

aids treatment update



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in this issue

It's really great news that people with multidrug-resistant HIV are now routinely expected to achieve an 'undetectable' viral load - as long they have expert HIV care and access to state-of-the-art HIV drugs.

And, as HIV treatment improves, fewer of us who are lucky enough to live in the UK (and have unrestricted access to HIV treatment and care) are likely to die of HIV-related illnesses.

But as we live longer, and are allowed to age, we are now more likely to die of all the other diseases that everyone else dies of.

Of course, there are many things we can do to make sure we live longer and healthier lives: take our anti-HIV combinations regularly and on time; don't do drugs; stop smoking; drink only in moderation; eat well; exercise regularly; and reduce our chances of acquiring new, potentially dangerous, sexually transmitted infections by having safer sex and regular sexual health check-ups.

The choice of whether you do any of this, of course, is yours to make.

After all, there's always the incredibly small chance that you might fall under that proverbial bus, despite your best efforts to live as healthy a life as possible.

Whatever you choose, make sure it's a choice that you can live with.

page 3 This month's *Upfront* finds that drug-resistant gonorrhoea is on the increase, particularly amongst HIV-positive gay men, and explains why this STI is becoming easier to acquire and harder to treat.

page 4 The main focus of this month's *ATU* is how new drugs and smarter strategies have changed the rules for what used to be known as 'salvage' therapy. In *From salvage to salvation?* we discover why even the most treatment-experienced person can now expect to have an 'undetectable' viral load as their treatment goal.

page 6 Want to know more about the anti-HIV drugs that are available now to treat highly drug-resistant HIV? The good and bad points of them all (as far as we know) are all here.

page 10 Three experts - Dr Anton Pozniak from London, Dr Clifford Leen from Edinburgh and Professor Sharon Walmsley from Toronto - explain the latest 'salvage' strategies.

page 12 Amongst the items in *News in Brief* is a new study which defines what puts you at risk for liver problems whilst taking anti-HIV drugs, as well as some surprising new findings for HPV in women and herpes in men.

page 14 Experts now tell us that HIV is a 'chronic, manageable' disease. In *Great expectations*, we wonder whether people with HIV can really expect to live a normal lifetime.



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Drug-resistant gonorrhoea on the increase

why this STI is becoming easier to acquire and harder to treat, by Edwin J Bernard

Gonorrhoea is the second most prevalent bacterial sexually transmitted infection (STI) in the UK, after Chlamydia. In the scheme of things, acquiring gonorrhoea might not seem so bad if you're already HIV-positive. After all, it's a bacterial infection that can easily be cured with antibiotics. But what if that gonorrhoea was drug-resistant, and the antibiotics you were given didn't work against that strain? That's the situation some HIV-positive gay men have been facing recently, and it's highlighted in a new report from the Health Protection Agency (HPA).

HIV-positive gay men disproportionately affected

The HPA report reveals that compared with the rest of the sexually active UK population, HIV-positive gay men were disproportionately affected by gonorrhoea in 2005. The situation appears to be getting worse, too, because although the total number of new cases of gonorrhoea in the UK fell by 13% last year, HIV-positive (as well as undiagnosed and HIV-negative) gay men are bucking the downward trend. About a third of all gonorrhoea cases diagnosed in 2005 were seen in gay men - up from 30% in 2004 - and about a third of the gonorrhoea cases diagnosed in gay men were seen in HIV-positive gay men. Therefore in 2005, about one in every eleven UK gonorrhoea diagnoses were made in gay HIV-positive men.

Easy to acquire, harder to diagnose

Gonorrhoea is relatively easy to acquire, since it can easily be passed on via oral sex. In fact, a recently published study of HIV-positive and HIV-negative men from San Francisco found that, although gonorrhoea can be found on the penis and in the rectum, it was most commonly found in the throat. Most of the time there weren't any symptoms. The researchers recommended that all sexually active gay men should have an annual throat swab to check for gonorrhoea in the throat, and that gay men who have multiple or anonymous partners should have such swabs every three to six months.

Drug-resistant gonorrhoea

Back in the UK, the HPA's GRASP programme has been testing for drug-resistant gonorrhoea since 1999. They found that more than 20% of the gonorrhoea they tested in 2005 was resistant to an antibiotic known as ciprofloxacin, a significant increase from the 14% observed in 2004. In addition, the HPA found that you were more than twice as likely to have ciprofloxacin-resistant gonorrhoea if you recently had sex abroad. And, although ciprofloxacin and other drugs from the same class (fluoroquinolones, including ofloxacin and levofloxacin) have not been recommended as a first-line treatment for gonorrhoea in the UK since 2003, about one-in-five of all

prescriptions to treat gonorrhoea in the UK in 2005 were still for drugs from this class.

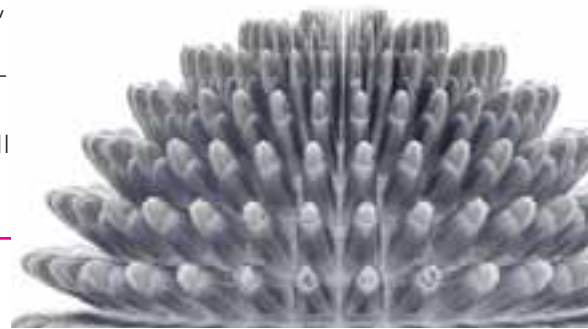
Multidrug-resistant gonorrhoea

The first cases of multidrug-resistant gonorrhoea were reported in the United States in 2003. Fortunately, the most commonly administered antibiotic treatments for gonorrhoea in 2005 - cefixime (*Suprax*) tablets or ceftriaxone (*Rocephin*) injections - still work against all the UK strains of gonorrhoea that were tested by the HPA.

However, the HPA did find that there was an increase in gonorrhoea that was resistant to other antibiotics. This included penicillin, tetracycline (doxycycline), and azithromycin: the latter two are often prescribed to individuals with both gonorrhoea and Chlamydia.

Get tested

If you are sexually active, consider having a sexual health screen at least once a year. If you have a lot of partners - even if it's just for oral sex - consider having a sexual health screen at least every six months. And if you are diagnosed with gonorrhoea, make sure that you are given the treatment that is most likely to work against all drug-resistant strains: either cefixime tablets or ceftriaxone injections. ■



from salvage t

how new drugs and smarter strategies have changed the rules for

A new goal for the highly treatment-experienced

Treating HIV is a constantly evolving balancing act; it's as much an art as a science. The idea is to improve the immune system to a point where the risk of HIV disease progression is low enough to warrant the inconvenience and side-effect risks of anti-HIV drugs.

The key to anti-HIV treatment's long-term success, however, is to reduce the measurement of HIV in the blood to the lowest point possible (commonly known as 'undetectable' because HIV is below the limits of detection of the viral load test). This prevents HIV from becoming resistant to anti-HIV drugs, allowing treatment to continue for as long as you can tolerate it.

Until recently, this goal had only been thought possible for people who take anti-HIV drugs for the first time (known as first-line therapy) because people who are new to treatment are least likely to harbour drug-resistant HIV. (However, non-exposure to treatment is no guarantee - the most recent data from the Health Protection Agency (HPA) suggest that about 9% of untreated individuals in the UK¹ have acquired HIV with some degree of drug resistance.)

Today, however, even resistance to one or more anti-HIV drugs is not an insurmountable challenge. There are now enough unique, potent anti-HIV drugs - currently 18 and growing - to mean that second-line and even third-line combinations still have a very good chance of long-term success if carefully chosen, and adhered to.

However, as resistance patterns accumulate, HIV can become resistant, to a greater or a lesser degree, to most or all approved drugs, making an effective anti-HIV combination difficult to put together. The best considered option in the past for highly treatment-experienced individuals in this situation was to keep the immune system as intact as possible. This was seen as a short-term goal, because it was thought that it was unlikely that anyone in this situation could achieve an 'undetectable' viral load, or if they did, keep it that way for long. In fact, the very term that has often been used for people in this situation - 'salvage therapy' - has always smacked of desperation: it sounds like a last-ditch attempt to keep someone alive. Once you were on 'salvage' you just hoped for better drugs to come along, and preferably more than one at a time.

Well, they're not perfect but these better drugs have now arrived, and the term 'salvage' really is no longer appropriate for the vast majority of highly treatment-experienced individuals in the UK. In fact, the

latest treatment guidelines from the British HIV Association (BHIVA) make this very clear: "The goals of treatment for the majority of treatment-experienced patients have changed and the new paradigm should be, wherever possible, maximal and durable HIV viral suppression."

Dr Anton Pozniak, from London's Chelsea and Westminster Hospital and one of the members of the BHIVA guidelines writing committee, explains what they mean to *AIDS Treatment Update*. "If you look at newly treated patients, you're able to achieve long-term success (sustained, 'undetectable' viral load) in 65% to 70% of the people you treat," he says. "It's nearly the same for second-line therapy."

And he stresses that most experts now agree that highly treatment-experienced individuals should be able to achieve the same degree of anti-HIV treatment success that anyone else on anti-HIV therapy. "If someone with multiple resistance mutations is asking me point-blank, 'Am I going to be alive or not in a few years time?' I'd say, 'Well, we've got all these new agents which we can use together, and you've got a very good chance of becoming 'undetectable'."

But how many people are we talking about? The most recent figures from the HPA (from 2004) estimated that about 8% of the UK's anti-HIV



no salvation ?

salvage' therapy, by Derek Thaczuk and Edwin J Bernard

drug-treated population has HIV that has some degree of resistance to all three major classes of anti-HIV drugs ¹. However, some doctors quote lower figures based on people who are truly in need of 'salvage' therapy - those who have HIV with extensive resistance to all three of the major drug classes, and possibly also to the one available drug in the fourth class of anti-HIV drugs, T-20.

Dr Pozniak tells *ATU* that "the numbers [of highly treatment-experienced individuals] vary from country to country, but in the UK we're probably talking about less than 5% of the treated population."

Some people in this situation are those who have been unable to adhere to anti-HIV combinations due to a variety of reasons. These unplanned short- or longer-term treatment interruptions could be due to intolerance; worry about side-effects; concern that taking treatment may lead to unwanted disclosure of HIV status; or being unable to fit often complex treatment regimens into their lives, because of difficult mental, emotional, social and/or economic situations.

"But the majority of highly treatment-experienced people are the early starters," notes Dr Pozniak, "the people who began therapy in the

early or mid-1990s with one or two drugs, because that's all we had. For those people, subsequent combinations usually amounted to sequential monotherapy (taking one drug, one a time). We're at great pains to avoid that now, but unfortunately those people can't reverse their treatment history.

Over the next six pages, we examine what is and what isn't known about the new 'salvage' drugs that are available for use today - or within the next few months - and talk to three experts about how best to use them.

class of 2006

As we go to press (November 2006), eighteen distinct anti-HIV drugs are approved for use in the United Kingdom, and we're expecting a nineteenth, the new protease inhibitor, darunavir, to be approved in the next few weeks.

These drugs belong to four different classes. The class that makes up the 'backbone' of anti-HIV therapy is called the nucleoside (and nucleotide) analogue class, or NRTIs. Examples include abacavir (*Ziagen*), tenofovir (*Viread*) as well as fixed-dosed combinations of these drugs, e.g. *Combivir*, which combines AZT and 3TC.

There are two further classes, from which one drug is added to the 'backbone' to make up potent anti-HIV combination therapy: non-nucleosides, or NNRTIs, and protease inhibitors, or PIs. Examples of NNRTIs include efavirenz (*Sustiva*) and nevirapine (*Viramune*); examples of PIs include lopinavir/ritonavir (*Kaletra*) and fosamprenavir (*Telzir*).

A fourth class became available in 2003. So far the only drug in the fusion inhibitor class is enfuvirtide (*Fuzeon*), commonly known by its development name, T-20.



Enfuvirtide

Approved since 2003, enfuvirtide (T-20, trade name *Fuzeon*) is the first, and still the only available, drug in the 'fusion inhibitor' class. Fusion inhibitors work in a completely different manner than the other classes of drugs: they prevent HIV from attaching to and entering cells. This, in itself, does not necessarily make for a better drug. However, a new drug class has one clear benefit for people who have experience of the other three classes: virtual certainty that HIV will be susceptible to it.

While T-20 is not exactly new it still plays a crucial role for highly treatment-experienced individuals. Clinical trials have shown modest benefits from adding T-20 to an otherwise failing drug regimen. The best results are repeatedly seen when T-20 is begun at the same time as another new drug.

However, T-20 costs much more than other anti-HIV drugs. It must also be taken by injection, twice a day - a laborious process that includes reconstituting the drug from a powdered formulation into an injectable liquid. This causes the only significant side-effect to T-20 - injection site reactions (itchy, swollen or hardened bumps on the skin). Still, some studies^{2,3} have hinted that doctors may perceive their patients to be more reluctant toward self-injection than they actually are. Although a needle-free injection system, the *Biojector 2000*, has been developed to mostly favourable reviews by users, approval for use with T-20 has been delayed in the United States until next year, and it is unlikely to be available in the UK for at least another year.

Regardless of cost and any reluctance towards needles, the most pertinent caution is T-20's limited usefulness as a single new drug. The new BHIVA guidelines note that T-20 "is most effective when used with other drugs to which the patient is susceptible, based on resistance testing and antiviral experience. When used as the only effective agent, resistance to it occurs within weeks and a future opportunity for constructing an effective regimen is lost." Still, now that there are several new drugs available it is possible that more people will give T-20 a try.

Tipranavir

Boehringer Ingelheim's protease inhibitor, tipranavir (*Aptivus*), is specifically approved for use in highly treatment-experienced individuals who have HIV that is resistant to other PIs. Like darunavir, it requires boosting with additional ritonavir (*Norvir*). Although it was approved by the European Agency for the Evaluation of Medical Products (EMA) in October 2005 and was made immediately available in England and Wales, HIV-positive individuals in Scotland had to wait almost a year, until September 2006, for the Scottish Medicines Consortium (SMC) to approve its use there. (For more on the approval process, see the box on 'Approval, Expanded Access and Named Patient Programmes'.)

Since this drug has been taken by many more people, and for longer, than the other oral drugs in this article, we know more about its good and bad points. The phase III clinical trials, RESIST-1 and RESIST-2, have now compared ritonavir-boosted tipranavir to most of the currently-approved PIs in individuals who have taken the three major drug classes. The most recent report⁴ suggests that ritonavir-boosted tipranavir results in greater viral load reductions than any of its comparison PIs, regardless of the initial viral load or CD4 count. After 48 weeks, between 17% and 24% of the people taking tipranavir achieved 'undetectable' viral loads (below 50 copies/mL), compared to 4% to 12% of those on other PIs.

Like most anti-HIV drugs, tipranavir can have short-term side-effects, such as nausea, vomiting, diarrhoea, tiredness, and headache. The drug should be used cautiously in people who have underlying liver problems (including coinfection with hepatitis B or C) because it has been associated with severe liver toxicity - although this usually reversible when the drug is stopped. Very rarely, intracranial bleeding (bleeding inside the brain) due to ruptured blood vessels, has occurred on tipranavir, so people with bleeding disorders or those who use blood-thinning drugs, should probably avoid it.

Because of the way tipranavir is broken down by the liver, and because it is taken with ritonavir, it can interact with many other medications, including most of the drugs in this article. As with all the drugs in this article, it is important that your HIV doctor and pharmacist monitor anything else you take carefully to make sure that they can be safely taken with ritonavir-boosted tipranavir, and that the doses are correct.

Darunavir

Darunavir (previously known as TMC114), a new protease inhibitor made by HIV drug newcomer, Tibotec, a division of Janssen-Cilag, is currently available in the UK via Expanded Access through a Named Patient Programme. It was approved in the US in June 2006, under the brand name *Prezista*, and EMEA approval is expected shortly.

In studies so far, ritonavir-boosted darunavir in combination with other drugs appears to be very effective for people who have HIV that is resistant to other protease inhibitors. These studies have all involved people on 'failing' drug combinations, with exposure to all three major drug classes, and resistance to PIs. All participants received 'optimised background therapy' (OBT - see box), plus either ritonavir-boosted darunavir, or one or more other boosted PIs selected by their doctor, based on resistance testing.

After 48 weeks, 46% of the individuals on boosted darunavir had 'undetectable' viral loads (below 50 copies/mL), versus only 10% of those on the other boosted PIs. The average drop in viral load was an impressive 1.63 log for the darunavir group, but only 0.35 log for the comparator group⁵.

The BHIVA guidelines note that the success rates "were related to the number of [darunavir-] sensitive drugs (including T-20) that the patients received, and the phenotypic [a resistance test that can help measure the amount of drug needed to overcome resistance] sensitivity to TMC114 at the start of the study."

So far, the short-term side-effects of darunavir seem comparable to many other ritonavir-boosted protease inhibitors, and diarrhoea, nausea, and headaches have been reported in 15%-20% of people in the studies. Since darunavir is also taken with ritonavir, it's important to be aware of ritonavir's drug interactions and long-term side-effects. In addition, the most recent report on darunavir's interactions concludes that its 'combination with any other PI is experimental and not recommended,'⁶ although it can be combined with T-20. In addition, Tibotec is also studying darunavir in combination with another of their experimental drugs, the NNRTI, etravirine.

For more information on accessing darunavir via Tibotec's Named Patient Expanded Access Programme, visit:
www.tibotec.com/bgdisplay.jhtml?itemname=EAP2_ROW

optimised background therapy

Clinical trials require a 'control arm' - a group that does not receive the experimental drug, against which that drug's performance can be measured. For highly treatment-experienced individuals, this becomes clinically and ethically difficult: how do you select a single standardised treatment regimen for such a diverse group of people?

The answer is - you don't! Most of the studies quoted here have taken a different approach, using resistance testing and expert judgement to select the best possible regimen for each individual participant (excluding the study drug).

Every study participant then receives a personalised 'optimised background therapy' (OBT) regimen. Those in the 'control arm' receive OBT only; those in the 'experimental arm' are given the experimental drug as well. Until (and if) the drug used in the 'experimental arm' proves more effective (and at least equally as safe), it is not considered unethical for the 'control' participants not to receive it.



Etravirine

While resistance to protease inhibitors tends to grow slowly, just one or two key mutations cause HIV to become highly resistant to the existing non-nucleoside (NNRTI) drugs, efavirenz and nevirapine. The experimental NNRTI, etravirine (TMC125) is specifically designed to be active against NNRTI-resistant HIV.

So far, we only have results from Phase II studies with which to judge this drug. Study TMC125-223 examined a small number (199) of individuals who had HIV that was resistant to drugs from the three major classes and whose viral loads were above 1000 copies/mL. These people received OBT, with or without etravirine. Although two different doses were studied, it is the higher dose in a new formulation (200mg, twice a day) that has been chosen for further study. At 48 weeks, results were modestly promising: only 9% of the people taking etravirine had 'virologic failure' (viral load rebound), versus 78% of those on OBT alone⁷.

No serious side-effects have yet been seen with etravirine. Dizziness, headache, blurred vision, mild diarrhoea, gas and mild rash have been reported, all of which seem to improve within a few days. Etravirine does appear to interact with most protease inhibitors, however, as well as the experimental integrase inhibitor, MK-0518, and this could affect drug levels with potentially serious results. It is clear that more detailed information on etravirine's drug interactions is needed.

Studies also suggest that another promising experimental NNRTI from Tibotec, TMC278 - and which is not yet available outside of clinical trials, none of which are taking place in the UK - will not be effective against TMC125-resistant virus. This becomes yet another factor in deciding whether to take this drug now, or to wait.

For more information on accessing etravirine via Tibotec's Named Patient Expanded Access Programme, visit: www.tibotec.com/bgdisplay.jhtml?itemname=EAP2_ROW

MK-0518

MK-0518, which has not yet been assigned any other name, is an experimental integrase inhibitor developed by US drug company Merck, known as Merck Sharp & Dohme (MSD) outside of the US. While several other integrase inhibitors are currently in trials (notably Gilead's GS-9137), MK-0518 is the furthest ahead in the development process.

Integrase inhibitors are another entirely new class of drugs. They work by blocking the integrase enzyme, which is used by HIV to splice ('integrate') its own DNA into a usable form once it is inside a cell. Experts are very excited about the possibility of this new class of anti-HIV drugs, in particular, because they can be taken by mouth (unlike T-20), and studies so far suggest they might be the most potent anti-HIV drug class yet.

An ongoing Phase II study has looked at MK-0518 in a small group of people whose HIV has resistance to the three major drug classes. In addition to OBT (and about a quarter of people included T-20 as part of their OBT), three different twice-daily doses of MK-0518 were studied (200, 400 or 600mg). Results from this study have been presented at conferences throughout 2006, and have been consistently positive. The most recent results⁸ - from 178 participants after 24 weeks - found that, depending on MK-0518 dose, 77-80% of participants saw at least a one log (tenfold) drop in viral load, compared with 18% on OBT alone. Viral loads fell to 'undetectable' (below 50 copies/mL) in between 57%-67% on the three different doses, compared to 14% on OBT alone.

Although all three doses worked equally well, prior research suggests that the 400mg twice-daily dose offers the best trade-off between potency and safety, and this dose has been selected for future trials.

While these results are extremely encouraging - in fact, practically unprecedented among 'salvage therapy' trials - they are drawn from a limited number of people, and only extend to 24 weeks so far. Larger, longer-term studies (such as the Phase III trial currently underway) are required to confirm that MK-0518 is as effective and durable as hoped. In addition test-tube studies suggest that etravirine and MK-0518 may interact, and we need to know more about other potential drug-drug interactions. "Durability and long-term toxicity have yet to be defined," notes BHIVA, "but importantly the drug... does not require ritonavir boosting. It is hoped that this drug will become an important new treatment option."

Maraviroc

Pfizer's first anti-HIV drug, maraviroc, belongs, like the fusion inhibitor T-20, to a broad drug class known as entry inhibitors, which work before HIV enters human cells. Many (but, crucially, not all) strains of HIV use a co-receptor known as 'CCR5' to bind to and infect the cell (these strains are called 'CCR5-tropic'). Maraviroc is a CCR5 antagonist, which prevents these 'CCR5-tropic' strains of HIV from entering the cell by interfering with a key chemical messenger. The main weakness of maraviroc is that it will not be effective against X4, the co-receptor used by other viral strains. In fact, there are some fears that it may 'drive' HIV to mutate to use this other co-receptor, which is associated with more advanced HIV disease.

The limited trials so far have not shown any sign that such harmful effects result from using maraviroc.⁹ Nor, however, have they shown any great reduction in viral load, although it is early days. Given that the studies were designed more around the safety issue than to show maraviroc's effectiveness, this drug may show more promise in further trials, and we should know more after this issue has gone to press (check out www.aidsmap.com for news stories about this drug from the Eighth International Congress on Drug Therapy in HIV Infection which took place in Glasgow in mid-November). The apparent safety and tolerability of the drug so far, BHIVA notes, "is reassuring, as it does not suggest that emergence of potentially more virulent X4 tropic strain will be a significant problem with this class of drugs."

Pfizer hopes to make maraviroc available through an EAP to people who need it to construct a viable 'salvage' regimen in the Spring of 2007. ATU will provide further details when they are known.



approval, expanded access and named patient programmes

Before a drug can be prescribed in the UK, the European Agency for the Evaluation of Medical Products (EMA) must grant approval. Other national agencies, like the National Institute of Clinical Excellence (NICE), the Medicines and Healthcare products Regulatory Agency (MHRA) and the Scottish Medicines Consortium (SMC) may also be involved before it is available on the NHS.

Approval is based on information gathered from studies in humans (clinical trials), which run in three phases: Phase I studies, the first in humans, are very small and focus on drug safety. Phase II trials involve more participants (a few dozen to a few hundred) and run for a few months: they continue to monitor safety and begin to study effectiveness ('efficacy'). Phase III trials involve larger numbers of people, run for longer periods, and provide data solid enough to evaluate and approve a drug.

While drugs are in the advanced stages of clinical trials, and before approval, the manufacturer may make them available to patients in most urgent need, through Expanded Access Programmes (EAPs), some of which can be considered to be clinical trials. However, some EAPs are Named Patient Programmes, which are very strictly regulated, and require a doctor to apply for a drug for a specific patient directly from the manufacturer.

interviews by Derek Thaczuk

strategies for salvage

Now that several new treatment options have become available for highly treatment-experienced individuals, it is crucial to take this lesson from past experience: even the brightest prospects can be wasted if not used strategically.

ATU spoke to three experts in patient care from both sides of the Atlantic about the impact of the new drugs on the lives of highly treatment-experienced individuals, and discuss various strategies to ensure their best possible use.

Dr Anton Pozniak (AP) is a Consultant Physician with the Department of HIV and Genitourinary Medicine, at Chelsea and Westminster Hospital in London. Dr Pozniak is a member of the BHIVA treatment guidelines writing committee.

Dr Clifford Leen (CL) is a Consultant Physician in Infectious Disease and HIV at Western General Hospital in Edinburgh. Dr Leen is also a member of the BHIVA treatment guidelines writing committee.

Professor Sharon Walmsley (SW) is Associate Professor of Medicine in the Division of Infectious Diseases at the Toronto Hospital, University Health Network, and Assistant Director of the Immunodeficiency Clinic at Toronto Hospital. She recently addressed the Autumn BHIVA conference on the subject of 'salvage' therapy.

Q

Several new anti-HIV drugs appear to be effective in highly treatment-experienced patients. What are the key strategies behind the optimal use of these new drugs?

AP: The best treatment strategies can't really be generalised, in the sense of having a mechanistic, 'cookbook' approach; this kind of treatment requires a more carefully individualised strategy. Nevertheless, there absolutely are general principles behind the treatment strategies, which are reflected in the new BHIVA guidelines.

These include the following:

- don't construct regimens with what is effectively monotherapy;
- use a multidisciplinary approach, involving everyone concerned in the major care of the patient;
- use resistance testing as a useful tool, not an infallible key to successful therapy;
- try to reach the goal of lowering viral load to undetectable levels, but realise that if this is not possible you may have to wait until it is.

CL: I'd like to stress how important it is to use as many active new drugs as possible - two or, preferably, three. If at all possible, use a new drug class.



Q

One of the most challenging treatment decisions would be whether to treat with what's available now, versus waiting for more information and more agents to become available. What are the factors influencing that choice?

SW: There's no generic answer to that question; you have to look closely at the specifics of the individual case. It depends on the level of risk that the patient is facing. If a patient is on failing therapy but is clinically stable, with little risk of disease progression, then it could very well be better to wait until we have more drugs to work with, as well as more data on those drugs. On the other hand, for someone whose treatment is failing and whose disease is progressing now, it's obviously more critical to treat now. Unfortunately in that situation you may not be able to optimise the use of that drug.

AP: Waiting is a balancing act between risk of progression and developing more mutations, versus the risk of giving ineffective therapy and inducing more resistance. In these cases, you would need a lot of input from a multidisciplinary team.

CL: Most particularly, we don't have all the information on how these drugs interact. There have been previous examples where using combinations of protease inhibitors led to negative drug interactions. So there could be a danger in earlier treatment without knowing enough about the interactions, which could have negative consequences for the patient. The key is balancing these risks against each other. For the purposes of the BHIVA guidelines, 50 CD4 cells/mm³ has been selected as a general 'cut-off point' for starting therapy - but that is subject to expert evaluation of the individual case. We encourage any clinicians who are uncertain to seek out expert advice.

We also need more information about durability. The data, for instance, from the Merck integrase inhibitor look great, but only time will tell if that response holds up in the long term. There is definitely great cause for optimism, but it is questionable as to when we can get 'gung-ho' and start guaranteeing positive outcomes.

Q

Another key factor is the lack of definitive 'head-to-head' data that compare some of these new drugs (e.g. darunavir vs. tipranavir). Given the lack, how do you go about making these 'either/or' decisions?

SW: Well, that's the million-dollar question. There is, in fact, a head-to-head study [between tipranavir and darunavir] planned, but we don't have any such data available at the present time. You really are comparing apples and oranges, in that clinical data is available for both of these drugs, but for very different groups of patients. Both agents have been shown to have good antiviral activity in patients with triple antiretroviral experience, relative to the comparator boosted PI, in combination with an optimised background therapy. They both also performed best when used in combination with another active agent. One should really not be comparing the results of these studies in any direct way.

CL: The point is well-taken that there is not always clear evidence as to whether agent A or B is going to play out better in the long run. There is the question of sequencing: having used one agent first, what will the consequences be for effectiveness of the other agent later? Both camps will probably try to show evidence that their drug is the better first choice, but at this time there are really no clear data.

AP: We definitely do need more data on this question. Darunavir has a different structure than tipranavir, and the resistance patterns defining susceptibility are probably different. Although it will be possible to be sensitive or resistant to both, the mutation pattern may guide us toward one drug or the other. Cost, tolerability and toxicity, of course, are always important considerations if both drugs are likely to be effective.

Q

In spite of the strategic challenges they present, how have these new drugs affected treatment prospects for highly treatment-experienced patients? Do you think we truly are seeing the emergence of a 'new paradigm'?

SW: Yes, definitely. Many of the specifics remain to be resolved, but there is a great deal of positive potential for treating our multiply drug-resistant patients.

CL: Yes, definitely. I can't think of a time when we've had so many options, so it looks very promising. If we can use all of these new agents effectively, then I think we will definitely have entered a new phase for this patient population.

AP: Yes, I think it's very exciting. I think we have a lot of patients who want to be on successful therapy but essentially have not had a chance to do so because of the incremental way in which therapies have been added. I think those people now stand a fantastic chance of becoming undetectable. Mind you, we're also old and wise enough to know that however great the data may be, unwelcome surprises can emerge.

news in brief

side-effects

New risk factors identified for liver problems on anti-HIV drugs

The largest ever clinical trial-based analysis of predictors of serious liver toxicity in HIV-positive individuals starting anti-HIV therapy has identified some new risk factors.

These include the liver damaging potential of other drugs being taken at the same time; pre-existing kidney problems; and a low platelet count (the blood cells that help blood to clot).

The study also found that after one year on anti-HIV drugs almost nine people out of every hundred had blood test results that showed that their liver was seriously harmed. Although this is often reversible once the drugs are stopped, this can occasionally lead to more permanent long-term damage.

The study found that the following factors - which can be checked before starting anti-HIV

therapy - led to an increased risk of liver problems: abnormal liver function tests; abnormal kidney function tests; low platelets; and coinfection with hepatitis B or C.

However, although it also found that taking the anti-HIV drugs, ddI (*Videx EC*), d4T (*Zerit*) or nevirapine (*Viramune*) increased the chances of someone experiencing liver problems, other drugs that may also be taken by people with HIV were also linked to an increased risk of liver problems. These include: most anti-TB drugs, including isoniazid, rifampicin, ethambutol, pyrazinamide, or rifabutin; certain antifungals, including fluconazole (*Diflucan*); certain antibiotics, including cotrimoxazole (*Bactrim/Septtrin*), erythromycin (*Erymax/Erythrocin/Erythroped*), co-amoxiclav (*Augmentin*), or dapsone; and certain anti-epilepsy drugs, phenytoin (*Epanutin*), or carbamazepine (*Tegretol*).

The investigators highlight the importance of checking for pre-existing risk factors before starting anti-HIV drugs, and recommend that people with either pre-existing risk factors or those taking other potentially liver-toxic drugs should have regular liver function tests.



sexual and reproductive health

BHIVA issues draft sexual and reproductive health guidelines

A draft version of the first-ever guidelines from the British HIV Association (BHIVA) to consolidate and review existing evidence on most aspects of sexual and reproductive health for HIV-positive individuals is now open for consultation.

The guidelines authors note that HIV-positive individuals "have the right to protect their own health, to enjoy meaningful sexual relationships, and reproductive health. These rights come with responsibilities however: in particular, to avoid passing infections on to others."

Consequently, although current guidelines exist from the British Association of Sexual Health and HIV (BASHH) regarding the management of sexually transmitted infections (STIs) in HIV-positive individuals, BHIVA's new draft guidelines cover much broader aspects of sexual and reproductive health needs of people living with HIV.

These include:

- contraception for HIV-positive women
- condom use in the era of criminalisation for HIV transmission
- HIV superinfection
- screening for, and management of, cervical and anal pre-cancer and cancer
- fertility issues for HIV-positive women and men, including assisted conception
- erectile dysfunction

The guidelines are also designed to complement existing guidance from BHIVA on the management of HIV in pregnancy, as well as guidelines on HIV transmission, the law and the work of the clinical team. They also refer to guidance from BASHH the use of HIV post-exposure prophylaxis following sexual exposure (PEPSE), but focus on making all HIV-positive individuals aware of PEP.

The draft guidelines can be downloaded from the BHIVA website (www.bhiva.org) and comments should be sent to the BHIVA Secretariat at: bhiva@bhiva.org by Wednesday 6th December 2006.

sexual health

Surprising new findings for HPV in women; herpes in men

Women-focused research on human papilloma virus (HPV) - the sexually-transmitted virus that causes genital warts and can lead to cervical cancer in women, or anal cancer in people of any gender or sexuality - has mostly looked at HPV in the cervix.

Now a team of American researchers have found that HIV-positive women are more likely to have HPV in the anus than in the cervix, whether or not they have ever had anal sex.

Most of the women in the study were found to have HPV infection, but surprisingly, whilst 92% had HPV in their anus, only 86% had HPV in their cervix. This was a small study, with 122 participants, however, and the investigators suggest that more studies are needed before we understand what this means.

A second study, this time in gay HIV-positive men, has found that active herpes simplex virus-2 (HSV-2) in the rectum can increase the shedding of HIV in the rectal tissue, which could increase the risk of HIV transmission to the insertive partner during unprotected sex.

The small study found that the men with active HSV-2 had HIV viral load in the rectum that was, on average, higher than the HIV viral load in the blood.

Since rectal HSV-2 is often hidden, but can be controlled with anti-herpes drugs if diagnosed, it makes good sense for all HIV-positive people who are sexually active to have a regular sexual health screen.

side-effects

Kaletra tablets better tolerated, according to patient survey

A survey of 332 people from 52 doctor's practices throughout the United States has found that 88% of respondents prefer the new tablet version of *Kaletra* (lopinavir/ritonavir) rather than the soft-gel version it replaced.

The tablet version has several practical benefits over its predecessor. Since it is heat-stable, it doesn't have to be stored in a fridge, and because more of the drug is absorbed, it no longer needs to be taken with a meal.

A small study in HIV-negative volunteers suggested that the tablet also resulted in less gastrointestinal problems (notably, diarrhoea, bloating and gas), but no studies have formally compared the two in terms of their side-effects.

The survey, sponsored by the drug's manufacturer, Abbott Laboratories, included 82% of people who had been taking *Kaletra* soft-gel capsules for at least a year. The majority (89%) had switched to *Kaletra* tablets less than three months prior to filling out a multiple choice questionnaire. Everyone took four tablets once a day, where previously they had taken the soft-gel capsules either once or twice a day. Although this is possible in the US, European regulations state that two



Kaletra tablets can only be taken twice a day when prescribed in the UK: this provides 400mg lopinavir and 100mg ritonavir every twelve hours.

The survey found that 80% of respondents were "very" or "extremely" satisfied with taking *Kaletra* tablets compared to 60% who had felt this way about taking the soft-gel capsules. In addition, 84% said they had experienced "very good" or "great" tolerability with the tablet compared to 63% with the soft-gel capsule.

The survey also found that diarrhoea tended to be a problem for fewer people with the new formulation, although it wasn't completely eliminated. Once they started taking *Kaletra* tablets, 82% reported either that they experienced no diarrhoea at all, or that their diarrhoea had improved compared to the soft-gel tablets. In addition, the proportion of people reporting severe diarrhoea fell from 12% with the soft-gel capsules to 3% with the tablets.

Talk to your doctor or HIV pharmacist if you are concerned about diarrhoea, or about any other side-effects that may be caused by *Kaletra* or any other anti-HIV drugs.

Earlier this year, at the International AIDS Conference in Toronto, Italy's Dr Stefano Vella - one of the most respected HIV clinicians in the world - stated that "HIV is a chronic disease. If patients stay on their medicines they will live a normal lifetime." Is it really true that HIV-positive people can now expect to have a "normal" life expectancy? What is "normal" anyway? And when we do die, what are we dying of? Several recent reports can help us figure out the answers.



How long will anti-HIV treatment work?

Researchers from the United States¹ recently calculated that someone who started treatment with anti-HIV drug combinations according to 2004's US treatment guidelines would benefit from these treatments for around 24 years before they finally stopped working. Their estimate included four separate attempts at suppressing HIV to 'undetectable' levels, from first-line therapy to 'salvage' therapy. However, new ways of treating HIV - such as new drug classes to fight HIV, or other methods to improve the immune system, like therapeutic vaccines - continue to be discovered that may mean successful anti-HIV treatment will last even longer.

What is "normal" life expectancy?

Calculations of life expectancy are based on statistical averages, and it's important to remember that these numbers are based on the mythical 'average' person. However, according to the Office of National Statistics², a 25 year-old (someone born in the UK in 1981) had a life expectancy at birth of just under 71 years if they were male, and 77 years if they were female. In the UK, life expectancy is continually increasing, however, and children born in 2004 can expect, on average, to live to 77 and 81 years of age, respectively.

On an individual level, many different and varying factors come into play, making it impossible to know how long you will actually live. Some of these factors are based on your genetics (including your ability to tolerate some anti-HIV drugs, as well as your risk of acquiring other life-threatening

illnesses, like cancer and cardiovascular disease), and personality traits, like your attitude to risk (which may affect your lifestyle choices).

Other important factors include social and economic status, including access to education and healthcare; your lifestyle, diet and exercise regimes (including whether you smoke, drink alcohol and take recreational drugs); and the stability of your everyday life.

It also will depend on other chronic infections that you may have at the same time as HIV, such as hepatitis B and hepatitis C, as well as other physical or mental illnesses.

How and why are HIV-positive people dying?

At the BHIVA Autumn conference, the results of BHIVA's mortality audit showed exactly how and why people with HIV die in the UK.

Although 133 HIV treatment centres throughout the United Kingdom were included in the audit, 40 centres reported no deaths at all. The remaining 89 centres reported just under 400 deaths between October 2004 and September 2005. Since over 40,000 diagnosed HIV-positive people were seen for HIV treatment and care in 2004, this suggests a death rate of less than 1%. In contrast, in 1995, there were around 14,000 people being seen for HIV treatment and care, and 1400 deaths - 10% of all diagnosed individuals. In other words, in the space of a decade there has been a 90% reduction in the death rate of people with HIV in the UK.

In the past, the collection of illnesses and infections that go to make up an

great expectations

AIDS diagnosis used to be the main cause of death for HIV-positive people in the UK. The most striking finding of the BHIVA audit was that one-in-three deaths were not directly related to HIV infection itself. In fact, these non-HIV-related deaths were the single largest cause of death for all HIV-positive people. In contrast, just under one-in-five deaths were due to untreatable complications of HIV.

The BHIVA audit found that cancers accounted for more deaths than any other cause, about one-in-six of all reported deaths. This includes those that are HIV-related (including lymphomas, and cervical cancer), as well as those not traditionally related to HIV (such as liver, lung, kidney and anal cancer).

Cardiovascular disease (heart attacks and strokes) was responsible for 1-in-15 of all reported deaths. We are still learning about the relative contributions of HIV itself, HIV's treatments and more traditional risk factors (such as smoking, obesity and genetics) to the risk of cardiovascular disease, although the majority of these deaths were attributed to traditional risk factors.

Liver disease due to hepatitis B or hepatitis C co-infection and/or alcohol accounted for a further 6% of all deaths.

The audit also found that deaths due to adverse reactions to anti-HIV therapy or multidrug-resistant HIV - each accounting for less than 3% of all deaths - were relatively rare.

However, almost 5% of all deaths were apparently due to an individual

“declining treatment”, and almost 7% of all deaths were considered to be due to “poor adherence”.

It is becoming increasingly likely that if you live in the UK, and are diagnosed and under care, that HIV/AIDS will not be the cause of your death. However, since the BHIVA audit also found that one-in-four deaths were due to people being diagnosed with HIV too late for effective anti-HIV treatment, it highlights how important it is that undiagnosed people with HIV know their HIV status in order to make the most of the latest advances in anti-HIV therapy.

Ultimately, what these data all suggest is that anti-HIV treatments are greatly extending the life expectancy of people with HIV, as long as you:

- know your HIV status early enough to get timely and effective treatment
- have access to good quality HIV treatment and care
- and can take anti-HIV combinations that are tolerable, in terms of both side-effects and convenience, so that you can adhere to the treatment.

can people with hiv really expect to live a normal lifetime?
asks Edwin J Bernard

references to all articles

upfront [page two]

1. GRASP Steering Group. *The Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP) Year 2005 report*. HPA, 2006.
2. Morris SR et al. *Prevalence and incidence of pharyngeal gonorrhoea in a longitudinal sample of gay men who have sex with men: the EXPLORE study*. CID 43: online edition, 2006.

from salvage to salvation [page four]

1. Health Protection Agency. *HIV Drug Resistance in the United Kingdom: data to end of 2004*. CDR Weekly 16(4), 2006.
2. Youle M et al. *Potential barriers and motivators to enfuvirtide use: physician perspectives of injectable antiretrovirals*. 10th EACS, Dublin, abstracts PE7.3/24, 2005.
3. Horne R et al. *Treatment-experienced patients' perceptions of self-injectable therapy*. 10th EACS, Dublin, abstract PE7.3/25, 2005.
4. Katlama C et al. *48 week RESIST 1 and 2 combined analyses*. 13th CROI, Denver, abstract 520, 2006.
5. Lazzarin A et al. *POWER 1 and 2 combined 48 week analysis*. 16th IAC Toronto, abstract TuAb0104, 2006.
6. Sekar V et al. *Pharmacokinetic interaction between the protease inhibitors TMC114 and lopinavir/ritonavir*. 46th ICAAC, San Francisco, abstract A-0367, 2006.
7. Cohen et al. *Efficacy and safety results at 48 weeks with the novel NNRTI, TMC125, and impact of baseline resistance on the virologic response in study TMC125-C223*. 16th IAC, Toronto, abstract TuPe0061, 2006.
8. Grinsztejn B et al. *Potent efficacy of MK-0518, a novel HIV-1 integrase inhibitor, in patients with triple-class resistant virus: 24-week data*. 46th ICAAC, San Francisco, abstract H-1670b, 2006.
9. Mayer et al. *24-Week Results of a Phase 2b Exploratory Trial*. 16th IAC, Toronto, abstract ThLb0215, 2006.

news in brief [page twelve]

New risk factors identified for liver problems on anti-HIV drugs

1. Servoss JC et al. *Predictors of Antiretroviral-Related Hepatotoxicity in the Adult AIDS Clinical Trial Group (1989-1999)*. JAIDS 43(3): 320-323, 2006.

Kaletra tablets better tolerated, according to patient survey

1. Schrader S et al. *Switching to lopinavir/ritonavir tablets once daily from soft-gel capsule dosed BID/QD led to significant improvements in tolerability, diarrhoea, anti-diarrhoeal medication use and satisfaction*. Eighth International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Francisco, 2006.

Surprising new findings for HPV in women; herpes in men

1. Kojic EM et al. *Human Papilloma Virus (HPV) infection of the anus is more prevalent and diverse than cervical HPV infection among HIV-infected women in the SUN study*. 44th Annual Meeting of the Infectious Diseases Society of America, Toronto, abstract 693, 2006.
2. Kim N et al. *Higher rectal HIV levels in men who have sex with men (MSM) with concurrent rectal HSV shedding*. 44th Annual Meeting of the Infectious Diseases Society of America, Toronto, abstract 57, 2006.

great expectations [page fourteen]

1. Schackman BR et al. *The lifetime cost of current HIV care in the United States*. Medical Care 44(11): 990-997, 2006.
2. Mandilia S et al. *Cause and time to treatment failure of HAART and cost of care in UK NPMS-HHC clinics, 1996 - 2002*. HIV Med 7 (supplement 1), abstract 033, 2006.
3. Available from: www.statistics.gov.uk

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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.

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On the last Monday of every month, an expert speaker discusses an HIV treatment related topic. Entry is free. The next topic is 'keeping healthy in 2007' and will be held on 27th January 2006. For more details, go to www.aidsmap.com/forums.

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