Although globally at least 170 million people are chronically infected with the hepatitis C virus (HCV), conservative estimates put the number in the UK at 0.33% of the general population, or 200,000, which is three-and-a-half times the number of people in the UK known to be infected with HIV.

The prevalence of HCV is highest in injection drug users, but it is also increasing in HIV-positive men who have sex with men (MSM). At the largest HIV centre in the UK, the Chelsea and Westminster Hospital in London, the prevalence of HIV and HCV co-infection is around seven percent; many of these are MSM who have been infected with HCV sexually.

The continuing outbreak of sexually transmitted hepatitis C infections in MSM in London and Brighton is a concern, because the exact means of transmission are still not yet known, and clear guidelines for the reduction of HCV sexual risk have not been drawn up.

Until then, there is information in this month's lead article on how to protect yourself, as well as the latest news on how to treat HIV/HCV co-infection.
Co-infection with HIV and hepatitis C virus (HCV) is a global problem and one that is of increasing concern in the UK. Because HIV and HCV are transmitted in some similar ways, many people are now infected with both viruses. It is estimated that 15-30% of all HIV-positive individuals also have HCV, but among haemophiliacs and injection drug users, the rate can be as high as 90%. Both the British HIV Association (BHIVA) and the US Public Health Service now recommend that all people with HIV should be regularly screened for hepatitis C.

Sexual transmission

HCV is most commonly transmitted through direct blood-to-blood contact, for example sharing needles to inject drugs. The issue of sexual transmission of HCV, however, remains unresolved. Research indicates that sexual transmission among monogamous heterosexual couples is rare, but the rate of sexual transmission appears to be higher among people with multiple sexual partners, particularly men who have sex with men (MSM). In September 2002, NAM broke the news of an emerging epidemic of apparently sexually transmitted HCV among MSM attending London HIV clinics. The first reports of the outbreak, presented at the April 2003 BHIVA conference, indicated that the new HCV infections were associated with sexually transmitted infections (STIs) including syphilis, non-injection recreational drug use, unprotected anal intercourse and fisting. Further analysis revealed that unprotected receptive anal intercourse and unprotected insertive fisting appeared to be the only common risk factors. Anal sex is a more efficient transmission route than vaginal intercourse, because the lining of the rectum is more prone to damage that could facilitate contact with blood.

A similar outbreak of sexually transmitted HCV in HIV-positive MSM has been taking place in Paris. Between June 2002 and July 2003, after their liver function tests were found to be abnormal, five HIV-positive MSM were found to be acutely infected with HCV, as well as syphilis. "Highly at-risk sexual behaviour, including unprotected anal intercourse and unsafe oral sex, with concomitant syphilis, was found to be the only identifiable important risk factor for transmission of HCV," wrote the authors, leading them to conclude that "sexual transmission may be fuelling a significant increase in HCV seroconversions among HIV-infected men" who are engaging in "highly risky" sex.1

"I think it's too early for anyone to give sexual transmission of HCV a rate, other than to say it's probably higher than previously thought," says Dr Martin Fisher of the Brighton and Sussex University Hospitals, where sexually transmitted HCV has also been seen in HIV-positive MSM. He believes the association between HCV and HIV among MSM may be explained by several factors, including higher HCV viral loads in people with HIV; more concurrent STIs, especially syphilis; generally more "risky" sexual behaviour and more frequent partner change. He also points out that individuals being treated for HIV are more likely to be told about their HCV status and are more likely to receive regular liver function monitoring tests that can provide an early indication of acute hepatitis C.

Treating acute HCV

Because it is typically asymptomatic, HCV
infection is rarely detected during the acute phase (within the first six months of infection). Among co-infected people on HAART who receive regular liver function tests, however, the detection rate is higher. Experts disagree about whether to treat acute HCV. On one hand, treatment is expensive and often causes difficult side-effects, and a proportion of people spontaneously clear HCV without therapy. This rate varies widely among studies, but is commonly estimated at 15-50%. Among patients seen in London HIV clinics, the rate of spontaneous clearance was 40-50%, at the high end of the estimated range. On the other hand, early treatment of acute HCV is highly successful. In a recent prospective study of 44 HCV mono-infected subjects with presumed acute infection, 98% had undetectable HCV viral loads after a 24-week post-treatment follow-up period. At the 2004 BHIVA conference, Sanjay Bhagani of London’s Royal Free Hospital reported that among HIV-positive men whose HCV was detected during the acute phase, the treatment response rate was 66%, and a similar rate, of about 60%, was seen at Chelsea and Westminster Hospital. Because the chances of success are so high, the BHIVA guidelines recommend that early treatment should be considered, but that it is prudent to wait to see if spontaneous clearance occurs.

How HIV and HCV interact
Chronic hepatitis C can lead to severe liver disease, including cirrhosis and hepatocellular carcinoma, usually over a period of 10–40 years. HCV is more likely to become chronic (last more than six months) in people with HIV. Also, HCV-related liver disease is more likely to progress — and to progress more rapidly — in HIV-positive people. At a June 2002 US National Institutes of Health consensus conference on the management of hepatitis C, David Thomas cited a meta-analysis showing that HIV/HCV co-infected people had a two-fold greater risk of progression to cirrhosis and a six-fold greater chance of developing end-stage liver disease than those with HCV alone. A recent British study estimated that the average time from HCV infection to the onset of cirrhosis was 23 years in co-infected people, compared with 32 years in people with HCV alone. However, recent research suggests that these differences in HCV disease progression may not be so stark for co-infected people with well-controlled HIV disease. For example, one study found that co-infected people taking protease inhibitors (PIs) had lower fibrosis scores and lower rates of progression to cirrhosis than those not taking PIs (9% vs. 27% at 25 years).

The issue of whether HCV affects HIV progression is more controversial. Most early co-infection studies showed that HCV infection did not appear to have an impact on HIV disease. In the international CAESAR study, a retrospective analysis of data collected prior to the advent of HAART, median changes in CD4 cell counts and the rate of progression to new AIDS-defining illnesses were similar in co-infected participants and those with HIV alone (11% vs 13%, respectively). The researchers concluded, “HCV has no significant impact on HIV disease progression.” But other research supports the opposite conclusion. In the Swiss HIV Cohort Study, co-infection was associated with greater HIV disease progression and higher mortality. The difference in study results may be due to the fact that both HIV and HCV progress so slowly. It may be that the case that any deleterious effects of HCV on HIV disease progression only become apparent after a person has been co-infected for many years or even decades. In addition, several studies have shown that co-infection appears to impair immune system recovery after starting HAART. For example, a Canadian study found that co-infected patients gained an average of 50 CD4 cells after 18 months on anti-HIV therapy, compared with an average gain of 190 cells in those with HIV alone.

Which to treat first?
There remains some disagreement about whether HIV or HCV should be treated first in co-infected individuals. It is often recommended that co-infected patients begin HIV therapy first, since once HIV is under control and CD4 cell counts rise, people respond better to interferon and are better able to tolerate the side-effects of HCV therapy. On the other hand, in people with mild HIV disease but progressive liver disease, it may be beneficial to treat HCV first. Furthermore, initial

Not my genotype
HCV has six genotypes, further divided into subtypes. Because they respond differently to interferon-based therapy, it is useful to break study results down by genotype. Genotype 1 is most common in Europe and the US — accounting for some 60-75% of cases — and is also the most difficult to treat. Genotypes 2 and 3 respond better to treatment. In most studies, response rates for genotypes 2 and 3 are at least twice as high as those for genotype 1. Relatively little research has been done on genotype 4, which is uncommon in Europe and the US. This genotype has traditionally been considered difficult to treat and is sometimes grouped with genotype 1 in studies, but recent research suggests genotype 4 may be easier to treat than previously believed.

What’s the difference between pegylated interferons?
Pegasys and Peg-Intron both include polyethylene glycol, which makes interferon last longer in the body. Pegasys comes pre-mixed and is administered at a standard dose, while Peg-Intron must be reconstituted and is dosed based on weight. In one small Italian study, individuals with genotype 1 HCV appeared to respond better to Peg-Intron, while those with more advanced liver disease seemed to respond better to Pegasys. An American study is currently underway to compare the two formulations head-to-head in nearly 3,000 HIV-negative individuals.
HCV therapy may improve patients’ ability to later tolerate HIV medications. An Italian study found that use of HCV therapy for six months prior to starting HAART reduced the chances that co-infected patients would discontinue HIV therapy due to drug-related liver toxicity. An international panel of experts recommended that co-infected patients starting HCV treatment should ideally have a CD4 cell count above 350 cells/mm³. HCV treatment is not recommended for those with CD4 cell counts below 200 cells/mm³ due to the low response rate when immune function is heavily compromised.

Comparing apricots to oranges

Treatment for hepatitis C has improved dramatically in recent years, first with the advent of standard interferon plus ribavirin combination therapy, and then in 2003 with the approval of a longer-lasting and more effective pegylated form of interferon (Schering-Plough’s Peg-Intron and Roche’s Pegasys). Overall, studies show that combination HCV therapy works better than interferon monotherapy, and pegylated interferon is more effective than standard interferon. But with all these regimens, response rates are lower in co-infected individuals than in those with HCV alone. In people with HCV mono-infection, sustained virological response (SVR; a continued undetectable HCV RNA six months after the end of treatment) rates using pegylated interferon plus ribavirin are around 50% overall, about 80% for HCV genotypes 2 and 3, and about 45% for genotype 1, which is harder to treat (see ‘Not my genotype’).

Results from four major studies of HCV treatment in co-infected patients have been reported this year, with conflicting results. The APRICOT study included 860 HIV/HCV-co-infected participants (about 60% with genotype 1) in 19 countries who were receiving HCV treatment for the first time. Participants, of whom about 85% were on HAART, were randomly assigned to receive thrice-weekly standard interferon-alfa-2a plus 800mcg ribavirin daily, 180mcg Pegasys once weekly plus placebo, or 180mcg Pegasys plus 800mcg ribavirin. After 48 weeks, 40% of those treated with pegylated interferon/ribavirin achieved SVR, compared with 20% of those receiving pegylated interferon monotherapy, and 12% of those receiving standard interferon/ribavirin. Individuals co-infected with genotypes 2 or 3 did much better, with SVR rates of 62%, 36%, and 20% respectively, while those with genotype 1 only achieved 29%, 14%, and 7% SVR respectively. In terms of safety and tolerability, 39% in the standard interferon/ribavirin arm, 31% in the pegylated interferon monotherapy group, and 25% in the pegylated interferon/ribavirin arm discontinued treatment. The rates of serious treatment-related adverse events were 5%, 10%, and 8% respectively.

US ACTG 5071 compared standard vs. pegylated interferon (Pegasys) plus ribavirin in 133 HIV/HCV-co-infected patients (78% with genotype 1) who were randomly assigned to receive either standard interferon-alfa-2a three times weekly or 180mcg Pegasys once weekly for 48 weeks. Both arms received daily ribavirin in escalating doses from 600mg to 1000mg. Here, too, about 86% were also receiving HAART. By 72 weeks, overall SVR rates were 27% in the pegylated interferon arm and 12% in the standard interferon arm. Among individuals with genotype 2 or 3, SVR rates were 73% and 33%, respectively. For those with genotype 1, the corresponding rates were 14% and 6%. Both regimens were generally well tolerated, with 12% in both arms prematurely discontinuing therapy.

The French RIBAVIC trial also compared standard and pegylated interferon, but used Peg-Intron instead of Pegasys. The 412 participants (58% with genotype 1 or 4) were randomly assigned to receive standard interferon three times weekly or 1.5 mcg/kg Peg-Intron once weekly, both with 800mg ribavirin daily. No information was provided regarding how many participants were also on HAART. Overall, at 72 weeks, 18% of participants receiving standard interferon achieved SVR, compared with 26% of those on pegylated interferon. In the pegylated interferon arm, individuals with genotypes 1 or 4 had an SVR rate of 11%, compared with 43% for genotypes 2 or 3 in terms of tolerability, 42% discontinued therapy in both arms.

Most recently, a Spanish study reported the highest SVR rates yet seen in a co-infected population; response rates were particularly...
impressive for individuals with genotype 1. In this study, 95 co-infected patients (63% with genotype 1 or 4, 94% on HAART) received either standard interferon or Peg-Intron plus daily ribavirin. Individuals with genotypes 1 or 4 were treated for 48 weeks, while those with genotypes 2 or 3 received therapy for 24 weeks. The overall SVR rates were 44% for pegylated interferon and 21% for standard interferon. Among those with genotypes 2 or 3, the SVR rates were 53% and 47%, respectively. The corresponding rates for genotypes 1 or 4 were 38% and 7%. Side-effect rates were similar in both arms; nine individuals in the pegylated interferon arm and six in the standard interferon arm discontinued due to side-effects.

It is currently unclear why the SVR rates were different in these four studies. While a good end-of-treatment response rate was seen in ACTG 5071, the relapse rate was high for genotype 1 patients, perhaps because the study started patients at a lower initial dosage of ribavirin. In addition, ACTG 5071 included more people of African heritage (about 33%) than APRICOT (about 10%), who respond less well to interferon-based therapy. RIBAVIC included patients with more advanced liver damage, and rates of severe adverse events and treatment discontinuation were considerably higher. The studies with the lowest and highest SVR rates used Peg-Intron, while the other two used Pegasys.

What next?
Given the side-effects and the cost of therapy, most experts believe it should be reserved for patients most likely to benefit – that is, those with progressive liver disease. Because liver disease can progress faster in people with HIV, many experts believe co-infected individuals should receive more frequent biopsies (every 2-3 years) to monitor liver damage. BHIVA recommends that people with co-infection consider early treatment. For a full discussion of the BHIVA HCV/HIV co-infection guidelines, see the June 2003 issue (126) of ATU, available online at: http://www.aidsmap.com/en/docs/pdf/atu126.pdf

Although co-infection undoubtedly presents challenges, most people with HIV and HCV can be successfully treated for both diseases. In fact, results from a recent Thai study indicate that co-infected people can do just as well on HAART as individuals with HIV alone. To achieve an optimal outcome, co-infected individuals ideally should be under the care of a physician or team that has experience with both diseases. Regular monitoring (including liver function tests and blood cell counts) and assistance in managing side-effects are keys to successful treatment.

Improvements in HCV therapy are continuing apace. New classes of drugs are under study, including HCV protease and polymerase inhibitors. Numerous studies show that even when therapy does not completely clear HCV, it can still help prevent, stabilise, or even improve liver fibrosis, and research is underway to determine whether long-term low-dose interferon can retard the development of liver damage. These advances offer the prospect that HCV – like HIV – can become a chronic, manageable illness.

References
children and hiv

why providing treatment and care for HIV-positive children is far from child's play,
by edwin j bernard

The treatment and management of HIV-positive infants, children and adolescents in the UK is complex. Paediatric HIV research still lags behind adult HIV research, and although children face the same treatment issues – potency, adherence, resistance, lipodystrophy and other side-effects – they are not just 'small adults'. Paediatricians treating HIV-positive children have to deal with issues unique to them; issues such as disclosure (both to and by the child), schooling and sexual development. Paediatric care is further complicated by the fact that drug companies have limited incentives to develop paediatric formulations of their antiretroviral drugs.

It is, therefore, truly remarkable that the state of paediatric HIV care is as good as it is in the UK, and that the marked decrease in illness and death seen in adults in the post-HAART era has been accompanied by similar results in children. Last year, Dr Di Gibb and colleagues published important results from the Collaborative HIV in Paediatric Study (CHIPS) cohort in the British Medical Journal. Around 75% of HIV-positive children in the UK and Ireland are being followed in centres participating in the CHIPS cohort, in which more detailed information on antiretroviral history, and clinical, immunological and virological status are collected annually. Additionally, details of service use, including hospital admissions, are also collated. The study reported that child mortality reduced from 9.3 per 100 child-years in 1996 to 2.0 in 2001-2 and hospital admission rates declined by 80%. The declines occurred in 1997 and paralleled the introduction and increased use of HAART in children.

Earlier this year, the latest treatment guidelines from the Paediatric European Network for Treatments of AIDS (PENTA) were published. The PENTA guidelines are endorsed by the Children's HIV Association (CHIVA), and are the paediatric equivalent of the adult BHIVA treatment guidelines. Later this month, at the CHIVA meeting in London, a draft report of the Children with HIV National Network (CHINN) review will outline the state of national paediatric HIV treatment, and recommend the development of regional networks in order to reduce the likelihood of postcode lottery-style variations in care throughout England, Scotland and Wales.

How many children?
There are currently around 1000 HIV-positive infants, children and adolescents under paediatric care in the UK; around two-thirds of them living in Greater London. *Thanks to the...
When to start therapy

*The concept of the PENTA guidelines is to review the state of the evidence, look at where future trials could be performed, and provide better guidelines for drug dosing,* says Dr Sharland. There have been few major advances in paediatric HIV management in the two years since the first PENTA guidelines were produced. Nevertheless, there is better information available now on the best time to start therapy. This comes primarily from a recent meta-analysis that identified CD4 percentage and viral load levels as independent predictors of clinical progression. The data has been translated into an online risk calculator which estimates the 6- and 12-month risk of progression to AIDS and death in the absence of therapy, based on the child’s age and either CD4 percentage or viral load.

Just as in adults, there has been a move from the hit-hard, hit-early treatment tactics pioneered in the US, to a more conservative approach. *It is important not to put children on treatment who do not need it,* says Dr Sharland, who adds that there needs to be a balance between treatment and quality of life.

The exception is in the treatment of infants. For example, a recent study found that starting antiretroviral therapy at younger ages and before severe immune suppression occurs appears to promote better CD4 cell recovery. Consequently, the PENTA guidelines say, *Many expert clinicians feel that the risk of progression is so high in infants that they would prefer to offer parents the option of treating (both symptomatic and) asymptomatic children identified in the first year of life.*

What to take

Dr Sharland points out, wryly, that although those not involved in paediatrics might be surprised to discover that there are still very limited data on how to use efavirenz, tenofovir, saquinavir, fosamprenavir, atazanavir, tipranavir and T-20 in children and infants, he isn’t surprised at all. *As always, we get drugs late,* he says. *And paediatric formulations lag behind adult drug availability, even in drugs that are well established in adults, like tenofovir and atazanavir. It’s a recurrent problem.*

Certain activists have dubbed children with HIV ‘therapeutic orphans’, and the issue of paediatric access to adult medicines has become a political issue. Currently, UK HIV-infected infants and children have only 12 of the 19 adult-approved antiretroviral armamentarium available to them, due to lack of dosage information or a paediatric formulation. In April 2000, the Food and Drug Administration (FDA) – who govern the approval of all US drugs – had implemented the ‘Pediatric Rule’, which forced drug manufacturers to provide paediatric...
data as a condition of approval of a new pharmaceutical product. However, a US Federal court decided in October 2002 that the FDA is unable to legally enforce the Pediatric Rule, which, notes Dr Sharland, "took paediatric pharmacy back to the Stone Age."

Fortunately, PENTA and its US counterpart, the Pediatric AIDS Clinical Trials Group (PACTG), are trying to rectify this. PENTA is running many trials in children as well as collaborating with the PACTG on the groundbreaking PENPACT 1. Currently there are limited data comparing the efficacy and tolerability of protease inhibitor (PI)-based therapy with non-nucleoside (NNRTI)-based therapy in children, as well as when and what to change to when first-line therapy fails, and so the currently-recruiting PENPACT 1 trial should provide many of the answers. This randomised trial compares starting with PI-based HAART versus NNRTI-based HAART, as well as trying to define at what HIV RNA viral load level one should change to a new regimen. The primary endpoint will be HIV viral load four years after randomisation.

### Summary of Penta Recommendations on Which HAART Combination to Start With

<table>
<thead>
<tr>
<th>Infants</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>either</td>
<td></td>
</tr>
<tr>
<td>2 NRTI(^1) + 1 PI (Kaletra or nelfinavir)</td>
<td>2 NRTI(^1) + 1 PI (Kaletra or nelfinavir)</td>
</tr>
<tr>
<td>or 2 NRTI(^1) + 1 NNRTI (nevirapine)</td>
<td>or 2 NRTI(^1) + 1 NNRTI (efavirenz or nevirapine(^2))</td>
</tr>
</tbody>
</table>

\(^1\)Dual NRTI combination recommended: AZT + 3TC or ddI; ddI + 3TC; abacavir + 3TC. d4T is not recommended as first-line therapy.

\(^2\)Nevirapine would be the preferred NNRTI for children under three years of age.

### Toxicity, Adherence & Resistance

One of the changes in the latest PENTA guidelines is an increased recognition of the toxicity associated with antiretroviral use. Lipodystrophy, in particular, "is of great concern", the guidelines note, "because of its potential metabolic consequences and the impact that body changes may have on self-image, leading to poor adherence and treatment failure." Consequently, they recommend that paediatricians perform a clinical examination for lipodystrophy every three months. Since there are fewer data on lipodystrophy in children than in adults, a PENPACT 1 substudy will look prospectively at the development of lipodystrophy and metabolic abnormalities in children.

The guidelines also place a greater emphasis on adherence monitoring and an increased awareness of the problem of drug resistance. However, interventions to improve adherence and tackle drug resistance are limited, again, because "the evidence base is almost zero," says Dr Sharland, "just a few scanty papers and abstracts. There is a lot more to be done and learned about adherence to one of the most complicated oral drug regimens we’ve ever used in paediatric practice. In the past, there has been a lot of focus on the efficacy of drugs, rather than a focus on actually getting the children to take them. However, the pendulum is swinging and I think we’re learning that adherence is very complicated and extremely
Paediatric HIV networks

Mike Sharland is also passionately involved in creating a series of co-operative paediatric HIV networks throughout London, and, eventually, the UK. "It's all about improving clinical care," he says with great enthusiasm, explaining that until recently, with over 20 different providers of paediatric services in London alone, "there was a certain variation in the care provided across London. The concept of networks is to try to smooth out that variation."

By focusing on providing hard data, publishing guidelines, and performing audits and regular training, the London network is "pretty much implemented now," says Dr Sharland, who took responsibility for co-ordinating a February 2004 report from the London HIV Consortium Paediatric Subgroup, entitled 'Developing Clinical Networks for Paediatric HIV Treatment and Care in London'.

Following an increase in the dispersal of asylum seekers throughout the UK, as well as the voluntary movement of families from high-prevalence countries to find work around the UK, there are now a considerable number of children with HIV being brought up outside London, with more than 300 children in paediatric care (compared with around 200 in each of three London network areas). "Many children are turning up in towns and cities where there have been few, if any, paediatric HIV services or experience," says Sharland. "For example, the paediatric HIV population of Birmingham has increased from two-three to 40-50 in the past few years. Paediatricians are, for the most part, working independently, and currently have no clear guidelines or structure for care."

Enter the CHINN (Children with HIV National Network) review, funded by the Department of Health, and co-ordinated by paediatric HIV nurse consultant, Sheila Donaghy, also of St. George's Hospital. Donaghy is currently midway through the CHINN review, and a report of her first draft will be presented at the CHIVA meeting. "The aim," says Dr Sharland, "is to develop regional family centres of HIV care in the UK because it's inappropriate and impossible for all these children to come to London for their care."

The proposed six regions are: Southwest, Northwest, Northeast, Midlands, Scotland, and Wales, with centres in the Southeast, like Brighton and Southampton, linked directly to a London centre. "The idea is that local paediatricians link into their local centre for advice and discussion, essentially sharing care," explains Dr Sharland. "Each of those local centres will then link in with one of the London centres."

"The hope is that nobody works in isolation anymore, that all clinicians have clear guidelines, and know exactly who to ring if they have any questions. The ultimate goal, however," an upbeat Sharland concludes, "is to 'skill people up' so they don't need to ask questions."

Streets ahead

HIV paediatrics in the UK may well be slightly behind when it comes to the timely availability of antiretroviral therapy for children with HIV. However, the enthusiasm, commitment and organisation of HIV paediatricians such as Drs Gibb and Sharland appear to be second to none, and with the establishment of the London and national networks, in collaboration with the NSPCC, CHIPS and PENTA, they may well be streets ahead of their adult equivalents in organisational terms.
Viral load below 20,000 copies/ml still confers survival benefit

Individuals with persistent, but modest HIV viral load (between 400 copies/ml and 20,000 copies/ml) are no more likely to die or develop new AIDS-defining illnesses than those with a viral load below 400 copies/ml, according to a US study on the effects of HAART in the Collaborations in HIV Outcomes Research (CHORUS) cohort. The study’s investigators believe that their findings demonstrate that efforts to control viral load, even when an individual is unable to achieve undetectable levels, can still provide important clinical and immunologic benefits, while also providing important new information for doctors and patients attempting to develop a treatment strategy in the face of continued HIV replication.


Nelfinavir: new issues for women

Two recent studies have found that the protease inhibitor nelfinavir (Viracept) may be problematic for pregnant women, and women who want to avoid pregnancy. A US study has found that nelfinavir reduces levels of oral contraceptives, and that women taking nelfinavir-containing HAART were significantly more likely to experience contraceptive failure and become pregnant than women taking HAART not containing nelfinavir. The results of this study were consistent with known pharmacological interactions between protease inhibitors and oral contraceptives: nelfinavir reduces levels of norethindrone by 18% and levels of ethinyl estradiol by 47%. "Women taking nelfinavir should use additional or alternative contraceptive methods," like condoms, the researchers conclude.

In another recent study, Dutch investigators found that plasma levels of nelfinavir were 34% lower in HIV-positive pregnant women than in HIV-positive women taking the drug who were not pregnant. However, all but one of the pregnant women maintained an undetectable viral load, and none of the women’s babies were infected with HIV. The investigators speculate that low concentrations of the drug during pregnancy could be due to the faster metabolism of nelfinavir by the liver, since production of CYP3A4, which plays a key role in processing the protease inhibitor, is increased during pregnancy. However, plasma concentration ratios of nelfinavir can be increased by taking nelfinavir with food, or failing that, by increasing the dose of the drug from 1250mg to 1500mg twice-daily, although that does mean six pills twice a day.

HAART increases stroke risk by 26% per year

More data from the landmark DAD (Data collection on Adverse event of anti-HIV Drugs) trial, which last year reported a 26% increased risk in the frequency of heart attacks per year of antiretroviral drug exposure, has found that HAART also increases the risk of stroke as well as other cardiovascular or cerebrovascular events - including the likelihood of bypass surgery - by the same amount. This means that after three years on HAART a non-smoker would increase their risk of a heart attack or stroke to that of an HIV-negative smoker. Frustratingly, however, the DAD study does not differentiate between different classes of antiretrovirals and their relative risk, since there have not been enough clinical endpoints for the investigators to be absolutely certain of the significance of their interpretations. These analyses are planned for the future.


New UK HIV diagnoses in 2003: a tale of two sex-driven epidemics

Near-complete numbers of new HIV UK diagnoses for 2003 were released by the Health Protection Agency (HPA) last week, and reveal that with over 90% of reports in, there were a record 6606 new HIV diagnoses last year. This confirms the HPA’s earlier estimate of over 7000 new HIV diagnoses in 2003 once all reports are in. Although only 26% of new HIV infections were diagnosed in men who have sex with men (MSM), they remain the group most at risk of acquiring HIV within the UK. This coincides with an increase in the reporting of riskier behaviours and other sexually transmitted infections (STIs), including syphilis and gonorrhoea. For new diagnoses among MSM made in 2003, where probable country of infection was known (950 of 1,735), 84% (796) were probably infected within the UK.

However, since 1999, the number of HIV infections diagnosed in heterosexual men and women has exceeded those in MSM. Although the increase in heterosexually-acquired HIV diagnoses has been substantial, the majority of these infections were acquired abroad. For diagnoses in heterosexual men and women made in 2003, 81% (2727/3359) were infected in African countries and 8.7% (291/3359) in other parts of the world than the UK and Africa. In addition, numbers of individuals infected through heterosexual contact within the UK, without evidence of a ‘high risk’ partner, have been increasing gradually, and in 2003 represented 10% (341/3359) of new diagnoses in heterosexual men and women where probable country of infection was known.


Viral load one month after starting HAART predicts six month outcome

Measuring viral load a month after starting highly-active antiretroviral therapy (HAART) can strongly predict which individuals will have a viral load below 50 copies/ml after six months of treatment, according to a joint UK and German study. The findings underline the importance of the British HIV Association’s recommendation that patients should receive a viral load test one month after starting treatment.


New competition for Combivir?

Preliminary results from a Gilead study comparing tenofovir/FTC with AZT/3TC (Combivir), both taken with efavirenz (Sustiva), suggests more antiretroviral-naïve patients reached and kept a viral load below 400 copies/ml in the tenofovir/FTC arm, boding well for the once-daily tenofovir/FTC pill, Truvada, now approved in the US, and due here early in 2005.

News from nam

atu research

Data from our in-depth research of AIDS Treatment Update readers are being collated as we go to press this month. Thank you to those who took part in this research. We will be analysing the results alongside feedback from the Readers’ Survey, and other feedback, which will help focus the changes needed to keep ATU an important, relevant, independent, cutting-edge and accessible source of HIV treatment information for all current, and future, readers.

nam forum

nam’s October forum will focus on issues around sex, and sexual problems. The forum will take place on Monday 25th October and will feature Dr Jose (Pepe) Catalan of London’s Chelsea and Westminster Hospital. Dr Catalan was interviewed on this subject in a recent ATU, and is one of the UK’s most knowledgeable experts in this area. The forum will start at 7pm at the University of London Union, Palms Room, 4th Floor, Malet Street, London, WC1. See http://www.aidsmap.com/en/events/forums.asp for more details.

next atu

The November issue of AIDS Treatment Update will feature an in-depth analysis of all the treatment simplification options reported on this year at both major conferences in the medical literature.