

# aids treatment update

## the sexual transmission of hepatitis C: has the risk been underestimated?

Last month the Government published its *Hepatitis C Strategy for England*, a plan intended to raise the profile of this blood-borne virus amongst health professionals and those at risk, and to improve NHS prevention, diagnosis and treatment facilities. The threat to both individual and public health is significant: it's estimated around 200,000 people are infected in England alone, and Scottish figures indicate that over 13,000 diagnoses have already been made there. In short, though hepatitis C (HCV) was identified several years later than HIV, the numbers of people affected in the UK are comparable, and in terms of undiagnosed cases, many more Britons have yet to discover they have HCV.

When it comes to public profile, service provision and access to *licensed* treatments, the association swiftly ends. In relation to HCV therapy, not only is the Postcode Lottery alive and well, but has been given an improved prognosis since the allocation of health commissioning responsibility to Primary Care Trusts – in many regions you (and your doctor) may struggle to identify your HCV treatment commissioner.

If you find them before we do, you might consider passing them a copy of the article over the page. Though the Government *Hepatitis C Strategy* rightly concentrates on improving drugs education and services (people who inject drugs are by far the worst hit by HCV), we've been aware of rumbling concern over the spread of HCV through sex – particularly amongst gay men – for some time. In our lead article this month, Edwin J Bernard speaks to two British doctors who have seen a rising number of new cases of HCV in people attending their HIV clinics. They are in no doubt that these individuals acquired HCV not through injecting drugs, but through their sexual behaviour.

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# sexual transmission of hep C

2 as uk doctors admit concern about rising numbers of people contracting hepatitis C through sex, we ask who is most at risk and how people with HIV may be affected by edwin j bernard

Coinfection with HIV and the hepatitis C virus (HCV) has increased in the past few years, as reported in the May 2002 issue of *AIDS Treatment Update*. Until very recently, the major risk factors for acquiring HCV were thought to be injection drug use (IDU), haemophilia and blood transfusion; sexual transmission was considered to be theoretical but insignificant.

Now, however, there is new evidence that sexual transmission of HCV is on the rise, particularly amongst gay men with HIV. Recent studies suggest that not only is sexual transmission of HCV possible, but that being infected with HIV, and/or having certain kinds of sex, are major risk factors for transmission of the virus.

In June 2002, the US government's National Institutes of Health issued a consensus statement by an independent panel of clinicians, researchers and community groups with expert knowledge of HCV. For the first time, they added sexual transmission to the list of exposure risks for HCV. Although they continued to say that the risk was extremely low for heterosexual monogamous couples, they added that "HCV-infected individuals with multiple sexual partners or in short-term relationships should be advised to use condoms to prevent transmission of HCV and other sexually transmitted diseases."<sup>1</sup>

Last month the UK Department of Health issued their *Hepatitis C Strategy for England*. The approach of the DoH is similar to that of their US equivalent. "There is evidence that both homosexual and heterosexual transmission of hepatitis C may occasionally

occur," the report states, before offering the somewhat contradictory advice to people with HCV to *discuss* the use of condoms with regular partners and *practice safer sex* with new partners.

Two large HIV clinics in London have seen an increase in new HCV infections over the past six months, causing concern that the risks of sexual transmission for gay men with HIV in particular have been underplayed. Is it possible that just like the delay that occurred over public health messages about the current syphilis outbreak amongst gay men, not enough people are taking the sexual HCV threat seriously? "I hope it isn't going to take us two years to realise that yes, it's here, and it's being sexually transmitted," says Dr. Sanjay Bhagani, specialist registrar in infectious diseases and HIV at London's Royal Free Hospital.

## Early evidence on HCV transmission

HCV was first identified in 1989 and although studies as far back as 1993 pointed to sexual transmission as a probable risk factor amongst gay men, the information did not translate into a public health message. This is likely because many more studies showed that the risk of sexual transmission was seen to be extremely low in the general population, and there may also have been an assumption that safer sex messages relating to HIV would also implicitly cover HCV transmission.

In these earlier studies, published between 1993-1996, data on three different cohorts of gay men without a history of IDU in the US showed that between 3-5% were infected with

HCV. Osmond found that HCV infection was marginally associated with more than 50 sex partners a year; or more than 25 oral receptive partners; or more than 25 anal receptive partners<sup>2</sup>. Buchbinder found that sexual risk factors for HCV infection included receptive anal intercourse, fisting, having a sexual partner with a history of IDU, a self-reported history of genital herpes and being HIV-positive<sup>3</sup>. Ndimbie found that whilst the number of sexual partners was not a significant risk factor, a history of syphilis, rectal gonorrhoea, insertive anal intercourse with ejaculation, and douche or enema use before anal receptive intercourse were statistically significant sexual risk factors<sup>4</sup>.

When Rooney<sup>5</sup> undertook a 1998 review of the literature into sexual transmission of HCV amongst the general population, he concluded that there was "a small but definite risk of sexual transmission of hepatitis C" of between 1-3%. Rooney did not look at the difference between heterosexual and gay sex transmission risks, however.

Since 1998, there have been many studies looking for a heterosexual transmission risk of HCV in monogamous couples that have found there is little to none. For example, Sciacca's Turin Study found that only three out of 196 long-term heterosexual spouses were infected with the same HCV viral genotype, and concluded that while sexual transmission of HCV was a possibility, "this method of transmission does not appear to be important if compared with that of other viruses (hepatitis B virus and HIV)<sup>6</sup>." Similar conclusions were drawn by Garcia<sup>7</sup> at the recent International AIDS Conference in Barcelona.

However, not all heterosexual transmission studies have come to the same conclusion, particularly those that include casual partners. Tenagan looked at the sexual partners of HCV-positive blood donors in Brazil from January 1992 to July 1996 and found that 11.76% were HCV-positive. Sexually transmitted infections (STIs) were found to be more prevalent among partners with HCV infection, suggesting that the high prevalence of HCV infection seen here may be attributed at least

partially to sexual transmission because they put themselves at risk of other STIs.

## HCV, HIV and sex

Though it has been suspected since 1994 that coinfection with HIV/HCV contributed to a higher risk of HCV transmission than being singularly infected with HCV (since HCV viral load was shown to be significantly higher in those coinfecting with HIV/HCV<sup>8</sup>), it was only towards the end of last year that a study confirmed that HIV/HCV coinfection magnified the risk of sexual transmission of HCV to both heterosexuals and gay men.

Researchers from Naples found that HCV infection was almost three times higher in those who were HIV-positive compared to HIV-negative controls (15.1% versus 5.2%). Significantly, 18.7% of those who had regular heterosexual or gay sex with an HIV-positive partner were HCV-positive, compared with only 1.6% for partners of HIV-negative controls. The authors concluded therefore, that "in subjects who had only a sexual risk factor for parenterally transmitted infections, HIV may enhance the sexual transmission of HCV<sup>9</sup>."

At the same time, another study found that HIV, certain sexual acts, and multiple sexual partners, correlated with a higher risk of sexually transmitted HCV amongst gay men. Here, 662 HIV-positive and HIV-negative men in the Vancouver Lymphadenopathy Cohort were investigated for HCV. 8.8% of HIV-positive men were HCV-positive compared with 2.6% of the HIV-negative men. Almost half (49%) of HCV-positive men reported never injecting drugs. The HCV-positive men were more likely to report the following: more than 20 sexual partners in the last year; more than 100 lifetime partners; practicing insertive fisting; practicing receptive anal sex, and practicing insertive oral-anal sex (rimming). A comparison of the non-IDU HCV-positive group with the non-IDU HCV-negative group found insertive rimming and insertive fisting associated with HCV infection. Multivariate analysis showed three factors independently associated with HCV infection: injecting drug use; HIV infection and more than 20 male partners in the last year<sup>10</sup>.

## glossary

See also pages 7, 9, 11  
**acute** A recently developed condition.

**antibody** Protein substance produced by the immune system in response to an organism.

**chronic** A long-term condition.

**cirrhosis/fibrosis** Scarring of the liver.

**cohort** A group of people who share at least one common

factor (e.g. being HIV-positive) and are studied over a period of time.

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

**hepatitis** Inflammation of the liver.

**seroconversion** The time at which a person's antibody status changes from negative to positive.

**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.

## coinfection seminars

The Haemophilia Society is organising two more HIV/HCV coinfection information evenings, in Glasgow on 30 October and Liverpool on 26 November. For details contact Babs Evans on 0800 018 6068 or via [babs@haemophilia.org.uk](mailto:babs@haemophilia.org.uk)

## more on treatment of HCV

Treatment for HCV and HCV/HIV coinfection was last covered in *ATU* issue 113. You can read more on NAM's website [aidsmap.com](http://aidsmap.com).



## sexual transmission of hep C continued

Three further studies confirming HIV as a cofactor for sexual HCV infection were reported at the recent International AIDS Conference in Barcelona. Risbud from India found that HIV infection was independently associated with more than a three-fold increased likelihood of HCV infection amongst STI clinic attendees<sup>11</sup>. Mendes-Correa from Brazil found that independent risk factors of HIV/HCV co-infection amongst male and female AIDS Outpatient Clinic attendees were (highest risk first): injecting drug use; a sexual partner with past history of chronic hepatic disease; a sexual partner who had received a transfusion; age above 30; anal intercourse; use of inhaled illicit drugs; and a history of an IDU sexual partner<sup>12</sup>. Finally, Abrescia from Italy found that 20% of women who had been infected with HIV by HIV/HCV coinfecting partners were also infected with HCV, leading the co-authors to conclude: "It's probable that HIV and its related opportunistic infections of the female genital tract could strongly facilitate HCV sexual transmission"<sup>13</sup>.

### Increasing UK cases

Mark Nelson, consultant in HIV at the Chelsea & Westminster Hospital, London, has been convinced for a long time that HCV is sexually transmitted. "What we've seen recently is an outbreak of syphilis (amongst gay men)," says Dr. Nelson, who also runs the HIV/HCV coinfection clinic, "and with the outbreak, what we've noted in the HIV clinic are small but increasing numbers of people seroconverting for HCV. Approximately a quarter of those have picked up syphilis at the same time, suggesting that HCV is sexually transmitted."

Dr. Sanjay Bhagani has been running the Royal Free's HIV/HCV coinfection clinic since last October. "In the last six months we have picked up six patients who have seroconverted for HCV," he says. "We've been through all of

them with a fine tooth comb in terms of risk factors and it seems that they have none of the other risk factors for HCV transmission," leading him to conclude that sexual transmission was the most likely route. "Two have an HCV-positive partner, and one had a gonorrhoea coinfection," he adds, "leaving me in no doubt that these were due to sexual transmission."

Both clinics only found these new HCV infections because of abnormal liver function tests (LFTs) since most acute HCV infections are clinically asymptomatic. "If we weren't doing the LFTs we wouldn't pick up (the acute infections)," says Dr. Nelson. This is because although most HIV clinics test for HCV during intake, regular screening is not commonplace. "Part of the problem is, once you've been tested you tend not to test again, so we're now promoting yearly testing for HCV," he adds.

"At the Royal Free we screen first for antibodies and do LFTs," says Dr. Bhagani. "If you have persistently abnormal LFTs, you're antibody negative for HCV, and your index of suspicion is high, we do an HCV PCR [viral load test]."

The most common way to measure HCV infection is the ELISA-2 anti-HCV (antibody) test. However, HIV infection can make the diagnosis of HCV more difficult since in a small minority, HCV infection may not show up on antibody tests in HIV-infected people. Last year, Bonacini found that 5.5% of people with HIV tested negative for HCV antibodies but were positive on the *Amplacor*<sup>TM</sup> PCR test for HCV viral load<sup>14</sup>.

Dr. Nelson estimates that around 7% of HIV-positive patients at Chelsea & Westminster are coinfecting with HCV. "A lot of them have none of the major risk factors of IDU or blood transfusion," he says. "Clearly a lot of people have tattoos, so you can't say it didn't come

from tattooing, but when we screened individuals in the GU clinic, a history of tattooing was not a significant risk factor for HCV. And of course you can't exclude toothbrushes and razors. But I think the majority is sexually transmitted."

"There is a strong biological probability as to why coinfecting men should be at higher risk of transmitting HCV," continues Dr. Bhagani. "If you look at the HCV viral loads in people who are coinfecting with HIV, as compared to singularly infected HCV patients, they are much, much higher. And the higher the viral load, the higher the risk of transmission."

The jury is still out, however, on the actual mechanism of HCV infection during sex. Nelson points to a recent study that found that the higher the HCV viral load, the higher the level of HCV in saliva<sup>15</sup>, "although we don't really know what that means," he admits. Many of the studies reviewed here point to fisting, rimming, and unprotected anal intercourse as being associated with a greater risk, leading Dr. Bhagani to speculate that "practices that involve blood may be more high risk."

### Safer sex, screening, treatment

Drs. Nelson and Bhagani both believe that people with HIV can best protect themselves from acquiring HCV sexually by continuing to practice protected anal intercourse, rimming and fisting. "Like everything, you're better off not getting it, and since there is no vaccine available, taking precautions is the only way," says Dr. Nelson.

They also strongly suggest that yearly screening for HCV should become the norm in all UK HIV clinics. "The first thing we really need to know in this country is what is the true prevalence of HCV in the HIV population," continues Dr. Nelson. "It is clearly something that people who have got HIV have put themselves at risk of. We need to make sure that everyone is screened for HCV. The advantage of picking it up early means you are much more likely to eradicate it."

Although similar evidence is lacking in those who are HIV/HCV coinfecting, last year,

Jaeckel showed that HCV can be eradicated in *HIV-negative* people during *acute* HCV infection after 24 weeks treatment with interferon alpha. The average time from infection until the start of therapy was 89 days, suggesting that screening every three to six months might be optimum for those who believe they are at the greatest risk of acquiring HCV sexually. In this trial, at the end of both therapy and follow-up, 98% had undetectable levels of HCV and normal LFTs<sup>16</sup>. "The data for treating acute HCV from the Jaeckel paper is using just interferon alone," says Dr. Bhagani. "At the Royal Free we use pegylated interferon and ribavirin since we feel we should be giving these people the best standard of care that we can."

Eradicating HCV during the acute stage "may be very important when you look at the data on HIV/HCV coinfection and higher rates of progression to end-stage liver disease," concurs Dr. Nelson. Many recent studies have confirmed the link between HIV/HCV coinfection and accelerated progression to fibrosis, cirrhosis, liver cancer and liver failure (including those by Martin-Carbonero<sup>17</sup>, Bica<sup>18</sup>, Monga<sup>19</sup>, Hatzakis<sup>20</sup>, Soto<sup>21</sup> and Garcia-Samaniego<sup>22</sup>). "Before HAART, everyone was saying you're going to die of your HIV, don't worry about your hepatitis C," continues Dr. Nelson. "Now suddenly people are living, and hepatitis is a major cause of morbidity and death in many people with HIV worldwide. It's something that we can't ignore anymore, and it's something that we've got to be much more proactive about."

### Take home messages

"I think the take home messages are that HCV is sexually transmissible amongst gay men and it may be more so than with heterosexual transmission," concludes Dr. Bhagani. "So gay men and people with HIV should always practice safer sex. In coinfecting patients, HCV is a particular concern because of the propensity for faster progression to end stage liver disease and complications with drug-related toxicity. We know from singularly infected patients that HCV is potentially curable if caught early. And so we should be making an effort to try and detect and treat early HCV seroconversion."

### references

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# once daily hiv therapy

6 many people with hiv say they'd rather take their hiv drugs just once a day. few drugs are licensed for this purpose but many more options are under investigation by anna poppa

With greater appreciation of the need to facilitate sustained, high levels of adherence to anti-HIV therapies, HIV physicians and the pharmaceutical industry have pursued a range of measures designed to ease the practical demands which HAART therapy involves.

Past examples include co-formulating drugs into one tablet or capsule (e.g. *Combivir*<sup>TM</sup>, *Trizivir*<sup>TM</sup>), and using drug interactions to boost drug exposure and so reduce the number of capsules or doses required (most commonly via a small dose of ritonavir taken with another protease inhibitor). More recently, the goal has become once daily therapy.

In both the general medical literature and in HIV research, treatment adherence has been shown to be governed by a great many factors, from cognitive issues such as one's beliefs and fears about medicine and health, to more practical issues such as the number and size of

pills to be taken, the number of doses per day, and whether the medicine is to be taken with food. (You can read more on this subject in *ATU* issue 91 and at [aidsmap.com](http://aidsmap.com)).

Though there is little research to indicate that once daily therapy results in better adherence than twice daily regimens (relative to regimens dosed more frequently), recent reports suggest that many people with HIV would *prefer* to take their treatment once a day if possible<sup>1</sup>. A number of initiatives designed to broaden access to HAART in resource-poor settings are working from an (untested) assumption that only low pill burden, low dosing frequency regimens will be feasible. Further, once daily regimens lend themselves best to 'directly observed' administration by health care professionals or trained volunteers, a strategy which has been shown to result in excellent adherence in 'vulnerable' communities (such as prisoners, drug users and in some settings

in the developing world). As a result, many pharmaceutical companies are now working to shoe-horn both licensed and experimental drugs into once daily regimens.

These moves are not without risks. Dosing regimens are established in the early stages of a drug's development, and aim to reflect the optimal balance between adequate drug potency and acceptable drug toxicity. Changing the dosing regimen can upset this balance and result in treatment failure. One of the earliest attempts at so-called 'treatment simplification' concerned indinavir, a drug which must be taken three times a day when it is the sole protease inhibitor (PI) in a HAART combination. Taken twice daily, without the assistance of a second PI, the drug failed after a lengthy research programme. Whilst indinavir is now routinely taken with ritonavir to allow twice daily dosing of both drugs, the optimal doses are still not agreed and some regimens appear to increase the risk of side-effects rather than reduce them.

Paradoxically, once daily regimens may raise the stakes in relation to adherence as a missed dose can leave drug levels to diminish for a longer period, theoretically increasing the risk of drug resistance emerging. This is particularly important because a number of drugs which can be (or are) taken once a day are those to which HIV most easily becomes resistant (3TC, efavirenz, nevirapine).

### Licensed once daily antiretrovirals

Currently only four drugs are licensed for once daily use: efavirenz, tenofovir, 3TC and ddI (both in the enteric-coated capsule and crushable tablet formulations). Because antiretrovirals are taken in combinations of three or more drugs, true once daily therapy requires the availability of at least three drugs which can be taken at the same time. Whereas efavirenz, 3TC and tenofovir can all be taken at the same time, ddI must be taken on an empty stomach. This raises potential problems for its use alongside efavirenz and tenofovir, which are best taken with food.

If tenofovir and ddI are taken at the same time, with a light meal (defined as 373 kCal, 20%

fat), ddI levels are raised to a degree that may cause an increased frequency of side-effects<sup>2</sup>.

### New research on once daily therapy

At the recent Barcelona International AIDS Conference, a number of research presentations concerning once daily therapy were reported.

Seventy-two week follow-up from a study comparing once daily with twice daily lopinavir/ritonavir was reported by Feinberg<sup>3</sup>. Thirty-eight treatment-naïve participants were randomised to receive either 800mg/200mg lopinavir/ritonavir once daily or 400mg/100mg twice daily, plus d4T/3TC twice daily. Virological efficacy (by both on treatment and intent to treat analyses) and toxicity were comparable across arms, with around 82% having viral load below 50 copies after 72 weeks by on treatment analysis. However, whilst peak lopinavir levels and total lopinavir exposure (called 'area under the curve' or AUC) were similar regardless of dosing regimen, those dosing the drug once a day had lower trough levels than those taking it twice daily. This may not be important for people who take lopinavir/ritonavir as a first-line PI, but it could reduce the benefit to be gained by those with PI resistance, because a lower trough level will mean a lower barrier against emerging resistant virus.

A group from Peru reported preliminary data from a trial comparing once daily ritonavir-boosted saquinavir, with saquinavir taken as a sole PI<sup>4</sup>. This was a randomised trial for advanced but treatment-naïve patients, and PIs were taken with two nucleoside analogues. Soft-gel saquinavir (*Fortovase*<sup>TM</sup>) was the formulation used and was dosed either as 1600mg once daily with 100mg ritonavir once daily, or 1200mg three times daily. *Fortovase*<sup>TM</sup> comes in 200mg capsules, so although the once daily group took fewer doses, their PI pill burden alone was nine capsules. Nevertheless, after 24 weeks follow-up, all study participants had undetectable viral load (below 400 copies), and there were no differences in the frequency of side-effects.

A small pharmacology study from Thailand compared once daily saquinavir/ritonavir

### glossary

See also pages 3, 9, 11

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

**antiretroviral** Substance which acts against retroviruses such as HIV.

**baseline** Starting point or value.

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

**cholesterol** A waxy substance, mostly made by the body to produce steroid hormones.

**double blind** A clinical trial where neither the researchers nor participants know which assigned treatment an individual participant in the trial is taking.

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

**intention to treat**

**analysis** A form of statistical analysis of clinical trials where data from all participants enrolled in the trial is evaluated, rather than only from those who complete the trial.

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

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

**NNRTI** Non nucleoside reverse transcriptase inhibitors, family of antiretrovirals including efavirenz, nevirapine.

**nucleoside analogues** Family of antiretrovirals which includes AZT, ddI, 3TC, d4T, abacavir, ddC.

## once daily hiv therapy continued

using both the hard gel (*Invirase*<sup>TM</sup>) and soft gel (*Fortovase*<sup>TM</sup>) formulations<sup>5</sup>. Though *Invirase*<sup>TM</sup> is also dispensed as a 200mg capsule, the pills are smaller; they can be stored at room temperature and this formulation is cheaper to manufacture. Drug exposure was measured in fourteen people who began treatment on *Fortovase*<sup>TM</sup> and switched to *Invirase*<sup>TM</sup>. Total saquinavir exposure (AUC) was greater in the *Invirase*<sup>TM</sup> period.

A group from Vertex Pharmaceuticals administered a once daily regimen containing 1200mg amprenavir with 200mg ritonavir, plus ddI and 3TC, to eighteen drug users<sup>6</sup>. Treatment was directly observed to maximise adherence. Over a 24 week period, trough levels of amprenavir were above those which would be expected when the drug is given as a single PI. Median viral load fell from 177,500 to 56 copies. However, eight of the eighteen participants were excluded from the study for non-compliance.

Atazanavir is an experimental once daily PI from Bristol-Myers Squibb (which was reviewed in *AIDS Treatment Update* 109). In studies so far, atazanavir has not been associated with the blood fat (lipid) increases commonly associated with drugs in this class. In Barcelona, Rob Murphy presented data from a study switching people on nelfinavir-containing HAART to an atazanavir-containing regimen<sup>7</sup>. These individuals had formerly been part of a trial comparing nelfinavir with atazanavir, allowing the switchers to be compared with those who started, and remained, on atazanavir. In 63 patients, after twelve weeks, the switch was associated with significant reductions in total cholesterol (16%), LDL or 'bad' cholesterol (21%), and triglycerides (28%), and a significant increase in HDL or 'good' cholesterol (5%). Minimal changes in

cholesterol and triglyceride levels were seen in patients who remained on the 400mg or 600mg dose of atazanavir. Atazanavir is available in the UK though clinical trials for people with PI experience (see [aidsmap.com](http://aidsmap.com)). An expanded access scheme is expected to begin late in 2002.

Turning to nucleosides, Bristol-Myers Squibb presented data on their new, once daily extended release d4T formulation, d4T XR/PRC<sup>8</sup>. 797 treatment naïve participants were randomised to receive either standard twice daily d4T or 100mg once daily d4T XR/PRC. d4T allocation was blinded by placebo and all participants also took once daily efavirenz and twice daily 3TC. After 48 weeks, there were no differences between arms in the proportions of participants with undetectable viral load (regardless of how the data were analysed); or in the overall reduction in viral load; or in CD4 response; or in the frequency of side-effects.

GlaxoSmithKline presented data from a pharmacological study comparing once daily with twice daily AZT<sup>9</sup>. This open-label study randomised 32 treatment naïve participants to receive either 600mg once daily AZT, or 300mg twice daily, for fourteen days. No other antiretrovirals were taken. Daily viral load testing revealed that viral load fell faster between days 1 and 10, and between days 3 and 10, in the twice daily group compared to the once daily group, though there was no difference overall in the level of viral load decrease by the end of the fourteen day period. Whether this difference is important clinically will not be known without further, larger studies.

FTC (emtricitabine, *Coviraci*<sup>TM</sup>) is a once daily 3TC-like nucleoside analogue in development from Triangle Pharmaceuticals. Data from two randomised studies comparing FTC with twice daily 3TC, within three drug HAART regimens, were presented at Barcelona<sup>10</sup>. FTC-303 was an open-label study switching 3TC for FTC in people with undetectable viral load, whilst FTC-302 was a blinded study comparing FTC with 3TC in naïve patients (who also received d4T and either nevirapine or efavirenz). FTC-

303 enrolled 440 patients, and FTC-302 enrolled 468. After 48 weeks, side-effects were described as mild to moderate and comparable in frequency, and the viral load response was equivalent across treatments.

Soon after the Barcelona conference, Triangle announced by press release that their FTC-301 study, comparing FTC with d4T, had been 'unblinded' after preliminary results revealed superior viral load results in the FTC arm. This randomised study offered naïve participants treatment with once daily efavirenz and enteric-coated ddI, plus either FTC or twice daily 3TC. Because this was a blinded study, everyone was taking a twice daily regimen. After 24 weeks, a greater proportion of FTC recipients had viral load below 50 copies, and a greater proportion of d4T recipients had left the trial early. This study will be presented at the forthcoming ICAAC conference in late September. FTC is not available in the UK at present, though Triangle plan to file for its approval in the European Union and USA soon.

### Other potential once daily options

Several other licensed treatments have been evaluated as once daily regimens, and at least one candidate in the drug pipeline may be suitable for once daily dosing.

The SCAN study randomised 94 individuals with viral load above 5,000 copies and CD4 counts above 500 to receive ddI/nevirapine once or twice daily in combination with twice daily d4T<sup>11</sup>. Intent to treat analysis at twelve months showed 68% and 45% of patients taking twice daily ddI/nevirapine had viral loads below 200 and 5 copies, respectively, compared to 73% and 40% of patients taking once daily ddI/nevirapine. Similar numbers stopped treatment for side-effects.

The VIRGO study randomised 100 treatment naïve participants to ddI/d4T plus nevirapine either once or twice daily<sup>12</sup>. At baseline, mean viral load was 4.7 log and mean CD4 count was 432. Intent to treat analysis at six months found 62% of those taking twice daily nevirapine, and 50% of those taking once daily nevirapine, had viral load below the 50 copy cut-off.

Efavirenz and nevirapine have been tested in combination with each other in a once daily regimen that also included ddI<sup>13</sup>. Twenty-six individuals received the regimen and after nine months, 25 out of 26 had viral load below 25 copies (with one viral rebound due to a treatment interruption). Mean viral load at baseline was 33,000 copies.

A number of researchers have evaluated once daily indinavir/ritonavir at a range of doses (see the detailed indinavir review on [aidsmap.com](http://aidsmap.com)), but these have generally been quite poorly tolerated, or have resulted in inadequate trough levels.

Finally, amongst the many therapies in development, DPC 083 (an NNRTI) may suit once daily dosing.

### Monitoring drug levels

In some circumstances where PIs or NNRTIs are taken once daily (bar efavirenz which is licensed for this purpose or atazanavir which is designed for once daily use) your doctor may want to check that your blood levels are adequate. In the UK, most manufacturers of PIs support the costs of drug level tests. This subject was reviewed in *AIDS Treatment Update* 114.

### key conclusions

- Taking treatment once a day may make anti-HIV therapy easier to stick to.
- A small number of anti-HIV drugs are licensed for once daily use.
- Several other drugs are being evaluated to see if they are effective and safe when taken once a day. This may involve taking the total daily dose all at once, or taking a new formulation, or boosting one drug with a small amount of ritonavir. Whilst these approaches remain experimental, changing your dosing regimen presents risks and should not be attempted without the support of your doctor.

### glossary

See also pages 3, 7, 11

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

**protease inhibitors** Family of antiretrovirals which includes amprenavir, lopinavir, indinavir, nelfinavir, ritonavir, saquinavir.

**randomisation** The process of selecting by chance the treatment that a clinical trial participant will receive.

**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.

**triglycerides** The basic 'building blocks' from which fats are formed.

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Except where stated, references are from XIV International AIDS Conference, Barcelona, 2002. Abstract numbers only are supplied.

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# anal cancer

as new research suggests hiv treatment has little effect on rates of anal cancer, we consider the potential role of anal pap smears in screening those at risk by edwin j bernard

Recent studies from the US<sup>1</sup> and Australia<sup>2</sup> show that anal cancer is currently the most common non-AIDS defining cancer amongst HIV-positive men who have sex with men (MSM). Current estimates are that 35 HIV-negative MSM per 100,000 will get anal cancer, and the risk is three to four times as high among MSM who are HIV-positive<sup>3</sup>. By comparison, the rate of anal cancer in the general population is 0.8 per 100,000. In fact, anal cancer in MSM regardless of HIV serostatus is currently more common than cervical cancer in HIV-negative women<sup>4</sup>.

## HPV and anal cancer

Like cervical cancer, anal cancer is caused by a family of viruses known as human papilloma virus (HPV)<sup>5</sup>. HPVs are very easy to acquire, and the majority of sexually active people are infected with one or more strain. The viruses normally cause lasting infection, which is why the prevalence of anal HPV is very high among MSM, reportedly as high as 93% in HIV-positive and 23% in HIV-negative men using PCR (viral load) detection techniques<sup>6</sup>.

However, HPV infection doesn't inevitably mean that anal cancer will develop and current research is trying to determine which other factors lead to the development of cancer: some evidence suggests that HIV-associated immune damage, abnormal hormone levels and viral mutations may play a role. Among the many strains of HPV, numbers 16, 18, 31, 33, 35 and 45 have been most strongly associated with the development of cancer. These strains are therefore the focus of work to develop both preventive and therapeutic vaccines, currently in clinical

trials in women. Most people associate HPV with genital warts, though these are usually caused by HPV strains other than those associated with genital cancers.

Anal HPV infection can vary in severity from no symptoms at all to benign anogenital warts, to grade 1 anal intraepithelial neoplasia (AIN), known as 'low grade squamous intraepithelial lesions' (LSIL), to grades 2 and 3 AIN, known as 'high grade squamous intraepithelial lesions' (HSIL).

Though it's not known how frequently or fast these lesions progress to cancer, prospective studies<sup>7</sup> have shown that the incidence of anal HSIL and progression of LSIL to HSIL within two years of follow-up is high in HIV-positive MSM and that these men may be at increased risk of developing anal cancer as a result.

## Anal cancer and HAART

At the recent International AIDS Conference in Barcelona, a presentation from Joel Palefsky and colleagues at the University of California, showed that HAART failed to prevent or reduce rates of pre-cancerous anal lesions in MSM<sup>8</sup>. In contrast, HAART has reduced rates of the most common AIDS-defining cancers, Kaposi's Sarcoma (KS) and non-Hodgkin's lymphoma (NHL)<sup>9</sup>.

"HPV-related lesions are different from the others to begin with because these happen quite commonly in HIV-negative people," explains Palefsky, an authority on HPV and anal cancer. "So the relationship between immune response and the lesions is different [to other cancers]. It's not surprising that

when you improve the immune response with HAART that it's not going to have the same dramatic impact that it does for KS or NHL".

Palefsky argues that since HAART is lengthening life expectancy, anal cancer will become increasingly common. "I'm guessing that the rates that are going up will continue to rise because we're now just starting to see the effect of the sexual revolution," he says, "because the people now entering their forties, fifties and sixties are the people who started to have more sex in the '70s and '80s."

### Is anal cancer preventable?

Though other HIV clinicians are less convinced, Palefsky himself makes a strong case that, unlike other cancers affecting people with HIV, anal cancer may be largely preventable through regular screening to identify and treat pre-cancerous anal lesions before they progress to cancer. He recommends that when HIV infection is first diagnosed, an anal Pap smear (where a tiny tissue sample is taken from the anus for examination) should be part of the initial evaluation. If the initial Pap smear is normal, then a second one could be obtained after six months. After two sequential normal smears, these patients could have a smear annually.

"I would suggest that anybody who's had receptive anal intercourse, whether it's protected or not, should consider [screening] because if condoms do have an effect on HPV transmission, it's relatively minor," he says.

US studies have concluded that such screening would be cost-effective for HIV-infected MSM at all CD4 cell count levels<sup>10</sup> and also for uninfected MSM<sup>11</sup>. And a recent review<sup>12</sup> of anal Pap smears at an HIV clinic in New York State found that screening identified problematic cases: 14% of patients had abnormal anal Pap smears over three years and 3% had lesions that required treatment.

### Women, anal sex and cancer

Palefsky's recommendations for anal Pap smears are also extended to women who have anal sex, although he admits that data collection on that population is in its early

stages. Studies do suggest that HIV-positive women have almost the same levels of anal HPV infection as HIV-positive men<sup>13</sup>. And since another Palefsky co-authored study at the Barcelona Conference reported that up to 30% of heterosexual couples have anal sex, the risk in women should not be understated<sup>14</sup>.

### Anal cancer in the UK

Here in the UK, despite data<sup>15</sup> that appear to concur with the US and Australian numbers, screening for anal cancer is not routine. One reason may be that no firm guidelines have yet been established due in part to a lack of large-scale prospective studies showing whether screening is beneficial, and the fact that treatment options at different stages of AIN are still being clarified.

Another could be lack of familiarity with the condition. "Many practitioners say, 'I've never seen a case, therefore it is not a big problem'", says Palefsky. "This confusion sometimes arises because an individual practitioner with a few hundred or even 1,000 patients is not statistically likely to see a case, when we're talking about rates of 30-100 per 100,000."

### Patient education

It is likely that those who are most at risk (HIV-positive MSM, HIV-negative MSM and women with HIV who practice anal sex) are not currently aware that they are at risk for anal cancer. If they did, perhaps there would be much more demand for anal Pap smears, and more discussion between patients and doctors about the potential use of treatment.

The implementation of screening programmes rests on our understanding of key criteria: examples being the reliability of the test, the natural history of the disease, the impact of early therapy on outcomes, the hazards of therapy and of screening itself, and health economic issues such as local cost-utility and cost-effectiveness. The use of Pap smears to screen women for cervical cancer coupled with the availability of appropriate treatment is clearly a success story. Before Pap smears became widespread in the 1960s, the rate of cervical cancer was about 40 per 100,000 women. It is now down to eight per 100,000<sup>16</sup>.

### glossary

See also pages 3, 7, 9  
**lesion** Any abnormal change in body tissue caused by disease or injury.

**neoplasia** Abnormal and uncontrolled growth of tissue, a tumour.

**strain** A variant characterised by a specific genotype.

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**editor**

Anna Poppa

AIDS Treatment Update  
founded by Peter Scott

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**design**

Alexander Boxill

**printing**

Cambrian Printers

**ISSN**

0969-4706

**charity number**

1011220

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

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