

# aids treatment update

## lie back and think of England Damning report into the UK's sexual health

"We have been appalled by the crisis in sexual health we have heard about during our enquiry. We do not use the word 'crisis' lightly but in this case it is appropriate. This is a major public health issue and the problems identified in this report must be addressed immediately." – Conclusions of the UK House of Commons Health Committee's report into Sexual Health, June 2003.

With the kind of fortuity that editors love, the rather shameful revelations of the Health Committee appeared within days of the publication of the British HIV Association's revised Antiretroviral Treatment Guidelines, the UK's national roadmap on the use of HIV therapies, and the subject of our lead story this month. As we reported in June, BHIVA's own efforts to audit compliance with their recommendations noted variations in the standard of care offered in HIV treatment centres around the country. During 2002, the HIV caseload in a majority of UK centres rose by over 15%. When we also consider that the workload in genitourinary settings leapt a staggering 155% in the decade from 1991, the harsh words of our Parliamentarians seem entirely apposite.

Amongst the Health Committee's proposed solutions is the expedited development of a National Service Framework on sexual health – a measure which would drive HIV further up the agendas of health commissioners. In their musings on how we got here in the first place, the Committee identify several factors, one being "the absence of a patient voice." Start shouting.

delivering HAART 2

UK testosterone deficiencies? 6

news in brief 10

# delivering HAART

## 2 the British HIV Association revise their guidelines on managing HIV infection with antiretroviral therapy by anna poppa

Since the introduction of anti-HIV therapy in the mid-1980s, fifteen antiretroviral drugs have been licensed for use in the European Union. Despite the major health gains these therapies have provided where they have been made available, a number of critical questions relating to their use remain unanswered today, just as they have since the early days of the epidemic.

When to begin treatment; which drugs to start with; and when to change – clinical practice in these areas is informed as much by expert opinion as gold-standard trial data. For people with HIV in the UK, the most significant barometer of changing opinion on HIV therapy is provided by the periodical revision of the British HIV Association's (BHIVA) Antiretroviral Treatment Guidelines. Last published in 2001, an update from BHIVA was released for consultation in early June, with a view to final publication in October.

These guidelines are intended to promote a uniformly high standard of care in HIV clinical settings across the UK, and to act as a reference document for both healthcare professionals and people with HIV. They strongly influence the treatment and care which local healthcare commissioners will purchase, and, as we reported last month, act as a benchmark for the purposes of medical audit.

The use of antiretroviral drugs remains a complex art, and whilst BHIVA have included a synopsis this year, there's no substitute for reading the guidance in full.

### When to start treatment

Having moved towards later initiation of HIV therapy in their 2001 guidance, BHIVA's advice here has not been altered significantly. At that

time, the main drivers of change were concerns about treatment tolerability, and a lack of evidence about the clinical benefit of intervening earlier, when the CD4 count remained high and viral load fairly low. Two years later, with little encouragement over the treatment of key side-effects such as lipodystrophy, and negative findings on the ability of structured treatment interruptions to modify the course of disease, if anything this viewpoint is more entrenched.

Relatively few people are diagnosed during primary infection, the period immediately after HIV is acquired. Evidence on the longer-term effects of intervening with treatment at this time is not available, though BHIVA note that it is plausible that this could have a role in supporting the immune system against the early, and sometimes dramatic burst of viral replication. Treatment may be useful in limiting symptoms of primary infection where they are severe, but otherwise, BHIVA suggest treatment should only be begun this early through participation in a clinical trial. The options for doing this in the UK are somewhat limited.

Turning to chronic infection, BHIVA continue to view the CD4 count as the primary guide to the timing of intervention rather than viral load level. This year they've strengthened their recommendation that treatment should be started before the CD4 count falls below 200, as delaying beyond this threshold increases the risk of opportunistic infections, and the risk of death. This is an important issue in the UK where a third of diagnoses are made in people whose CD4 is already below 200. As we reported last month, BHIVA's own audit of UK practice during 2002 indicates that a significant number of these individuals remain off treatment some months after their diagnosis.

Regardless of CD4 count, those with severe HIV-related symptoms (apart perhaps from TB which can occur at higher CD4 levels) are also advised to begin treatment in order to prevent further immune damage.

Follow-up of a number of cohorts of people with HIV, including a large collaborative effort, has failed to detect a benefit in beginning treatment at CD4 counts above 350 compared to starting in the range between 200 and 350. BHIVA accordingly advise in favour of beginning therapy in this range, and against starting any earlier. Several additional factors govern the rate of disease progression and are likely to influence the timing of intervention once the CD4 count is between 200 and 350:

- The rate of loss of CD4 cells; a fall of more than 80 cells per year increases the risk of disease progression.
- The viral load level, particularly where it is above 60,000 to 100,000 copies.
- Hepatitis co-infection, as liver disease may worsen at lower CD4 counts.
- Age, as response to HAART is poorer in older people.

## Choice of initial therapy

Some of the more significant revisions of opinion occur within BHIVA's discussion of preferred treatment options for those who start HIV treatment for the first time. BHIVA continue to advise that NNRTI-based HAART will generally be the most suitable choice for first-line therapy. However, the advantages of drugs in this class (efavirenz and nevirapine) largely concern their lower pill burden, and lesser effect on metabolism and body shape relative to PIs. If PIs become available which do not present these problems (as is hoped, but not proven in the case of atazanavir, for example), these class-based distinctions may become less pronounced.

Efavirenz-containing combinations have performed well in a series of recent studies, particularly when combined with AZT/3TC (see ATU 116), though the findings of the 2NN study, which directly compared efavirenz with nevirapine, suggest there is little difference

between the two drugs in terms of efficacy (see ATU 123). 2NN demonstrated these drugs' respective side-effect profiles well, and this is likely to influence many people's choice between the two. Toxicity related to efavirenz typically features psychological effects such as abnormal dreams, insomnia, depression and euphoria, whilst nevirapine can cause rashes, which may be severe.

Where PIs are used in initial therapy, BHIVA now advise that they should be boosted with ritonavir rather than used singly. Ritonavir boosting slows the progress of several drugs through the body, which has enabled a reduction in pill burden and dosing for some PIs. Ritonavir boosted indinavir is not recommended, however, following reports of increased toxicity. BHIVA instead advise the use of lopinavir/ritonavir or hard gel saquinavir/ritonavir, whilst noting that these combinations may have a harmful effect on lipids.

Other initial strategies which have lost favour include the use of four drug combinations in people who start treatment with high viral load, and the use of d4T (where alternatives exist) because of the accumulating evidence linking the drug with a more rapid onset of fat loss (see ATU 119). BHIVA advise the combination of d4T with ddI should be avoided where possible, again due to toxicity.

The triple NRTI combination *Trizivir* (AZT/3TC/abacavir) has also dropped off BHIVA's list of preferred options for first-line therapy, following the early closure of ACTG 5095, a trial comparing this regimen with two efavirenz-containing combinations (see ATU 124). An earlier, blinded comparison of this three NRTI regimen with indinavir/AZT/3TC found the former was outperformed in people who began treatment with viral load over 100,000 copies. For some, this trial has left a persistent question mark over *Trizivir's* potency relative to other combinations. Nevertheless, BHIVA continue to see a role for the drug in people who are expected to struggle with adherence (the combined formulation consists of one pill taken twice daily); those whose parallel use of other medicines means that their antiretroviral options are limited by potential drug interactions; and perhaps those who begin treatment with low viral load.

## glossary

**adherence** The act of taking a treatment exactly as prescribed.

**antiretroviral** A substance that acts against retroviruses such as HIV.

**CD4** A molecule on the surface of some cells onto which HIV can bind. The CD4 cell count roughly reflects the state of the immune system.

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

**co-infection** Having more than one infection at the same time. For example, when a person with HIV has hepatitis B or C. This can make disease worse and treatment more difficult.

**cytokine** A natural chemical used to pass signals between cells.

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

**hepatitis** Inflammation or infection of the liver.

**hormone** A chemical which stimulates or suppresses cell and tissue activity.

**insulin** A hormone produced by the pancreas that tends to lower blood sugar levels.

**lipids** A general term for fats.

**lipodystrophy** A disruption to the way the body produces, uses and distributes fat.

**median** The central value of the distribution, so that half the values are less than or equal to it and half are greater than or equal to it.

**metabolism** The mechanisms which sustain life, turning sugar and fat into energy.

continued on page seven

## delivering HAART continued

Individual needs and preferences are important drivers of treatment choice, and BHIVA stress that issues of tolerability – the likely burden of adherence requirements and side-effects – should take precedence over predicted resistance patterns following treatment failure, when initial therapy is considered. People with hepatitis B co-infection are one example of this individualisation – BHIVA suggest the use of tenofovir and 3TC, both dually active against HIV and hepatitis B, in these circumstances. (See ATU 126 for a review of BHIVA's draft recommendations on the management of HIV and hepatitis co-infection).

It's issues such as these which have necessitated the evaluation of a growing range of patient risk factors prior to initial therapy selection. BHIVA now advise that all patients undergo assessment for hepatitis B or C co-infection, cardiovascular disease, diabetes, and psychiatric conditions, along with lifestyle factors such as smoking, obesity, and drug and alcohol use, before beginning HIV treatment.

### Changing treatment

When to change HIV treatments is no less complex an area of HIV medicine than when to start and what to start with. Definitions of treatment failure have arguably broadened since BHIVA's previous treatment guidelines, with perhaps less emphasis on the importance of viral load failure above failure for toxicity or adherence. Moreover, there's been a move to change treatment in order to reduce the future risk of failure, adding to the complexity of choices which people on therapy face.

Given the change in their advice on treatments which are recommended for use in first-line therapy, BHIVA acknowledge that some people may be prompted to consider switching off treatments now on the 'not preferred' list. Those who are not experiencing side-effects, and who have maintained a viral load below 50 copies for at least six months, may feel happy to remain on their established therapy.

If viral load is suppressed, and treatment is being switched either for toxicity or to ease adherence, it's possible to change the 'offending' drug(s) only. Where the failure is virological, the initial step should be to consider the potential role of poor adherence or inadequate drug exposure in driving the failure.

Resistance tests should be used to guide treatment choices wherever there is a rebound in viral load. However the lack of accuracy associated with resistance testing at viral load levels below 1,000 copies continues to present a dilemma over the timing of a switch. BHIVA suggest that in those who are likely to be able to re-suppress their viral load with available treatment options, first-line treatment should be changed if viral load is above 400 copies on two consecutive tests.

Where a change of treatment is unlikely to suppress viral load fully (a more common prospect for people who have taken several HIV treatment combinations already rather than just one), and the risk of imminent death is low, it may be appropriate to remain on the current regimen. Where the risk of death is high, changing drugs in order to derive some degree of viral load suppression is another option.

### Managing lipodystrophy

Side-effects associated with long-term exposure to HIV treatments – particularly the lipodystrophy syndrome – continue to dominate debate about their use. Current strategies for managing body fat changes and abnormal metabolic values are based on assumptions about the cause of these problems, and these assumptions may prove to be incorrect, or to be an incomplete explanation of their origins. Given the limitations of the evidence base in this area, BHIVA's emphasis is on preventing the problem from occurring – based on current knowledge. Table 1 summarises BHIVA's conclusions on management of lipodystrophy. These should be read in the context of the full discussion of drug toxicities.

**Table 1: BHIVA DRAFT ANTIRETROVIRAL TREATMENT GUIDELINES 2003  
Issues concerning use of HIV treatment: Lipodystrophy**

Fat loss is difficult to treat and so is best avoided. Its appearance may be delayed by avoiding d4T in first-line therapy.

Insulin resistance should be treated with metformin.

Abnormal lipids should be treated by switching drugs where possible and by the use of statins and fibrates.

Exercise and diet may have a modest effect on body shape and lipids.

Controlled trial evidence exists for the use of *New-Fill* injections for facial fat loss.

### Resistance testing

BHIVA recommend testing for drug resistance at each viral load rebound in order to inform the selection of new treatments. Because some people are infected with drug resistant virus, testing prior to starting therapy may be useful, and this should be performed on the earliest blood sample available.

A meta-analysis of results from six randomised trials which investigated the use of resistance tests when changing treatment found the best virological responses following the switch were seen in those who received a genotypic resistance test, which was interpreted by an expert. Since then, the recent results from the UK ERA study, which evaluated the use of resistance testing to inform treatment changes, found no benefit from the additional use of a phenotypic test over a genotypic test alone. Given that phenotypic testing is the more lengthy, complex and expensive of the two approaches available, it seems these data will likely encourage greater use of genotypic testing than of phenotyping.

### Drug level testing

BHIVA's assessment of the limited evidence base regarding the use of drug level testing (most commonly referred to as Therapeutic Drug Monitoring or TDM) is that it may be useful in some circumstances:

- To reduce side-effects.
- For dose adjustment in people with liver or kidney damage, or with very low or high body weight.
- To assist understanding of treatment failure.
- To assist management of multiple drug interactions.

### Treatment interruptions

BHIVA continue to advise against the use of structured treatment interruptions or cycled HIV therapy unless conducted within a clinical trial (see *ATU 123* for more on this, and this month's News in Brief for details of one such UK-based trial).

## key conclusions

- Revised expert guidance on the use of HIV treatments in the UK is under consultation, online at [aidsmap.com](http://aidsmap.com)
- It is recommended that HIV treatment is begun before the CD4 count falls below 200, and whilst it is somewhere between 200 and 350.
- NNRTI-based drug combinations are the preferred choice for starting HIV therapy.
- Treating body fat changes (lipodystrophy) remains difficult and so these are best avoided.

### BHIVA guidelines consultation

The draft BHIVA Antiretroviral Treatment Guidelines 2003 are open for consultation at <http://www.aidsmap.com>. These should be read alongside guidance from BHIVA on treatment adherence (see *ATU* issue 121), and on co-infection with hepatitis viruses (see *ATU* issue 126). All available guidelines from BHIVA are online at [aidsmap.com](http://aidsmap.com).

### references

For references to data discussed in this article, please see the draft BHIVA Guidelines online at <http://www.aidsmap.com>



# UK testosterone deficiencies?

6 new testosterone gel launched in the UK – but how will it be used in people with HIV?  
by edwin j bernard

Testosterone isn't just a drug for bodybuilders. It's a vital natural sex hormone that does much more than give men their male attributes. Whilst it is also necessary for muscle-building, lack of testosterone affects us in myriad and subtle ways, and has recently been linked with depression. Interestingly, here in the UK, the diagnosis and treatment of HIV-related testosterone deficiency (also known as hypogonadism) has not been in step with North America. This could be for several reasons including the fact that American HIV treatment philosophy tends towards the more aggressive, whereas UK clinicians generally lean towards a more cautious approach, as well as the lack of availability of satisfactory testosterone replacement therapies in the UK – that is, until now. Last month, Schering launched the first testosterone gel available on prescription in the UK, *Testogel*, which offers a new treatment choice for those with HIV-related testosterone deficiency.

## Definitions & prevalence

Exactly what constitutes low testosterone levels is open to interpretation. There are two measures of testosterone levels: total and free. Free testosterone measurements are considered more accurate and reliable, but cost more and therefore many studies looking at the prevalence and treatment of hypogonadism have only included total testosterone levels.

Additionally, although the normal range of total testosterone (as measured in the blood) is 9.7-38.2 nmol/L, some clinicians feel that testosterone levels need to be interpreted contextually: ie so-called normal levels (especially at the low end of the normal range) may not be normal for that particular individual. Pre-HAART, it was found that up to 50% of men with AIDS, and 25% of men with HIV were hypogonadal.<sup>1</sup> A much-referenced post-HAART study reported at the 1998 International AIDS

Conference in Geneva found that out of 127 HIV-positive men with or without wasting, 21 (16.5%) had total testosterone levels below 6.73 nmol/L, well below the lower limit of normal; interestingly, seven (31.8%) were on testosterone replacement therapy at the time.<sup>2</sup> A study of 587 HIV-positive males between August 1997 and January 1999 found that 119 (20.3%) had total testosterone levels below 13.9 nmol/L.<sup>3</sup> However, a 1999 study by Arver and colleagues of 148 HIV-positive men compared with 42 HIV-negative men found that 31% of the HIV-positive men had testosterone levels less than 9.7 nmol/L. In this study, testosterone levels were generally lower in all HIV-positive men compared to HIV-negative men, and were lowest in HIV-positive men who had lost 2.3 kilograms or more of weight in the preceding 12 months.<sup>4</sup>

## Causes of hypogonadism

Low levels of testosterone can occur in both men and women with HIV disease, although much more is known about testosterone deficiency in relation to men. The majority of testosterone deficiency in HIV disease is not caused by testicular failure (also known as primary hypogonadism), but by secondary hypogonadism. This happens when there is a disruption of hormone secretion between the hypothalamus (located in the brain) and the pituitary gland (located near the brain). Since the pituitary gland secretes hormones that stimulate the production of testosterone in the testes, a disruption in this hormonal cascade can cause secondary hypogonadism. Arver and colleagues discovered that out of the 31% of HIV-positive men with low testosterone in their study, 19% had primary and 81% had secondary hypogonadism.<sup>4</sup> Although both are associated with having low levels of testosterone, in secondary hypogonadism you also see low levels

of other sex hormones, including luteinising hormone and follicle-stimulating hormone, whereas in primary hypogonadism these other sex hormones are raised.

HIV-related hypogonadism can be caused by a variety of factors including opportunistic infections (particularly wasting), HIV-associated malignancies, the effects of the virus itself (including increased cytokines seen in chronic infection), and antiretrovirals and/or other HIV-related medications. In general, the longer you have been infected with HIV and/or the more ill you have been, the more likely it is that you may be testosterone deficient.

## Red flags

What are the symptoms of testosterone deficiency that might cause you to suggest that your HIV consultant test for levels of testosterone? Hypogonadism can cause physical symptoms that clinically may appear to overlap with depression and other physical illnesses: chronic fatigue, loss of interest in sex and food, depressed mood and a general sense of not feeling well. Lack of testosterone can also lead to anaemia and osteopenia (lowered bone mineral density). Wasting (loss of lean body mass) and hypogonadism are also linked, although differentiating between cause and effect is not easy. For example, Berger and colleagues found no significant relationship between low testosterone and wasting, concluding that having low testosterone levels did not necessarily mean wasting occurred.<sup>2</sup> And although a systematic review conducted in 2002 found that testosterone replacement therapy was more likely to increase lean body mass compared to nothing, that does not necessarily mean all wasting is caused by hypogonadism (or that hypogonadism always leads to wasting).<sup>5</sup>

Dr Graeme Moyle, Associate HIV Research Director at the Chelsea and Westminster Hospital, London screens for hypogonadism when his patients present with problems like anaemia, fatigue, and reduced libido, involuntary weight loss and lipoatrophy, although generally not depression. Prevalence of hypogonadism amongst his patients is "about 5%, depending on how you define it," he says. "In my experience, individuals don't always become

symptomatic until their total testosterone level is about 5 nmol/L, about 50% below the lower end of the normal range." As well as testing for free and total testosterone levels, he will often also measure sex hormone binding globulin (SHBG) levels. "Chronic infections can cause an increase in SHBG levels so you end up with hypogonadism despite the presence of a normal total testosterone values," he says.

## Testosterone, depression & fatigue

A recent study on the use of testosterone replacement therapy in depressed HIV-negative men aged 30 and over indicates that hypogonadism may cause more depression than previously thought. Researchers from Harvard Medical School found that 43% of 22 men who had not responded to antidepressant medications had total testosterone levels below 12.15 nmol/L. About a third of the men with these low or low-normal levels who received 10g of 1% testosterone gel daily showed dramatic improvement in mood, anxiety, and other measures of depression after eight weeks, compared with placebo.<sup>6</sup> An earlier open-label study of hypogonadal HIV-negative men treated with intramuscular or oral testosterone replacement therapy found that significant reductions in anger, irritability, sadness, tiredness and nervousness, and significant improvements in energy levels, friendliness and sense of well-being were seen in all men on therapy compared with being off-therapy.<sup>7</sup>

Grinspoon and colleagues found that men with HIV-related wasting and total testosterone levels below 14.8 nmol/L were more likely to be depressed than those men with higher total testosterone, and those who received testosterone replacement therapy were less depressed than those who received placebo.<sup>8</sup> Fatigue has also been seen to be greatly alleviated in an open-label trial of testosterone for 108 HIV-positive men with clinical symptoms of hypogonadism and a total testosterone level below 17.35 nmol/L; 79% were rated as having much improved energy level by the study doctor at the study's end.<sup>9</sup>

## To replace or not?

Before deciding on which testosterone replacement therapy is right for you, serious

## glossary contd

**naive** Never having taken anti-HIV treatments before.

**NNRTI** Non nucleoside reverse transcriptase inhibitor, the family of antiretrovirals which includes efavirenz, nevirapine and delavirdine.

**NRTI** Nucleoside analogue reverse transcriptase inhibitor, the family of antiretrovirals which includes AZT, ddI, 3TC, d4T, ddC and abacavir.

**open-label** A clinical trial where both the researcher and participants know who is taking the experimental treatment.

**phenotype** Trait or behaviour which results from a particular genotype.

**PI** Family of antiretrovirals which target the protease enzyme. Includes amprenavir, indinavir, lopinavir, ritonavir, saquinavir, nelfinavir, and atazanavir.

**placebo** A pill or liquid which looks and tastes exactly like a real drug, but contains no active substance.

**resistance A** drug-resistant HIV strain is one which is less susceptible to the effects of one or more anti-HIV drugs because of its genotype.

**TB** A disease caused by the bacterium *Mycobacterium tuberculosis*.

**toxicity** The extent or ways in which a drug is poisonous to the body.

**undetectable viral load** A level of viral load that is too low to be picked up by the particular viral load test being used.

**viral load** Measurement of the amount of virus in a sample. HIV viral load indicates the extent to which HIV is reproducing in the body.

## UK testosterone deficiencies? continued

consideration should be given as to whether to treat at all. "I've seen people with testosterone levels of six or seven that have returned to normal levels without treatment," says Dr Moyle, arguing for repeat testing to be absolutely certain these levels are not transitory. "When you decide to replace testosterone you are embarking down the pathway of something that is semi-permanent," he warns. "Many people do not appreciate that they are committing to something that will be part of their life for a long period of time."

Little to nothing is known about how or whether HIV-related hypogonadism can correct itself once treatment has begun, but the only way to discover this is to stop replacement therapy for several months, until the body's own testosterone production can begin again (known as the refraction period). During this time all the symptoms of low testosterone will reoccur and you will very likely feel quite unwell. Since the male produces somewhere between 3 and 10 mg of testosterone daily, mostly in the morning and again in the evening (in women it is closer to 10% of this amount), the ideal replacement would mimic our own natural production.

Until last month there were two main treatment options for testosterone deficiency available to HIV-positive people in the UK: intramuscular injections of two strengths of *Sustanon*, or the transdermal (through the skin) testosterone patch, *Andropatch*.

### Injection, patch or gel?

*Sustanon 250* is the most common method of testosterone replacement in the UK. It is made up of four different testosterone esters (providing a total of 176 mg of testosterone), which affect how quickly or slowly the testosterone is absorbed after injection. It is popular amongst clinicians because it is cheaper than patches. It is administered by deep, and often painful, intramuscular injection into the buttocks or thigh, usually by a nurse, every two to three weeks.

*Sustanon 100* contains three shorter-lasting testosterone esters (equivalent to a total of 74 mg of testosterone) requiring more frequent administration. However, these two standardised dosing regimens can create several problems due to high post-injection peaks and low pre-injection trough levels. "*Sustanon* creates a non physiological profile of testosterone," explains Dr Moyle. "It's a dump of testosterone that gets absorbed relatively quickly in the first week and there's relatively less to get absorbed in the second and third week. You get a situation where people feel good at first and less good in the second and third weeks." Also such high supra-physiological doses can create problematic feelings of aggression (known popularly as 'roid rage'), insomnia or feeling 'wired', and an abnormally high interest in sex than can feel all-consuming.

*Andropatch 5 mg* is an oval, sticky patch applied to the back, stomach, upper arms or thighs which slowly releases 5 mg testosterone over 24 hours. The patch is also available in a 2.5 mg version, so there can be some individual dose adjustment upwards or downwards. This provides closer to a physiological replacement level dose compared with *Sustanon*, avoiding the peak and troughs, although it provides a constant flow of testosterone through the skin, rather than mimicking the daily production cycle. However, up to 30% of users experience skin irritation and "if people don't rotate sites frequently, then they start to get localised skin reactions," says Dr Moyle. There is also the problem of patch visibility, which may be considered stigmatising.

Manufactured by Laboratoires Besins International in France, 1% testosterone gel was first licensed in the US three years ago by Solvay Pharmaceuticals who market it as *AndroGel*. The German company Schering own the European distribution rights and finally launched *Testogel* in the UK on June 9th 2003. The alcohol-based gel comes in 5 g pouches, to be applied each morning to the belly, shoulders or inner thighs (but not genitals) and dries

within minutes. Last year, preliminary reports from a study of 30 hypogonadal HIV-positive males who had been receiving a stable regimen of intramuscular testosterone (cypionate) and then switched to *AndroGel* were very promising.<sup>10</sup> The gel was well-tolerated and testosterone levels were stable and physiological. Quality of life (physical, emotional well-being and cognitive function) also improved by an average of 10% compared with the intramuscular testosterone. "There do seem to be clinical advantages and improved patient acceptance of testosterone gel compared with testosterone ester injections," notes Dr Moyle.

Two further gel formulations are also waiting in the wings. *Andractim*, also manufactured by Besins, is a dihydrotestosterone (DHT) gel, which may be comparable to testosterone gel, although no studies comparing them exist. It is available in France over-the-counter at a cost of 14 euros a month. Another 1% testosterone gel, *Testim*, manufactured by the US company Auxilium, was launched in the US in February 2003, and although a European application was filed in April 2002, there is no word on a UK launch date. An Auxilium-sponsored trial recently found that 30% more testosterone was absorbed per dose in hypogonadal HIV-negative men on *Testim* compared with *AndroGel*.<sup>11</sup> The clinical significance of this is unknown, however.

People using testosterone gels should be advised to avoid physical contact for 30 minutes after application, as this may result in testosterone being absorbed by the partner.

### What next?

Finding the right method and dose of testosterone replacement may take time. As well as reporting clinical signs and symptoms to your clinician, measuring free and total testosterone levels, particularly if you are using patches or gels, is useful to make sure adequate replacement levels are being reached. Although replacement doses of intramuscular or transdermal testosterone are not as toxic as chronic cycles of supra-physiological doses of either testosterone or anabolic steroids, there are still a variety of adverse effects of, and contraindications to, testosterone replacement therapy. Replacement doses of testosterone do not appear to affect HIV viral load or CD4 and CD8 cell counts,<sup>12</sup> but should be avoided in people

with polycythemia (excess red blood cell counts). Men with prostate cancer or enlarged prostate should also avoid using testosterone replacement therapy.

A 2001 meta-analysis of hypogonadal HIV-negative men on intramuscular testosterone replacement therapy found that it was associated with a fall in HDL cholesterol as well as declines in LDL and total cholesterol levels.<sup>13</sup> Since HIV disease and PI-containing HAART can also cause HDL (so-called good cholesterol) reductions, the additive effect of testosterone on HDL levels should be monitored.

Liver function problems are not usually seen with replacement levels of testosterone, although acne can be a problem.

### Women & testosterone

Although testosterone is considered to be a male hormone, it also occurs naturally in women. A recent study found that 26% of HIV-infected women with significant weight loss had total testosterone levels below the normal range, even in the era of HAART.<sup>14</sup> Laboratory diagnosis of testosterone deficiency among women is difficult, however. Total testosterone levels may be increased as a result of increased serum concentrations of SHBG in HIV-positive women, and although testing for free testosterone levels may be more accurate, the normal ranges for women are not standardised. There has been little research into testosterone replacement in women generally, so it is no surprise that treating low testosterone among women with HIV has received scant attention. However, Miller and colleagues found that when low-dose testosterone patches were used on women with HIV-related wasting, both weight and quality of life improved and the development of 'masculine' features was not reported.<sup>15</sup>

### Conclusion

Misinformation and confusion still exist over the use of testosterone and other anabolic steroids in the treatment of HIV disease. But as you can see there are often good reasons to replace the body's natural testosterone when one is found to be deficient, as is the case in a significant minority of men and a smaller minority of women living with HIV.

### references

1. Dobbs AS. *Am J Med* 1988;84(pt 2):611-616
2. Berger D. 12th Intl Conf on AIDS, abs 32174, 1998
3. Kopicko JJ. *Int J STD AIDS* 1999;10(12):817-20
4. Arver S. *J Androl* 1999;20(5):611-8
5. Kong A & Edmonds P. *Lancet Infect Dis* 2002;2(11):692-9
6. Pope HG. *Am J Psychiatry* 2003;160:105-111
7. Wang C. *J Clin Endocrinol Metab* 1996;81(10):3578-83
8. Grinspoon. *J Clin Endocrinol Metab* 2000;85(1):60-65
9. Wagner GJ. *Gen Hosp Psychiatry* 1998;20(4):209-13
10. Cohan GR. 42nd ICAAC, abs H-1912, 2002
11. Marbury T. *Biopharm Drug Dispos* 2003;24(3):115-20
12. Bhasin. *J Clin Endocrinol Metab* 1998;83:33155-62
13. Whitsel EA. *Am J Med* 2001;111(4):261-9
14. Huang JS. *CID* 2003;36(4):499-506
15. Miller K. *J Clin Endocrinol Metab* 1998;83(8):2717-25



## Our sexually unhealthy nation

England is facing a crisis in the spread of sexually transmitted diseases according to an extensive report into sexual health conducted by the House of Commons Health Select Committee, a cross-party body made up of Members of Parliament. The report, released in early June, made headlines both here and abroad and is an embarrassing indictment of the state of service provision in this area. Here in England:

- Rates of teenage pregnancy are the highest in Europe.
- Around one in ten sexually active young women have chlamydia.
- Syphilis rates have increased by 500% in the last six years.
- Gonorrhoea rates have doubled in this period.
- The number of HIV diagnoses made during 2002 (around 6,600) was the biggest year-on-year increase reported so far.
- The median waiting time for sexual health services is around 10-12 days.

As we reported in *ATU* last December, the Government's National Strategy on Sexual Health and HIV has delegated responsibility for the commissioning of sexual health services to newly-established Primary Care Trusts. But as the Select Committee report, "We [the Select Committee] have received little evidence to suggest PCTs were ready to take on these responsibilities."

Crucial amongst the 'urgent steps' the Committee advises is the development of a National Service Framework on sexual health, as exists for other prioritised health areas such

as cancer, mental health and coronary heart disease. Read the full report online at <http://www.parliament.the-stationery-office.co.uk/pa/cm200203/cmselect/cmhealth/69/69.pdf>

## OPTIMA trial adds entry options

OPTIMA, a clinical trial for people with experience of HIV drugs from all three main classes, has altered its protocol to allow more people to consider joining the study. OPTIMA is a UK Medical Research Council-led international study investigating the role of treatment interruptions, and 'mega' versus standard HAART, in salvage therapy.

The original trial design includes a 'double-randomisation' at entry to one of the following groups:

- A mega-HAART regimen of at least five drugs begun immediately
- A standard HAART regimen of up to four drugs begun immediately
- A mega-HAART regimen of at least five drugs begun after a treatment break
- A standard HAART regimen of up to four drugs begun after a treatment break.

Now a new pilot study has opened, titled Options in OPTIMA. This effectively 'uncouples' the original randomisation plan by allowing participants to opt out of *either* the randomisation to mega versus standard HAART; *or* the randomisation to begin treatment with or without a treatment interruption.

OPTIMA is open to people who have experienced treatment failure on at least two multi-drug combinations, including drugs from the NNRTI, PI and NRTI classes. Your two most recent monitoring results, taken on your current HAART combination, must show your CD4 count to be below 300 cells (or 15%), and your viral load to be above 2,500 copies. You should have been on your current treatment for at least three months, and will not be prevented from participating in other suitable clinical trials and early access programmes as a consequence of joining OPTIMA. Full details of OPTIMA are available from your doctor or research nurse, and via [aidsmap.com](http://aidsmap.com).

The use of treatment interruptions prior to beginning a salvage regimen are intended to allow the viral population within your body to 'revert' to one which is predominantly drug-sensitive rather than drug-resistant. Studies have reported conflicting results on this strategy so far, and these were covered in the March 2003 issue of *ATU*.

## Atazanavir: US approval expected

Atazanavir, a new protease inhibitor (PI) from Bristol-Myers Squibb, has been recommended for approval in the US by the Food and Drug Administration (FDA) Antiviral Advisory Drugs Committee. The FDA is expected to make a final decision on the drug's indication – specifically on whether it will be licensed for use in treatment experienced people as well as those beginning therapy for the first time – towards the end of June, when this newsletter goes to press.

Atazanavir, branded *Reyataz*, has attracted interest after trials have shown the drug to have little effect on blood lipids; fats such as cholesterol and triglycerides which can become abnormally high as a side-effect of other drugs in the PI class. These lipid increases (termed hyperlipidemia) are worrisome because, in the general population, there is a well-established association between high levels of blood fats and heart disease. The drug is dosed just once daily, which is a further plus point.

In people new to therapy, atazanavir-based HAART has been shown to be of comparable efficacy to HAART regimens containing either efavirenz or nelfinavir. Its role in people who've

previously taken PIs is less well understood – as a single PI it was out-performed in this setting by the boosted PI lopinavir/ritonavir. Whilst BMS presented new data on ritonavir-boosted atazanavir at the FDA Committee hearing in May, these appear to have been submitted too late for proper consideration by the Committee.

The use of atazanavir following other PIs is likely to be further scrutinised following the publication of new data from a German group in the May 23rd issue of *AIDS*. In a test-tube study, viral samples which were phenotypically resistant to either ritonavir, saquinavir, nelfinavir or indinavir (defined as more than a 3.5 fold loss of susceptibility) were evaluated for cross-resistance to three newer PIs. This phenomenon was observed more frequently with atazanavir than with either lopinavir or amprenavir, though cross-resistance was common in all three cases.

Atazanavir was reviewed alongside other new PIs in the January 2003 issue of *ATU*. More detailed information is available at [aidsmap.com](http://aidsmap.com). A position paper on the US indication for atazanavir, prepared by the New York-based Treatment Action Group, can be read online at <http://www.aidsinfonyc.org/tag/activism/atazanavir.html>

## T-20 & tenofovir: Final EU approval

The European Medicines Evaluation Agency gave final approval for the marketing of two anti-HIV drugs at the end of May. This means that T-20 (*Fuzeon*), a new type of HIV treatment which prevents fusion between the virus and immune cells, can now be prescribed across the European Union for the treatment of HIV in people who have experienced treatment failure on drugs from other available classes. T-20 was reviewed in *ATU* 125.

Tenofovir (*Viread*) is an NRTI which was previously licensed for use in treatment experienced people only. Its indication has now been extended to include first-line use. There's more on tenofovir in *ATU* 118, and more detailed information on all antiretrovirals at [aidsmap.com](http://aidsmap.com).

### International AIDS Society meeting

The 2nd International AIDS Society Conference on HIV Pathogenesis and Treatment takes place in Paris on July 13th to 16th. One of this year's key clinical meetings, *ATU* will be carrying a full report next month. Daily news stories from the conference, reported by NAM's editors, will be posted to [aidsmap.com](http://aidsmap.com).

### correction: Entecavir

Thanks to Paul Slade from BMS for pointing out an error in last month's *ATU*. Entecavir is not dually active against HIV and hepatitis B as we reported – its activity is against hepatitis B alone. And the generic name for FTC is emtricitabine. Apologies.

## credits

### editor

Anna Poppa

founded by Peter Scott

### typesetting & layout

Thomas Paterson

### design

Alexander Boxill

### printing

Cambrian Printers

### ISSN

0969-4706

### copyright

©NAM Publications 2003  
All rights reserved

### charity number

1011220

## medical advisory panel

Dr Fiona Boag  
Dr Ray Brettle  
Professor Janet Darbyshire  
Dr Martin Fisher  
Professor Brian Gazzard  
Dr Diana Gibb  
Professor Frances Gotch  
Professor Paul Griffiths  
Dr Margaret Johnson  
Dr Jacqueline Mok  
Dr Graeme Moyle  
Dr Barry Peters  
Dr Gareth Tudor-Williams  
Professor Jonathan Weber  
Dr Ian Williams  
Dr Mike Youle

## about NAM

NAM is a charity that exists to support the fight against HIV and AIDS with independent, accurate, up-to-date and accessible information for affected communities, and those working to support them.

For more information, and details of our other publications and services, please contact us, or visit our website, [www.aidsmap.com](http://www.aidsmap.com).

### disclaimer

The publishers have taken all such care as they consider reasonable in preparing this newsletter. But they will not be held responsible for any inaccuracies or mis-statements of fact contained herein. Inclusion in this newsletter of information on any drug or clinical trial in no way represents an endorsement of that drug or trial. This newsletter should always be used in conjunction with professional medical advice.

## thanks to our funders

NAM's treatments information for people living with HIV is provided free thanks to the generosity of:

African HIV Policy Network, British HIV Association, International HIV/AIDS Alliance, Scottish Voluntary HIV & AIDS Forum, The European Commission, Government of the United Kingdom - Department of Health, London HIV & GUM Commissioning Consortium, Birmingham area PCTs, East Surrey area PCTs, East Sussex, Brighton & Hove area PCTs, Manchester area PCTs, Manchester City Council, Newcastle PCT, Norfolk area PCTs, Salford Primary Care Trust, Stockport Social Services, Trafford North PCT, Trafford South PCT, West Sussex area PCTs, Body Shop Foundation, Crusaid, The Elton John AIDS Foundation, Lloyds TSB Foundation for England & Wales, M-A-C AIDS Fund, Peter Moores Foundation, St Stephen's AIDS Trust, Abbott Laboratories, Boehringer Ingelheim (UK & International), Bristol-Myers Squibb Pharmaceuticals, Delphic Europe (for Tibotec Virco), Gilead Sciences, GlaxoSmithKline, Merck Sharp and Dohme, Positive Action GlaxoSmithKline, Visible Genetics, Roche Hepatitis C, Roche Molecular Systems (UK & International), Roche Products, Serono.

## order form

Please set up my subscription to AIDS Treatment Update at the following rate:

- free (for personally affected individuals)  
 £75 (professional rate)  
 £55 (voluntary organisations rate)

### format required

(please tick the format you require):

- paper       email (pdf)       audio tape

### overseas postage costs

(for paper and audio subscriptions only)

within EU please add £10/year  
outside EU please add £15/year

name \_\_\_\_\_

address \_\_\_\_\_

postcode \_\_\_\_\_

email address (if applicable) \_\_\_\_\_

signature \_\_\_\_\_

**total payment due: £ \_\_\_\_\_ (if applicable)**

Payment can be made by cheque (payable to NAM), or call +44 (0) 20 7840 0050 with your credit card details.

- NAM publishes a complete range of information resources about HIV and AIDS. Please tick this box if you would **not** like to receive information about them.  
 NAM occasionally undertakes fundraising campaigns to help support its work. Please tick this box if you would **not** like to receive information about them.

## subscriptions

### free subscriptions for individuals

AIDS Treatment Update is available free to individuals in the UK affected by HIV or AIDS. We ask individuals from overseas to contribute to postage costs.

### costs to professionals and organisations

professional/organisational rate: £75/year  
voluntary organisation rate: £55/year

To begin your subscription simply complete the form opposite and return it to NAM, or call or email us.

**AIDS Treatment Update is also available on audio tape, and can be emailed to you as a pdf file. Call NAM on +44 (0)20 7840 0050 for details.**

## any questions

### for an introduction to HIV treatment issues

NAM's information booklets are free to people with HIV. Titles include: **adherence, anti-HIV drugs, clinical trials, glossary, HIV & hepatitis, HIV therapy, lipodystrophy, nutrition, resistance, and viral load & CD4**. Please contact NAM for your copies.

### HIV & AIDS Treatments Directory

This is a comprehensive guide to the medical aspects of HIV. Available at only £12.95 to people with HIV and £64.95 to professionals. Please contact us to order your copy.

### www.aidsmap.com

Visit our website for the latest news and conference reports, a fully searchable treatments database, and The Wheel – your personal pill planer.

### information forums in London

Each month an expert speaker discusses an HIV treatment-related topic. Entry is free. Future forums are advertised inside this newsletter and on our website.

### THT Direct Phoneline

0845 1221 200  
Mon-Fri 10am-10pm Sat-Sun 12-6pm

### i-Base Treatment Phoneline

0808 8006013  
Mon-Wed 12-4pm

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