

# aids treatment update

## End the US HIV Tourist Ban

In this month's lead article, we discover that the 17 year-old US policy barring HIV-positive visitors is not only unnecessary and unworkable, it is also damaging the physical and mental health of people with HIV.

By forcing some people into taking treatment holidays, and causing mental anguish to anyone considering travelling to the US for whatever reason, it is clear that this anachronistic policy is dangerous and discriminatory.

Ironically, many with power in the US argued against adding HIV to the list of communicable diseases that bar entry to the States when the policy was first put into place in 1987. However, due to the occult intricacies of the US political system, a minority right-wing letter-writing campaign appears to have allowed this policy to become firmly entrenched. And when former President Clinton – who today attempts to do so much for people with HIV – had an opportunity to veto the bill before it became law in 1993, he balked for currently unfathomable reasons.

In 2004, the forced repatriation of HIV-positive tourists still happens. Last week my HIV clinician put me in touch with a fellow patient who had just been forcefully returned to the UK after he was repeatedly asked if he had AIDS by New York immigration officials, and who finally admitted he was positive under great duress. Shocked and angry, he had no idea until that point that he was an "undesirable": in fact, few people are even aware that this ban exists.

This law can only be repealed by an act of Congress, and so I appeal to anyone who has any influence in the US to put pressure on the government to end the HIV tourist ban. Wouldn't it be great if President Clinton himself campaigned to undo the damage he caused eleven years ago?

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# US travel health warning!

2 why the US hiv travel ban is seriously damaging our health by edwin j bernard

This month, ahead of the 15th International AIDS Conference in Bangkok, the US city of San Francisco hosts the 11th Conference on Retroviruses and Opportunistic Infections (CROI), generally considered to be the major scientific AIDS meeting of the year.

Fourteen years ago, San Francisco was the location for the 6th International AIDS Conference, which saw international boycotts and mass demonstrations due to the then three-year-old US policy of barring visitors with HIV. This was the last time a US city played host to *any* International AIDS Conference: the 1992 International AIDS Conference was moved from Harvard University to Amsterdam.

## End the ban

Currently, the US is one of only 15 countries to effectively ban HIV-positive visitors – along with the likes of Iraq, Libya, Russia and Saudi Arabia – according to the latest information from the Swiss HIV information site, [aidsnet.ch](http://aidsnet.ch).<sup>1</sup> Although the US HIV tourist ban has been almost universally criticised – both within and outside the US – the restriction remains after 17 years, and due to the convoluted nature of the history of this

discriminatory piece of legislation, requires an act of Congress to remove it.

It *is* possible to enter the US legally with HIV under certain circumstances – to attend conferences, receive medical treatment, visit close family members, or conduct business – but this requires applying for a stigmatising HIV visa waiver. Even if the waiver is granted – which may take three months or longer to obtain, and requires a personal interview at the US Embassy – the person's passport is endorsed to show that this person may not enter the US without the waiver, which must be renegotiated on each entry. This can cause further HIV disclosure issues on entering other countries, where immigration officers may want to know why the passport holder is barred from the US.

Two years ago, the UK AIDS charity, THT, began a campaign to raise awareness of the ban on US entry restriction for HIV-positive visitors.<sup>2</sup> Martin Kirk, THT's Parliamentary and Campaigns officer, acknowledges the limitations of the campaign in terms of changing US policy, but "having said that, we have raised the issue with the US Ambassador, the US Secretary of State for Health, and Bill Clinton. However,

apart from Clinton – who said the policy ought to be reviewed – most US officials have been very defensive, citing the other countries that ban visitors with HIV, and will not engage in a proper dialogue.”

### First-ever study on ban’s health effects

Until recently, there had been no research on the physical, emotional and psychological effects of the ban on HIV-positive people. Late last year, however, a study from Brighton and Sussex University Hospitals was presented as a poster at the 2003 European AIDS Conference in Warsaw.<sup>3</sup>

The study sought to determine whether those attending the Lawson Unit HIV Outpatients’ Clinic in Brighton travelled with a visa waiver and/or medical insurance, and to establish how they managed their HAART medications when travelling.

A self-completion questionnaire was given to everyone who attended the clinic in February and March last year. Of 642 attendees, 346 completed the questionnaire, of which 96.5% were male (compared with 90% of all clinic attendees) with an average age of 41 (compared with the clinic average of 40). In total, 135 (39%) respondents had travelled to the US since their HIV diagnosis, all but two of them “illegally.”

### One-in-eight interrupted treatment

The most striking – and worrying – finding of the Brighton study was the way people travelling to the US without an HIV waiver managed their drugs.

Of the 83 respondents on HAART who travelled to the US, 10 (12.5%) stopped their drugs for the duration of their stay. Five chose to take treatment interruptions prior to leaving for the States, and five had problems with mailing their drugs. “We found that people either stopped HAART themselves because of the trip to the States or they attempted to mail their drugs, which was often problematic”, says Dr Duncan Churchill, co-author of the Brighton study.

Of the ten who interrupted their treatment, five were on NNRTI-based HAART, which, due to its longer half-life, must be stopped ahead of the

other HAART components in order to reduce the likelihood of NNRTI mutations that could lead to clinical resistance. Current BHIVA guidelines<sup>4</sup> suggest that the NNRTI should be replaced with a drug with a shorter half-life two weeks prior to stopping all drugs.

In the Brighton study, only one of the five on NNRTI-based regimens stopped their NNRTI in the best-possible way after consulting with their HIV clinician. This person switched from efavirenz to tenofovir two weeks prior to stopping all drugs. The remaining four stopped their NNRTI two days, one day or at the same time as the rest of their HAART combination.

Of the three people who had short- or long-term problems due to their treatment interruption, one subsequently developed NNRTI drug resistance (Y188L). “This was a highly drug experienced patient who has subsequently run out of options now that he has also developed resistance to T-20,” notes Dr Churchill.

The other two developed intermittent fevers, arthralgia, headaches and diarrhoea, symptomatic of a viral load rebound, whilst in the US.

### Afflicted with a communicable disease

THT’s Kirk is not surprised by these results. “I think it just confirms our fears that people with HIV are still travelling to the US and it seems they choose to go on an unplanned drug holiday because they fear they will have their drugs found on them. It’s what we’ve always said will happen.”

All the people who stopped their treatment travelled on the green I94-W form which allows citizens of EU countries to enter the US for up to 90 days without any visa, as long as they are not terrorists, communists, convicts or “afflicted with a communicable disease.”

According to the website *AIDSandtheLaw.com* “if the applicant is not aware that HIV is such a disease under US immigration law, he or she could respond ‘no.’ In that case, the application would not be fraudulent. But if the applicant answers ‘no,’ while knowing that individuals with HIV are barred from entry, then the applicant has committed immigration fraud, which, if discovered, is a permanent, non-waivable, basis for inadmissibility.”<sup>5</sup>

### Timeline

**1987** President Reagan and Congress add AIDS to the list of “dangerous, contagious diseases for excluding persons from the United States.”

Senator Jesse Helms’ “Helms amendment” adds HIV to the exclusion list

**1989** Dutch HIV-prevention expert Hans Paul Verhoef jailed for four days in Minneapolis en route to an AIDS meeting in San Francisco, after AZT discovered in his suitcase.

**1990** Mass boycott of Sixth International AIDS Conference in San Francisco; thousands demonstrate.

**1992** International AIDS Conference moves from Boston to Amsterdam; Clinton campaign promises end to the ban by executive order.

**1993** Congress adds amendment to NIH Reauthorization Act adding HIV to the list of “communicable diseases for excluding people from the United States.” Clinton signs the bill, making the policy law.

**2001** 9/11 results in increased security and bag searches, increasing concerns that HIV medications would be found.

**2002** THT launches ‘End The Ban’ campaign.

### hiv+ tourists unwelcome

Armenia, Bangladesh, Brunei, Iraq, Libya, Moldavia, Oman, Qatar, Russian Federation, Salomon Islands, Saudi Arabia, Sri Lanka, South Korea, Sudan, USA.

## US travel health warning! continued

“The fear of being stopped by immigration officials is entirely understandable and is possibly more damaging than the reality,” notes Dr Churchill. “If you don’t realise what is at stake, health-wise, then you may think that stopping your drugs for a fortnight has less consequences than the potential of what could go wrong: ‘my holiday will be ruined, I’ll have to come straight back, my name will be forever be on a computer, I’ll never be able to go back there, I’ll have broken the law, they may even take it further, I may have to pay for all of this’...all those fears.”

### US fear culture

It seems that the US HIV visitor ban’s biggest impact is to create a culture of fear around travelling to the US.

The reasons given for temporarily stopping HAART in the Brighton study include a variety of fears. All ten had a fear of being searched at the airport and were afraid of their status being known to immigration. Three also feared that their drugs would be confiscated.

According to Robert Goodman, counselling supervisor for Brighton Body Positive, the psychological burden of “this insidious ban creates a great deal of apprehension for most HIV travellers to the US. The ‘culture of fear’ you mention I think sits alongside other feelings of anger, outrage, bitterness, and frustration. This may ‘feed’ other fears around living with HIV, such as being seen as ‘unclean’, being denied the choice not to disclose one’s status, the implications of that disclosure, and all other forms of discrimination that the HIV population experiences.”

“The fact that this is the position of one of the world’s most powerful nations feels deeply threatening – and fear-promoting – in itself.”

*AIDSandtheLaw.com* reports that the “Bureau of Citizenship and Immigration Services (BCIS)

has issued an ‘advisory’ policy regarding border inspections regarding HIV/AIDS. BCIS officials should not inquire about HIV status unless there are physical symptoms of illness or the individual makes an unambiguous and unsolicited statement of his or her status. Carrying literature pertaining to HIV/AIDS or related materials should not cause questioning regarding HIV status.”

“However, discovery of medications used to treat HIV illness may result in questioning and a referral for a medical examination. As a result, some travellers carry their HIV-related medication in unmarked containers. A written prescription pertaining to the medication, however, should be carried in order to comply with US customs laws.”

“If an individual with HIV is identified at the border, however, the BCIS has the authority to detain the individual indefinitely, without any right to release on bail. The individual has no right to counsel and may not be permitted to communicate with others who may be able to help the individual.”<sup>5</sup>

Since 69% of US visits in the Brighton study were for tourism – which, according the latest INS factsheet<sup>6</sup> is not a valid reason to be granted an HIV visa waiver – many (43.4%) were concerned that they would be denied a visa if they did declare their status.

However, the media often report conflicting and confusing (mis)information regarding who exactly is eligible for the HIV waiver, including this article from *The Guardian* two years ago. “Inadmissibility because of HIV/AIDS ‘is routinely waived’, a [US Embassy] spokesman said. ‘People are given visas and the waiver many times and do travel on holidays, business and as students. It is a public health issue. In some cases it is a financial concern as well. It is not saying there is anything wrong with the person.’”<sup>8</sup>

## Inadequate insurance

Despite the fact that 62% (n=215) of all respondents were aware that an HIV waiver was required, more than two-thirds (n=88) of all those who travelled to the US did so without adequate HIV medical insurance. This is not only risky, it is also another reason that the US says the HIV travel ban is in place: to make sure that foreigners do not place undue stress upon the US public health system.

Indeed, according to Section 212(a)(1)(A)(i) of the *Immigration and Nationality Act*: "The applicant must demonstrate that he or she is not currently afflicted with symptoms of the disease; there are sufficient assets, such as insurance, that would cover any medical care that might be required in the event of illness while in the United States; the proposed visit to the United States is for 30 days or less; and that the visit will not pose a danger to public health in the United States."<sup>9</sup>

Even though NAM, THT, *Positive Nation* and other HIV information resources make information available that explains that HIV-specific travel insurance is readily available for those who require it, Dr Churchill speculates that "few people want to disclose their HIV status to an insurance company. Or it could be as simple as: 'I just want to have a holiday, I don't want to have to think about all this stuff.'"

## A blunt instrument

Although one of the reasons for the US HIV ban is to control and monitor HIV-positive people entering the country, of the 135 who travelled to the US, only two (1.5%) actually travelled with an HIV waiver: 98.5% entered the country without the US knowing their HIV status. The most common reason (83%) given for not applying for an HIV waiver concerned disclosure to both the US and travelling companions.

"They think this law stops people with HIV from coming in unless they have a special waiver, and this is not the case," says THT's Kirk. "People keep coming in. It's a fairly blunt instrument and it's not working."

Ironically, if the law is there to prevent onwards transmission of HIV from foreign visitors, by forcing a significant minority into treatment

interruptions – which invariably leads to a rise in viral load and therefore, theoretically, a rise in the likelihood of transmission – it is counterproductive.

"I don't think they've thought it through," comments THT's Kirk.

## Please Mr Postman

The most surprising conclusion of the Brighton study was that those people who took up the option of mailing their drugs to the US were more likely to stop treatment than those who chose to carry their drugs with them.

This was because of the 12 people who attempted to mail their drugs ahead of time, only seven were successful (42%). This compares with 62/83 (75%) of those who took their drugs with them.

Of the five who were unsuccessful, two reported that their drugs did not reach the USA (most likely prevented from entering by US customs); one reported that their drugs arrived late; and a further two found that they were unable to mail their drugs at all. Since 9/11 the Post Office and courier firms now require a detailed description of the contents of any package sent to the US, with full details of the sender as well as the addressee. This makes the sending of antiretrovirals anonymously impossible, and once the sender includes their details, the same fears of discovery by US officials would then apply.

Consequently, Dr Churchill advises "to take enough medication with you to cover delays, as well as a letter from your doctor that doesn't mention HIV but does say that you need to be on these medications."

## key conclusions

If you are thinking of stopping your medications when travelling to the US it is imperative that you consult with either your HIV clinician or pharmacist before doing so, otherwise you run the risk of acquiring new or further resistance that could have significant future health risks. Remember also that if you do stop HAART that you may feel ill during your trip, and that you may also be more infectious.

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# no nukes?

## 6 is there a place for triple nucleoside haart in 2004? by megan nicholson

Hopes that triple nucleoside therapy could provide a simple and effective means of treating HIV have been severely quashed by the findings of several recent studies. In particular, it has been established that once-daily triple nucleoside regimens including tenofovir and abacavir are suboptimal, and switching to abacavir/ AZT/ 3TC (*Trizivir*) is associated with an increased risk of viral rebound.

Triple nucleoside therapy involves the use of only nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs). This single class approach has been promoted as a means of keeping protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) in reserve for later treatment.

However, current British and US antiretroviral guidelines do not endorse triple nucleoside regimens as first line treatment. According to guidelines published by the US Department of Health and Human Services (DHHS), *Trizivir* and abacavir/ d4T/ 3TC "should ONLY be used when an NNRTI-based or a PI-based regimen cannot or should not be used as initial therapy (e.g. for important drug-drug interactions)".<sup>1</sup> The British HIV Association (BHIVA) guidelines make a similar recommendation.<sup>2</sup>

The guidelines take an even tougher stance on tenofovir/ abacavir/ 3TC and tenofovir/ ddI/ 3TC. Following very poor efficacy in several studies, drug regulatory authorities in Europe and the US and pharmaceutical companies Gilead Sciences and GlaxoSmithKline have warned against the use of these two triple nucleoside regimens in any circumstances.

### First line therapy: *Trizivir*

The recommendation against the use of *Trizivir* (AZT/ 3TC/ abacavir) was made following the interim analysis of the ACTG 5095 study, which

showed that *Trizivir* alone was less effective than the efavirenz-containing combinations it was compared with in the study.

ACTG 5095 was a randomised, double-blind study comparing *Trizivir*, efavirenz/ AZT/ 3TC and efavirenz/ *Trizivir*. After an average of 32 weeks treatment, 79% of the triple nucleoside recipients had a viral load below 200 copies/ml compared with 90% of people taking efavirenz-containing HAART. After 48 weeks, the efavirenz arms of the study were performing significantly better than the triple nucleoside (89% versus 74% with viral load below 200 copies/ ml).<sup>3</sup>

A retrospective, non-randomised study of people who started efavirenz/ AZT/ 3TC or abacavir/ AZT/ 3TC confirmed this finding. The average time to treatment failure was 441 days in the triple nucleoside group and 1222 days in the efavirenz group.<sup>4</sup>

However, ACTG 5095 did not verify earlier findings that triple nucleoside therapy was less effective in people with baseline viral loads above 100,000 copies/ ml.<sup>5</sup> Instead, *Trizivir* was found to be less effective than recommended regimens regardless of baseline viral load.

In contrast to ACTG 5095, several earlier studies had suggested that *Trizivir* was roughly equivalent to indinavir/ AZT/ 3TC and nelfinavir/ AZT/ 3TC.<sup>5,6</sup> However, these combinations are no longer the yardstick of antiviral efficacy. Response rates of 40-58% (viral load below 50 copies/ ml at 48 weeks), as achieved in these studies, would now be regarded as below par. Recommended combinations with efavirenz or lopinavir/ ritonavir achieve undetectable viral load in up to 90% of participants in clinical trials.

Although the triple nucleoside arm of ACTG 5095 was halted because it was clearly less effective than the efavirenz-based combinations,

it still performed reasonably well with viral suppression in three quarters of patients at one year.<sup>7</sup> However, given the evidence that first line *Trizivir* is inferior to other combinations, both BHIVA and the US DHHS recommend that *Trizivir* should not be considered for first line therapy unless specific circumstances mean that more potent regimens cannot be taken.

### First line therapy: tenofovir/ abacavir

Tenofovir/ abacavir/ 3TC has also proved to be an inferior first line combination. The ESS30009 study compared once-daily tenofovir/ abacavir/ 3TC with efavirenz/ abacavir/ 3TC in treatment-naïve patients. Data on 194 people who completed at least eight weeks of treatment showed that 49% of those randomised to tenofovir/ abacavir/ 3TC were classified as virologic failures, compared to 5% in the efavirenz/ abacavir/ 3TC arm ( $p < 0.001$ ). Virologic failure was defined as a viral load reduction of less than 2 logs or an increase of 1 log following an initial drop in viral load.<sup>7</sup>

ESS30009 corroborated the findings of a pilot study of 19 people who took tenofovir/ abacavir/ 3TC. A high rate of non response or treatment failure was found, with only eight achieving a viral load reduction of 2 logs out to 16 weeks.<sup>8</sup>

Tenofovir/ abacavir/ ddI has also performed badly in a small pilot study of 24 treatment-naïve people. Twenty-two patients (91%) failed to achieve a 2 log reduction in viral load after 12 weeks of treatment. Of 21 people who underwent resistance testing, 95% had the M184I/ V mutation and 50% had the K65R mutation.<sup>9</sup>

As a result, the US DHHS have added tenofovir/ abacavir/ ddI and tenofovir/ abacavir/ 3TC to the list of combinations which should not be offered at any time.

### Not fully understood

The reasons these combinations have performed so poorly are not fully understood. Dr Martin Fisher of Brighton and Sussex University Hospitals told *ATU* that previously undescribed drug interactions, once-daily dosing, common resistance pathways, and inherent lack of potency may all have contributed to lower-than-expected efficacy.

“None of these individually stand up to scrutiny,” Dr Fisher said. “Initial data show no apparent

unexpected interactions, the Zodiac study<sup>10</sup> suggests that abacavir/ 3TC can be given once daily (with efavirenz), since not all individuals with virological failure demonstrate the K65R [mutation] common resistance pathways cannot explain all, and inherent lack of potency seems unlikely if one considers the individual drug effects on viral load when used as monotherapy. It may be that there are components of each that add up to explain the findings.”

Dr Joel Gallant, one of the authors of the ESS30009 study, has discussed the reasons for the poor performance of tenofovir/ abacavir/ 3TC on the Clinical Care Options website. Although he admits that there is a possible role for dosing and drug interactions, his focus is on the issue of resistance. Genotypic data on 36 people in the ESS30009 study found all had the M184V mutation associated with resistance to 3TC and abacavir, and 23 (64%) had the K65R mutation associated with resistance to tenofovir and abacavir. The overlapping pathways to resistance of the three drugs in this combination may be a major factor in its poor clinical efficacy.<sup>11</sup>

However, some people have failed the tenofovir/ abacavir combinations without detectable resistance, suggesting that other factors are at play. In the pilot study of tenofovir/ abacavir/ 3TC, only one third of people with treatment failure had the K65R mutation but nine had a baseline viral load over 100,000 copies/ ml. This points to a possible lack of potency with the once-daily tenofovir/ abacavir combinations.

### First line: other triple nuke regimens

Two randomised studies – CLASS and Atlantic – have compared d4T-containing triple nucleoside regimens with PI and NNRTI-based regimens. The CLASS study found that the efavirenz regimen was superior to ritonavir-boosted amprenavir and d4T regimens when combined with abacavir/ 3TC after a year.<sup>12</sup> In the Atlantic study, the d4T-containing regimen was inferior to nevirapine and nelfinavir when combined with ddI/ 3TC after two years of therapy.<sup>13</sup>

A Danish team has compared three first line regimens in 180 people. Once again, the triple nucleoside regimen performed badly: 43% of people taking d4T/ abacavir/ ddI had viral load below 20 copies/ ml after 48 weeks compared

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## Triple NRTI study chart

Regimen	Trial	Number of naive patients	Time	Results
TNF/ ABV/ 3TC vs EFV/ NRTIs	ESS30009 Gallant 03	194	12 weeks interim	49% TNF vs 5% EFV without virological response (-2 log or 1 log rebound after initial response)
TNF/ ABV/ 3TC	Farthing 03	20 (3 dropped out)	16 weeks	9/ 17 had viral rebound
TRV vs EFV/ AZT/ 3TC vs EFV/ TRV	Gulick 03 ACTG 5095	1147	48 weeks	74% TRV vs 89% EFV arms VL < 200 copies/ ml. BL VL >100,000 copies/ ml didnt impact on response
TRV vs IDV/ AZT/ 3TC	Staszewski 01	562	48 weeks	40% TRV vs 46% IDV <50 copies/ ml. BL VL >100,000 31% TRV vs 45% IDV <50 copies/ ml
TRV vs NFV/ AZT/ 3TC	Matheron 03	195	48 weeks	57% TRV vs 58% NFV < 50 copies/ ml
TNF/ 3TC/ ddi	Winston	24	12 weeks	91% failed to reduce VL by 2 log

abacavir = ABV, baseline = BL, efavirenz = EFV, indinavir = IDV, nelfinavir = NFV, tenofovir = TNF, *Trizivir* (AZT/ 3TC/ ABV) = TRV, viral load = VL, 3TC = lamivudine

with 69% of people on nevirapine/ nelfinavir/ AZT/ 3TC and 62% of the ritonavir/ saquinavir/ AZT/ 3TC group.<sup>14</sup>

These studies point to the inferiority of d4T-containing triple nucleoside regimens compared to recommended highly active antiretroviral therapy (HAART), which may be due in part to the role of d4T-associated side effects in treatment failure.

In the UK, d4T is no longer recommended as first line therapy because of its association with long-term toxicities, including lipoatrophy. Furthermore, US guidelines now recommend against the d4T/ ddi nucleoside 'backbone'.

### Triple nukes for switch maintenance?

Triple nucleoside regimens are sometimes used to simplify dosing or to reduce toxicities in people who are on suppressive NNRTI- or PI-based HAART. This approach has been dubbed 'switch-maintenance' therapy.

Several studies have looked at the use of triple nucleoside regimens in this context.

An early randomised study reported that replacing a PI with abacavir was associated with sustained viral suppression and improved lipids.<sup>15</sup> However subsequent studies have not been as encouraging, suggesting that abacavir is not the best switch option.

A Spanish study called NEFA was published in the *New England Journal of Medicine* in September 2003.<sup>16</sup> Four hundred and sixty people who had a viral load suppressed to below 200 copies/ ml for at least six months were randomised to replace their PI with either efavirenz, nevirapine, or abacavir. After twelve months follow-up abacavir-treated patients showed a trend towards greater likelihood of viral rebound. However, rebound was most common among people who had previously taken suboptimal dual or single NRTI therapy, as found in a previous *Trizivir* 'switch-maintenance' study.<sup>17</sup> This indicates that people with underlying NRTI resistance may be most vulnerable to treatment failure when switching to a triple nucleoside regimen.

A meta-analysis of nine randomised studies confirmed that a switch to abacavir is associated with increased risk of viral rebound, although the extent to which prior suboptimal nucleoside treatment contributed to this higher failure rate is not clear.<sup>18</sup>

Another important switching study, known as Trizal, investigated a switch from PI- or NNRTI-based therapy to *Trizivir*. Sponsored by GlaxoSmithKline, the marketers of *Trizivir*, and conducted in nine European countries, 219 people with viral load below 400 copies/ ml with an average CD4 count of approximately 500 were randomised to

continue their PI or NNRTI, or to switch to *Trizivir*. There was no difference in the rate of treatment failure between the two groups (22% of each group stopped treatment due to viral rebound or adverse events).<sup>19</sup>

## Some benefits

Despite the evidence of poorer virological outcomes with triple NRTI therapy, studies have found some benefits associated with the *Trizivir* switch. In the NEFA study, people taking abacavir were less likely to report side effects and were less likely to stop treatment due to toxicity. Another positive feature of the triple nucleoside regimen was the improvement in blood lipids after the switch to abacavir. Improvements in cholesterol (but not triglycerides) were also reported among switchers in the Trizal study.

Given that *Trizivir* involves simply taking one pill twice daily, it is not surprising that some *Trizivir* 'switch-maintenance' studies have reported boosted patient adherence to medication.

The benefits of switching to *Trizivir*, in terms of improved adherence and lower cholesterol, point to the potential usefulness of *Trizivir* for people struggling with complex dosing or high pill burden, and those who develop elevated lipids.

Despite inferior efficacy, there remains a role for *Trizivir* in treatment-experienced people in some contexts. For example, for a person with resistance to the NNRTIs who is experiencing high lipids on PI-based therapy may consider a switch to *Trizivir*. Alternatively, a person commencing treatment for tuberculosis may elect to take *Trizivir* for the duration of their TB therapy to minimise the risk of drug interactions.

However, the potential role of *Trizivir* should not be extrapolated to all triple nucleoside regimens. For instance, data shows that

replacing a suppressive HAART regimen with tenofovir/ abacavir/ 3TC is a risky strategy. A small pilot study from the Netherlands found that five of eight people who made such a switch experienced virological failure after an average of 19 weeks. None had previously experienced virological failure, yet four of the five had developed key NRTI resistance mutations at positions 194 and 65.<sup>20</sup> As noted above, US guidelines recommend against the use of tenofovir/ abacavir/ 3TC and tenofovir/ abacavir/ ddI under any circumstances.

## A future for triple nukes?

Leading UK HIV clinician, Dr Martin Fisher acknowledges an ongoing role for *Trizivir* in patients experiencing adherence difficulties, side effects, or drug interactions due to use of other medications. In particular, the use of *Trizivir* may become more attractive when doctors begin screening patients for abacavir hypersensitivity using a genetic test that is currently available but not widely used. However, Dr Fisher adds that *Trizivir* should not be used if there has been prior treatment with nukes in a non-suppressive regimen.

The poor results with tenofovir/ abacavir/ 3TC highlight the importance of treatment decisions that are informed by clinical trial evidence. "I think this serves as a reminder that we still live in an era of uncertainty and practice should still be data driven," comments Dr Fisher. "These unorthodox triple nuke combinations (TDF/ ABC/ 3TC and ddI/ 3TC/ TDF) should be avoided completely."

Although triple nucleoside therapy took a battering in 2003, there is still hope that four-drug nucleoside/ nucleotide treatment may be effective. So far, ongoing UK and US studies involving tenofovir/ *Trizivir* have not been discontinued, suggesting no early evidence of poor performance.

## glossary

**adherence** the act of taking a treatment exactly as prescribed.  
**genotype** the genetic make-up of an organism.  
**lipid** a general term for fats.  
**lipatrophy** loss of body fat.  
**mutation** a single change in gene sequence.  
**nucleoside (analogue)** family of antiretrovirals which includes azt, ddi, ddc, 3tc, d4t and abacavir.  
**nucleotide (analogue)** family of antiretrovirals which includes tenofovir.  
**nnrti** non nucleoside reverse transcriptase inhibitor, the family of antiretrovirals which includes efavirenz, nevirapine and delavirdine.  
**protease inhibitor** family of antiretrovirals which target the protease enzyme. includes amprenavir, indinavir, lopinavir, ritonavir, saquinavir, nelfinavir, and atazanavir.  
**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.  
**toxicity** the extent or ways in which a drug is poisonous to the body.  
**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.  
**virologic failure** a term to describe when an anti-hiv medication is no longer controlling hiv replication.

## key conclusions

- Tenofovir/ ddI/ 3TC: should not be used at any time due to extremely poor efficacy.
- Tenofovir/ abacavir/ 3TC: should not be used at any time due to extremely poor efficacy.
- *Trizivir* (AZT/ 3TC/ abacavir): not recommended as first line therapy because less effective than recommended first line regimens. May be used where alternative regimens will cause more severe toxicities, drug interactions, or regimen complexity, but poor efficacy in those with prior NRTI resistance.

For more about the what the Dica case means to English law and HIV transmission, see Issue 131 of *ATU* (November 2003) which is now available online at [www.aidsmap.com/publications/atu/index.asp](http://www.aidsmap.com/publications/atu/index.asp)

## HIV transmission legal briefs

Since last October's first successful prosecution of HIV transmission in England and Wales resulted in an eight year prison sentence for Mohammed Dica after infecting two women with HIV and being convicted of grievous bodily harm, several other prosecutions have taken place.

Less than two weeks after Dica's sentence, another man was charged with the more serious offence of grievous bodily harm with intent. Although not yet brought to trial, it is alleged that Malawi-born Teesside resident Feston Konzani, 27, deliberately infected two women and a teenage girl with HIV between February 2000 and May 2003. This more serious offence carries a maximum penalty of life imprisonment.

Last month in Liverpool, a 40-year-old South African man, Kouassi Michel Adaye, was convicted of grievous bodily harm after he pleaded guilty of infecting a 48-year-old woman with HIV. Judge David Lynch told the man, "I cannot imagine a greater degree of grievous bodily harm than infecting a person with a virus of this nature," before passing a six year sentence, with an order for his deportation to South Africa on his release from prison.

The same week, a San Francisco Superior Court judge threw out a high profile HIV transmission prosecution after finding insufficient evidence to support charges that a former San Francisco health commissioner had intentionally infected his sexual partners with HIV. This came after the first-ever judicial review of a 1998 California law against knowingly and deliberately infecting partners. The review found that the law means that someone could not be prosecuted simply for withholding his or her HIV status from a partner.

## Efavirenz levels affect sleep

The February 1st edition of *Clinical Infectious Diseases* features a report that high blood concentrations of efavirenz (Sustiva) are correlated with poor sleep.

This Spanish study also found that compared to those people taking efavirenz without sleep disturbances, and HIV-negative controls, those who had sleep problems whilst taking efavirenz were more likely to have reduced sleep efficiency, to spend more time awake during the night, to have less REM sleep, and to wake up more often during the night.

Poor sleep efficiency was almost twice as common in those who had peak plasma concentrations of efavirenz measuring 4mg/L or more, compared to those with lower peak plasma levels (62.5% versus 37.5%,  $p=0.04$ ) and the authors suggest that measuring efavirenz levels through therapeutic drug monitoring (TDM), and consequently adjusting the efavirenz dose might solve the problem. Currently TDM is not routinely performed in the UK. However, if you are having sleep problems with efavirenz, it is worth asking your HIV clinician if TDM might be a useful tool to help overcome what appears to be a relatively common problem that can seriously affect quality of life.

*Gallego L et al. Analyzing sleep abnormalities in HIV-infected patients treated with efavirenz. CID 38 (3):430-432, 2004.*

### new-fill update

*New-Fill* is now available at the Bloomsbury Clinic, Mortimer Market Centre, London. Also, in last month's *ATU*, we listed the wrong address and phone number for accessing *New-Fill* in Portsmouth. The correct details are: St Mary's Hospital GUM Department, Milton Road, Portsmouth, PO3 6AD. Tel: 023 9286 6796. Dr Harindra's name and email address were correct, however. Additionally, it appears that not everyone who wants *New-Fill* in Manchester can access it through the clinical trial run by Dr Chapondra. Apologies to those inconvenienced.

## T-1249 on hold

New concerns about what to use after *Fuzeon*, the expensive new fusion inhibitor from Roche, also known as T-20, fails in salvage therapy, have emerged since Roche's announcement last month that its experimental second-generation fusion inhibitor T-1249 will not be suitable for large scale trials.

Although uptake of *Fuzeon* in the UK has been slow since its approval last year, some who have accessed the drug have already developed resistance to it, and were hoping that T-1249 would provide another chance at salvage therapy. Last year, a small T-1249 study showed that after ten days, people who had experienced viral load rebound on T-20 had sustained viral load reductions when treated only with T-1249.

However, Roche have now discovered that the formulation of T-1249 is not suitable for large-scale production, and have gone back to the drawing board, delaying its development by at least several years. With new agents unlikely to be available for T-20 resistant patients until 2006 – Pfizer's chemokine antagonist UK-427,857 is the most likely candidate – choosing an optimal background regimen, and combining *Fuzeon* with at least one other new antiretroviral to which your virus may still be susceptible now appears to be more important than ever.

## Durex finally removes dangerous spermicide from condoms

SSL International Plc, the makers of Britain's best-known condom brand, Durex, have finally agreed to stop producing condoms containing nonoxynol-9 (N-9), four years after the disgraced spermicide was proven ineffective against preventing HIV infection.

N-9 blocks HIV infection of cells in the test tube. However, a 2000 study from Phillips and colleagues found that it causes inflammation of the vagina and cervix and shedding of cells from the lining of the rectum. Additionally, there is no evidence that N-9 reduces the incidence of any sexually transmitted infections and its use may actually increase the likelihood of HIV transmission.

It is particularly important that products containing N-9 should not be used for anal sex. Since many heterosexual couples practise anal sex on occasion, it seems unreasonable to expect them to decide in advance, when buying condoms, on what sort of sex they are going to have.

There is an even greater risk for gay men, since in many settings they are more likely to be exposed to HIV, yet there is evidence that gay men continue to use N-9 products despite publicity that these are dangerous.

A survey of gay men in San Francisco carried out in 2001 – a year after the publication of data showing that N-9 may increase the risk of HIV transmission – found that of the 349 men out of 573 who had heard of N-9, 55% had used products containing it for anal sex in the previous year. It had been used in a median of 50% of acts of anal sex in the past twelve months and 23% had actually used it without a condom in the mistaken belief that it reduced their risk of HIV infection.

Other companies, including Johnson and Johnson, manufacturers of the popular lubricant KY have already ceased making products containing N-9. However, there had been resistance from SSL to calls to remove 'spermicidal lubrication' with N-9 from their products, because they perceived that it met a demand for 'extra safety' from some users.

However, in a statement released last month, the company who make Durex said: "SSL is anticipating a material reduction in demand for spermicidally-lubricated condoms following a recent WHO report which questioned the level of additional protection provided by such condoms when compared to non-spermicidally lubricated condoms."

"In light of this, SSL decided to discontinue using the spermicide N9 in our condom manufacturing process."

In the UK, the only condom made by Durex that still contains N-9 is the, ironically-named, *Extra Safe* brand. All other Durex condoms, including *Ultra Strong*, contain a non-spermicidal lubricant and are safe to use.

According to recent studies, regular thickness condoms for anal sex are just as safe as thicker condoms, as long as they are used with plenty of water-based lubricant and do not contain N-9. Those that do contain N-9 will say so on the label.

### nam news

#### friends of nam

This month we will be inviting *ATU* readers and others to become a 'Friend of NAM' and to support our work with a monthly donation. With your assistance we can provide an increasing number of people with free information resources - like *ATU* and [aidsmap.com](http://aidsmap.com) - resources that help people live longer, healthier lives. When you receive a letter from Caspar Thomson, NAM's director, later this month, please seriously consider supporting our work.

#### nam forum

The next forum will take place on Monday March 1st and focus on reporting the most important information gleaned from the 11th Conference on Retroviruses and Opportunistic Infections (CROI), held this year in San Francisco, and generally considered to be the major scientific HIV/AIDS meeting of the year. Usual time (7-9pm), usual place: University of London Union, Palms Room, 4th Floor, Malet Street, London, WC1. See [www.aidsmap.com](http://www.aidsmap.com) for a map and more details.

#### march atu

Next month's issue will feature an article on the latest UK guidelines for providing Post Exposure Prophylaxis (PEP) after accidental sexual transmission of HIV.

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For more information, and details of our other publications and services, please contact us, or visit our website, [www.aidsmap.com](http://www.aidsmap.com).

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