based triple therapy. The researchers could not explain why this was the case, since they found that both drugs were tolerated equally well, and similar numbers of participants stopped their treatment due to toxicity.

On the other hand, CD4 cell count increases appeared to be greater in the people taking *Kaletra*: 285 cells/mm³ versus 241 cells/mm³ after two years. However, the clinical significance of this is unknown.

integrase inhibitors can prevent HIV from replicating.

So far, MK-0518 seems to be well tolerated, although only a few hundred people have taken it for longer than a few weeks. However, it doesn't have to be boosted with ritonavir and it doesn't have the central nervous system side-effects associated with efavirenz. In fact, the only

Which boosted PI?

Kaletra was the preferred boosted PI choice in the 2005 BHIVA guidelines, but other boosted PIs are catching up: the IAS guidelines now place atazanavir, saquinavir and fosamprenavir (all boosted) on an equally preferred footing for the first time.

The draft BHIVA guidelines are currently more cautious, still recommending the same four PIs, but placing *Kaletra* above the others as the preferred regimen.

Although atazanavir is not yet approved for first-line therapy in the EU, BHIVA does recommend that since this is the only boosted PI not associated with increased blood fats, atazanavir could be used in individuals starting therapy for the first time, as long as its use is "restricted to those with established cardiovascular risk factors and where a PI is required."

The BHIVA authors say in their draft guidelines that they wanted to wait until detailed results of head-to-head comparisons with *Kaletra* were announced before considering elevating fosamprenavir or saquinavir to *Kaletra*'s preferred level.

Well, the final results of the KLEAN study⁴ were published in *The Lancet* just prior to their Toronto presentation. This large, randomised study found that

side-effect reported so far that wasn't experienced more by the participants taking efavirenz is flatulence.

A new larger study comparing MK-0518 with efavirenz, both with *Truvada* (tenofovir/FTC) as the dual nucleotide/nucleoside 'backbone' has just begun to enrol an expected 550 treatment-naïve individuals. The results of this year-long study are likely to influence

boosted fosamprenavir was "not inferior" to *Kaletra*: in other words, the two were comparable in terms of effectiveness, safety, and tolerability over 48 weeks. Both produced similar side-effects, too; primarily diarrhoea and increased blood fats.

Nevertheless, when patients and their doctors come to choose between the two, they will probably take into consideration the fact that the new tablet formulation of *Kaletra* does not need to be refrigerated, unlike the ritonavir capsule that must be taken to boost fosamprenavir. Cost may also be an issue, since the BHIVA guidelines say that when everything else is equal, cost should be considered.

This has already resulted in a pricing war between Abbott (who market both *Kaletra* and ritonavir) and GSK, who substantially reduced the cost of fosamprenavir in the UK on September 1st, making it the cheapest PI as we go to press. Abbott - who have said that a heat-stable tablet version of ritonavir is proving difficult to create - may still have the upper hand, since they control the price of ritonavir, which is needed to boost fosamprenavir. Several years ago they increased the price by 400% in the US, which made *Kaletra* the cheapest boosted PI, helping it gain the lion's share of the PI market.

whether MK-0518 will be approved for people who haven't taken anti-HIV treatment before.

Merck took the opportunity of the conference's limelight to announce that they will soon make MK-0518 available through a worldwide expanded access programme to treatment-experienced individuals who cannot construct a viable anti-HIV regimen without it.

understanding treatment experienced

Great news for the treatment-experienced

Even before the expanded access availability of the highly promising Merck integrase inhibitor, both the IAS and BHIVA guidelines are tremendously upbeat regarding the prospects of treatment-experienced people. The term 'salvage therapy', which had implied treatment that was rescuing someone from potential destruction, seems outdated today: "Our new treatment guidelines encourage doctors to treat even the most-experienced patients with an eye to suppressing the disease," noted IAS guidelines co-author, Professor Scott Hammer, of Columbia University, New York, at the Toronto conference.

The BHIVA guidelines authors also write that "the goals of treatment for majority of treatment-experienced patients have changed, and the new paradigm should be wherever possible maximal and durable HIV viral suppression leading to immunological improvement with lack of clinical progression and improvement in quality of life."

They now recommend that individuals with the option of at least two - and preferably three - new active drugs should switch "as soon as possible [after virological failure] when the CD4 count is higher and viral load lower".

Tipranavir or darunavir?

Tipranavir (*Aptivus*), which was approved in the EU a year ago - and darunavir - which should be approved in the EU before the end of the year - are both ritonavir-boosted PIs that appear to be quite effective against virus resistant to current PIs, and are the two available PI options for the highly treatment-experienced.

Now that 48-week data have been presented on darunavir in Toronto, it should be possible to compare the two in terms of potency and tolerability. However, there are some differences in the way the studies were designed, and in the people treated, so direct comparisons are never straightforward, and should be interpreted with caution. Nevertheless, both PIs were compared with lopinavir/ritonavir (*Kaletra*), boosted saquinavir (*Invirase*), boosted amprenavir (*Agenerase*) and boosted atazanavir (*Reyataz*) in highly treatment-experienced people, and some comparisons are inevitable.

The combined results of the POWER 1 and POWER 2 studies⁶ presented in Toronto found that in highly treatment-experienced individuals ritonavir-boosted darunavir proved superior to the other boosted PIs, with almost half of the study participants having viral loads below 50 copies/ml 48 weeks after starting treatment with darunavir.

The combined results of the RESIST 1 and RESIST 2 studies⁷ that were presented last year at the Tenth European AIDS Conference in Dublin showed that although ritonavir-boosted tipranavir was superior to the other boosted PIs, just 23% of tipranavir-treated individuals had viral loads below 50 copies/ml after 48 weeks.

Darunavir appears more tolerable, too. Whilst darunavir had a side-effect profile similar to that of the other boosted PIs, it was less likely to cause diarrhoea. On the other hand, whilst tipranavir's side-effect profile was also similar to the other boosted PIs, more people taking tipranavir experienced elevations in liver enzymes and blood fats.

Don't forget the *Fuzeon!*

Both the IAS and the BHIVA treatment guidelines note that people who had never taken enfuvirtide (T-20, *Fuzeon*) before were significantly more likely to achieve an undetectable viral load when they added it to either tipranavir or darunavir as part of an optimised background regimen.

Enfuvirtide is the only drug currently available in the fusion inhibitor class of antiretrovirals. Unlike all other anti-HIV drugs, enfuvirtide can only be given by twice-daily injection and although the drug is not associated with side-effects commonly caused by other classes of antiretrovirals, using it can lead to the development of injection site reactions - often angry red bumps - and needle fatigue. In addition many people are needle-phobic and some doctors worry their patients won't want to self-inject the drug.

At Toronto we heard more about a needle-free delivery system known as the *Biojector B2000*. This is quite a large, clunky device about the size of a desktop stapler that is placed against the skin and delivers enfuvirtide through the skin at high pressure.

A US community pharmacy, BioScrip, has been providing the *B2000* to 726 individuals, of whom 85% had previously used a needle to self-inject enfuvirtide. They are evaluating it for a year, and in Toronto they presented their first six months of data.

They found that injection site reactions and fear of using enfuvirtide improved significantly, with 75% saying that they preferred the *B2000* to syringes so far⁸.

The *B2000* is not yet widely available for use with enfuvirtide, but Roche and Trimeris, who market the drug, will soon present data from their own WAND study, which, if positive, may lead to more widespread availability soon.

toronto



drugs in the pipeline

More on CCR5 antagonists

A year ago, everyone was excited about a new class of anti-HIV drugs known as CCR5 antagonists. However, development of aplaviroc - which was developed by the Japanese company Ono and went on to be developed by GlaxoSmithKline - was stopped in late 2005, following the discovery that it led to severe liver toxicity in two studies which were halted early.

Some studies of a second CCR5 antagonist, vicriviroc - developed by Schering-Plough - were also halted last year due to poor responses in individuals who had not taken anti-HIV therapy before, although an ACTG study of the drug in 118 treatment-experienced individuals has continued. Results of this study, known as ACTG A521, were presented in Toronto⁹.

Although the people who added vicriviroc to their 'failing' boosted PI regimen had much greater viral load reductions and larger CD4 cell count rises after 24 weeks than those who took a pill that looked like vicriviroc but contained no active ingredient, there were no data presented on how many people ended up with a viral load below 50 copies/ml.

In addition, there were some other concerns about vicriviroc, in particular the fact that five cases of cancer occurred in the people taking the drug, although several of these cases were in people with a previous history of cancer. Since two cancers were diagnosed in the group of patients who were not taking vicriviroc, the investigators concluded that "the

relationship of vicriviroc to malignancy is uncertain".

A third CCR5 antagonist - Pfizer's maraviroc - has also had some development problems. A study of once-daily maraviroc involving people who had never taken HIV therapy before was stopped earlier this year because it appeared to be less potent than efavirenz. However, a study comparing twice-daily maraviroc against efavirenz in treatment-naïve individuals continues, as do several studies examining the effects of maraviroc in treatment-experienced individuals.

Late in 2005, a treatment-naïve patient enrolled in the maraviroc study experienced severe liver toxicities.

Although the drug safety and monitoring board concluded that these were probably due to other medications she was taking that are known to cause liver problems, they could not rule out the possible involvement of maraviroc.

Data presented in Toronto¹⁰ suggest that maraviroc is safe and well-tolerated in highly treatment-experienced individuals who are infected with HIV that uses both the CCR5 and CXCR4 co-receptors to enter CD4 cells. Although it doesn't appear to be very effective in reducing viral loads in people who have so-called 'dual-tropic' HIV, maraviroc did appear to increase CD4 cell counts a little. Notably, people who also used enfuvirtide had the best results.

Promising future therapies

TNX-355 is an artificial antibody developed by biotech company, Tanox,

which attaches to the CD4 receptor on the surface of CD4 cells, preventing HIV from entering CD4 cells. Results from a small randomised phase II trial presented at Toronto¹¹ found that TNX-355 can reduce viral loads and allow CD4 cell counts to rise, when combined with an optimised background regimen.

If development continues, it is likely to be seen as a competitor to enfuvirtide, since this fusion inhibitor can be dosed once a week for the first eight weeks, and then taken every other week. However, unlike enfuvirtide - which can be self-injected under the skin - TNX-355 must be infused into a vein, which requires regular visits to the doctor.

Trimeris - who developed enfuvirtide - are already working on two new fusion inhibitors that they think will require once-weekly self-administered injections, and in Toronto they reported on test tube¹² and animal studies¹³ of TRI-1144 and TRI-999 which showed that this was possible, and that these investigative compounds were also active against enfuvirtide-resistant HIV.

Data were also presented on two PIs in early development. GlaxoSmithKline's brexanavir appears to work well against HIV that is resistant to other PIs¹⁴, and PPL-100 - from biotech company Ambrilia - may be able to be dosed once daily without the need for ritonavir boosting. In fact, test-tube studies presented in Toronto¹⁵ suggest that PPL-100 may also boost other PIs, although not quite as potently as ritonavir.

understanding

alternative treatment strategies

A variety of alternatives to the currently recommended NNRTI or boosted PI plus a dual nucleotide/nucleoside 'backbone' were examined in Toronto. Although results are promising, most experts agree that they are not ready for prime time.

Kaletra monotherapy

Four studies examined either starting therapy with, or switching first-time therapy to, *Kaletra* monotherapy which appeared to be an attractive option when the studies were conceived, since it was thought that this may reduce both side-effects and cost. However, this may come at a price: it is still unclear whether *Kaletra* alone can control levels of HIV in places other than the blood, such as the brain, the gut, and the genitals - known as 'sanctuary sites' - where it may be possible for the virus to replicate at high enough levels to eventually create resistant strains.

Three of the studies - M03-613¹⁶, OK40¹⁷ and KaMo¹⁸ - were similar in design. They all found that most individuals whose HIV was controlled with combination therapy could safely switch to using *Kaletra* alone for up to two years, with controlled viral loads and few cases of resistance. A fourth study, the MONARK trial¹⁹, found that starting HIV treatment with *Kaletra* alone may be safe for some people for up to a year. Most of

the people who experienced an increase in viral loads managed to reduce HIV to undetectable levels by adding a dual nucleotide/nucleoside 'backbone' to *Kaletra*.

Still, all of the *Kaletra* monotherapy studies found that people who received *Kaletra* alone were more likely to experience 'viral blips' (where viral loads jump temporarily to between 50 and 400 copies/ml) than those who received triple combination therapy. Although we don't know if this means anything in the long-term, it might mean that HIV is still replicating in sanctuary sites and may eventually become resistant to the active ingredient in *Kaletra*, lopinavir. This suggests that more data are needed before this strategy could ever be recommended in treatment guidelines; at the moment it remains an experimental strategy.

No nukes?

The same ACTG study that compared efavirenz with *Kaletra* as a first-line therapy also examined whether efavirenz plus *Kaletra*, but with no nucleotide/nucleoside 'backbone', was possible in people taking anti-HIV therapy for the first time. The ACTG 5142 study³ concluded that this nucleoside-sparing regimen was almost as effective as the now 'gold-standard' efavirenz-based triple therapy.

The study's lead author, Dr Sharon Riddler, told that conference that since "we found that the NRTI-sparing two-drug combination of efavirenz and lopinavir had a similar level of effectiveness to the efavirenz plus two-NRTI regimen...there should be little doubt that patients can benefit from this 'nuke'-sparing treatment regimen when NRTI side-effects are a problem."

However, the preliminary resistance analysis showed that people who experienced virological failure on efavirenz plus *Kaletra* showed a trend towards a higher rate of NNRTI resistance when compared with the people on efavirenz-based triple therapy.

In addition, since efavirenz lowers levels of lopinavir, a higher dose of *Kaletra* must be used. In this study, this was easily obtained by increasing the *Kaletra* dose from three capsules twice daily to four capsules twice daily. Now that *Kaletra* is only available in tablet form, increasing the dose from two tablets twice daily to three tablets twice daily would mean taking substantially higher levels of ritonavir (200mg twice a day, compared with 133.33mg twice a day in the soft gel capsules). This may well result in a lot more ritonavir-associated side-effects, like increased blood fats and diarrhoea.

toronto treatment interruptions

Earlier this year, SMART - the largest-ever study of an HIV treatment strategy - was terminated early after it became clear that people in the treatment interruption arm were 2.6 times more likely to experience HIV disease progression or death than people who continued taking their anti-HIV drugs.

The Toronto conference heard several reports from the SMART study team, examining why this happened, and if there were any benefits at all from interrupting treatment.

Dr Jens Lundgren's analysis²⁰ found that the risk of opportunistic infections or death was similar to what might be expected among participants with CD4 cell counts below 350 cells/mm³, but significantly greater in the treatment interruption arm among participants with CD4 cell counts of 350 cells/mm³ or more. While lower CD4 cell counts in the treatment interruption arm accounted for some of the differences in the rates of illness and death between the two arms, CD4 cell levels could only provide a "partial explanation," he told the conference.

Some experts have suggested that going off treatment may create an inflammatory immune system response which can't be measured by CD4 cell counts alone, and that this may be the reason that stopping treatment - even at higher CD4 cell counts - appears to be riskier than previously thought.

A second analysis, presented by Dr Wafaa El-Sadr²¹, found that no particular group of people appeared to benefit from treatment interruptions. However, she told the conference that people who were doing best on their anti-HIV therapy before interrupting treatment (those with 'undetectable' viral loads and higher CD4 cell counts) experienced the worst outcomes using the treatment interruption strategy.

A third analysis found that people who interrupted their treatment in the SMART study had a worse quality of life as the study progressed²². This came as a surprise, since it had been thought that interrupting anti-HIV therapy would improve quality of life by reducing exposure to potentially toxic drugs, and relieving the burden of remembering to take drugs once or twice a day.

In fact, the people who interrupted their treatment reported worse physical health, less energy, had poorer mental health and experienced greater levels of pain than the people who remained on treatment throughout the study.

What if you still have to interrupt treatment?

Both the IAS and BHIVA guidelines do provide some guidance, however, on treatment interruptions. The IAS guidelines authors acknowledge that "treatment fatigue, when a patient strongly requests that treatment be stopped temporarily, is a common reason to consider" a structured treatment interruption. They recommend, however, that it should be explained to the individual who wants to stop treatment that there are risks of both disease progression and of drug resistance, but that if they still want to stop therapy they should be allowed to do so, and then monitored closely until they are ready to restart.

Other reasons for interrupting treatment cited by the IAS guidelines authors include "significant antiretroviral toxic effects" and situations where the treatment of another infection - such as TB - might jeopardise the effectiveness of either treatment.

In those cases they recommend that anti-HIV drugs should be restarted as soon as possible after the symptoms have resolved, or when the treatment of the other infection has been successful.

The BHIVA guideline authors suggest an alternative strategy to interrupting treatment for those highly treatment-experienced individuals who are unable to construct a regimen with at least two new active drugs.

They point to a recent study²³ examining the possibility of using 3TC (lamivudine, *Epivir*) monotherapy. This study found that 3TC monotherapy "significantly delayed CD4 count decline and reduced viral load rebound compared to treatment interruption" in people with more than 500 CD4 cells/mm³ whose current regimen was failing and who had 3TC resistance (the M184V mutation). They add, however, that this strategy should only be considered in the "short term" and "is only relevant until a regimen likely to suppress viral replication completely can be found."

complementary therapies

Are you risking your health with 'complementary' therapies?



A survey of 293 HIV-positive individuals attending several large London HIV clinics has found that one-in-nine (11%) were taking complementary or alternative treatments that were potentially dangerous to their health, according to a study that was presented at the International AIDS Conference in Toronto.

The survey found that two-thirds of respondents were taking herbal or alternative remedies which have the potential to cause side-effects and/or have interactions with drugs used to treat HIV. Since only half of the people using alternative therapies had told their HIV healthcare provider what they were using, many were unaware of the risks.

The majority (8%) of respondents taking potentially dangerous therapies were using the herb echinacea. Test-tube studies have shown that the herb stimulates white blood cells, known as macrophages, to release certain immune system messengers, known as cytokines, including tumour necrosis factor (TNF) and interleukin-1. However, many HIV-positive people already have excessively high levels of these cytokines, and they are associated with some of HIV's symptoms, including weight loss, persistent fevers and diarrhoea. It is possible, then, that further immune stimulation with echinacea may well be counterproductive.

Another 3% of respondents were taking products that can lower the amount of anti-HIV drugs in the blood, which could lead to resistance and treatment failure. These include garlic supplements, and the herbs, kava and St John's wort.

The study highlights the importance of informing your HIV healthcare provider about the non-prescription therapies that you are taking. Even if you think your doctor won't approve of you using alternative medicine, it is important to inform someone in your healthcare team. Your HIV pharmacist may well be the ideal person to help you assess the potential risks and benefits arising from the use of herbal, complementary and other over-the-counter medicines.

hiv transmission

Two-in-five HIV-positive gay men don't know they're positive

On average, of every five HIV-positive urban gay men, two are undiagnosed, according to research from five English and Scottish cities by the Medical Research Council and University College London. This involved surveys at gay bars and clubs linked to anonymous HIV antibody testing (so no-one was told their results).

In total, 41% of HIV-positive gay men in all five cities were found to be undiagnosed. Over half of these men (53%) reported that their most recent HIV antibody test was negative and, consequently, they falsely believed themselves to be HIV-negative.

The city with the highest HIV prevalence was Brighton, where one-in-seven were found to be HIV-positive. However, Brighton had the lowest percentage of undiagnosed men: one in three were unaware of their infection.

One-in-eight of gay men in London were found to be HIV-positive, but almost half of them (44%) were unaware of their positive status.

Although almost one out of every two HIV-positive gay men in Glasgow were unaware of their positive status, HIV prevalence was the lowest of the five cities: just one in 28.

Just over one-in-three HIV-positive gay men in Manchester and Edinburgh were undiagnosed, although there were more people living with HIV in Manchester (one-in-eleven) than in Edinburgh (one-in-18).

The researchers told the conference that "given the high level of sexual risk behaviour, undiagnosed infection and incorrect assumptions of status, the potential for HIV transmission is of concern".

clinical trials

Controlling HIV long-term without drugs?

An international appeal was launched in Toronto to find people who are controlling HIV at very low viral load levels without any medication in order to learn how they control HIV, and to use this information to design potential vaccines.

The HIV Elite Controllers Consortium is looking for two groups of people with HIV: 'elite controllers' - people who have been living with diagnosed HIV infection for at least a year and who have had a viral load below 50 copies/ml throughout that period without any treatment); and viral controllers - people who have been living with diagnosed HIV infection for at least a year and who have had a viral load below 2000 copies/ml throughout that period without treatment.

Professor Bruce Walker of Harvard University Medical School said they were looking for between 700-800 people worldwide. Participation in the study is a very simple process: researchers need only a blood sample to be drawn by your doctor, which is then sent by post for analysis. A small number of participants may be invited to the United States for more intensive immunological studies.

To volunteer to join the study, contact the researchers directly by emailing Rachel Rosenberg at rosenberg2@partners.org.

travel

Travel update

German and Swiss HIV activists have developed a guide for HIV-positive travellers, providing details of the entry restrictions which some countries place on HIV-positive individuals. The guide, *Quick Reference: Travel and Residence Regulations for People with HIV and AIDS 2005*, can now be accessed in English via the website of the International Lesbian and Gay Association: <http://doc.ilga.org>.



criminalisation

Confidentiality update

The UK Department of Health has opened up a consultation on the confidentiality of HIV and sexual health records and the circumstances in which disclosure without a patient's consent may be possible. This follows concerns highlighted by the British HIV Association's preliminary guidance document on confidentiality in the light of recent prosecutions for the transmission of HIV (see ATU 159).

The consultation document is available at: www.dh.gov.uk/Consultations/LiveConsultations and the deadline for the receipt of comments is October 31st.

criminalisation

HIV transmission prosecutions: have your say

The long-awaited consultation by the Crown Prosecution Service (CPS) on their policy for prosecuting HIV transmission is taking place right now, with a deadline for comments by November 3rd.

Considering that the CPS have already consulted with a variety of HIV and sexual health organisations, as well as doctors and legal experts, the draft document is hugely disappointing and ill-conceived.

For example, although they say that they want to prosecute 'intentional' or 'reckless' transmission of most sexually transmitted infections that "cause grievous bodily harm" - not just HIV - they include the relatively innocuous STI, non-specific urethritis (NSU), but exclude human papilloma virus (HPV), responsible for cervical and anal cancer as well as genital and anal warts.

There are many areas of the document that require further comment and change before the final version is published in

February 2007, and as Lisa Power, THT's Head of Policy says, "it's vital that people who have something to say about the way in which people are being prosecuted for sexual transmission of HIV respond to this consultation. The CPS need to hear what is really happening and how it affects the ability of people with HIV to live their lives, and the ability of doctors and others to provide services for them."

THT and the National AIDS Trust have joined together to provide further information on prosecutions for transmitting HIV and other STIs as well as guidelines for commenting on the CPS consultation document. These are available from <http://www.tht.org.uk/informationresources/prosecutions>. The consultation document is also available to view on the UKC website (<http://www.ukcoalition.org/law>) which also includes an anonymous online response form for individuals who would like the UKC to respond on their behalf.



about our readers*

What was the survey respondents'...?

...gender?

a total of **86%** were male and **13%** were female.

...ethnicity?

the majority (**71%**) were white British, another **15%** were white European, and **4%** were black African.

...sexuality?

the majority (**79%**) were gay, lesbian or bisexual, and **18%** were heterosexual.

...age group?

close to **10%** were aged 25-34; **36%** aged 35-44; **35%** aged 45-54; and **14%** aged 55-64.

...first language?

English was the first language for **88%**; other first languages included Spanish, Italian, German, French, Portuguese, Shona (spoken in Zimbabwe), Chichewa (spoken in Malawi) and Welsh.

...educational achievement?

49% were educated to degree level or higher; **16%** left education at 18; **19%** left education at 16; and **2%** were still in education.

...HIV status?

89% of survey respondents were HIV-positive, **8%** reported that they are HIV-negative, and **3%** said that did not know their HIV status.

When were the HIV-positive survey respondents diagnosed?

Of the **89%** who said they were HIV-positive, **23%** were diagnosed up to four years ago; **24%** were diagnosed between five and nine years ago; **25%** were diagnosed between ten and 14 years ago; **15%** were diagnosed 15-19 years ago; and **13%** were diagnosed more than 20 years ago.

How many are on treatment?

The vast majority (**84%**) of HIV-positive survey respondents said they were currently taking anti-HIV treatment.

“ All the info provided is always of utmost interest and very useful ”

readers' survey results

who are you, and what do you think of *atu*? by Edwin J Bernard

Earlier this year, NAM surveyed the 5,700 or so HIV-affected individuals that had received a free subscription to *AIDS Treatment Update* in the past year.

This was our first readers' survey in more than two years; we had previously undertaken a great deal of other kinds of research prior to our redesign in October 2005.

The survey helps us learn more about the people using our UK-focused resources, and how effectively they are meeting needs.

As well as using this information internally in order to generate ideas for the development of new resources, and to help improve current ones, these data are crucial in supporting funding applications.

So, a huge 'thank you' to the almost 600 of you who responded - a response rate of 11.5%.

about *ATU**

How many people read *ATU*?

A remarkable 59% of respondents regularly share their copy of *ATU* with at least one other person, which suggests that an estimated 14,200 people read NAM's newsletter each month. That means we're reaching the equivalent of one-in-three of the entire diagnosed UK population.

What do they read?

Two-thirds of all readers, new and old, say that they regularly read *ATU* from cover to cover. Most are happy with the content, language and tone, with just five percent finding the language too complicated and only two percent finding *ATU* too technical.

How helpful is *ATU*?

A very satisfying 93% of respondents said that they find *ATU* very or fairly useful in helping them make decisions about their health and treatment; and 56% discussed the information they read in *ATU* with their doctor/nurse clinician/health specialist.

What impact has the redesign had?

The new design of *ATU* appears to have had a very positive impact on how the newsletter is read and rated. Of those respondents who had been readers prior to October 2005, and who expressed an opinion, 99% (335 out of 339) found the new look *ATU* easier to navigate, 96% (332 out of 347) found it more appealing to read, and 94% (63 out of 67) found it more trustworthy since the redesign.

ATU readers' panel

We had a surprisingly large number of readers who were willing to join our new readers panel. We ended up spoiled for choice, and have picked fifteen to represent the many different people living with HIV in the UK today. You'll be hearing more about the panel - and more *from* them, too - in the very near future. Thank you again to everyone who responded.

*Not everyone answered all the questions we asked, so the percentages may not always add up to 100%.

“ I like the current mix of treatment and social issues and would like to see this pattern continue ”

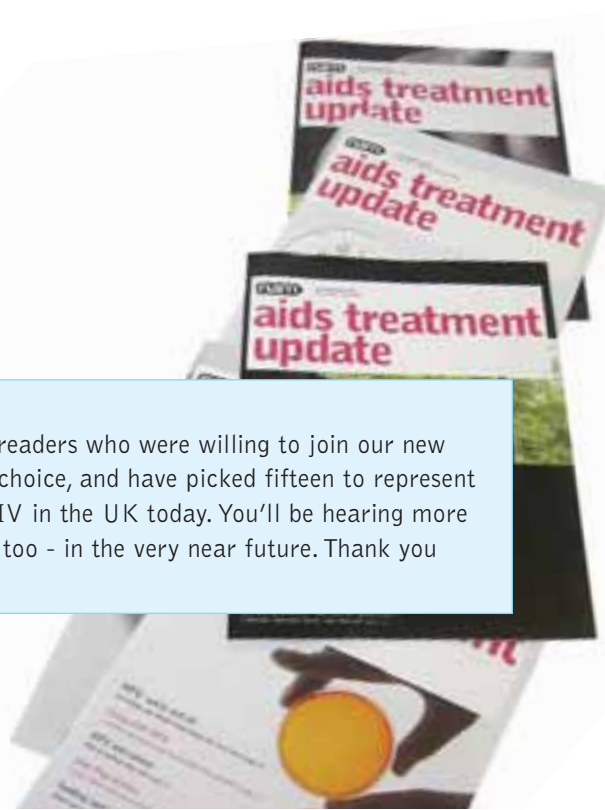
What would you like to read about?

An open question invited respondents to suggest subjects that future issues of *ATU* might cover. Of the 244 people who made suggestions, it was striking how many wanted the newsletter to cover issues that weren't strictly treatment-related, including the social, emotional, financial and legal ramifications of living with HIV.

Many respondents still wanted to know more about new drugs and new treatment strategies, and other ways of staying well - including healthy living choices and complementary therapies - but the two areas that received more requests than any others were side-effects and mental health.

We shall be covering all of these issues - and many more - in the future.

“ Keep covering mental/social aspects of HIV - very useful ”



references to all articles

Understanding Toronto [page four]

- All are abstracts from the 16th International AIDS Conference, Toronto, 2006, unless otherwise indicated.
1. IAS-USA 2006 guidelines: www.iasusa.org/pub/arv_2006.pdf
 2. Draft BHIVA treatment guidelines 2006: www.bhiva.org/guidelines/2006/hiv/hivfs06.html
 3. Riddler SA et al. ThLB0204
 4. Eron J et al. Lancet 368: 476-482, 2006.
 5. Markowitz M et al. ThLB0214
 6. Lazzarin A et al. TuAb0104
 7. Cahn P et al. 10th EAC, Dublin, abstract PS3/8, 2005.
 8. Tschida S et al. TuPE0147
 9. Gulick R et al. ThLB0217
 10. Mayer H et al. ThLB0215
 11. Norris D et al. ThLB0218
 12. Davison DK et al. ThPE0021
 13. Delmedico M et al. ThAA0303
 14. Craig C et al. ThPE0023
 15. Dandache S et al. ThAA0304
 16. Cameron W et al. ThLB0201
 17. Arribas J et al. ThLB0203
 18. Nunes EP et al. TuAb0103
 19. Delfraissy JF et al. ThLB0202
 20. Lundgren JD et al. WeAB0203
 21. El-Sadr W et al. WeAB0204
 22. Burman W et al. ThPE0145
 23. Castagna A et al. AIDS 20; 795-803, 2006.

news in brief [page twelve]

Are you risking your health with 'complementary' therapies?

1. Ladenheim D et al. Potential health risks of complementary alternative therapies in HIV-positive patients. 16th Intl. AIDS Conf, Toronto, abs MOPE0219, 2006.

Two-in-five HIV-positive gay men don't know they're positive

1. Williamson L et al. HIV prevalence and undiagnosed infection among community samples of gay men in the United Kingdom: five city comparison. 16th Intl. AIDS Conf, Toronto, abs MoPe0517, 2006.

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Where to find out more about HIV

■ Find out more about HIV treatment:

NAM's factsheets, booklets, directories and website, keep you up to date about key topics, and are designed to help you make your healthcare and HIV treatment decisions. Contact NAM to find out more and order your copies.

■ Information events in London

On the last Monday of every month, an expert speaker discusses an HIV treatment related topic. Entry is free. The next topic is 'The doctor is in', and will be held on 30th October 2006. For more details, go to www.aidsmap.com/forums.

■ www.aidsmap.com

Visit our website for the latest news about HIV & AIDS and a fully searchable treatments database and a complete list of HIV treatment centres in the UK.

■ THT Direct Phonenumber

Offers information and advice to anyone infected, affected or concerned about issues relating to HIV and sexual health.

0845 1221 200

Mon-Fri, 10am-10pm Sat-Sun, 12pm-6pm

■ i-Base Treatment Phonenumber

A HIV Treatment phonenumber; where you can discuss your issues with a treatment expert.

0808 8006 013

Mon-Wed, 12pm-4pm

nam

living with hiv

2006 edition

Whether recently diagnosed, thinking about starting or changing treatment or have lived with HIV for a long time, NAM's book *Living with HIV* provides answers to the questions you might find yourself asking.

“ it's absolutely great; so practical and easy to read and the personal stories really bring everything to life. I am finding useful information that I never knew and I can't believe that it is free! ”

This book is free to people personally affected by HIV, there is a charge for professionals.

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