

aids treatment update

The shape of things to come

The first thing people often do at the start of a new year is decide to get fit. There are plenty of reasons why HIV-positive people might want to consider getting fitter and stronger - to counteract an increased risk of heart disease, say, or simply to feel better about ourselves - but should we be using anabolic steroids in our quest for a better body? The answer from the HIV-experienced endocrinologist, Dr Pierre Bouloux, is a resounding 'no'. You can read why inside this bumper issue of *ATU*, which also includes a round-up of the new treatment options that will become available to us this year. With the arrival of one new drug, tipranavir, there's some good news for people looking to construct a so-called 'salvage' regimen, but only if you can find other potent drugs to go along with it, and can tolerate its side-effects. There will also be easier-to-take combinations of existing drugs, although, of course, not all of them are as easy to tolerate.

Finally, in *The Shape of Things to Come*, Gus Cairns examines whether the immune system can rebuild itself with HAART alone. It's a complicated subject, but one well worth looking into.

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2 a look at the latest treatments options, by paul kidd

Will 2005 be remembered as a year of great leaps forward in HIV medicine, or of just marking time? Fortunately, the slow and careful fashion in which treatments research progresses makes it possible to look at least a short distance into the future, and the news is generally good. Not exactly earth shattering, but encouraging.

For most of the last few years, new anti-HIV drugs have become available in the UK at a fairly steady rate of one or two a year, and that's not going to change in 2005 - only one genuinely new anti-HIV drug is expected to make it onto pharmacy shelves.

But there are new formulations of existing drugs that promise more convenient dosing, some good news on the drugs we already have, and encouraging signs from further back in the drug development pipeline.

The unfortunate truth is that there are never enough treatment options, especially for very treatment-experienced people. The encouraging news is that next year's new kid on the block may well have the greatest impact right where it is needed most.

Tipranavir

Boehringer Ingelheim's new protease inhibitor will likely be the first, and perhaps the only, new HIV drug to come into widespread use in 2005. Originally developed by Pharmacia and Upjohn, but later acquired by Boehringer Ingelheim, tipranavir has been available in the UK on a named-patient basis since November 2003, and

is now moving through the approvals pipeline, after Boehringer lodged marketing authorisation applications to the European Medicines Agency and the US Food and Drug Administration (FDA) in October. Boehringer is confident it will have marketing approvals for tipranavir in place in both the US and Europe by mid-2005.

Tipranavir is the first *non-peptidic* protease inhibitor. Existing PIs are derived from peptides, short chains of amino acids, which are the building blocks of protein. Tipranavir's non-peptidic molecular structure is designed to make it more effective against virus that has become resistant to other PIs, and, in theory, less likely to lead to resistance itself. Because of this, much of the excitement about tipranavir, and all of the clinical research to date, has focused on its potential as salvage therapy.

The RESIST-1 and RESIST-2 studies examined tipranavir's effectiveness in heavily pre-treated patients. Participants in these trials had all previously been treated with an average of twelve antiretroviral drugs from all three major drug classes, and had at least one clinically important PI resistance mutation determined by genotypic testing. The RESIST-1 study enrolled 620 patients in the United States, Canada and Australia; RESIST-2 enrolled 863 patients in Europe and Latin America.

Participants in both trials were randomised to receive either 500mg tipranavir boosted with 200mg ritonavir twice daily, or another boosted PI chosen on the basis of the individual's

resistance test result. All patients also took an optimised background nucleoside regimen, again chosen on the basis of their HIV genotype. This is because, like all other drugs, tipranavir works best with other anti-HIV drugs that are at least partially active against HIV. Some patients also took T-20 (enfuvirtide, *Fuzeon*).

Interim results, up to week 24, from RESIST-1 were presented at a late-breaker session of the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in Washington DC in early November¹. After 24 weeks, 41.5% of patients in the tipranavir arm achieved a treatment response (defined as a 1 log or greater decrease in viral load) compared with 22.3% of those in the comparison arm. Participants in the tipranavir arm were also much more likely to have undetectable viral load: 34.7% had viral load levels below 400 copies/ml, compared with 16.5% of those taking other PIs. For viral load below 50 copies/ml, the numbers were 25.1% versus 10% respectively. All results were statistically significant.

Among participants also taking T-20, the response rates were even higher, despite the fact that these patients tended to be more severely immunocompromised at baseline. In this subgroup, 47.1% versus 21.9% of patients achieved viral loads below 400 copies/ml, and 32.8% versus 14.3% below 50 copies/ml. Tipranavir and T-20 together could give some treatment-experienced patients just the break they have been waiting for.

A similar, but smaller, interim analysis was presented for RESIST-2 a few weeks later, at the Seventh International Congress on Drug Therapy in HIV Infection in Glasgow, with similarly encouraging results².

In both trials, participants in the tipranavir arm were more likely to experience increased liver enzyme (ALT/AST) levels, and had a higher rate of blood fat (lipid) elevations; however, the changes did not lead to symptomatic illness or discontinuation of treatment. Other side-effects reported for tipranavir are similar to other PIs, including diarrhoea, nausea and stomach cramps.

Apart from side-effects, tipranavir's other main limitation is that it interacts negatively with many other anti-HIV medications, which could

mean that the ability to assemble a viable salvage option may be very limited. The lessons learned from recent T-20 studies tell us that the more new agents that are included in a salvage regimen, the better. This could be difficult when tipranavir has been reported to reduce levels of ritonavir-boosted saquinavir (*Invirase*, *Fortovase*), ritonavir-boosted amprenavir (*Agenerase*) and lopinavir/r (*Kaletra*). Tipranavir also reduces blood levels of delavirdine (*Rescriptor*) by 95%, ruling out a combination of the two drugs. As a consequence, caution and therapeutic drug monitoring will be required for many people taking tipranavir.

T-20 less often?

T-20 (enfuvirtide, *Fuzeon*) continues to perform as the 'big gun' of salvage therapy. Long-term follow-up from the TORO-1 and TORO-2 clinical trials has shown that T-20 continues to be effective in a substantial number of patients up to two years after starting the drug³. Despite the immense inconvenience of twice-daily injections, more than a quarter of patients are still taking the treatment and still maintaining undetectable viral loads after 96 weeks. However, a poster presentation at the 44th ICAAC in Washington reported on a small study looking at whether T-20 could be dosed once instead of twice daily, with encouraging results⁴. Halving the number of daily injections (and halving the considerable time involved in preparing the drug for injection) would obviously have a substantial positive effect on the lives of people taking this treatment, although more studies are needed before once-daily dosing of T-20 can be considered as effective as twice-daily dosing.

New combos of existing drugs

Two new fixed-dose combination antiretrovirals will become available in 2005, joining GlaxoSmithKline's *Combivir* (AZT plus 3TC) and *Trizivir* (AZT, 3TC plus abacavir). The first is Gilead Science's *Truvada*, which combines two existing treatments, FTC (emtricitabine, *Emtriva*) and tenofovir (tenofovir disoproxil fumarate, *Viread*) in a single tablet taken once daily.

Combivir is one of the most-prescribed HIV medicines in the UK, often in combination with

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efavirenz (*Sustiva*), and *Truvada* is intended to provide an attractive alternative. An antiretroviral regimen of *Truvada* plus efavirenz means taking just two pills once a day, adding a significant premium of convenience and simplicity.

The Gilead 934 study is directly comparing these two regimens, although it is using separate tenofovir and FTC pills, not the *Truvada* combined formulation. Interim 24-week data from this study was presented at the 44th ICAAC meeting in November⁵. Five hundred and seventeen previously untreated people with HIV were enrolled, with a baseline median viral load of 100,000 copies/ml and median CD4 count of 237 cells/mm³.

Participants were randomly assigned to two groups; the first group received FTC, tenofovir and efavirenz, and the second group received 3TC and AZT (as *Combivir*) and efavirenz. After 24 weeks, the proportion of trial participants with viral load below 400 copies/ml was 87% in the FTC/tenofovir/efavirenz group, and 78% in the 3TC/AZT/efavirenz group. The difference between the groups was statistically significant. Average increases in CD4 counts were 129 and 111 cells/mm³ respectively.

The key to the superior showing of FTC/tenofovir so far seems to be that it was better tolerated than 3TC/AZT, with 9% of participants in the 3TC/AZT group withdrawing due to side-effects (primarily anaemia, nausea, fatigue and vomiting) compared with only 3% in the FTC/tenofovir group. This study will continue for another 24 weeks but it would be interesting to see if FTC/tenofovir's tolerability advantage lasts longer than this planned 48-week study.

The second fixed-dose combination that will arrive in 2005 is GlaxoSmithKline's once-daily *Kivexa*, which combines 3TC (lamivudine, *Epivir*) and abacavir (*Ziagen*). This formulation is already available in the US, where it is sold under the brand name *Epzicom*.

The two component medicines in *Kivexa* are well established and have been in use since the 1990s, but both have recently been re-approved for once-daily dosing following clinical studies that showed the one-a-day regimens were as

effective as the earlier twice-daily dose. Abacavir plus 3TC is a popular and effective antiretroviral regimen 'backbone' - the CNA30024 study found that 3TC/abacavir/efavirenz was as good as, and perhaps slightly better than, 3TC/AZT/efavirenz in people who had not taken treatment before. Switching from the twice-daily to the once-daily doses of 3TC or abacavir (or both) has also been shown to be safe, but of course you should always discuss any variation in your antiretroviral dosing with your HIV care provider before making any changes.

Nelfinavir no-show

One previously announced new treatment that we won't be seeing in 2005 is the 625mg formulation of nelfinavir (*Viracept*). A 625mg version of nelfinavir has been available in North America since mid-2004, substantially reducing the pill burden for this medicine. But the European manufacturer, Roche, announced in November that "insurmountable production problems" with the film coating on the tablets meant that the more convenient version wouldn't be available in Europe as previously planned. This is a double blow for people taking nelfinavir, as the 625mg tablets were reported to cause less diarrhoea and other gastrointestinal problems in clinical trials⁶.

By May, those people on nelfinavir 625mg will have been switched to the 250mg tablets, but they will have options around dose frequency. The recommended adult dose is either three tablets three times a day, or five tablets twice a day - a total of nine or ten pills a day, compared with four of the now-abandoned 625mg tabs. Research has shown that both the twice-daily and three times daily doses are equivalent, so it's worth giving some thought to which dosing option fits in best with your lifestyle, and discussing with your doctor if you want to change⁷. Nelfinavir should be taken with a meal or a substantial snack, so the twice-daily dosing may better suit some people, even though the number of pills is amongst the highest for any anti-HIV drug. On the other hand, nelfinavir is notorious for causing diarrhoea in people who take it, and the higher peak drug levels produced by the twice-daily dose might make this worse.

Beyond 2005

Although we won't see any of them on our pharmacy shelves this year, there are several promising anti-HIV drugs in development that are now being examined, or will soon be tested, in major clinical trials. Trying to predict which anti-HIV drugs will survive the clinical trials process and make it into widespread use is a hazardous business. But here's a brief list of promising contenders from each of the major drug classes:

Nukes:

Reverset (D-D4FC) is a second-generation nucleoside analogue. It has only been studied in very small trials, but with striking results. The ICAAC conference heard results from a ten-day phase I/II trial of *Reverset* monotherapy in ten treatment-experienced patients; eight received *Reverset*, two received sugar pills⁸. The average reduction in viral load among those receiving the drug was 0.8 logs, and four of the eight achieved viral loads below 400 copies/ml. While there are limitations on the conclusions that can be drawn from clinical trials as small as this, these numbers are very encouraging. A larger phase II trial with 180 participants is planned for 2005.

Non-nukes:

Two 'second-generation' NNRTIs lead the field. The drug most likely to appear first, capravirine, developed by Agouron-Pfizer, appears to be highly potent and effective against efavirenz-resistant HIV, but resistance to nevirapine would render capravirine useless. It also requires ritonavir boosting to be most effective, and is currently being studied in combination with *Kaletra*.

Next in line is Tibotec-Virco's etravirine, also known as TMC125. Several small dosing and efficacy studies have been presented at conferences and results show significant reductions in viral load after just one week of treatment. Virus which has high level resistance to efavirenz and nevirapine is susceptible to etravirine, but interactions with PIs (e.g. ritonavir reduces etravirine levels by 45%) will make combinations involving etravirine complicated.

Protease inhibitors:

TMC-114 is an experimental protease inhibitor developed by Tibotec-Virco. It appears to be effective against HIV that has become resistant to other protease inhibitors. In 2003, a small phase IIa study reported viral load reductions of 1.35 logs in heavily pre-treated patients. A study examining the use of TMC-114 in salvage therapy is about to get underway; it will be particularly important to investigate interactions with other PIs given the interactions that have emerged between tipranavir and other PIs.

Entry inhibitors:

Pfizer's chemokine antagonist, UK-427, is already halfway through phase II studies with several worldwide phase III studies starting this year. UK-427 promises to be the most important new agent on the horizon because it opens up another drug class. The main question for people who need the drug as a salvage option is whether it will be appropriate for people who have previously had low CD4 cell counts and experienced some degree of immune restoration, and whether it will be possible to use it in people with CD4 cell counts below 200.

Conclusions

The good news about all of these drugs is that they promise a great deal - a whole new generation of anti-HIV treatments. But that promise needs to be taken with a grain of salt: the vast majority of potential HIV treatments don't make it, and all of these drugs are yet to be tested in phase III trials, meaning their eventual arrival into widespread clinical use - if it happens at all - could be 2007 or even later. Where will we be a year from now? Despite the much-anticipated arrival of tipranavir, and the increased convenience that the new fixed-dose formulations will offer, we'll still be battling HIV with much the same weapons as now, and doing so in the face of the challenges presented by long-term side-effects such as lipodystrophy and increased heart disease risk.

But while 2005 is looking like a lean year, 2006 is unlikely to be significantly better, and that reinforces the importance of careful adherence, preservation of treatment options, and taking care of ourselves.

steroids, testosterone and hiv

6 could anabolic steroids be beneficial for people with hiv? asks edwin j bernard

Q&A with dr pierre-marc bouloux

Low levels of testosterone can occur in both men and women with HIV disease, although much more is known about testosterone deficiency in men. In recent years, it appears that the use of both testosterone and anabolic steroids amongst some HIV-positive men has become quite commonplace. A 2002 study¹ examining the use of anabolic steroids amongst HIV-positive gay men in London gyms found that over 30% had used testosterone and/or steroids in the past year. However, not all of the testosterone and/or steroids were obtained from their doctor.

Although today anabolic steroid use and misuse appears to be a less taboo topic than ever before, the medical profession as a whole is still very cautious when it comes to prescribing anabolic steroids, since they are not licensed in the UK for any HIV-related condition. They can, however, prescribe testosterone replacement when medically necessary.

AIDS Treatment Update spoke with Dr Pierre-Marc Bouloux (PMB), reader in endocrinology at London's Royal Free, who has many HIV-positive patients, about the use of anabolic steroids and testosterone replacement in HIV disease.

ATU: *Who do you see in your clinic at the Royal Free?*

PMB: The vast majority of the HIV-positive people that I see are men with borderline low testosterone. They have this for different reasons, sometimes as a consequence of their HIV disease, and sometimes as a consequence of previous use of anabolics that has put them into a switched-off mode, so that they need to be given something while their body recovers. In both these cases, the idea is to replace either partial or complete testosterone deficiencies. In a small proportion of these patients, I use testosterone in a slightly pharmacological way, giving larger amounts of male hormones to people who have lost a lot of muscle bulk and who have been in a truly wasting state. I have found that larger than normal doses of testosterone can be quite effective in slowing down muscle loss, particularly following a severe illness.

ATU: *Do you prescribe anabolic steroids in your clinic?*

PMB: Anabolic steroids are not agents that I deal with, although I am somewhat familiar with their misuse. Anabolic steroids like

Deca-Durabolin (nandrolone, an injectable steroid), *Oxandrin* (oxandrolone, a steroid tablet) and *Winstrol* (stanozolol, a steroid tablet) are not licensed in the UK for any HIV-related indication and most people get them from various, rather suspect, sources. Anabolic steroids are derivatives of testosterone; they mimic the effects of testosterone but they are semi-synthetic and have been modified so that they are either more muscle-building (anabolic), or more likely to affect sexual function (androgenic). Some can be taken by mouth, unlike natural testosterone. My biggest concern regarding steroids is that they go through the liver.

ATU: *What is the problem with steroids going through the liver?*

PMB: There's little doubt that a proportion of patients will suffer consequences in terms of potentially irreversible changes in their liver. They can certainly become jaundiced and there's a much greater risk, in terms of long-term use, of getting liver problems with non-cancerous (benign) or cancerous (malignant) tumour formation. Some of the tumours are full of blood vessels (vascular) and can bleed, and you can occasionally get abdominal or liver catastrophe, or sudden death, from a massive bleed from one of these lumps in the liver.

ATU: *Is the risk to the liver as great from an injectable steroid?*

PMB: I think the oral steroids are more problematic because they would definitely go first-pass into the liver; if you take them by mouth and they get absorbed directly into the liver, the liver gets quite a hard hit in terms of concentration, whereas if you give something by intramuscular injection, the amount getting through to the liver will be less, because it is diluted.

ATU: *How soon could liver damage occur?*

PMB: It depends on the individual. Not everybody gets liver damage, but some people can get severe liver damage on the very first 'cycle' of treatment. It's not dose-dependent, it's not duration dependent, but if a person happens to be sensitised in some way to that kind of

molecule, then there's no way of predicting it. It's important to bear in mind that many HIV-positive patients already have liver disturbances; some of them have hepatitis B and/or C and some are taking anti-HIV drugs or other related medicines that are already slightly liver-toxic. It would be very risky to add another chemical that might provoke a disastrous adverse reaction. A liver tumour doesn't just suddenly go when you stop taking the steroids; it may remain a benign tumour but it may have a potential to bleed with critical, or fatal consequences. I never use these agents unless there are some very unusual circumstances.

steroids and the law

Anabolic steroids are Class C drugs; it's legal to possess or import steroids as long as they're for personal use. But possession or importing with intent to supply (which includes giving them to friends) is illegal and could lead to 14 years in prison and an unlimited fine.

ATU: *The injectable steroid, nandrolone, is only licensed for use in the UK to treat osteoporosis in post-menopausal women and aplastic anaemia (a bone marrow disease resulting in low red and white blood cell and platelet counts). However, it is commonly used in the US in combination with testosterone in HIV-positive men who currently have, or are at risk of, wasting. Why isn't it approved for that purpose in the UK?*

PMB: No standard textbook or mainstream clinical investigation has ever looked at nandrolone use in a clinical context in a sustained and scientific manner. A lot of the knowledge we have from nandrolone in the context of muscle building is from its 30 years of misuse, and the 'experts' are often the guys who use it themselves. There's no doubt that nandrolone can get muscle to grow very impressively, and that gives some people confidence and makes them feel good. However, it's important to realise that there are problems associated with using nandrolone and other anabolic steroids. You can achieve the effects in muscle, but you don't know what you're doing to your blood cells, the fats in your blood, or your prostate.

steroids, testosterone and hiv continued

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ATU: *Could there be an argument for the medical use of steroids, in lower doses than those often advocated by misusers, in order to deal with the real psychological body image issues of lipodystrophy? Is it possible that, just like New-Fill for fat loss in the face, anabolic steroids could be used, alongside weight training and diet, to reshape the body where fat has been lost in the arms, legs and buttocks?*

PMB: Anabolic steroids might reduce visceral, tummy fat, but they will not regenerate fat that has been lost. Yes, what they can do is fill the space by increasing muscle bulk, and that will regenerate some contours around the buttocks, for example. So, I accept that, if quality of life suffers as a consequence of changes in bodily appearance, anabolic steroids are potentially beneficial agents. However, having exaggerated muscle definition would not completely hide that this was an abnormal appearance. As a therapy to deal with lipodystrophy, it becomes an issue of risk versus benefit, particularly if you are looking long-term. Given current predictions on HIV survival, people living with HIV in the UK can conceivably live another 30-40 years and so we are talking about the side-effects of treatment being the real issues of living with HIV and not the disease itself. In the future there may be other ways that can regenerate lost fat tissue, but in the present, if you're saying 'it's anabolics or nothing'; well, if we can accept that premise, which I don't particularly support, I would have to ask the following question: how can we use anabolics to achieve those effects in the safest possible way? And I would tend to say use naturally occurring ones, like testosterone.

ATU: *So you recommend that your HIV-positive patients don't use anabolic steroids at all, but that if they have to use anything, they should consider testosterone?*

PMB: With the best will in the world, if someone is prepared to go to a gym and buy something in a brown envelope and inject

steroid use in north america

Certain clinicians and HIV-positive individuals in the US and Canada use steroids to combat wasting and lipodystrophy in a more pro-active and aggressive way than we do in the UK. For more information, visit the *medibolics* website at: www.medibolics.com

themselves with it, or take tablets, I can't stop that. There's a culture out there, and that's what people do. And I try to put people off doing that. However, provided I monitor these people carefully, and check their red blood cells, their prostates, and the fat levels in their blood, then it's cautious, pragmatic medicine. However, safe practice says, if the effect you're trying for is a muscle-building effect, then you are best using a substance which occurs naturally in the body, and that would be testosterone. You can vary the dose of that if you like, and push it to high levels, but at least you're not dealing with a foreign chemical in the body. Testosterone is converted into at least two other beneficial hormones; oestrogen, which may be important for bones and sexual function; and DHT or dihydrotestosterone, which is converted in places like hair follicles, muscles and the prostate and appears to be important in certain facets of testosterone's action. Now you miss all of that, of course, if you go for an anabolic steroid, which is structurally related to testosterone but can't be converted into oestrogen or DHT. So, there are many theoretical and practical reasons for staying with a natural substance like testosterone.

ATU: *Do you differentiate between patients who need testosterone replacement because their body no longer makes enough due to their HIV disease, and those who feel they need replacement because they constantly feel tired and/or depressed?*

PMB: In my clinic, I tend to deal with the more severe end of the spectrum, and these are the people who have a long-term requirement and will probably be on testosterone replacement for life. But I'm also prepared to accept that under certain circumstances there are a number of HIV-positive patients who might not have low enough testosterone levels to fit into the deficiency category, but who may well benefit from having additional male hormone in their bodies. But I think the issue of low testosterone is becoming less of a problem than it used to be, affecting mostly people who have been very ill in the past.

There are other causes of low testosterone that can confuse the issue, not least previous use of anabolics, as well as heavy smoking, and regular marijuana use, all of which can chronically reduce testosterone levels. It's also possible that bad snoring at night, particularly when it causes sleep apnea [an interruption in regular breathing, reducing the quality of sleep], can cause low testosterone. Also, depression in younger HIV-positive men is unlikely to be caused by low testosterone. So it is important to be absolutely sure that the symptoms you are treating are clearly those that relate to testosterone deficiency. If that is the case, the issue, then, is how best to administer replacement therapy.

ATU: *The last time ATU covered testosterone replacement therapy, we found that there were no ideal solutions. Which methods do your patients prefer?*

PMB: There are several choices. First, there are intramuscular injections with testosterone preparations like *Sustanon*, but as well as a regular painful injection in the buttock or thigh, there are the up and down cycles of mood, sexual urge and aggression. There are also gels like *Testogel*; however one needs to apply rather a lot of gel in order for it to be absorbed through the skin, and there isn't always a desired or appropriate effect. I use a lot of testosterone implants on the men in my clinic who require long-term testosterone replacement therapy. Most of my patients who are on long-term replacement therapy prefer it to injections or gels because it is so convenient. These are tiny pellets of testosterone that I

implant in the buttocks during a four-minute procedure, and these pellets release a replacement amount of testosterone steadily over a six-month period. We can often get levels to the high end of the normal range, and in terms of the 'feel good' factor, and energy - the usual reasons people receive testosterone replacement - we've had a lot of success. The only downside is that it leaves a half a centimetre scar on the buttock.

ATU: *Once testosterone therapy is started, how likely is it that your HIV-positive patients will be able to stop?*

PMB: I have been treating some people for four or five years consistently and I haven't thought of stopping, since they feel well, and when their testosterone is low, their symptoms come back. Provided I monitor safety, they can continue. Whether I have been rigorous in closely examining if they actually need it for life is another question. We get in to this problem where if you replace testosterone, your body may switch off its own production. And then you may have to wait until it recovers. And during that period of waiting, you're going to get symptoms. Are you prepared to wait three months feeling tired and depressed? It's a vicious circle.

ATU: *There has been some anecdotal success in 'kick-starting' the body's natural testosterone production with anti-oestrogen drugs like clomifene (Clomid) and tamoxifen (Nolvadex, Soltamox). Have you had any experience with them?*

PMB: I have tried both drugs in a few patients, but I have more experience with tamoxifen. It's been around for breast cancer for about 25 years. While you remain on the tamoxifen, undoubtedly your testosterone levels rise, but in some of these people something has happened whereby they do not recover very easily, and you don't know if that's the effects of the previous drugs, the disease, or if there are other issues. However, there are risks to using either of these drugs; both increase the risk of blood clot formation. So, in the long term, it's an individual decision of risk versus benefit; but that would be one way to try to encourage spontaneous recovery.

further reading

For more on testosterone replacement, see the July 2003 issue (*ATU 127*) available online at: www.aidsmap.com/en/docs/pdf/atu127.pdf

An excellent, practical guide to steroids, aimed at gay men, has been produced by the Camden and Islington Gay Men's Team. *In Gear - A gay man's guide to steroids* can be found in many London gay bars and clubs. To obtain a copy contact David Smith on 020 7530 3956 or email david.smith@camdenpct.nhs.uk

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the shape of things to come?

10 is haart enough to keep our immune systems working in the long term? asks gus cairns

When people who have been very sick start taking highly active antiretroviral therapy (HAART), their immune systems begin to regenerate. Once their CD4 count has risen above 200 cells/mm³, their chances of getting sick again, in the short term at least, fall to almost nil.

But what is the long-term legacy of HIV infection? Can HAART give a normal lifespan to people whose CD4 cells had dropped way below 200 cells at some point in their HIV history? Or has HIV left them with long-term damage to their immune system that antiretrovirals alone can't fix?

Is long-term HAART enough?

The latest findings of the ACTG 375 study¹, which was designed to evaluate the long-term success of HAART soon after it became available, suggest that long-term HAART - or, at least, this now-outdated regimen - might not be enough to restore the immune system.

The study was designed to look in detail at what happened to the immune systems of 53 people treated with the then-new HAART regimen of AZT, 3TC and (full dose) ritonavir.

Six years later, 19 out of the original 53 patients have remained in the study with, remarkably, all but two still taking the original regimen. These 19 patients present us with the only detailed long-term glimpse of what happens to a post-AIDS immune system once HIV replication has been suppressed.

Good news, worrying news

Over the six years, the average CD4 count of the participants went up by nearly 300 cells, from an average starting point of about 230. After an initial spurt in the first year, there was hardly any increase in years 2 and 3. The study looked as if it might back up a similar Spanish study², which suggested that CD4 counts don't improve any further after 4-5 years on HAART.

However, between years 3 and 6 there was an average increase of about 42 cells a year. Increases were also reported in certain kinds of T cells. The number of 'memory' CD4 cells, which recognise specific infections, (see *CD sorter*) increased, as did the number of 'naïve' cells, which are freshly-minted CD4 cells that have been taught to recognise specific infections but haven't met them yet. That's the good news.

The worrying news was that in the fifth year of the study, the CD4 counts of eleven of the 19 patients dropped - by between 20 to 178 cells. Even more troubling was that the level of activation of the immune system - which should continuously decline after HAART stops HIV from overstimulating it - started going up again after year one; over three-quarters of the 19 patients had persistently hyped-up immune responses. It was as if they were responding to an ongoing HIV infection, despite HIV replication being suppressed.

What's going on?

"We don't know if these people all had fully suppressed virus," says immunologist Gareth Hardy, from London's Royal Free and University College Medical School. "We are only told that none of them had a viral load over 1,000 at any time. However, immune activation should be going down, not up, over time. Due to the small sample size, we can't draw too many conclusions, but if these findings were repeated in a larger trial, with viral loads maintained under 50 with no

CD sorter

CD means Cluster of Differentiation. It's a way of distinguishing between different cells in the immune system - or, more precisely, what 'job' they are currently engaged in. Immune cells have different proteins on their surfaces according to their function, and these can be detected by seeing which combination of artificial antibodies (proteins designed to attach to specific cell-surface molecules) attaches to them. This combination is given a CD number. Cells may have several different CD numbers according to which antibodies they do and do not react to. There are 247 different CD patterns determined so far.

CD4 is the marker that differentiates T-helper cells, it is also the cell-surface molecule to which HIV first links. T-helper cells do not kill foreign substances or infected cells themselves, but serve as the 'traffic cops' of the immune system, telling other cells where to go and what to do.

CD8 is the marker that distinguishes T-suppressor cells. The job of these cells is to seek out and destroy cells infected with viruses. In untreated HIV infection there is a permanent, extremely high rate of CD8 (and CD4) activation, some three to six times higher than in other infections. Most of the immune damage in AIDS is not due to HIV directly killing CD4 cells, but to the fact that the immune system becomes exhausted by the effort of cells continually dividing and to the toxic effects this has on the system.

CD28 Naïve cells (see below) have to express the CD28 molecule in order to be able to recognise new infections and become memory cells. Having CD4 cells that also express CD28 seems to be essential if you are to get back any kind of natural immune response to HIV. Most people do not regain this response despite HAART.

CD38 A marker of whether CD4 or CD8 cells are 'activated' in response to an infection. In HIV infection, too many cells become permanently CD38-positive, and high CD38 levels are a more accurate marker of progression to AIDS than either low CD4 counts or high viral loads.

CD45 RA Cells with this marker are naïve cells. These are programmed to react - slowly - to a specific foreign invader, but have not yet met it. Before HAART came along, immunologists were worried that people who'd had very low CD4 counts would never get back their naïve cells and would therefore be vulnerable to new infections. Luckily, this doesn't seem to be the case, although it is possible that 'gaps' remain in the immune system that could predispose people to certain infections or cancers in the future. The second, slow phase of CD4 cell recovery on HAART partly consists of newly made naïve cells repopulating the immune system.

CD45 RO Cells with this marker are **memory** cells. After naïve cells have met their specific foreign invader and killed it, they become memory cells. Most memory cells die after they have won their battle, but a few persist in a resting state, ready to quickly proliferate if that specific infection occurs again. Resting CD4 cells infected with HIV cannot be detected and destroyed by the rest of the immune system and so become the source of new HIV when HAART is stopped. The first, fast phase of CD4 recovery mainly consists of memory cells 'flooding' out of the lymph nodes, where they have been trapped, and repopulating the bloodstream.

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"My personal view is that most people on HAART will have a normal lifespan"

Professor Brian Gazzard

'blips', and no drug resistance... well, then this would raise a lot of eyebrows in the immunology community.

"It may mean that HAART was possibly failing to correct long-term immune activation. There are very few clinical situations like HIV, where part, rather than all, of the immune system is knocked out and then allowed to reconstitute. We don't know what we'll see in the long term."

Are there holes in the immune system?

Like many immunologists, Hardy is frustrated. "I think your lowest-ever CD4 count is of immense importance; more than clinicians think, even now. I think having had virtually no CD4 cells may leave people with long-term 'holes' in their immune system. The trouble is, when you show clinicians that certain immune responses are sluggish, they say,

"Yes, but do these test-tube results correspond to any clinical effect?"

What Hardy means is that, as the immune system recovers, certain sets of 'memory T cells' which recognise infections that most of us carry around anyway - such as herpes, CMV and candida - can easily return. However other infections that the immune system only 'sees' intermittently (which Hardy terms as 'transient antigens') generate more sluggish responses - tetanus, influenza and TB among them. For instance, when they looked at this group of 53 patients after their first year of therapy³, only 48% of them developed a satisfactory response to a tetanus vaccine.

Of more concern are immune responses to viruses implicated in cancers, including human papilloma virus (HPV), which causes most cervical and anal cancers, and Epstein-Barr virus (EBV), implicated in lymphomas. Hardy is one of the researchers in a soon-to-be-published study in which patients were vaccinated with a 'transient antigen' and then stimulated with an immune chemical called interleukin-2 (IL-2) to see if their immune responses could be improved. "We have examples from other illnesses where an incomplete immune response to the original disease results in problems in later life," says Hardy. "An example is post-polio syndrome, where a much slower muscle paralysis starts to happen in some people decades after the original infection. The immune system probably also only has so much capacity to revive itself after decimation. Every cell in the body only has so much capacity to divide; that's basically why we age."

Welcome back, thymus

"However, there is some hope," Hardy continues. "It seems that the thymus gland, which generates naïve cells, is able to regenerate. Normally only about 2% of the thymus remains active in people aged 25-50, but after HAART successfully suppresses HIV, the thymus can re-grow. There must be a mechanism whereby the body recognises a fall in T cell numbers and can generate more of them. However, we think that the body can't distinguish between CD4 and CD8 cells. So while the CD4 count may rise to normal levels, the CD4/CD8 ratio rarely normalises."

The CD4/CD8 ratio should be about 1:1, but in HIV infection there can be four times as many CD8 cells as CD4 cells, and it very rare that anyone achieves a ratio above one CD4 cell for every two CD8 cells. This leads Hardy to wonder if people with long-term HIV infection and recovered CD4 counts may still be vulnerable to opportunistic infections and tumours.

"My personal view is that most people on HAART will have a normal lifespan," says Professor Brian Gazzard, former chair of the British HIV Association. "I feel that the results of the recent Swiss HIV Cohort Study⁴, which found that non-intravenous drug users on HAART still had seven times the death rate of HIV-negative people, is due to several factors. First, there is the legacy of suboptimal treatment before HAART, and there is also the notion that people with HIV tend to be risk-takers anyway.

"The challenge with immunology is that we don't know which immune indicators correlate with clinical outcomes. It's difficult enough to find immune indicators that show if vaccines will work, let alone what will protect you against opportunistic infections."

Keep taking HAART

However, Professor Gazzard has high hopes for the ESPRIT trial of interleukin-2; the immune-modulating chemical that boosts CD4 counts. "It does this not by creating new CD4 cells, but by doing the opposite - it stops them going through their life cycle too fast, so that they live much longer." The ESPRIT trial is not due to be completed until 2011, but Professor

Gazzard hopes that if a difference in the illness rates between the IL-2 and untreated patients becomes obvious, it could produce results before then.

Gareth Hardy has a very personal interest in CD4 cell counts and immune recovery. His own lowest-ever CD4 count was zero. "I was diagnosed with HIV in January 1990 at the age of 19, and must have been a 'fast progressor', because my CD4s were below 200 within a year of infection. I held on with various combinations of AZT, ddI, 3TC and d4T until 1996, when full-blown AIDS hit me like a tidal wave. "Because I was a researcher I'd seen all the data at the Retroviruses Conference that February, showing patients' viral loads going undetectable - previously unthinkable - and I remember saying to another patient in my hospital ward in the summer of 1996, 'You realise we are either going to be the last patients to die of AIDS or the first to survive?' I've no idea what happened to him."

There have also been numerous attempts to stimulate an immune response to HIV itself by using a therapeutic vaccine. The limited success of this approach is illustrated by the fact that one of the most promising was a recent Brazilian study⁵ where cells that 'present' HIV to the immune system were taken out of patients' bodies, loaded with an inactivated preparation of their own HIV, and transfused back in. Eight of the 18 patients achieved a 90% reduction in viral load for a period of about a year. But at a cost of up to £5000 per patient for a year's treatment, this approach is no cheaper than HAART.

"Can we produce a therapeutic vaccine that has everything structured in the right way and combine it with just the right kind of stimulant therapy to reconstitute the immune system?" asks Hardy, pointedly. "At present we just don't know. At the moment there's not a lot we can do except keep people on HAART. But there should be more research into agents that can remove rather than just suppress the virus. But I wonder if it would be advantageous to the pharmaceutical industry to provide a drug that would wipe out HIV."

Further reading

Visit [aidsmap.com](http://www.aidsmap.com) for more on:

Eradicating HIV
<http://www.aidsmap.com/en/docs/1AD7D076-DF8B-4D4A-82CA-F9CC2F1E6773.asp>

Restoring the immune system
<http://www.aidsmap.com/en/docs/8312D5CD-E74D-4BEC-B847-2441E0C945A9.asp>



Is combining ddI and tenofovir problematic?

Two separate issues regarding the use of ddI (*Videx*, *VidexEC*) with tenofovir (*Viread*) suggests that this combination may be problematic. The first concerns the use of ddI and tenofovir as the nucleoside backbones in a first HAART regimen where the third drug is a non-nucleoside reverse transcriptase inhibitor (NNRTI). Several studies have found early virologic failure in patients with high viral loads who begin first-time antiretroviral treatment with regimens that combine ddI and tenofovir with either efavirenz (*Sustiva*) or nevirapine (*Viramune*). In addition, an open-label comparative trial at London's Chelsea and Westminster Hospital, in which patients were randomised to receive ddI and efavirenz with either tenofovir or 3TC, was stopped early because higher rates of treatment failure were seen in patients taking tenofovir.

There is also some concern for treatment-experienced patients who take tenofovir and ddI together in a HAART regimen. Preliminary data, based on two Spanish studies, suggest that in some cases this may lead to either a drop in CD4 cell counts or a slower-than-expected increase. Dosing the two drugs together allows for ddI to be taken with food, and switching to HAART that contains ddI/tenofovir has become a relatively common simplification strategy in recent months. It had been thought that since tenofovir increases levels of ddI, a ddI dose reduction from 400mg/day to 250mg/day was a safe and

effective option, although no official guidelines support the dosing of ddI and tenofovir together at any level. The studies found that it was mainly patients who took the full dose of ddI that experienced these CD4 anomalies.

In a letter to US clinicians, ddI manufacturer, Bristol-Myers Squibb (BMS), warned doctors that ddI/tenofovir plus efavirenz or nevirapine should be used with caution in patients with a high baseline viral load about to take HAART for the first time. However, it points out that in treatment-experienced patients there is no evidence that the combination of ddI and tenofovir is associated with higher rates of virologic failure. Further data concerning both issues will become available in the next few months, and we are likely to know more after the 12th Conference on Retroviruses and Opportunistic Infections (CROI), to be held at the end of February.

If you have any concerns about this, or any anti-HIV drug combination, talk to your HIV clinic about current and future options before stopping or making any changes.

One-in-eight HIV-positive Europeans need salvage therapy

Nearly 13% of individuals taking HAART throughout Europe have experienced the failure of all of the three main classes of

antiretrovirals. This includes 16.6% who were treatment-experienced when the study began and 5.9% of individuals who were treatment-naïve. The study, from the EuroSIDA cohort (which involves 3500 treatment-naïve and -experienced individuals throughout Europe, along with Israel and Argentina) found that drug resistance was not necessarily the cause of this failure, since intolerance to a class of drug's side-effects (e.g. rash for NNRTIs) may also preclude use of that class. However, since the study ran from 1994 to 2002, more than 60% of participants had received either single drug or dual drug therapy before starting HAART, which suggests that many do have multidrug-resistant HIV strains.

"By 2003, one in 20 treatment-naïve and one in six treatment-experienced patients from the EuroSIDA study who started receiving HAART experienced triple class failure," the investigators wrote, adding that "for the individual, this may lead to a poorer prognosis and to potential transmission of resistant virus to others. For the clinics, it may lead to increased cost due to more-intensive diagnostic tests, the use of more expensive drugs such as enfuvirtide [T-20], and the use of more drugs in each regimen."

Mocroft A et al. *Time to virological failure of three classes of antiretrovirals after initiation of highly active antiretroviral therapy: results from the EuroSIDA study group.* J Infect Dis 190: 1947 - 46, 2004.

Boosted atazanavir as effective as *Kaletra*

The protease inhibitor (PI) atazanavir (*Reyataz*) boosted by low dose ritonavir works as well as *Kaletra* (lopinavir/ritonavir) for up to two years in patients who have experienced failure of at least one PI-containing regimen. At the end of 96 weeks, 33% of people who began the study taking *Kaletra*-based HAART and 30% of people who started with atazanavir-based HAART had viral loads below 50 copies/ml. As suspected, *Kaletra* caused more gastrointestinal side-effects such as diarrhoea, and atazanavir caused hyperbilirubinemia in some cases: leading to mild jaundice and the yellowing of the whites of the eyes. Although it has been suggested that atazanavir has a more favourable effect on

blood fats than lopinavir, close examination of the data suggests that, in fact, in the study there was little clinically meaningful difference.

Johnson M et al. *Long-term efficacy and durability of atazanavir (ATV) with ritonavir (RTV) or saquinavir (SQV) versus lopinavir/ritonavir (LPV/RTV) in HIV-infected patients with multiple virologic failures: 96-week results from a randomized, open label trial, BMS A1424045.* Seventh International Congress on Drug Therapy in HIV Infection, Glasgow, abstract PL14.4, 2004.

HAART use in pregnant women associated with premature delivery

Up to one in four women who take highly active antiretroviral therapy (HAART) during pregnancy are likely to give birth prematurely, according to two recent long-term studies from the UK and Ireland and Europe-wide. And although there appears to be no higher risk of congenital abnormalities due to HAART, the incidence of spontaneous abortion has increased over time, with 23% occurring between weeks 20 and 23 of gestation, according to fourteen-year data from the National Study of HIV in Pregnancy and Childhood (NSHPC).

Both the NSHPC and the European Collaborative Study (ECS) also found that infants born prematurely had a high mortality rate. "Our findings of a substantially increased risk of severely curtailed pregnancy duration among women taking HAART antenatally, particularly when initiated pre-pregnancy, coupled with very high neonatal mortality rate associated with delivery at these early gestations, are very concerning," write the ECS investigators, who added that HAART is effective at preventing mother-to-baby transmission of HIV but who also suggest "that these data are taken into consideration when making therapeutic decisions for HIV-positive women of childbearing ages whose clinical, immunological and virological status does not indicate a need for early initiation of HAART."

Thorne C et al. *Increased risk of adverse pregnancy outcomes in HIV-infected women treated with highly active antiretroviral therapy in Europe.* AIDS 18: 2337 - 2339, 2004.

Tookey P et al. *Antiretroviral therapy and pregnancy outcome: UK/Ireland surveillance data 1990-2004.* Seventh International Congress on Drug Therapy in HIV Infection, Glasgow, abstract PL11.3, 2004.

news from

living with hiv

NAM has just published a new book, *Living with HIV*. It is an introduction to the key issues involved in life with HIV, and aims to provide basic answers to some of the questions you may find yourself asking. The book is available free to anyone personally affected by HIV. For organisations and professionals there is a charge of £14.95. Call NAM on 020 7840 0050 or email info@nam.org.uk for more information or to request your copy.

thanks to the lsgo

NAM would like to thank the London Gay Symphony Orchestra, and all those who attended their World AIDS Day concert, for their generous donations to NAM. The Orchestra's next concert will be held from 7pm on February 20th at St John's Church, Waterloo Road, London. For more information please call the Orchestra on 079 6385 3099 or email tickets@lsgo.org.uk

nam forum

NAM's Patient Information Editor, Michael Carter, who edited *Living with HIV*, will chair a panel of people living with HIV on Monday January 31st to discuss life with the virus. The forum will start at 7pm at the University of London Union, Palms Room, 4th Floor, Malet Street, London, WC1. See <http://www.aidsmap.com/en/events/forums.asp> for more details.

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