

aids treatment update

Know all your options

Undiagnosed, untreated and under-treated syphilis is still harming HIV-positive people in the UK; many new infections are occurring in gay white men, although heterosexual men and women from Africa may also have previously undiagnosed syphilis.

Although every HIV treatment centre is supposed to routinely test for syphilis and other sexually transmitted infections (STIs), it has come to our attention that screening for STIs is not routine at all centres. Ask your healthcare provider if it is being done in your centre - if not, you have every right to ask why not.

Treatments for syphilis are also different across the country, despite clear UK guidelines. Some doctors argue that the guidelines are not based on studies, just "expert opinion" - which they disagree with. However, it is important that every person with HIV is aware of all the available treatments, as well as with the risks associated with the easier options.

New *ATU* contributor Bridget Haire immersed herself in both the old and new pregnancy guidelines from the British HIV Association (BHIVA), which we are previewing in this issue. "I was quite astounded at the difference between the 2001 and 2005 documents," she says. "There was a noticeable, and welcome, shift from a pedantic, almost anti-woman stance to one that seems to embrace the complexities of health for women with HIV and their babies."

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hiv & pregnancy

2 new pregnancy guidelines will provide more choice for hiv-positive women, by bridget haire

Summary

- The latest BHIVA pregnancy guidelines show a highly developed understanding that management of HIV during pregnancy is not simply a matter of reducing the risk of mother-to-child transmission, but is also about planning a strategy that takes into account the long-term health of both mother and baby.
- A balance needs to be struck when there is a potential conflict between the best interests of the mother and those of her baby, with careful regard to weighing the likelihood of potentially adverse consequences for either.
- These guidelines support recommendations with carefully graded levels of evidence. This allows women with HIV and their health care providers to assess the values and evidence base of particular management strategies to determine their usefulness for individual circumstances.
- Choice is encouraged where evidence is not conclusive. But perhaps most importantly, these guidelines do not reduce the concept of health to a couple of clinical markers, but instead take a more holistic approach and focus on the overall health and well-being of women and their babies.

The British HIV Association (BHIVA) will soon finalise its new guidelines for the management of HIV infection in pregnant women and the prevention of mother-to-child transmission. European Collaborative Study These new guidelines have a broader remit than earlier versions, and tackle a wide range of health concerns facing HIV-positive pregnant women in the UK.

For instance, for the first time, specific recommendations are provided regarding both the differing stages of HIV infection and the

different stages of pregnancy: prior to conception, early pregnancy, late pregnancy, during labour, and after giving birth. Most importantly, the recommendations leave room for women to make informed choices about their treatment and delivery strategies.

In addition, the guidelines move away from the recommendation that all women with HIV should opt for pre-labour Caesarean, and instead outline a detailed strategy for reducing the risk of transmission in vaginal delivery for women with very low viral loads.

Summary of BHIVA antiretroviral recommendations

- For women who do not yet require antiretroviral treatment for their own health (usually because they have CD4 counts above 200 cells/mm³), the guidelines recommend holding off taking anti-HIV therapy until mid-way through the pregnancy. They recommend starting at between week 20 and 32, and the choice is to begin with *either* AZT (zidovudine, *Retrovir*) alone *or* a triple drug combination, known as combination antiretroviral therapy, or Highly Active Antiretroviral Therapy (HAART).
- Vaginal delivery is an option for women opting for HAART, if viral load is undetectable (below 50 copies/ml) at weeks 36-40. Intravenous AZT during delivery is not required for women taking HAART.
- For women opting to take AZT alone, pre-labour Caesarean and intravenous AZT during delivery is recommended.

- For women with higher viral loads (above 10,000 copies/ml) who still do not require treatment for their own health, short-term HAART is also recommended. In all cases, if viral load is undetectable after 30 weeks of pregnancy, vaginal delivery is an option.
- Short-term HAART should stop after delivery, except where viral load is still above 50 copies/ml, when treatment should be continued until the viral load becomes undetectable.
- Women who have not previously taken anti-HIV treatment but who require it for their own health are advised to wait to start HAART until after the first three months of pregnancy, and then to use a regimen that contains both AZT and 3TC (lamivudine, *Epivir*; both drugs are also available in one pill called *Combivir*). However, if they have very advanced HIV disease they are advised to commence treatment immediately.
- Women who become pregnant while on HAART and who have an undetectable viral load are advised to continue on therapy. Those who are on HAART that isn't achieving undetectable viral load are advised to have genotypic resistance testing done in order to determine their best option, and then to change to a better regimen.
- Although mother-to-child transmission is rare in women with HIV-2, they should follow the same guidelines as those infected with HIV-1. However, the anti-HIV drugs nevirapine (*Viramune*) and efavirenz (*Sustiva*) should be avoided.

Precautions for specific drugs

Nevirapine has been widely prescribed in pregnancy and is effective. However, the manufacturers, Boehringer Ingelheim, caution that women "with higher CD4 counts are at increased risk of hepatic [liver] adverse events, often associated with rash, especially women with pre-treatment CD4 counts greater than 250cells/mm³." Pregnant women may fit this description.

The BHIVA guidelines caution against efavirenz (*Sustiva*), as severe birth defects were noted in studies of the drug in monkeys (three

out of 29 had foetal abnormalities). However, similar studies have not been conducted on other antiretroviral drugs, either singly or in combination.

Women taking protease inhibitors during pregnancy have a higher risk of developing diabetes during pregnancy than either HIV-negative women or HIV-positive women not taking protease inhibitors.

The US Food and Drug Administration has recently warned against the use of the protease inhibitor indinavir (*Crixivan*) in pregnancy, as blood levels of the drug in pregnant women were found to be below therapeutic levels.

Liver function and blood lactate should be monitored in women taking HAART that includes both ddI (didanosone, *Videx*) and d4T (stavudine, *Zerit*), as three pregnant women have died of lactic acidosis. If possible, this combination should be avoided in pregnancy.

Resistance

Current treatment guidelines for adults with HIV recommend anti-HIV therapy that reduces viral load to less than 50 copies/ml where possible, in order to avoid the development of drug-resistant virus. The choice of short-term AZT monotherapy in pregnancy where a mother does not require therapy for her own health and wishes to limit infant exposure to drugs is an exception to this. There is now evidence¹ that AZT monotherapy used in the short term is not associated with resistance that affects future treatment options.

Single doses of nevirapine, however, do have a negative impact on future regimens containing drugs of the same class (the class of non-nucleoside reverse transcriptase inhibitors, or NNRTIs, which also includes efavirenz)².

A recent study from Ireland³ found that women who take HAART in order to prevent mother-to-child transmission, and who stop nevirapine-containing HAART after giving birth, may still be at risk of acquiring resistance when stopping nevirapine, as has been suggested, five days prior to the rest of the combination. The majority of the women in the study were from sub-Saharan Africa and had a wide variety of HIV-1 subtypes.

further reading

bhiva guidelines
The draft 2005 BHIVA pregnancy guidelines are available for download from the BHIVA website: www.bhiva.org. Comments should be sent by March 12th to Dr David Hawkins (david.hawkins@chelwest.nhs.uk). The final version of the guidelines be presented at the Spring BHIVA Conference, to be held in Dublin in April.

hiv & women booklet
NAM's Patient Information Booklet for women with HIV includes chapters on preventing mother-to-baby transmission, conception and pregnancy. It is available free by emailing info@nam.org.uk

www.aidsmap.com
Visit www.aidsmap.com for the latest news and information on pregnancy and HIV.

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New data on HAART and prematurity

The BHIVA guidelines suggest that women can choose between taking AZT alone or HAART, depending on their own health and their attitude to risk. However, two recent studies raise concerns about premature delivery in women taking HAART. The European Collaborative Study⁵ looked at 4372 mother-infant pairs and found that HAART, particularly if started before pregnancy, was strongly associated with prematurity (defined as birth before 37 weeks gestation) or severe prematurity (birth before 34 weeks).

In addition, a strong relationship was found between prematurity and neonatal death (defined as death within the first 28 days of life). The prematurity rate among women taking HAART was 25.5%, compared with 16.8% among those taking a single anti-HIV drug (usually AZT). The perinatal mortality rate (defined as stillbirths and deaths within the first week of life) in babies born to women taking HAART was 21.7 per 1000 in 2003, compared with nine per 1000 in the general European population.

In total, there were 28 neonatal deaths between 1986 and 2004; eight of these

occurred in four years between 2000-2004, compared with 20 in the fourteen years between 1986 and 2000. Although this sounds alarming, the numbers are still very small when compared with the number of healthy babies born.

The association of HAART with prematurity is strengthened by a survey conducted in the UK and Ireland, the National Study of HIV in Pregnancy and Childhood⁶, which found that mothers taking HAART were almost one-and-a-half times more likely to give birth prematurely.

However, this study did not find that HAART was associated with either stillbirth or congenital abnormalities.

These data raise as yet unanswerable questions about the relative safety of particular drugs or particular classes of drugs. However, the latest BHIVA pregnancy guidelines take all current knowledge into account and provide more guidance and information than ever before to help reduce the risks to both mother and baby. If you have any concerns about taking HAART during pregnancy, talk with someone at your clinic.

Reducing risk at birth

Previous BHIVA guidelines have recommended pre-labour Caesarean delivery in every instance. The new guidelines say that vaginal delivery is an option for women who have an undetectable viral load at weeks 36-40.

Risk of transmission is increased approximately two percent for every hour following waters breaking, up to 24 hours⁴. Emergency Caesareans after waters break are not associated with the same reduction in mother-to-child transmission as those done before waters break.

Pre-labour Caesarean at week 38 is recommended for all women with obstetric complications, those co-infected with hepatitis C

and those with viral loads above 50 copies/ml. The guideline authors discuss evidence that emergency Caesareans in particular are associated with greater complications in HIV-positive women (especially higher incidence of fevers); however, they point out that this finding pre-dated the use of antibiotics before, during and after surgery, which is now commonplace.

Antibiotics are also recommended if waters break during the first stage of labour. If premature delivery is threatened, corticosteroids are recommended to aid the baby's lungs.

The guidelines recommend that written birth plans should cover every contingency that might arise, in the event of an emergency hospital admission.

Other maternal health issues

Genital infections such as *Chlamydia* and herpes need to be treated in order to lower the amount of HIV present in the birth canal and genital secretions. A Pap smear is also very important, particularly if this is overdue.

However, the guidelines advise that treatment of any Pap smear abnormalities is deferred until six weeks after delivery, unless invasive cervical cancer is suspected.

If a woman is co-infected with hepatitis B (HBV), HBV immunoglobulin and vaccination of their babies usually prevents transmission. The guidelines suggest that women co-infected with HIV/HBV should use anti-HIV medicines that are active against both viruses, such as 3TC and tenofovir (*Viread*).

Around 6% of HIV-negative women infected with hepatitis C (HCV) will infect their babies with HCV. This risk doubles or triples when women are co-infected with HIV and HCV. When and how this happens (in the womb or during birth) is not clear, but it is thought that the use of forceps in vaginal delivery increases the risk of HCV transmission. Recommendations are that women with HIV/HCV co-infection should take HAART and deliver by planned pre-labour Caesarean.

Psychological and social issues

HIV testing is offered to all pregnant women in the UK, and this practice has significantly reduced mother-to-child transmission. However, being given an HIV diagnosis when pregnant can be a major shock - and can be a more radically life-changing event than motherhood itself.

The guidelines recommend an antenatal multi-disciplinary team consisting of at least: an HIV specialist, an obstetrician, a specialist midwife and a paediatrician. Peer and voluntary sector support may be necessary, as may patients' advocates, social workers, legal advocacy, psychologists, counsellors, health advisors, citizens' advice bureaux, interpreters, community midwives, community nurse specialists and health visitors.

The guidelines discuss treatment adherence, HIV testing of existing children, eligibility for treatment, post-natal depression, referral

pathways, welfare and immigration support and access to infant formula. This is an excellent overview of the myriad of social factors that may impact on a pregnant HIV-positive woman's health. Potentially volatile subjects, such as failure to disclose to a partner, refusal of interventions and child protection issues are also discussed in a sensitive manner. A thorough understanding of these guidelines will doubtless help clinicians, nurses, social workers and others involved in caring for pregnant women with HIV provide the best possible service.

Infant feeding

There is currently no evidence that any kind of anti-HIV therapy can protect against transmission through breast-feeding. The guideline authors cite studies that indicate the "random" nature of virus shedding into milk⁷. As infant formula is available and safe in the UK, it remains the recommended option, and the guidelines recommend avoidance of breast-feeding in all instances.

Infant treatment

AZT alone is recommended for an infant for four weeks after delivery when the mother has taken AZT alone and delivered by pre-labour Caesarean, or the mother was on HAART that contained AZT and which reduced viral load to less than 50 copies/ml. Four weeks of single therapy with a different reverse transcriptase inhibitor, such as 3TC, d4T, ddI or abacavir (*Ziagen*), is recommended if the mother was on non-AZT-containing HAART that reduced viral load to less than 50 copies/ml.

Four weeks of HAART with AZT, 3TC and nevirapine is recommended where a mother presents at full term or in labour with no previous anti-HIV medicine experience, or where the maternal HIV diagnosis is determined after delivery (and she has no previous treatment experience).

"Expert advice" regarding infant treatment is recommended where a mother presents with non-suppressed HIV and previous antiretroviral exposure, or where the mother has a history of multiple antiretroviral exposure and drug resistance.

glossary

antenatal before birth
antiretroviral a substance that acts against retroviruses, such as HIV

cervical intraepithelial neoplasia (CIN) an abnormal growth on the surface of the cervix which, when observed with a microscope, suggests that the cells could be cancerous
caesarean a method of delivery where the child is born via a cut made through the abdomen and womb

genotypic resistance testing a test that looks for drug-resistant HIV strains.

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

HIV-1 the most common kind of HIV in the world

HIV-2 occurs mostly in West Africa, is less infectious and has a slower rate of disease progression than HIV-1
obstetrics the branch of medicine dealing with childbirth and care of the mother

pap smear an examination of cells from the cervix used to detect early changes that could lead to cancer

subtypes different strains of HIV, which can be grouped according to their genes. Subtype B is commonest in the UK, but many other subtypes are now being seen here, too.

the hiv/syphilis connection

6 what every hiv-positive person should know about syphilis, by edwin j bernard

Summary

- Syphilis is currently affecting a disproportionate amount of HIV-positive gay men
- Prevention (i.e. using condoms for oral, vaginal and anal sex) may be easier to deal with than either treatment or the complications of untreated syphilis. Using a condom for oral, anal, or vaginal sex offers protection from infection with syphilis, or from passing on the bacteria to somebody else. However, protection is not complete because lesions and rashes may not necessarily be in the genital area.
- Symptoms are often harder to diagnose because syphilis behaves differently in HIV-positive people.
- Syphilis can increase viral loads, making you potentially more infectious, and reduce CD4 counts, making you potentially more ill.
- It's best to catch syphilis early in the disease, with regular blood tests, so that treatment is more likely to be successful.
- If syphilis affects the brain or nervous system, it can create lasting damage. It might be best to consider using the strongest, but most inconvenient and painful, treatment in order to avoid this possibility.

The 21st century has seen the return of an ancient sexually transmitted infection (STI), syphilis - caused by a bacterium called *Treponema pallidum*. After almost disappearing in the 1990s, syphilis has re-emerged as a relatively common STI in the UK, and in 2005 it continues to affect HIV-positive gay men disproportionately. Of particular concern is the fact that the symptoms of syphilis can appear faster and be more aggressive in HIV-positive people. "We are seeing syphilis present in so many different - and often unusual and even unreported - ways," notes Dr Martin Fisher of Brighton and Sussex University Hospital. "Even the best textbooks were written before the HIV epidemic and so we are having to learn from new experiences, and, hopefully, rewrite the old texts."

Who is at risk?

The Health Protection Agency (HPA) reports that in 2003 (the last year for which there are available reporting figures) there were 1647 new cases of syphilis diagnosed in the UK, an increase of about 30% on 2002, mainly clustered in London and Manchester, but also affecting Brighton, Edinburgh and Glasgow. Since then, most major cities in the UK have seen and continue to see an increased incidence of syphilis.

About two-thirds of all UK syphilis infections are being reported in gay men, over half of whom are HIV-positive. In contrast, only a minority (7%) of heterosexual men and women diagnosed with syphilis in 2003 were also known to be HIV-positive.

However, the HIV clinicians that *AIDS Treatment Update* spoke to from three major UK cities (Birmingham, Brighton and Manchester) note that although the majority of their HIV-positive patients with recently-acquired syphilis are gay men, they are also sometimes seeing latent (or hidden) syphilis in their male and female heterosexual African patients.

The HPA examined the various factors that put people at highest risk of acquiring syphilis, and found that people who have "high rates of partner change within risk groups and with concurrent HIV infection"¹ are at greatest risk. They also found that the average number of partners of a gay man diagnosed with syphilis in 2003 was one a month. In addition, HIV-positive gay men diagnosed with syphilis were more likely to have sex in public places (e.g. saunas, backrooms) and be older than HIV-negative gay men diagnosed with syphilis.

However, HIV-positive gay men may be being diagnosed with syphilis more often than HIV-negative people due, in part, to the routine

testing of all sexually active HIV-positive people for syphilis at most (but not all) HIV treatment centres. In addition, "I think HIV-positive men are more likely to present to an HIV/GUM clinic with a rash or fever, etc. than those without HIV who would probably go to their GP," says Martin Fisher, acknowledging that HIV/GUM clinics are probably more experienced than GPs at recognising and diagnosing the symptoms of syphilis.

A difficult infection to diagnose

Syphilis can cause a range of symptoms or none at all, but if left untreated can have very serious effects on the brain and the rest of the nervous system (known as *neurosyphilis*). In HIV-positive people, the small sore or ulcer (chancre) associated with initial infection (primary syphilis) can appear as unusual or multiple ulcers, and may be mistaken for an attack of genital herpes, which can happen at the same time. It can also be totally missed by both patient and doctor. Consequently, syphilis is more often diagnosed in HIV-positive people when it has progressed to the often symptomatic secondary stage, when it shows up in blood tests. "The experience in Manchester is that more patients with HIV are likely to be symptom-free with their primary disease and yet present with more florid secondary disease," says Dr Ed Wilkins of North Manchester General Hospital. "In our clinic we have certainly picked up more cases of secondary syphilis due to the characteristic rash affecting the palms and soles," confirms Birmingham's Stephen Taylor.

It can take up to 90 days for the body to develop antibodies to the bacteria that cause syphilis, so a blood test immediately after exposure to syphilis may not detect infection. Some studies have suggested that these tests are not as effective in people with HIV; in fact, some HIV-infected people who do have syphilis may test negative. Since 2002, the HIV Special Interest Group of the British Association of Sexual Health and HIV (BASHH), chaired by Martin Fisher, has recommended that in an outbreak situation, a blood test for syphilis should take place every three months, at the same time as routine CD4 counts and viral

Symptoms of syphilis can include:

- Swollen glands
- Enlarged spleen
- Skin rashes and/or hair loss
- Mouth problems
- Memory problems
- Meningitis
- Double vision (*cranial nerve palsies*)
- Weakness, pain or co-ordination problems in the arms and legs (*myelopathies*)
- Inflammation of the eye (*uveitis*)

loads. This has been the case in Brighton, Birmingham and Manchester, but might not be the case in your clinic - if it isn't, ask why. As a result of regular testing, even where there are no symptoms, cases of syphilis have been found. "Since we have been testing for syphilis regularly we have seen a lot of cases where the change from negative to positive antibody tests is the only indication of recently acquired infection," notes Stephen Taylor. Brighton's Martin Fisher adds: "A significant proportion of our syphilis diagnoses have been picked up by a policy of routine frequent screening in the absence of any symptoms."

Syphilis, CD4 counts and viral loads

There is new evidence that on an individual level, an HIV-positive person with untreated syphilis has a higher HIV viral load, and could therefore be more infectious. A recent study² in the journal *AIDS* found that syphilis can lower CD4 cell counts and raise viral loads in HIV-positive men. Medical records from 52 HIV-positive men with primary or secondary syphilis seen at three clinics in San Francisco and Los Angeles between January 2001 and April 2003 were analysed. More than half (58%) of the men were receiving antiretroviral therapy. On average, HIV viral loads were higher during infection with syphilis than before the infection by 0.22 log, and CD4 cell counts were 62 cells/mm³ lower. After treatment, viral loads

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fell by 0.10 log and CD4 cell counts rose by 33 cells/mm³. The effects of syphilis infection were greatest in men with secondary syphilis and those not receiving antiretroviral therapy.

"We have seen drops in CD4 counts in some patients with secondary syphilis," says Stephen Taylor. "However, this has not so far translated into clinical problems." The Birmingham experience is echoed in Manchester, but not in Brighton. "We haven't encountered this phenomenon," says Martin Fisher. "A look-back at our co-infected cohort, after the *AIDS* paper was published, suggested no apparent significant effect on CD4 or viral load."

Treating syphilis

There is much divided opinion on the treatment of syphilis in HIV-infected people. There is some evidence that, in people with HIV, standard treatment may be inadequate. A number of reports have described cases when ulcers did not heal, the syphilis bacteria were still detectable or neurosyphilis developed after standard therapy had been completed. Because of this, and the concern that neurosyphilis may occur more often in HIV-positive people, a set of treatment guidelines were created in 2002 by the HIV Special Interest Group of the British Association of Sexual Health and HIV (BASHH). However, these differ from guidelines from the US Centres for Disease Control (CDC), the World Health Organisation (WHO) and the International Union against Sexually Transmitted Infections (IUSTI), and not all clinicians in the UK subscribe to them.

The minimum standard of treatment set out by the BASHH guidelines is to treat syphilis with drugs that are strong enough to cause the syphilis bacteria to drop to a level in both the blood and cerebrospinal fluid (CSF, the fluid found in the brain and spinal cord) that will prevent future neurosyphilis. "By treating all stages of syphilis in HIV adequately [with a

regimen that is known to completely kill the bacterium that causes syphilis], future confusion about suboptimal therapy will be avoided should the patient develop neurological or psychiatric symptoms or signs," say the guidelines³. However, some clinicians argue that there is no hard evidence to support these recommendations; rather, they are based on expert opinion. Because of this, and also due in part to patient preference, there is currently great variation in treatments across the country.

The first-line treatment recommended by the BASHH guidelines, *Jenacillin A* (which contains both procaine and benzathine penicillin), requires between 17 and 21 consecutive days of somewhat painful intramuscular injections (usually into the buttock) along with four probenecid tablets a day to keep blood levels of penicillin high.

In contrast, the standard penicillin treatment for HIV-negative people (and given to HIV-positive people with syphilis in some London treatment centres) is one to three intramuscular injections of benzathine penicillin (*Crystapen*) over one to three weeks. However, there have been studies that found that 20 - 25% of people with HIV are not completely cured of syphilis with this treatment⁴.

"Our first-line treatment is to offer all HIV-positive patients daily procaine penicillin," notes Stephen Taylor. "However, many still choose to take weekly benzathene penicillin, despite us explaining the potential risks of treatment failure."

It is also the case that at clinics all over the country some patients are opting not to have injections at all, and choosing oral antibiotics, which are even less likely to completely eradicate the syphilis bacteria in HIV-positive people.

The World Health Organisation's preferred treatment for all forms of syphilis is penicillin injections. Only if someone is truly allergic to

penicillin should other treatments be given. Until recently, the oral antibiotic azithromycin (*Zithromax*) had been used by some doctors to treat syphilis. However, since reports emerged of azithromycin-resistant syphilis in gay men in San Francisco, Baltimore, Seattle and, notably, Dublin, where 88% of samples analysed were found to be resistant to the drug, it is no longer considered to be a viable treatment.

prevention is better than cure, and earlier detection better than later detection

Since there have been no reports of penicillin-resistant syphilis, the first option for patients in Brighton who are allergic to penicillin is to attempt a desensitisation protocol, which requires a day in hospital. "If this is unsuccessful, we use doxycycline (*Vibramycin/ Vibramycin D*)," says Martin Fisher. The same is true in both Birmingham and Manchester: "If there is significant penicillin allergy and we are certain there is no evidence of neurosyphilis, then oral doxycycline for two to four weeks is appropriate, depending on the stage of disease and their HIV status," says Ed Wilkins. However, doxycycline should only be considered in the case of true penicillin allergy, according to the BASHH guidelines, because of the risk that it might not completely eradicate the syphilis bacteria.

Syphilis and the nervous system

Although the bacteria that cause syphilis can infect the cerebrospinal fluid in around 70-80% of cases, doctors are still debating whether HIV-positive patients are more likely to experience syphilis symptoms that affect the brain and the rest of the nervous system.

"Neurosyphilis is more common in HIV-infected persons at all stages of the infection, with several units reporting rates of 21-28%," says Ed Wilkins. "Although we have seen several cases of early neurosyphilis presenting with meningitis," he adds, "we have not seen any late cases in our unit to date. Most patients are presenting with minor symptoms such as headache, and are found to have abnormal CSF findings on lumbar puncture [also known as a spinal tap, an invasive procedure that involves the insertion of a needle into the lower spine]. Others are presenting with more florid features of meningitis, including headache, neck stiffness, and photophobia [sensitivity to light]." Martin Fisher concurs: "We really haven't seen much true late neurosyphilis, apart from the odd case in HIV-uninfected individuals who have never been tested before and who almost certainly acquired their syphilis a long time ago, although we have seen eye and ear involvement during secondary syphilis."

Treatment for neurosyphilis is similar to that for primary and secondary syphilis. However, last year, a study found that HIV-positive people were two-and-a-half times less likely, and those with CD4 cell counts below 200 cells/mm³ almost four times less likely, to completely eradicate the bacteria that cause syphilis from their CSF⁵, when using any one of three recommended treatments for neurosyphilis. However, it remains uncertain whether this reflects a need for more aggressive treatment in neurosyphilis patients with HIV. This is worrying, but, as Martin Fisher says, "hopefully a proactive approach to identifying early syphilis and a concerted effort for optimal therapy will mean that true neurosyphilis will remain relatively rare."

Early detection better, prevention best

HIV disease is not an easy disease to live with, and adding the burden of new infections can make life much harder. At best, the treatment for syphilis is inconvenient and painful; at worst, even when it has been treated there may be long-term repercussions, for example hearing loss, which could be experienced early on in the infection. It's worth remembering that prevention is better than cure, and earlier detection better than later detection.

further reading

The BASHH guidelines for the screening and management of acquired syphilis in HIV-positive people can be downloaded from the BASHH website: http://www.bashh.org/committees/sig/hiv_sig/syphilis_hiv_standards_v8.pdf

NAM has recently produced a patient information booklet on HIV and sex that includes information on all sexually transmitted infections, including syphilis. It can be obtained free of charge from NAM by emailing: info@nam.org.uk

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Paradoxical relationship found between HAART and peripheral neuropathy

A study of 4,400 HIV-positive Americans has found that the incidence of peripheral neuropathy has declined since the introduction of HAART. However, drugs from all the three main classes of antiretrovirals are associated with peripheral neuropathy. The investigators were surprised to find that several protease inhibitors (indinavir, ritonavir, nelfinavir and saquinavir) were revealed by their study to be associated with peripheral neuropathy. They suggest that this could be because they were acting "synergistically" with nucleoside analogues. Paradoxically, however, the investigators found that a year or longer on HAART protected against any further risk of developing peripheral neuropathy, unless full-dose d4T was part of the HAART regimen.

They also found that having a lowest-ever CD4 cell count of below 200 cells/mm³ was associated with an increased incidence of peripheral neuropathy. Having ever had a CD4 count less than 50 cells/mm³ and a first-ever viral load test higher than 10,000 copies/ml made an individual even more likely to experience peripheral neuropathy. Other factors that made HIV-positive people more likely to experience peripheral neuropathy included being older than 40, being white and having diabetes.

Lichtenstein KA et al. Modification of the incidence of drug-associated symmetrical peripheral neuropathy by host and disease factors in the HIV Outpatient Study Cohort. J Infect Dis: 40 (online edition), 2005.

Protease inhibitors can increase cardiovascular disease risk

HIV-positive patients who take a protease inhibitor as part of their HAART regimen have a significantly increased risk of experiencing cardiovascular events like heart and angina attacks, or the need to have coronary bypass surgery, according to new research. However, the risk is still low: of more than 7500 patients in the study, only 127 on HAART experienced cardiovascular events. However 112 of the 127 were taking a protease inhibitor. Nevertheless, the researchers found that traditional risk factors for cardiovascular disease (including current smoking, past smoking, age over 65 years, diabetes, and pre-existing cardiovascular disease) were much more likely than protease inhibitor use to lead to these cardiovascular events. They conclude, however, that people taking protease inhibitors, or those about to start therapy, should have their cardiovascular disease risk assessed.

Iloeje UH et al. Protease inhibitor exposure and the increased risk of cardiovascular disease in HIV-infected patients. HIV Medicine 6: 37 - 44, 2005.

Warning over boosted saquinavir with anti-TB drug

The protease inhibitor, saquinavir (*Invirase/Fortovase*) boosted with ritonavir should not be taken with the anti-tuberculosis

drug rifampicin because of the risks of drug-induced hepatitis, according to a new warning issued by saquinavir's manufacturer, Roche. The drug company is advising anyone taking boosted saquinavir and rifampicin to contact their doctor immediately.

Don't mix atazanavir and antacid drugs

Bristol-Myers Squibb, who produce atazanavir (*Reyataz*), have warned doctors and patients not to combine atazanavir with the antacid drug *Prilosec* (omeprazole). If you have to take *Prilosec* and atazanavir, they recommend that you take them "as far apart as possible, preferably 12 hours apart." The company also reminds patients to be cautious when taking medicines such as cimetidine (*Tagamet*) and ranitidine (*Zantac*) with atazanavir, until further research is carried out.

Shingles virus common in HIV-positive women

Herpes zoster, the virus that causes chickenpox and shingles (a painful rash of small fluid-filled blisters, usually on one side of the trunk of the body), occurs with greater frequency in HIV-positive women than in HIV-negative women, according to a new US study. More information on shingles and its treatments can be found on www.aidsmap.com.

Glesby MJ et al. Herpes zoster in women with and at risk for HIV. J Acquir Immune Defic Syndr 37: 1604 - 1609, 2004.

New HAART 'backbone' news

Since last month's new drugs feature, 'Treatments Outlook 2005', went to press, GlaxoSmithKline's new single-pill combination of abacavir and 3TC (*Kivexa*) has been licensed by the European drug approval authorities and is now available on prescription. The combination of abacavir/3TC has proved to be a

more potent NRTI 'backbone' in children than AZT/3TC, and interim results from the CNA30024 study suggest abacavir/3TC may also be a superior NRTI 'backbone' in adults. Taking *Kivexa* with efavirenz (*Sustiva*) requires just two pills twice a day.

Meanwhile, Gilead's tenofovir (*Viread*) and FTC (emtricitabine, *Emtriva*) combination has been found to be "not inferior" to AZT/3TC, when taken along with efavirenz (*Sustiva*). European marketing approval for Gilead's single-pill combination of tenofovir/FTC, called *Truvada*, is expected within the next few months.

Significant interaction between some African herbal medicines and anti-HIV drugs

Two herbs widely used to treat individuals with HIV in Africa have significant interactions with anti-HIV medications, potentially leading to reduced drug levels, according to a recent test-tube study. Extreme caution should be taken if using herbal medicines in the treatment of HIV, stress the investigators. Next month, *ATU* will examine these and other herbal/HIV drug interactions in more detail.

Mills E et al. Impact of African herbal medicines on antiretroviral metabolism. AIDS 19: 95 - 97, 2005.

Most children thriving on HAART

After four years of HAART, the majority of a small group of Dutch children have continued to thrive, with most achieving and maintaining undetectable viral loads and increased CD4 cell counts. However, the researchers found that as the children got older they were more likely to have detectable virus, possibly because of poorer adherence during puberty.

Fraaij PLA et al. Sustained viral suppression and immune recovery in HIV type 1-infected children after 4 years of Highly Active Antiretroviral Therapy. Clin Inf Dis 40: 604-8, 2005.

news from



nam forum

The March NAM Forum will feature feedback from one of the most important HIV science meetings of the year, the Retroviruses Conference (CROI) held in Boston in late February. It takes place on Monday 21st March from 7pm at the University of London Union, Palms Room, 4th Floor, Malet Street, London, WC1. See www.aidsmap.com/en/events/forums.asp for more details.

hiv & aids treatments directory

Last month NAM published a new edition of the HIV & AIDS Treatments Directory. This comprehensive and clearly written book covers a wide range of topics including the immune system and HIV, starting and changing treatment, and side effects. It also contains A-Z sections on symptoms, illnesses and treatments.

The HIV & AIDS Treatments Directory costs £12.95 to people directly affected by HIV, or £64.95 to professionals or organisations. To order your copy, or for more information, please call NAM on 020 7840 0050 or email info@nam.org.uk.

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For more information, and details of our other publications and services, please contact us, or visit our website, www.aidsmap.com.

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