

aids treatment update

Prevention matters

As a positive gay man, one of my chief concerns is that I keep my HIV infection to myself. That is not to say that my sexual partners are not equally responsible for their own health, sexual or otherwise. However, I feel better about myself knowing that I continue to do everything I can to prevent passing on my HIV during the most intimate of acts.

Current prevention methods – I hesitate to call condoms and safer sex negotiation 'prevention technology' – are not even close to 100% effective. Our knowledge of HIV transmission risks continues to evolve; people are human and make mistakes; condoms – even when used correctly – can fail; and the fundamentalist notion of abstinence and/or lifelong monogamy, is laughably, perhaps even tragically, unworkable in the real world.

These grey areas around HIV transmission have led to a huge amount of personal anxiety around sex during the past two decades, which has frequently impacted upon the quality of my life. And so I welcome the forthcoming UK guidelines on PEP for sexual transmission – and more importantly, the imminent promotion of PEP's availability to those who are most at-risk of either passing on or acquiring HIV-infection.

The availability of PEP certainly isn't going to make me any less careful, or caring, during sex. After all, PEP is not 100% guaranteed to work, either: it relies on accessing the drugs as soon as possible after likely transmission – ideally within 24 hours – and requires the PEP recipient to stick to the regime. But knowing that there is a safety net – let's think of PEP as a last-ditch attempt to prevent HIV infection after a possible act (or acts) of sexual transmission – helps to alleviate my anxiety as I continue to walk the sexual tightrope.

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HIV's morning after pill(s)?

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For the past twenty years or so, condoms, safer sex negotiation and – in many countries outside of the UK – abstinence have been the holy trinity of HIV prevention work. With the unveiling of the first UK guidelines regarding the use of PEP for sexual transmission of HIV, there is now the possibility of a last-ditch attempt to stop HIV taking hold when the other three have failed. But just how effective is PEP, and what does it mean for prevention work as a whole?

What is PEP?

PEP is short for the term **Post-Exposure Prophylaxis**, which literally means preventing infection after exposure to a pathogen – in this case to HIV. PEP requires a short course of antiretrovirals, although the exact length of time PEP is taken for – and number of drugs given – varies from country to country and even from treatment centre to treatment centre, and is currently under debate.

The concept of PEP has been around almost as long as antiretrovirals themselves, but for many years was used only for healthcare workers who were accidentally exposed to HIV, usually after being unintentionally pricked by a *sharp* or needle that they had used on someone who was – or was likely to be – HIV-positive. The US term *needlestick injury* is now the usual phrase for this kind of accident, which may result in *occupational* exposure to HIV.

More recently, PEP has been used as a way of attempting to prevent HIV infection following possible exposure to HIV through both gay and heterosexual sex, as well as injecting drug use (IDU). This is known as *community* or *non-occupational* exposure.

PEP in the UK

The most recent review of prescriptions for non-occupational PEP in the UK covered events in 1999¹. Of 242 requests in that year, 130 people were prescribed PEP. Half of the requests followed sexual exposures between known HIV discordant couples. Requests for PEP were received by 56 of the UK's 132 GUM clinics (42%). However, just nine clinics received over 60% of all requests, and of the 39 clinics that actually prescribed PEP, just six clinics issued 64% of prescriptions.

Though this could simply reflect supply and demand, it seems much more likely that the reasons for this unequal access are at least partly due to the lack of clear guidance on using PEP in non-occupational settings. The Department of Health's (DoH) PEP Guidelines² deal largely with occupational exposure. Just three of its 20 pages are devoted to sexual exposure, and it makes few specific recommendations.

In fact, a recent survey of UK gay men found that 22% knew someone who had sought PEP, but that only 4% had tried to get it themselves and only 2% had actually taken it. Seventy-one per cent of respondents said they would take PEP if they needed it and it was easily available³.

This summer, PEP should become much more widely available in the UK following the release of detailed guidelines regarding the use of PEP in response to sexual exposure of HIV by the British Association for Sexual Health and HIV (BASHH). The draft guidelines will be available for consultation online soon, at www.bashh.org.

At the same time, the first CHAPS awareness campaign for 2004/5, due to be launched in July,

will aim to increase gay men's awareness of PEP and its availability, especially in cities with larger gay scenes, such as Brighton, London and Manchester.

The effectiveness of PEP

Large-scale prospective, placebo-controlled trials have not been carried out for PEP, and so a definitive answer regarding the effectiveness of PEP cannot be given at this time. A much-cited 1997 case control study of health care workers from France, Italy, the UK, and the US came to the conclusion that PEP (in this case AZT monotherapy) reduced the risk of becoming infected with HIV by 48-94%⁴. However, there is much less solid data on PEP's effectiveness after sexual exposure.

One of the more convincing studies was conducted in Brazil and reported two years ago at the 9th Retroviruses Conference in Seattle⁵. Here, 202 HIV-negative gay men were enrolled and followed for an average of two years. At the time of enrolment, 57% of the group reported "high-risk behaviour". PEP, consisting of four weeks of AZT/3TC, was used 100 times by 73 of the participants, 91% of whom completed the course.

There were 11 seroconversions among the group; however, only one occurred in someone who had taken PEP. Analysis of the strain of HIV that infected him despite using PEP showed that it harboured the *M184V* mutation which is likely to lead to high-level resistance to 3TC. The researchers calculated that PEP reduced the seroconversion rate by 83%, from 4.1 cases per 100 patients a year to 0.7 cases.

Several other interesting findings came from this study. One was that "high-risk" behaviour declined during the study from 56% to 40%. Although it has been suggested from other studies that people reporting declines in risky behaviour may sometimes not be reporting the whole story due, possibly, to guilt at being a 'study failure', this finding may help allay fears that the widespread availability of PEP for sexual exposure will cause an increase in condomless intercourse.

Furthermore, 92% of the time, PEP was taken appropriately, i.e. after an exposure that researchers considered "high risk". This seems to offer a degree of assurance that PEP will not be

abused by the 'worried well' concerned by very low-risk incidents.

Finally, the study issued people with 'starter packs' – ready-wrapped doses of AZT/3TC with instructions that participants should take them immediately following exposure. Other PEP schemes have relied on people reporting to A&E departments after weekend incidents. Since one of the key components to successful PEP is prompt treatment – ideally within 24 hours – this may explain some of the difference between the reported effectiveness rate of 83% in the Brazil study and the 53% rate in the study detailed below.

The cost-effectiveness of PEP

A major concern about PEP is cost. Since the end of 'ring-fenced' money for HIV from the Government coffers, lack of funding for prevention work has become, and remains, a major stumbling block. It could be argued that offering everybody anti-HIV drugs as a preventative measure is a lot more expensive than offering condoms. However, it could also be argued that PEP is HIV treatment rather than HIV prevention, and should therefore be paid for out of treatment budgets.

A study published in January⁶ attempted to calculate the cost-effectiveness of PEP. Here, Pinkerton and colleagues looked at 401 people who had sought PEP in San Francisco.

The group included men and women who sought PEP for incidents of unprotected anal and/or vaginal intercourse and needle-sharing. The researchers concluded that PEP reduced expected HIV infections by 53% by calculating that, according to types of risk reported by the study participants, an average of 2.36 HIV infections would have been expected: PEP reduced this to 1.1 infections.

This 53% reduction saved 11.74 quality adjusted life years (QALYs). This measurement, frequently used in cost-benefit calculations, means that, for those that used it successfully, PEP should lead to an extra 11.74 years of reasonable health. This in turn, it was calculated, would save a total of US\$281,323 in future HIV-related medical costs. When all factors were taken into account, the cost of PEP per QALY saved was US\$14,449 – approximately £9,500.

PEP not 100% effective in gay men

A California PEP study presented last month at CROI in San Francisco found that of the 702 gay men in the study, seven (1%) of those receiving PEP after a possible sexual exposure to HIV went on to become infected with HIV.

All the men had requested PEP after having unprotected receptive anal sex with another man (compared to 50% of non-seroconverters, $p=0.03$), and in four instances their partners were known to be HIV-positive.

All seven seroconverters were provided with their PEP medications within 72 hours of exposure to HIV (median 45.5 hours). Only four of the seven men seroconverting were assessed as having excellent adherence to their PEP regimens; two had poor adherence and one man's adherence was fair. Additionally, all seven men had had other instances of unprotected anal sex in the six months prior to being provided with PEP. Furthermore, in the period between being provided with PEP and seroconversion, one man also reported high-risk sex with a known HIV-positive man and two reported high-risk sex with men of unknown HIV status.

The PEP regimen usually consisted of two nucleoside analogues (AZT/3TC, d4T/3TC, or d4T/ddI) but if the infecting partner was known to be HIV-positive with a detectable viral load, a triple regimen including two nucleoside analogues and the protease inhibitor nelfinavir was prescribed¹³.

This may sound a lot, but in the US programmes costing \$40,000 – \$60,000 per QALY are seen as cost-effective. By comparison, similar cost-effectiveness studies⁷ showed that HIV combination therapy resulted in a cost of US\$23,000 per QALY saved. There is no official figure for the UK, but it is thought that the National Institute of Clinical Excellence (NICE), which guides Primary Care Trust spending, considers anything below £30,000 per QALY saved to be cost-effective.

By including a varied population with different risks, this study found that PEP *given to the general at-risk population* did work out to be much less cost-effective than other HIV prevention methods. One risk-reduction programme for at-risk women⁸ attending an urban primary health care clinic was successful at increasing condom use and cost about US\$260 per client or about US\$2,000 per QALY. A similar programme for gay men⁹, although costing US\$470 per client, was not only cost-effective but also *cost-saving*: the cost of likely future treatment and care of those infected without the programme outweighed the cost of delivering the programme to the whole group. This compares with an average cost of US\$8,607 per QALY saved for PEP for gay men as a whole as reported by Pinkerton. However, when it came to gay men who had been on the receiving end of unprotected anal sex (i.e. 'bottoms'), the Pinkerton study found that PEP was not merely cost-effective, but actually cost-saving. The cost per infection averted for this group was US\$177,293 – which is less than the likely cost of their lifetime HIV treatment if they had not received successful PEP. On the other hand, PEP for gay men on the insertive end of unprotected anal sex (i.e. 'tops') was not considered cost-effective.

The variation seen in cost-effectiveness between subgroups of different populations is not surprising, given that you need to provide PEP to the people most at-risk for it to be cost-effective. As we go to press, the Health Protection Agency (HPA) are attempting to define the risks of HIV transmission in the UK – based on mathematical probability. They are currently estimating that gay men who are the passive partner in unprotected anal intercourse have a 1-in-33 risk of being infected with HIV if they are certain their partner

is HIV-positive, but a 1-in-222 risk if they do not know the HIV status of their partner. They estimate that gay men who are the active partner in unprotected anal intercourse have a 1-in-555 risk of being infected with HIV if they are certain their partner is HIV-positive, but a 1-in-11,111 risk if they do not know the HIV status of their partner. However, other factors such as geographical location, STIs, viral load and bleeding may affect the risk estimate, so there is likely to be a range of risk of transmission rather than an exact value¹⁰.

In short, if PEP in the UK is offered to gay men who have been the passive partner in unprotected anal intercourse and/or who have known HIV positive partners, PEP could potentially save as much money as providing condoms and safer-sex education, as long as PEP is not routinely relied upon as a substitute for these other safer-sex practices.

What the draft UK guidelines recommend

Last December, HIV prevention experts and community activists met in London to discuss a draft of the BASHH guidelines at a round table session organised by Terrence Higgins Trust (THT). The first guest speaker was Dr. Martin Fisher of Brighton and Sussex University Hospitals, who is lead author of the guidelines writing group.

There was a wide variation in the availability of PEP at STD clinics, he told the meeting. For example, one HIV-negative partner of a serodiscordant couple who sought (and received) PEP at Brighton had been refused by three other clinics.

The guidelines would cover, among other things:

- The scientific basis for recommending PEP
- A guide to calculating the risk of a given exposure
- The pros and cons of PEP as a prevention measure
- Recommended protocols
- Pathways for access
- An emphasis that PEP is only one strand in HIV prevention

The draft recommendations are open for discussion, and therefore may be amended. For who might be eligible for PEP, see table 1 below: Draft BASHH guidelines on PEP provision.

Draft recommendations for PEP regimens are:

- *Combivir* (zidovudine, AZT + lamivudine, 3TC)
or
- *Zerit* (*stavudine*, D4T) + *Epivir* (lamivudine, 3TC)
or
- *Viread* (tenofovir, TDF) + *Epivir* (lamivudine, 3TC)
plus *either*
- *Viracept* (nelfinavir)
or
- *Kaletra* (lopinavir/ritonavir)

Although *Combivir* is suggested as one of the nucleoside components, as Dr. Fisher explains below, this may be ruled out due to high rates of pre-existing HIV strains resistant to both drugs that are currently circulating within the UK. NNRTIs are not recommended because of the likelihood of short-term side-effects: central nervous system problems such as sleep disturbance and depression with efavirenz and liver toxicity with nevirapine. (see *The Night Before...* on pages 8-9 for more on nevirapine and PEP).

Other draft recommendations include:

- 24-hour access and expertise via A&E
- Baseline HIV test mandatory

- Rapid GUM/HIV clinic referral
- Weekly follow-up during PEP period
- Three- and six-month HIV antibody test

No limit on repeat requests, but an appointment with a psychologist or health advisor should be mandatory after several repeats.

This last recommendation contrasts with Australia's 'three strikes and you're out' policy. France and Spain allow a maximum of four and five repeats respectively.

Behavioural implications

Dr. Oliver Davidson, Head of Sexual Health Psychology at London's Mortimer Market Centre, addressed the possible impact of PEP on subsequent perceptions of risk behaviour.

In the San Francisco study reported above, only 10% of people seeking PEP reported an increase in risk behaviour following a PEP consultation. This compares with 74% reporting a decrease in risk behaviour and 16% no change. Consequently, Davidson commented: "Health-related interventions such as PEP may help capitalise on 'close calls' to motivate and sustain risk reduction."

A US survey of gay men in 1998¹¹ attending a large Pride festival in Atlanta found that 3% of those surveyed had used PEP, 26% planned to use it, and 74% doubted if they would need to use PEP. Those planning to use PEP were younger, less educated, more likely to have used recreational drugs and have a history of IDU. They were also more likely to have had unprotected receptive anal sex.

glossary

A&E the accident & emergency, or casualty, department of a hospital.

antiretroviral a substance that acts against retroviruses such as HIV.

autoimmunity a condition in which an individual's immune system starts reacting against his or her own tissues, causing disease.

baseline a starting point or value.

chemoprophylaxis taking a drug to prevent an illness.

discordant another word for different.

serodiscordant couples include one HIV-positive and one HIV-negative person.

efficacy how well something works.

GUM clinic genito-urinary clinic: where sexually transmitted infections are treated.

hepatotoxicity side-effects affecting the liver.

monotherapy taking a drug on its own, as opposed to in combination with other drugs.

pathogen any micro-organism which can cause disease.

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

pharmacologic the properties and reactions of drugs.

prophylaxis see *hemoprophylaxis*

serodiscordant see *discordant*

table 1: Draft BASHH guidelines on PEP provision*

	Partner status HIV+	Partner Status Unknown
Receptive anal intercourse	Recommended	Recommended if partner high risk
Insertive anal intercourse	Recommended	Consider if partner high risk
Receptive vaginal	Recommended	Not recommended
Insertive vaginal	Recommended	Not recommended

*Other factors to consider include whether either partner has a concurrent STI, the viral load in the HIV positive partner, and whether there was sexual assault/trauma.

As others at the seminar noted, this user profile could be seen either as a problem or as an opportunity. Does the availability of PEP mean that young, drug-using gay men have an 'excuse' not to try to maintain safer sex habits? Or, conversely, are they taking a realistic look at their behaviour and its likely risks and seizing upon a technology that may protect them?

Davidson was also concerned about the potential cost (as opposed to cost-effectiveness) of PEP if taken up as a mass prevention measure. One of the implications of the San Francisco study is that if the entire annual US HIV prevention budget was used for PEP, it would fund 550,000 treatments and prevent a mere 880 new infections, or 2.2% of the estimated US annual incidence.

Putting PEP into practice

Rod Watson of THT reported on his experience of promoting a PEP programme for gay men in his former capacity as Health Promotion Manager for SE Sydney Health Authority in Australia. The Australian policy on PEP for sexual exposure – the first of its kind – was first written in 1998, although the decision to actively promote PEP as a prevention tool was not taken until June 2000.

The high-risk groups targeted initially were gay men and people in serodiscordant relationships; subsequently, IDUs and sex workers were also targeted.

A phonenumber with the number 1-800-PEP-NOW was publicised, posters were placed in community press and information was issued in leaflets and on the web. There were 493 calls for the January – November 2001 duration of the helpline, of which 88% were direct requests for PEP. Sixty one percent met guidelines for PEP prescription; 28% did not because they were considered low risk, and 11% fell outside the 72-hour time limit.

Interestingly, and contrary to some other surveys, only 7.2% of callers were seeking PEP for exposure with regular partners.

In terms of community awareness of PEP, 64% of those polled in the target groups had not heard of PEP in February 2001. Six months later, 58.5% *had* heard of PEP. Triple combination therapy was prescribed at the start of the programme, but cost pressure meant that HAART

was reduced to the dual nucleoside therapy, AZT/3TC.

Q&A with Dr. Martin Fisher, Chair of the BASHH HIV Special Interest Group

ATU: Are you satisfied that PEP represents an important part of the HIV prevention arsenal?

MF: I certainly think that it's one part, but it's only one part – essentially, the last part, when everything else has gone wrong. The problem about when to use it is due to the relative lack of any clear guidelines or consistent message up to now.

ATU: Animal studies have concentrated on, and demonstrated much less effectiveness after, the first 24 hours. Why do the guidelines recommend PEP up to 72 hours after exposure?

MF: The key is not to think that it's fine up to 72 hours. It's just that after 72 hours it can be shown to have little or no effect. If people want to consider PEP they need to enquire as early as possible. All the data suggests the earlier the better.

ATU: Why do you recommend triple combination therapy when studies seem to show that dual or single therapy can work?

MF: This *is* just a draft, and there are a few places where we've tried to be a little provocative to generate a reaction and get suggestions. The regimen recommendations are one of those places.

There aren't any randomised controlled studies of PEP in humans and it's difficult to imagine how you would design one, from an ethical point of view. Who would be the control group? You have to extrapolate from animal studies, retrospective studies and studies of the prevention of mother-to-child-transmission – which is, after all, HIV prophylaxis by means of drugs – to decide on the best regimen.

We have mainly stuck with the current DoH guidelines. We are flagging up the possibility of tenofovir monotherapy, as this has proved to be 100% effective in some animal studies¹². There are no published studies of tenofovir monotherapy

in humans, and we know it's well tolerated in the short term – the kidney toxicity associated with tenofovir comes from long-term exposure.

The Australian guidelines say there is a role for dual nukes, but we won't say that. I have concerns, in particular with increasing rates of primary resistance, that AZT/3TC may not be effective, as with the one failure in the Brazil study.

ATU: Why do you recommend PEP for all kinds of sexual intercourse when the partner is known to be HIV+ but only for receptive anal intercourse where their status is unknown?

MF: My guess is some will say we're being too conservative about this, others too aggressive. We regard receptive anal sex as 'high risk', remember, not just because it transmits quite efficiently but because it's likely to be with a high-risk partner, i.e. a gay man. When the partner's HIV status is unknown and they are of a low-prevalence population, e.g. a straight non-IDU European man, we might just say 'consider' and not 'recommend' PEP, even if the risk behaviour is receptive anal intercourse.

ATU: You place no limit on the number of repeat prescriptions. Why?

MF: Because we felt you had to treat each individual instance on its own merits. But if people are repeatedly presenting, then something clearly isn't working for them, and we'd like them to go to a health adviser or psychologist to explore that.

That being said, it's very important to note that repeat presentation is not common, and reported incidence of unprotected sex among people who've had PEP has usually gone down, not up.

ATU: Cost is clearly a concern. What if raising awareness of PEP proves to be too effective?

MF: Remember 'cost-effective' isn't the same as 'cost-saving'. Most medical interventions come at a net cost; it's usually cheaper to do nothing.

All the experience so far – as with with the Australian campaign, for example – indicates that vast numbers of people are *not* going to come forward and demand PEP as their prevention method of choice. Introducing the "morning after" pill for women has not resulted in it becoming the only form of family planning for women, but it has provided a fallback strategy for some.

The point about increasing awareness is that at present it's only those who know about PEP and know how to access it that can get it, and that's not equitable.

My personal preference is that we need to notch up services a bit and find ways of providing PEP so people don't miss out. It needs to be provided locally. There is a very clear role for the non-statutory sector here. I don't mean getting your PEP pack from the THT, but I do mean that they could be acting as gatekeepers, filtering out inappropriate requests.

ATU: What about the idea of 'starter packs' for weekend incidents, as in the Brazilian study?

MF: It's something some physicians have done informally before, for instance issuing them to a serodiscordant couple who live a long way from the clinic. The main problem there is one of drug storage: for example, you couldn't keep your *Kaletra* on the bathroom shelf for months.

ATU: The 'starter pack' idea blurs the distinction between post-exposure prophylaxis and PRE-exposure. You could, after all, take your starter pack before you think you are likely to be exposed to HIV. What do you think of pre-exposure prophylaxis, which is currently the subject of some high-profile studies?

MF: If it's shown to work, then it too is another addition to the arsenal. It could have a particular role in developing countries where condom use simply isn't possible for some women. Twenty years of HIV prevention has shown there is no magic bullet that will prevent HIV. We have to explore all the options.

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the night before...

8 in the absence of a preventative vaccine, PREP could be the prevention tool of the future, says edwin j bernard

If antiretrovirals can be used to prevent HIV infection taking hold after exposure to HIV, then it's not a giant leap to imagine that taking antiretrovirals prior to HIV exposure might be a good idea for those at high risk.

Pre-exposure Prophylaxis (PREP) has been proven effective in preventing mother-to-infant (vertical) transmission, when expectant HIV positive mothers are treated with HAART (if their own HIV infection warrants treatment) or AZT or nevirapine (as monotherapy) prior to, during and, if breast-feeding, after birth.

A report on the first feasibility study for this strategy was delivered two years ago at the XVth International AIDS Conference in Barcelona¹, and involved the use of the NNRTI nevirapine. This Phase I/II trial (known as *HIVHOP 101* provided a 200mg tablet of nevirapine once weekly (n = 12), twice weekly (n = 12), or every other day (n = 9) to a group of men or women in

the Baltimore area who were at high risk of contracting HIV. The cohort included gay men, injecting drug users (IDUs) and sex partners of HIV-positive people.

None of the participants experienced physical side-effects associated with the drug, including rash, although increases in GGT (a liver function test) were seen in those receiving higher levels of nevirapine. Additionally, nine of the 33 dropped out of the study before the end of the 12 weeks, most of whom were receiving the higher doses of nevirapine, suggesting a possible toxicity problem.

Although the study did not set out to assess the effectiveness of PREP nor its effect on the risk behaviour of the participants, the authors reported that risk-taking did not increase during the study and that no-one became HIV-positive.

This was a successful "proof of concept" study, even if the drug used was not ideal: there

continue to be concerns about nevirapine's short and mid-term liver toxicity, particularly in women and those who have more intact immune systems. Last month Boehringer Ingelheim, who market nevirapine as *Viramune*, issued important new safety information in a letter to US doctors, which cautioned that women with CD4 cell counts above 250 cells/mm³ (including pregnant women) who are taking nevirapine for chronic HIV infection have a twelve-fold greater risk of serious liver side-effects, and that these have sometimes been fatal.

Additionally, a study published last month in the *Journal of Acquired Immune Deficiency Syndromes* found that HIV-negative people appear to have a higher risk of side-effects when exposed to nevirapine, according to a review of case reports and toxicity reports from people exposed to the drug as a component of PEP after potential exposure to HIV. The authors suggest that autoimmunity may be at the root of these toxicities, since when severe adverse reactions have occurred in HIV-positive people (at a rate of less than 1%), they have tended to be when CD4 counts were high. They conclude that "although precise estimates of the risk for severe hepatotoxicity are not available, the risk appears to be higher than in HIV-infected persons... therefore non-HIV infected individuals should not receive PEP or other prophylaxis regimens that include multiple doses of nevirapine."

For these reasons, tenofovir (*Viread*, TDF) has now become the drug of choice for use in PREP studies, the first of which was announced in Barcelona 18 months ago and is currently in the final planning stages. The trial will focus on sexually active heterosexual women in resource-poor countries in Africa and Asia with high HIV incidence. Additionally, the US Centers for Disease Control (CDC) are planning a PREP trial in Atlanta and San Francisco which will include 400 men who have sex with men (MSM) for at least 18 months, with a tentative completion date for phase 1 of July 31 2004.

The CDC explains the rationale behind the use of tenofovir in their PREP study. "TDF has been selected for investigation as chemoprophylaxis against HIV in high-risk individuals because of its unique pharmacologic profile. In addition to the

convenience of being a once-daily single tablet with a safety profile comparable to placebo among HIV-infected persons, it has striking anti-HIV potency and a low potential for selection of resistant viruses. Each of these properties is necessary given the realities of the intended target populations."

Just as there are concerns that the availability of PEP may increase risky behaviour, particularly amongst gay men, so the CDC are aware that PREP may do the same. "The availability of an oral agent may induce some men to switch from the most effective prevention method (condoms) to one that is less effective (TDF). It is likely that TDF may be highly effective against HIV (i.e. < 80%), but it has no efficacy against other sexually transmitted infections (STIs) such as syphilis and gonorrhoea. Modelling exercises have indicated that the availability of a less-effective method, but one which is used more often, can result in a large decrease in HIV transmission. However, decreases in transmission of HIV would need to be considered in the context of the potential for increased transmission of other serious, although generally non-fatal, STIs."

A smaller-scale trial, to be led by Dr. Mike Youle at the Royal Free in London, has been planned for some time, but is currently awaiting funding before he can recruit serodiscordant gay couples for his PREP study. Writing about the urgent need for PREP trials in the *Journal of the International Association of Physicians in AIDS Care*⁵, Dr Youle wrote that "While barrier methods remain the gold standard for HIV prevention, the use of chemoprophylaxis against HIV infection could benefit those who may be less empowered to insist on condom usage – such as women in commercial sex work, or gay men who choose not to use them..."

"HIV serodiscordant couples, commercial sex workers, women wishing to conceive, and individuals unwilling to use condoms are groups that are regularly at significantly higher risk of HIV infection than the general population.

"Could these groups now benefit from HIV pre-exposure chemoprophylaxis with current or soon-to-be available drugs?"

Watch this space.

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Ritonavir rebellion spreads

Anger among doctors over Abbott's decision to quadruple the price of its protease inhibitor Norvir (ritonavir) in the US is growing; a boycott of the company's products and promotional activities is now supported by more than 200 leading HIV prescribers in the United States. Physicians have pledged to boycott Abbott promotional events and advisory boards, will no longer permit Abbott sales representatives to visit their practices, and will seek to ensure that their practices or hospitals prescribe alternatives to Abbott products where those exist and it is not harmful to the care of a patient to do so. Abbott's actions have also attracted the attention of state attorney generals in Illinois and New York who last month issued subpoenas to Abbott, requiring the company to disclose information for investigations into unfair pricing of Norvir. Abbott announced a number of concessions last month including a promise to make Norvir available free of charge to anyone who does not have insurance coverage, or who exceeds their annual maximum budget for prescription drug costs, and to maintain this offer permanently.

Record UK HIV diagnoses in 2003

According to figures published last month by the Health Protection Agency (HPA), a record 7,000+ people were newly diagnosed with HIV in the UK in 2003, a 20% increase on 2002.

So far a total 5,047 new HIV diagnoses have been reported, compared with 4,204 at the same time last year. However, when all reports are received, the total figure is expected to increase to over 7,000, and the HPA is warning of an impending HIV crisis.

New diagnoses in gay men are expected to reach a record 2,000 in 2003 after remaining stable for over a decade at around 1,500 a year. At least 10% of the gay men diagnosed with HIV in 2003 are thought to have been recently infected, providing sobering evidence that HIV transmission is continuing unabated amongst gay men.

New heterosexual HIV diagnoses increased by 27% in 2003, and although 80% involved infection with HIV outside the UK, over 250 heterosexuals acquired HIV in this country, a figure that is expected to increase to 400 once all reports are in.

Dr Barry Evans of the HPA attributes the increases to several factors: a rise in the number of some sexually transmitted infections that can facilitate HIV transmission; increased HIV testing; and migration to the UK from countries with a high HIV prevalence. However he notes that, "increases in unsafe sex are

undoubtedly the main driving force behind this epidemic. Changing people's sexual behaviour so they use a condom with all new and casual partners is one of the most effective ways of reversing this trend. People must be encouraged to take responsibility for their own sexual health.

"HIV is an infection that is here to stay," he adds. "With almost a third of the 49,500 people currently living with HIV in the UK still unaware they are infected, the rising trend in new diagnoses is liable to get worse before it gets better."

Superinfection occurs at 5% a year in recently infected gay men not on therapy

Investigators from California provided long-awaited information on the incidence of sexually-acquired HIV superinfection, concluding that, amongst their cohort of 78 recently infected individuals not on therapy, the annual rate of superinfection was 5%. The data was reported at the Eleventh Conference on Retroviruses and Opportunistic Infections in San Francisco last month.

Superinfection is the re-infection of an HIV-positive person with a slightly different strain of HIV. Although a series of case reports have documented that superinfection is

definitely possible under certain circumstances, until now there had been no data regarding how often this occurs.

Smith and colleagues retrospectively analysed blood plasma samples from 78 individuals – the majority of whom (90%) were gay men – who were enrolled in a study for new and recently infected people. When superinfection was suspected, they rigorously tested the samples using four different lines of molecular investigation.

Three cases of superinfection were identified in the cohort, two of which have previously been reported as individual cases. In each instance, the superinfecting HIV strain was associated with a change in susceptibility to antiretrovirals, even though none of the men were on therapy. Two were initially infected with drug-resistant HIV and then became superinfected with a wild-type strain, while the other was initially infected with a wild-type strain and then was superinfected with a drug-resistant strain. Within six months of acquiring the superinfecting strain, their viral loads increased by an average of 1.6 logs and their CD4 counts decreased by an average of 132 cells/mm³ (p < .05).

All three of the cases were gay men who had multiple sexual partners, making identification of the person who superinfected them (the index case) impossible. This is frustrating, because without the index cases, the possibility of co-infection – that is, infection with two different viruses at the same time – cannot be completely ruled out. However, the researchers' rigorous testing appeared to satisfy the eminent members of the San Francisco audience, who concurred that Smith provided compelling evidence in his oral presentation that these were, indeed, cases of HIV-1 clade-B superinfection.

Smith D et al. 11th CROI, San Francisco, abs 21, 2004.

Gottlieb G et al. 11th CROI, San Francisco, abs 454, 2004.

Gene commonly seen in Africans increases efavirenz levels

Three studies presented on the last day of the Retroviruses Conference in San Francisco

suggest that efavirenz is metabolised differently in a significant number of Africans.

Taylor presented data from the STOP study, which was originally designed to discover the ideal time to stop efavirenz (EFV) when discontinuing HAART. However, the most important finding was that EFV levels in African women can persist up to five-times longer and reach peak levels almost three times higher than average.

Ribaudo found that ethnicity (which she termed "race") was very strongly associated with how fast EFV was cleared by the liver: African-Americans and Hispanics had, on average, a 32% slower clearance of EFV than Caucasians. Weight was also a significant factor, although there was no apparent association with gender.

Haas examined the relationships between CNS toxicity, pharmacokinetics, and genetic polymorphisms (i.e. common DNA variations found in genes). EFV is metabolised in the liver by an enzyme known as CYP2B6; variations in this gene include the T/T genotype which is associated with slower clearance and higher plasma EFV levels in all subjects. Haas found that the T/T genotype was more common in African-Americans (20%) than Caucasians (3%) and concluded that "racial differences may be largely explained by this T/T genotype".

The take-home message for the UK is that since current BHIVA guidelines recommend that therapeutic drug monitoring "may have a role in reducing toxicity in individual patients and in adjusting doses in those with ...extremes of body weight", perhaps this technology could be used in the UK clinic whenever NNRTI-based regimes are prescribed to Africans and/or people with low body weight. Additionally, when stopping an NNRTI, perhaps drug-switching strategies should be preferred to stopping the NNRTI seven or more days earlier.

Taylor S et al. 11th CROI, San Francisco, abs 131, 2004.

Ribaudo H et al. 11th CROI, San Francisco, abs 132, 2004.

Haas D et al. 11th CROI, San Francisco, abs 133, 2004.

news from nam

Over the last few weeks, many of you will have received a letter from Caspar Thomson, NAM's director, inviting you to become a Friend of NAM and to support our work with a monthly donation. With your help we can provide more people with free information resources – like ATU and aidsmap – resources that help people live longer, healthier lives. In this month's edition we have included a donation form. If you haven't already, please consider supporting our work.

nam forums

Two NAM forums will be held this month from 7–9pm at the usual location: University of London Union, Palms Room, 4th Floor, Malet St., London, WC1. On Monday March 1st discover what the experts are saying about the latest advances in HIV treatment, in a feedback session from last month's Retrovirus Conference in San Francisco. Then, on Monday 29th March, there will be a discussion of the issues surrounding travelling with HIV medications, with a special focus on the United States' HIV-positive visitors' ban. Questions and experiences from the audience are welcome, and you can email your questions or comments in advance to forums@nam.org.uk

next month's ATU

The April edition of AIDS Treatment Update will feature an article on alternatives to ritonavir for boosting protease inhibitors, plus an in-depth analysis of the most important news from last month's 11th Conference on Retroviruses and Opportunistic Infections in San Francisco.

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