UK syphilis outbreak continues to spread

As recently as 1996, syphilis had become so rare a disease in the UK that only one or two new cases a year were reported. This would soon change – there were over two hundred cases in 1999, and soon-to-be-released figures for last year are expected to show a continuing spread.

The eruption of syphilis across Europe towards the close of the Fifteenth Century was blamed alternatively on the return of Christopher Columbus from the Americas, and the involvement of mercenaries of disparate European origins in the Siege of Naples. How times change. The clusters of cases recently appearing in British cities have been linked to an internet chat room, and the use of ecstasy and GHB.

Two other associations are particularly striking. Firstly, of a group of affected men from Manchester, many didn’t know how to recognise signs of syphilis, or how the disease is transmitted. Secondly, in several of the UK outbreaks noted so far, a significant proportion of those affected also had HIV infection.

In this month’s lead article, Robert Fieldhouse writes on syphilis transmission, testing and treatment, and provides a timely reminder to HIV-positive readers that HIV treatment centres do not routinely screen for sexually transmitted diseases. If you’re concerned about your sexual health, you’ll need to ask for advice and testing.
the return of syphilis

A re-emergence of syphilis has been reported in several UK cities, and now London appears to be the latest region to be experiencing an outbreak by Robert Fieldhouse.

From 1998 to 1999, diagnoses of syphilis in the UK rose 58% among men and 27% among women. Similar increases have been witnessed across Europe and the USA. This recent increase in new diagnoses in the UK has been attributed to increased transmission within the UK, rather than abroad.

Recent outbreaks: Bristol
Between 1994 and 1997 just one or two cases of syphilis were seen each year at GUM clinics in Bristol. In the eighteen months between January 1997 and May 1998, however, 45 cases of early syphilis were diagnosed. Unlike later outbreaks in Manchester and Brighton, in Bristol the number of women who contracted syphilis during the outbreak outnumbered the number of men affected (26 versus 19).

Most transmission occurred among people living in the inner city areas of Bristol and almost all were thought to have acquired the infection within the UK. Most cases could be linked through sexual and social networks. Female sex workers and drug users (including those who smoked crack or heroin) were disproportionately affected. Four of the women affected were diagnosed through antenatal screening. There were no cases acquired through homosexual contact, and no associated cases of HIV transmission were reported.

Manchester
Between January 1st 1999 and January 31st 2000, a total of 34 cases of early infectious syphilis were diagnosed at three genitourinary medicine (GUM) clinics in Manchester. By June 2001 the total had risen to 140. The highest number of new syphilis diagnoses, in any month so far, occurred in January 2001, when seven new cases were diagnosed.

This outbreak is affecting both the heterosexual and gay community, though a high proportion (86%) of infections reported since January 1999 have been among men who have sex with men. At the beginning of the outbreak there were more cases in heterosexual people than in gay men, but there has since been a rapid increase in the gay community.

To June 2001, 30% of those diagnosed with syphilis had also been diagnosed as HIV-positive. In North Manchester General Hospital GUM department, 50 cases of infectious syphilis have been diagnosed, 55% of which are in people who also have HIV infection.

Brighton and Hove
Between June 1999 and May 2001 a total of 26 cases of syphilis have been diagnosed in the Brighton and Hove area. In total, nine were diagnosed with primary syphilis and ten displayed symptoms of secondary syphilis. Seven cases had no symptoms and were diagnosed with early latent disease on routine blood testing. An association with oral sex was identified in this cluster of cases. Eight of the 26 were also HIV-positive, ten were HIV-negative, and eight remained untested. According to local health care professionals, new cases are still occurring suggesting that transmission in this region is continuing.

Dublin
Since March 2000, ninety cases of syphilis have been reported in Dublin, the majority of which have affected gay men. It is suggested...
that this outbreak is associated with sex overseas and with use of ecstasy. Twenty-one of the 90 cases are in people who are also diagnosed HIV-positive.

Peterborough
A recent outbreak affecting the heterosexual community has been reported in Peterborough. These cases have been linked via an internet chat room.

Enhanced surveillance in London
In the UK in 1999 there were 217 cases of infectious syphilis diagnosed in the UK. Infectious syphilis usually reflects recent infection. Seventy-nine (36%) of the 217 cases were in London. Complete data regarding new diagnoses of sexually transmitted diseases such as syphilis in the UK in 2000 were not available at the time this article went to press. However, the Public Health Laboratory Service (PHLS) was due to publish the latest figures on its website (http://www.phls.co.uk) in early July, and these will be reported accordingly on NAM’s site (http://www.aidsmap.com) and in a future issue of AIDS Treatment Update.

However, we anticipate that the new figures will show the continuation of transmission of syphilis across the UK, especially in cities where outbreaks have already been reported, particularly Manchester and Brighton. In addition, it appears that London should be added to this list. Tom Paine of the PHLS told AIDS Treatment Update that the service “is concerned about the syphilis situation in London, and is carrying out enhanced surveillance to assess the extent of the problem”.

Dr Mike Youle, Director of HIV Clinical Research at the Royal Free Hospital in London, confirmed to AIDS Treatment Update that he has seen an increase in the number of new diagnoses of syphilis among his patients, saying that “it is very contagious and easily missed [by health care workers].”

Assessing the cause of the problem
Research from the School of Health and Human Sciences at Liverpool John Moores University, published in January, has illustrated that there is a lack of awareness among both HIV-positive and HIV-negative individuals regarding both how syphilis is transmitted and the symptoms it may cause.

Interviews with 27 people, seven of whom were HIV-positive, who had been diagnosed with syphilis in Manchester between May 1999 and August 2000, reported that almost all (24 of 27) said they had little or no information on syphilis and were not aware of its symptoms and treatment.

Oral sex a key factor
Of particular note was a misconception regarding the risk of unprotected (without condoms) oral sex. Whereas the majority of individuals (20 of 27) thought that the likelihood of catching syphilis from unprotected anal sex was high, there was confusion over the risk associated with unprotected oral sex. Twenty six per cent thought that oral sex was a low-risk activity for syphilis transmission, 22% thought it was medium-risk, just over one third (37%) regarded oral sex as a high-risk activity, and 15% did not to know how risky it was. In fact, syphilis is readily transmitted through this route (see below).

This study identified oral sex as the biggest source of syphilis risk behaviour. Eight individuals stated there was no other way they could have contracted syphilis, including one man who reported not having had anal sex for over three years. It was also noted that participants expressed an overwhelming reluctance to use condoms for oral sex.

Increased risk taking
Research in the UK has suggested that since 1996 there has been a gradual increase in unprotected sex among men who have sex with men. There have been sharp rises in diagnoses of several sexually transmitted diseases in the gay and other populations during this time.

A report in the February 10th 2001 issue of The Lancet showed that people with AIDS on HAART in the US were more likely to acquire a sexually transmitted infection compared to untreated people with AIDS. It is a concern therefore, that a syphilis outbreak among HIV-positive people may prompt an increase in

Further reading
Statistics on syphilis and other sexually transmitted disease are available from the Public Health Laboratory Service. See their publication CDR Weekly available at their website http://www.phls.co.uk. A report titled Re-emerging syphilis in the North West: Lessons from the Manchester outbreak is available from the North West Public Health Observatory website at http://www.nwpho.org.uk. Click on Published documents, and then the Ad-hoc button.
transmission of HIV infection, particularly in gay and bisexual men, as the presence of untreated sexually transmitted infections make HIV transmission more likely.

How is syphilis transmitted?
Syphilis is caused by a bacterium called Treponema pallidum. It can be transmitted through unprotected vaginal, anal and oral sex. It can also be transmitted through contact with syphilitic sores, lesions and rashes as well as blood-to-blood contact. The transmission rate for syphilis is relatively high – unlike HIV, for example, it is very easily passed on.

Syphilis can also be transmitted from mother to baby. This is known as congenital syphilis and if left undetected and untreated can cause miscarriage, foetal abnormalities or death.

The likelihood of transmission depends upon the infectiousness of the individual, something which is determined by disease stage. Syphilis is at its most infectious in the primary and secondary stages, sometimes called ‘early syphilis’. Early detection of individuals with syphilis by testing, and the provision of treatment, reduces the period when individuals are infectious, and is therefore critically important to containing spread of the infection.

Testing for syphilis infection
It can take up to ninety days for the body to develop antibodies to the bacterium that causes syphilis. A blood test is used to identify antibodies to syphilis, but it is also possible to detect syphilis through swabbing syphilitic ulcers, which may require an internal genital examination in the case of women. In addition, all pregnant women should be offered screening to prevent mother-to-baby transmission.

If neurological (brain) involvement is suspected, a lumbar puncture is carried out to assess the extent of the disease.

Symptoms of syphilis
Soon after the organism enters the body it spreads via the blood stream or the lymphatic system. Initial symptoms may not be obvious enough to cause any discomfort. Usually a painless ulcer known as a chancre will appear where the bacterium entered the body, e.g. mouth, genitals, anus, though such ulcers can appear anywhere on the body. This usually clears up within two to eight weeks. This phase is known as primary syphilis.

Secondary syphilis occurs six weeks to six months after the appearance of the chancre. At this stage a non-itchy rash may develop on the body, often on the hands or feet. This rash is infectious. Some people experience a flu-like illness, tiredness and loss of appetite, which can be accompanied by swollen glands and may last for several months. Less frequently, meningitis may occur at this stage. Of course many of these symptoms are not specific to syphilis but are also common to other infections, including HIV and other viral illnesses, and this is one reason why syphilis may go undiagnosed.

After around two years of infection, if left untreated, syphilis develops into an asymptomatic, latent stage. Up to 40% of individuals may then go on to develop clinical manifestations in which the heart, joints and the nervous system may be affected. The time frame for this progression is extremely variable; from three to ten or more years. Syphilis is rarely transmitted sexually at this stage. Brain disease relating to syphilis (neurosyphilis) may occur at any stage.

Treating syphilis
Treatment in primary or secondary stages of infection will cure the infection. Some people may experience a flu-like illness, called a Jarisch-Herxheimer reaction, at the onset of treatment, as the syphilis bacteria begin to die off. This is treated with paracetamol.

Treatment of primary and secondary syphilis, among HIV-negative people, consists of fourteen daily intramuscular procaine penicillin injections at a dose of 750,000 units. HIV-positive individuals, or HIV-negative individuals with suspected neurological syphilis, are usually
prescribed a course of 21 daily procaine penicillin injections at a dose of 2 mega units (2,000,000), with a tablet of probenecid four times a day to delay excretion of the penicillin from the body.

Individuals who are allergic to penicillin will be offered a course of antibiotic tablets or capsules. This is usually doxycycline. The standard dose for HIV-negative individuals is two 100mg capsules once daily for 14 days, unless neurological syphilis is suspected, in which case the dose is two 100mg capsules daily for 21 days. This longer course is also prescribed to HIV-positive individuals with primary or secondary syphilis.

Treatment of latent infection may be as long as 28 days with a further increased dose of penicillin or doxycycline. Treatment at this stage can still cure infection. However, if damage to the heart and nervous system has occurred before the initiation of treatment, this may be irreversible.

Follow-up blood tests will be carried out at intervals of 1, 2, 3, 6, 12 and 24 months to ensure that the organism has been eradicated.

**Syphilis and HIV**

Syphilis appears to facilitate HIV transmission more efficiently than any other sexually transmitted infection. HIV-positive people with untreated syphilis are two to five times more likely to transmit HIV to others. This is probably due to trauma in the mucous membranes caused by syphilitic ulceration.

Some studies have shown that the antibody tests used to identify syphilis are not as effective in HIV-positive people. In people with HIV the course of the disease may be different; it is possible that HIV speeds up the course of syphilis. There may be an increased risk of brain involvement, and unusual symptoms may include skin and mouth ulcers and fever.

However, provided HIV-positive people are prescribed the recommended longer course of treatment the response to treatment should be as good as that seen in HIV-negative people.

**Raising awareness**

According to Gay Men Fighting AIDS (GMFA, a London-based HIV prevention organisation) many HIV-positive gay men are unaware that they are unlikely to be routinely screened for syphilis when they have blood samples taken routinely at their treatment centre. Matthew Hodson, Project Worker for the Positive Campaign Group at GMFA told *AIDS Treatment Update*, “Many HIV-positive people mistakenly believe that they do not need to specifically access sexual health screening”.

**key conclusions**

- **Enhanced syphilis surveillance is currently underway in London, which is understood to be the latest UK city to be affected by a syphilis outbreak.**

- **Unprotected oral sex is a significant risk factor for syphilis transmission, though syphilis is also readily transmitted through unprotected anal or vaginal sex.**

- **If you are concerned that you may have been exposed to syphilis or any other sexually transmitted infection, take a test at your HIV treatment centre or at a genitourinary medicine clinic.**

- **Symptoms of syphilis may not always be present despite having acquired the infection.**

- **Syphilis is completely curable if detected in the early stages. It can be cured later but may leave permanent damage.**

- **Syphilis appears to facilitate HIV transmission.**

- **Progression of syphilis may be more rapid among HIV-positive people.**

- **HIV-positive people should routinely be offered screening for sexually transmitted infections.**

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is phenotyping useful?

According to current guidelines in both the UK and US, changes in anti-HIV therapy which is failing to suppress viral load to undetectable levels should be guided by the results of a drug resistance test. In practice, in the UK at least, the testing method used most commonly is genotyping, which detects mutations in HIV's genes which are known to cause resistance to specific drugs.

Phenotyping is an alternative method which measures the amount of a drug which is needed to stop HIV reproducing. Where the amount is in excess of that normally required, HIV is considered to be drug resistant, (or of reduced susceptibility or sensitivity). Whilst theoretically more useful because it is intended to provide a direct measure of a given drug’s activity against a sample virus, phenotyping is the more costly of the two methods and results are generated more slowly.

As we have reported in a recent issue of AIDS Treatment Update (issue number 99, March 2001), four randomised, controlled trials have reported improved short-term treatment responses in people who change anti-HIV regimen with guidance from the results of a genotypic resistance test, rather than without this information.

In comparison, the case for using phenotypic resistance tests is somewhat less robust. Of two studies presented at last year’s Fourth International Resistance Workshop in Sitges, one demonstrated a benefit in favour of phenotyping (VIRA3001), whilst another (NARVAL) found no benefit. A third study, CCTG 575, reported at the Fifth Resistance Workshop in Scottsdale, Arizona, last month, found no benefit in recipients of phenotypic testing overall, but did find the test improved treatment response in some subgroups1.
CCTG 575
CCTG 575 was designed to evaluate the usefulness of phenotypic testing (using the Virologic test, Phenosense) when changing treatment. This randomised, prospective study compared treatment response in two groups of participants. The first group (PHENO) changed their failing anti-HIV therapy with the results from a phenotypic resistance test performed while still on the failing regimen; whilst the second (SOC; standard of care) changed without a test.

All 256 participants had been taking anti-HIV therapy for at least six months, and had viral load above 400 copies. They had previously taken one protease inhibitor (PI), (though the protocol was later amended to allow those who had received two PIs to be included as well). That participants should have ‘viable treatment options’ was also an entry requirement, (though this criteria was not well defined).

Entry characteristics, and treatment responses for 119 PHENO participants and 119 SOC participants are shown in the table below. As the table demonstrates, CCTG 575 found no difference overall between those who received a phenotypic test and those who did not in their response to their new regimen at either six or twelve months.

However, there was a subgroup of patients in the PHENO arm who do appear to have benefited from phenotyping. Of those who began with resistance to at least three PIs, PHENO participants were more likely to have viral load below 400 copies at six months than SOC participants (50% versus 17%). A subgroup analysis of participants who began the study with more than sixty months prior experience of anti-HIV therapy, (and so may have been expected to have acquired more drug resistance), showed a trend towards a benefit in the PHENO arm, but this did not quite reach statistical significance, meaning it could have been due to chance.

The CCTG 575 study team have proposed a series of possible explanations for the lack of benefit associated with phenotypic testing observed in their study, given that this result does not appear to fit with that of other trials. In comparison with other studies, participants in CCTG 575 were not particularly drug experienced and many had yet to use drugs from the NNRTI class. It is suggested therefore that participants in both trial groups should have had a range of viable treatment options available to them.

A further important consideration is that phenotypic tests are currently basing predictions of drug sensitivity on break-points which have not been clinically validated. While this affects all current antiretrovirals to a greater or lesser extent, it is suggested that it may be a particular problem for the nucleoside analogues ddi and d4T. In CCTG 575, there was a tendency for these two drugs to be used more often in the PHENO arm than the SOC arm. If the break-points used for these drugs were inaccurate, then one would expect the PHENO arm to have under-performed. When the study team reanalysed the data excluding these two drugs, there was no difference in the change in viral load at twelve months (median) or the proportion with viral load below 400 copies at six months. However, treatment response in the PHENO arm to have under-performed. When the study team reanalysed the data excluding these two drugs, there was no difference in the change in viral load at twelve months (median) or the proportion with viral load below 400 copies at six months.

<table>
<thead>
<tr>
<th>Entry characteristics</th>
<th>PHENO</th>
<th>SOC</th>
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</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>119</td>
<td>119</td>
</tr>
<tr>
<td>Viral load (median)</td>
<td>12,589 copies</td>
<td>12,589 copies</td>
</tr>
<tr>
<td>Duration of prior NRTI therapy (median)</td>
<td>36 months</td>
<td>36 months</td>
</tr>
<tr>
<td>Experience of NNRTI class</td>
<td>24%</td>
<td>24%</td>
</tr>
<tr>
<td>Experience of PI class</td>
<td>85%</td>
<td>86%</td>
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<tr>
<td>Experience of three drug classes</td>
<td>15%</td>
<td>18%</td>
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<table>
<thead>
<tr>
<th>Treatment response</th>
<th></th>
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<tbody>
<tr>
<td>Change in viral load at six months (median)</td>
<td>-0.71 log</td>
<td>-0.69 log</td>
</tr>
<tr>
<td>Proportion with viral load below 400 copies at six months</td>
<td>48%</td>
<td>48%</td>
</tr>
<tr>
<td>Change in viral load at twelve months (median)</td>
<td>-0.71 log</td>
<td>-0.7 log</td>
</tr>
</tbody>
</table>

glossary

**gene** A DNA sequence which determines the structure of a protein.

**genotype** The genetic make-up of an organism.

**intent to treat** A form of statistical analysis where data from all participants in a trial are evaluated, rather than data only from those who complete the trial.

**log** Short for logarithm, a scale of measurement often used when describing viral load.

**mutation** A single change in gene sequence.

**NNRTI** Non nucleoside reverse transcriptase inhibitor; a family of anti-HIV drugs.

**NRTI** Nucleoside analogue reverse transcriptase inhibitor; a family of anti-HIV drugs.

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

**protease inhibitor** Family of anti-HIV drugs which target the protease enzyme.

**regimen** A drug or treatment combination and the way it is taken.

**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.

**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.

**wild-type virus** Virus which has not been exposed to anti-HIV drugs before.
phenotyping useful? continued

number of sensitive drugs available to participants in each arm. In these circumstances, resistance testing may have been expected to add no extra value.

**VIRA 3001**

Final results from VIRA 3001 were reported at last year’s Resistance Workshop. 273 people with viral load above 2,000 copies were randomised to change their failing therapy with the results of a phenotypic resistance test (PRT, using Virco’s Antivirogram), or without (SOC). All had previously taken at least two nucleoside analogues and one PI.

Median viral load at enrollment for 221 participants was 4.2 log in the PRT arm and 3.9 log in the SOC arm. Median CD4 was 340 cells. Phenotyping demonstrated that a greater number of people in the SOC arm switched to nucleoside analogues to which they were resistant than in the PRT arm. A greater fall in viral load was observed in the PRT participants after sixteen weeks on the new regimen than in the SOC arm. At this point, 45% of PRT participants had viral load below 400 copies by intent to treat analysis, compared with 34% of the SOC arm.

**NARVAL**

The NARVAL study was designed to evaluate the use of either genotypic (arm G) or phenotypic (arm P) resistance tests for choosing a new anti-HIV regimen, compared to changing treatment without a test (arm SOC). All participants were taking a PI-containing regimen and had viral load over 1,000 copies.

Of 541 people enrolled, median viral load at baseline was 4.3 log, and median CD4 count was 280 cells. The median number of prior drugs used was seven. After twelve weeks on the new regimen, there were no differences between the three groups in the proportion of people whose viral load had fallen below 200 copies, or in the proportion who had achieved a fall in viral load of at least one log. By 24 weeks, there was a trend towards a benefit in those in the genotyping arm, but there was no advantage seen in those who received phenotyping compared with those who did not receive a resistance test.

At the time the results of this study were reported, it was proposed that the lack of benefit associated with resistance testing observed may have been related to participants’ lengthy drug experience, and subsequent shortage of viable treatment options. However, the accuracy of resistance test results may also have played a part. The French team behind the study presented data showing discrepancies between the predictions regarding likely drug susceptibility arising from genotypic compared to phenotypic tests. For example, 56% of samples were deemed resistant to d4T by genotyping, but only 24% were resistant by phenotyping. In the cases of 3TC and abacavir, the differentials were 62% G, 81% P; and 84% G, 41% P respectively. Whilst these differences may be due to a delay between changes in genotype and changes in phenotype, it seems likely they are also a reflection of the inadequacy of the break-points used to define phenotypic resistance versus susceptibility, particularly those in use at the time this trial took place.

**Debate over break-points**

Though these three studies suggest that phenotyping may be useful in some circumstances, there are those who believe that the case for using these tests within routine clinical practice has yet to be made. One of these is Stefano Vella, President of the International AIDS Society. During the discussion that followed the presentation of the CCTG 575 data at the recent Resistance Workshop, Vella argued strongly that, while acknowledging the range of potential confounders, the burden remained with industry and trial investigators to design and
complete trials which more clearly delineate the specific patient populations who may benefit from phenotypic testing. Richard Haubrich, lead investigator on CCTG 575 agreed, but cautioned that current studies may be under-powered (i.e. do not include an adequate number of participants) to perform this task.

That there is a pressing need for the establishment of more accurate breakpoints between different levels of drug susceptibility is very clear. Phenotypic resistance tests give results in the form of a ‘fold-change’ in the susceptibility of a given HIV strain to a given HIV drug. Historically, Virco phenotypes were defined as sensitive if the fold-change was less than four, intermediate for fold-changes between four and ten, and resistant for fold-changes above ten, whereas for Virologics, the cut-off between sensitive and resistant virus was 2.5. These cut-offs failed to distinguish between differences in the emergence of resistance to different drugs. Moreover, HIV drug resistance is a continuum rather than a choice between yes, no, and maybe. This distinction becomes particularly relevant to treatment decision-making when one considers that anti-HIV regimens involve several drugs. In practice, patients and doctors need to be able to weigh up whether the inclusion of a specific drug in a new regimen will offer enough antiviral activity to merit the risks it may pose in terms of toxicity.

In response, biotechnology companies such as Virco are now evolving ‘biological cut-offs’ for individual antiretrovirals, (see sidebar to right of this page). These are calculated statistically, based on the normal distribution of drug susceptibilities found in 1,000 ‘field samples’ of HIV from HIV-positive people who have not used anti-HIV treatment. These cut-offs therefore take into account the natural variation between circulating viruses (because these viruses are not genetically identical), rather than being based purely on laboratory variability. Though these biological cut-offs remain somewhat arbitrary, and so have their critics, many resistance experts consider them to be an improvement on the old system. Nevertheless, it is still important to recognise that these biological cut-off values do not necessarily determine which individual will or will not respond to a particular drug. There is far less data on ‘clinical cut-offs’, and identifying such values for each drug is now the focus of attention.

**key conclusions**

- Anti-HIV therapy which is failing to suppress viral load fully should be changed with guidance from a drug resistance test, according to HIV treatment guidelines.

- Four clinical trials have shown that genotypic resistance testing is of some benefit when changing treatment.

- There is less evidence to support the use of phenotypic resistance tests, and more research is needed to establish the patient groups and clinical circumstances in which these tests may have a role.

- The break-points used to distinguish levels of drug resistance in phenotypic resistance tests have been revised, but they are likely still to be sub-optimal. However, there is some optimism that their accuracy will continue to be refined as research progresses over the coming year.

**new Virco cut-offs**

For Virco’s *Antivirogram*, the move to biological cut-offs has altered the proportion of tests which will report resistance. Lower cut-offs for ddI, d4T and ddC reflect the likely under-reporting of resistance to these drugs previously, while cut-offs for the NNRTIs have been raised. The new biological cut-offs for Virco’s *Antivirogram*, expressed as a fold loss of susceptibility compared to a reference wild-type virus from untreated individuals, are:

- AZT 4.0
- 3TC 4.5
- ddI 3.5
- ddC 3.5
- d4T 3.0
- abacavir 3.0
- nevirapine 8.0
- efavirenz 6.0
- delavirdine 10.0
- indinavir 3.0
- ritonavir 3.5
- nelfinavir 4.0
- saquinavir 2.5
- amprenavir 2.5
- lopinavir 2.5

**references**

1 Haubrich R et al. Antiviral Therapy 2001; 6(Supplement 1):63.
**OPTIMA to begin**

A major new clinical trial for people with multi-drug experience is due to begin recruiting participants at sites across the UK soon.

The OPTIMA trial (Options in Management with Antiretrovirals), is designed to compare the effect of different management strategies on clinical outcomes (survival, time to AIDS-defining event, time to serious adverse event), virologic and immunologic response, and other healthcare outcomes (quality of life measures, cost-effectiveness) in people who have failed several HAART regimens.

OPTIMA is a tri-national trial, involving the UK, Canada, and the USA. People with advanced HIV disease will be followed for one to three and a half years. This trial will help delineate the most effective therapeutic strategies for their management. The strategies to be compared in this open, randomised study are:

- An HIV drug-free period of 3 months followed by HIV treatment with up to 4 drugs (“standard ART”)

- An HIV drug-free period of 3 months followed by HIV treatment with 5 or more drugs (“mega-ART”)

- Immediate start of HIV treatment with up to 4 drugs

- Immediate start of HIV treatment with 5 or more drugs.

A total of 1700 people, including 400 from the UK, will be randomised. At the time this issue went to press, details of participating sites were not yet available, but will be listed on NAM’s website http://www.aidsmap.com soon.

If you are interested in entering OPTIMA you can discuss this with your HIV treatment centre. If you are interested in offering this trial at your site contact the Medical Research Council Clinical Trials Unit, who are responsible for OPTIMA in the UK, (http://www.ctu.mrc.ac.uk).

To be eligible to join OPTIMA you should be aged 18 years or more; have confirmed HIV infection; have experienced failure of at least two different multi-drug regimens, which included drugs of all classes that you could tolerate; and have a history of at least three months continuous HAART and still be on treatment. In addition, your last two sets of lab results should be either CD4 below 100 plus viral load over 5,000 copies; or CD4 between 100 and 199 and viral load over 10,000 copies.

You will be ineligible if you are pregnant or planning to become so, or are breast-feeding; or if mega-ART is contraindicated, e.g. by intolerance; or if your current drug regimen includes more than 5 drugs; or if you have a serious, uncontrolled opportunistic infection (OI); or if you are considered likely to be poorly adherent.
Resistance after STIs

According to two research groups, supervised treatment interruptions (STIs) in people taking 3TC-containing regimens, can result in the emergence of 3TC resistance. These data were presented at the Fifth Resistance Workshop in Arizona last month.

The first study, from Bruce Walker’s lab at Massachusetts General Hospital and Havard Medical School, found the 3TC signature mutation M184V emerged during periods off therapy in one of fourteen people undergoing STIs after beginning anti-HIV therapy very soon after infection. M184V was not detected by genotypic resistance testing in this person prior to treatment, nor in a further test at day 3 of the first STI, but had emerged by day 21.

A team from Badalona, Spain, similarly detected the 3TC mutation in two of twelve people participating in a study of STIs in chronically infected people. M184V emerged at the end of the second and third STIs.

Both groups hypothesise that 3TC’s long half-life may have been the cause of the problem. After stopping treatment, the drug remains at tapering levels in the blood for some time. These low levels create the right climate for selection of 3TC resistance mutations.

Other anti-HIV drugs which also have long half-lives, such as efavirenz and nevirapine, are expected to be affected by the same problem. People who want to take a break from a treatment combination which involves one of these drugs, therefore need to discuss this with their doctor beforehand to minimise the risks involved.


Treating fatigue

A controlled trial of two psychostimulant drugs has found that both treatments were effective in reducing fatigue experienced by people with HIV. This US study recruited 144 people with persistent and severe fatigue, and then randomised them to receive either a dummy pill (placebo), or one of two active psychostimulants, methylphenidate (Ritalin) or pemoline (Cylert). Allocation of treatment was blinded to both patients and their doctors. Both of these psychostimulants have been found effective in treating fatigue experienced by cancer and multiple sclerosis patients.

One hundred and nine people finished the six week treatment course. After this time, 41% of methylphenidate recipients and 36% of pemoline recipients reported an improvement in their condition, compared with 15% of those receiving placebo. The difference between the two active drugs was not significant, though this study was not powered to detect a difference.

Improvement in quality of life and less depression were also associated with the improvement in fatigue. Side-effects were reported in a minority of participants. As expected, jitteriness and hyperactivity occurred more frequently in those receiving psychostimulants than placebo.


BMS buy DuPont drugs

Last month DuPont Pharmaceuticals was sold to Bristol-Myers Squibb. DuPont’s biggest selling drug is the anti-HIV drug efavirenz. This acquisition means that BMS now own three licensed antiretrovirals, including the nucleoside analogues ddI and d4T, and have a protease inhibitor, currently known as BMS 232632, in development.

NAM forum

July’s NAM Information Forum will provide feedback from two key HIV research meetings due to take place in early July: The International AIDS Society Conference, a medical meeting to be held in Buenos Aires, and AIDS Impact, a social science conference to be held in Brighton.

The Forum takes place on July 23rd at the University of London Union, Malet Street, London WC1 from 7 to 9pm. Note this month a room change to Room 101, First Floor. A sign language interpreter is available and everyone is welcome to this free event.

For an introduction to HIV treatment issues
The booklets in NAM's Information Series for Positive People are free to people with HIV. This easy-to-read series covers six key topics: Viral Load, Clinical Trials, Nutrition, Anti-HIV Drugs, Resistance, and a Glossary.

The HIV & AIDS Treatments Directory
This 600-page book, published twice a year, is a comprehensive guide to the medical aspects of HIV. Available at only £12.95 to people with HIV, £64.95 to professionals.

http://www.aidsmap.com
NAM's resources are also available online at aidsmap.com. These include our extensive and searchable treatments database, the latest news on treatment developments, our online directory of AIDS organisations, hundreds of links to recommended HIV-related sites, and free downloadable resources.

Monthly NAM information forums in London
Each month an expert speaker discusses a treatment-related topic. Entry is free. Future forums are advertised inside this newsletter.

AIDS Treatment Phoneline 0845 9470 047
From Terrence Higgins Trust: Mon & Wed 3–9pm, Tue 3–6pm.

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

AIDS Treatment Update is available on audio tape, and can be emailed to you as a pdf file for viewing with Acrobat Reader. Telephone 020 7627 3200 for details.