

# aids treatment update

## HAART & HIV transmission

Writing in the medical journal, *The Lancet*, this year, Elliot Marseille of the Center for AIDS Prevention Studies at the University of California, caused controversy when he suggested that, in sub-Saharan Africa, an ounce of HIV prevention was worth rather more than a pound of HIV treatment. How best to spend inadequate resources is undoubtedly a very different problem for AIDS policy makers in Africa than for those in San Francisco. Nevertheless, even in well-resourced settings, from the beginning of the epidemic, prevention and treatment have been viewed competitively.

In this month's *ATU*, our lead article considers the complex relationship between the two. In both the sexual and vertical transmission of HIV, the probability of transmission is associated with viral load – the higher the viral load, the higher the risk. Anti-HIV drugs are extremely effective in preventing mother-to-baby HIV transmission, but their effect on sexual transmission is more difficult to understand. HAART's effect appears much more than biological, though this effect is central to the equation – reductions in viral load in the blood are often, but not always, accompanied by reductions in virus in the genital areas. The evidence suggests that for some gay men – though clearly not all – viral load levels may influence sexual activity and practice. Treatment-driven health improvements may foster renewed interest and confidence in sexual relationships. In other words, there are many variables to this issue – even if effective treatment reduces infectivity substantially, any potential benefit in terms of reduced transmission may be offset if those receiving treatment not only live longer but also engage in more risky behaviour.

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# haart & hiv transmission

2 moves to widen global access to anti-HIV drugs are raising debate over the relative merits of treatment and prevention, but must the two be seen to be in conflict? by edwin j bernard

Since 1996, the widespread use of Highly Active Antiretroviral Therapy (HAART) in wealthy, industrialised countries has resulted in a sharp decline in AIDS mortality and a significant improvement in the general health of people infected with HIV.

Although there are no conclusive data on use of HAART and the risk of sexual HIV transmission, there are good biological reasons to assume that, in general, the use of HAART may lower the probability of transmission. This, in turn, ought to mean that in populations where the majority of those infected with HIV are on HAART, the sexual transmission of HIV should be declining. But epidemiological data on men who have sex with men (MSM) in the United States and the UK show that, at best, the number of new infections of HIV has remained stable, and, in some cases, has actually increased.

What then, is the relationship between HAART and HIV transmission? Has treatment succeeded and prevention failed? And what are the future public health consequences for both the industrialised and developing worlds?

## HAART and infectiousness

Although we do not know for certain that HAART reduces the probability of HIV transmission, there is a mounting body of evidence that suggests that reductions in viral load in blood caused by HAART correlate with the amount of HIV in semen<sup>1</sup>. But this is not always the case, and it is not easy to predict who will shed HIV via genital secretions and when. Dr Steve Taylor, Clinical Research Fellow and Specialist Registrar in

GU & HIV Medicine at Birmingham Heartlands and Coventry Hospitals, is known for his expertise in this area. He and his colleagues have found that a significant minority of men continue to shed HIV in their semen despite HAART. "As a generalisation, seminal plasma viral load tends to be about one log lower than corresponding blood plasma viral load," he says. "However, there are individuals in whom the seminal plasma viral load is in excess of the blood plasma viral load. There appears to be a handful of such people in each cohort studied."

Additionally, recent studies by Dr. Taylor and others have shown that not all antiretrovirals penetrate into the seminal plasma equally<sup>2</sup>. "All protease inhibitors [PIs], with the exception of indinavir and to a lesser extent amprenavir, reach the semen at low concentrations, at around 5% of blood levels," he notes<sup>3</sup>. "When indinavir is combined with ritonavir, seminal plasma levels of indinavir can exceed blood plasma levels, although this does not appear to be the case when ritonavir is combined with other PIs<sup>4</sup>."

Both currently approved NNRTIs, nevirapine<sup>5</sup> and efavirenz<sup>6</sup>, appear to reach therapeutic levels in the semen. However, data on the nucleoside analogues are less clear. "AZT and 3TC appear to accumulate in semen," Dr. Taylor says. "There are less data on abacavir, ddI and d4T but [these] suggest that they all reach the semen at therapeutic concentrations."

## Research needed on receptive partners

Though the focus of current clinical research remains somewhat phallogocentric, the effect of

HAART on the genital tracts of the male or female receptive partner is also important, and needs to be considered when it comes to sexual transmission of HIV. Limited data suggest that HAART penetration into female genital secretions is similar to that of the male genital tract, although there is evidence that detectable amounts of HIV may be found in both cervicovaginal fluid<sup>7</sup> and anorectal tissue<sup>8</sup> despite HAART. Kovacs and colleagues found that 27 of 83 women on HAART had detectable levels of HIV in their cervicovaginal fluid, despite having blood plasma viral load of below 500 copies. Brodie and colleagues found that the rectal mucosa is a site of persistent HIV replication and shedding, and that treatment with HAART did not reduce HIV to untransmittable levels in many patients.

“I think that one must assume that a person with HIV is always infectious,” asserts Dr. Taylor. “This is what I tell my patients.”

### Other factors at play

It is also clear that other factors besides HAART must be taken into account when it comes to the sexual transmission of HIV.

“I think sexually transmitted infections are hugely important in influencing the infectiousness of individuals,” says Dr. Taylor. “There are biological data to suggest that these infections can increase the amount of virus in both semen and cervical secretions in the developing world<sup>9</sup>. There are much less data from the developed world,” Dr. Taylor notes, “but we are currently investigating the effects of sexually transmitted infections on seminal shedding in a UK study. So far we have found that four out of six of the unsuppressed individuals had multi-drug resistant mutations in their semen, some at high levels<sup>10</sup>.”

“The other crucial factor is sexual behaviour,” states Dr. Taylor. “The potential benefit of reducing a person’s infectiousness with drugs may be entirely compromised if high risk sexual behaviour increases and the incidence of sexually transmitted infections continues to rise among people with HIV.”

### HAART and sexual transmission

The only clinical data so far on the effect of antiretrovirals on sexual transmission are from observational cohorts or retrospective analyses of heterosexual couples. In 1994, use of AZT was associated with a 50% reduction in the risk of HIV transmission from 436 heterosexual men to their female partners<sup>11</sup>. In 2000, Quinn and colleagues found that no HIV transmission was observed in 90 monogamous, serodiscordant heterosexuals in Uganda when blood plasma viral load was less than 1,500 copies<sup>12</sup>. The following year, using the same cohort, Gray and colleagues calculated that when blood plasma viral load was less than 3,500 copies, transmission probability was 1 per 10,000 acts of unprotected vaginal intercourse. This rose to 1 in 200 when viral load was 50,000 copies or more<sup>13</sup>. Clearly more clinical data are needed.

The HIV Prevention Trials Network is currently planning a large-scale, randomised study (HPTN052) to evaluate the effect of HAART on HIV transmission. This study will last five years, examines heterosexual couples, and takes place in developing countries. There are no plans to study HAART and HIV transmission in men who have sex with men.

### HAART and sexual behaviour in MSM

At the recent International AIDS Conference in Barcelona, UK figures on HIV incidence in MSM between 1995 and 2000 showed that HIV transmission in this group is continuing at the same level despite widespread HAART<sup>14</sup>. Figures from San Francisco<sup>15</sup> show that HIV transmission amongst MSM in the city is actually rising. Epidemiological studies and mathematical modelling go some way to explain why this is happening.

In the gay community, the success of HAART in the treatment of HIV has affected sexual behaviour at both individual and community levels. Some recent epidemiological studies have shown that ‘HAART optimism’ (a term that can mean many different things depending on the study, but in general relates to the feeling that HIV is less of a concern since the advent of HAART) plays a factor in the individual’s decision-making regarding

### glossary

Glossary words are found on pages 7 and 10.

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## haart & hiv transmission continued

safer sex<sup>16</sup>. But an international comparison of MSM in Australia, Canada, France and the UK<sup>17</sup> could not detect a significant association between 'HAART optimism' and risky behaviour, and another study concluded that perceptions of HIV risk were often at odds with actual sexual behaviour<sup>18</sup>.

A recent study from San Francisco<sup>19</sup> found that a significant minority of gay men were using viral load levels to make decisions about unsafe sex. But another study from Amsterdam found that whilst men on HAART were having more risky sex than before HAART, men *not* on HAART with very high viral loads were also having more risky sex<sup>20</sup>, suggesting that perceptions regarding risky sex have changed within the gay community as a whole.

A group of epidemiologists from Canada have developed a behavioural model suggesting that a "large fraction of individual behaviour changes may be due to the pressure exerted by a new sexual environment, rather than a cognitive process (e.g. prevention fatigue or complacency)"<sup>21</sup>. In other words, the effect that HAART has had on the gay community as a whole – the overall reduced mortality and morbidity of AIDS – has renewed the sexual vigour of the whole community. Since more people feel that HIV is less harmful than before, and there are more people with HIV having sex, individual and community behaviours act to enhance each other.

Recent models from the US and Australia have suggested that HAART can reduce HIV transmission and make a difference to the scale of the HIV epidemic within that community<sup>22</sup>. But increases in risky behaviour could mean the benefit of HAART is outweighed. In 2000, Blower and colleagues predicted that even a 10% increase in unsafe

sex amongst gay men in San Francisco would mean that the HIV incidence rate would increase, despite HAART. This was confirmed by studies showing that a greater than 10% increase of unsafe sex *was* occurring in San Francisco<sup>23</sup>, and empirical data from the San Francisco Department of Public Health<sup>24</sup> which showed that although more than 70% of MSM with AIDS were on HAART in 2000, the incidence of new HIV infections amongst MSM doubled from approximately 2% in 1998 to around 4% in 2000.

### HAART, transmission and resistance

Recently, there has been much interest in the public health ramifications of the sexual transmission of HAART-resistant virus. This year there have been conflicting reports claiming there has either been a rise or a decline in the number of people who are acquiring resistant strains of HIV sexually. According to a recent US study<sup>25</sup>, resistance to at least one antiretroviral increased from 3.4% in the period 1995-1998 to 12.4% in the period 1999-2000, and multi-drug resistance increased from 1.1% to 6.2% in the same timeframe. The picture is not the same everywhere that HAART is in use, however. A group of Spanish researchers recently found that prevalence of antiretroviral drug resistance mutations fell during a similar period<sup>26</sup>. Explaining the differences in these findings, Dr Taylor states: "The study populations are extremely diverse, as are the definitions of newly-infected individuals. The bottom line is that drug resistant HIV can be transmitted."

Complicating matters is the fact that resistance in the blood and semen are not always concordant<sup>27</sup>. "Some studies have found that resistance develops first in the genital tract, and others that resistance can occur in the blood but be absent in the genital tract," says Dr Taylor. "Most of the cases that we have investigated so far have identical mutations in blood and semen<sup>30</sup>, but more data are required."

### HAART and HIV prevention

It is entirely possible that it is not chronically-infected people with HIV on HAART who are

responsible for the majority of new sexual transmissions, but those who are currently untested, untreated, or experiencing primary infection<sup>29</sup>. Since it has proven difficult to detect and treat those who have recently acquired HIV sexually, research is beginning on the effectiveness of anti-HIV drugs as pre-exposure prophylaxis in high-risk individuals, as reported in August's *ATU*.

In resource-poor countries, where the majority of people infected with HIV are untreated, it has been argued that the availability of HAART will provide more incentives for testing, leading to more people on treatment, and theoretically, a reduction in the prevalence of sexually transmitted HIV.

Despite the uncertainties and limitations of HAART as a prevention tool, many prominent figures are advocating that in the absence of a vaccine, HAART remains the most promising currently-available method to prevent transmission of HIV on a global scale. The Pan-African HIV/AIDS Treatment Access Movement recently issued a policy document outlining their demands for the future: "We insist that access to [HAART] is not only an ethical imperative, but will also strengthen prevention efforts, increase uptake of voluntary counselling and testing, reduce the incidence of opportunistic infections, and reduce the burden of HIV/AIDS on families, communities, and economies."

Others argue that HAART is too difficult, too expensive, too likely to lead to large-scale drug resistance and too prone to divert resources from other priority health investments. Marseille and colleagues wrote recently in *The Lancet* that "Data on the cost-effectiveness of HIV prevention in sub-Saharan Africa and on [HAART] indicate that prevention is at least 28 times more cost effective than HAART. We aim to show that funding HAART at the expense of prevention means greater loss of life<sup>30</sup>."

For some, these same criticisms might be levied towards prevention activities. Professor Brian Gazzard, commenting on *The Lancet* paper said: "The data that we have on

effective prevention measures are very poor, and even if the costs of prevention are modest compared with the cost of HAART, if it does no good it is still expensive."

### More hard data needed

At a meeting in Atlanta earlier this year, a panel of experts discussed the role of HAART and prevention<sup>31</sup>. The contrasting needs of the individual as opposed to public health benefits were weighed, and it was felt that there were no conclusive data supporting the use of HAART in all people with HIV as a way to reduce transmission (though clearly there are other reasons for its use); individual health needs must come first, they concluded.

In the absence of hard clinical data, it is impossible to conclude that HAART reduces sexual HIV transmission at a community level. It is imperative, however, that further clinical research is completed in a timely manner in both heterosexual and MSM populations, in both industrialised and developing countries. Until then, prevention campaigns must attempt to bridge the gap between perceptions about HAART, HIV infectivity and individual and community behaviour, and encourage safer sex; and more effort must be made to prevent, diagnose and treat all sexually transmitted infections.

### key conclusions

- Anti-HIV therapy (called HAART) which suppresses viral load in the blood may also reduce viral load in genital fluids and linings, but this is not always the case.
- Some people with undetectable viral load on HAART continue to shed HIV in their genital fluids. This means that people taking HAART who have undetectable viral load should not assume that they are no longer infectious.
- The use of HAART may reduce HIV transmission within communities, but this will be influenced by many local factors; including the incidence of sexually transmitted diseases, and the prevalence of behaviour which presents a risk of HIV transmission.

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# new nrti backbones

drugs from the nucleoside analogue class continue to be the foundation of anti-hiv therapy: how will new treatment options affect how haart's backbone is chosen? by anna poppa

Long before the approval of NNRTIs and protease inhibitors, the first antiretrovirals to be used to treat HIV were AZT, ddI and other drugs from the nucleoside analogue reverse transcriptase inhibitor (NRTI) class. In most cases, the foundation of HIV treatment continues to be a combination of two NRTIs. The availability of six licensed NRTIs, plus the recent addition of a similar drug, tenofovir, seemingly offers ample choice for HAART's dual backbone. But are some backbones stronger than others, and how has access to newer options changed prescribing habits?

## How to choose

As there is no clear agreement over which is the best HIV drug combination, individuals select a regimen by considering the following:

- potency against HIV (in the blood and in other body compartments)
- dosing requirements
- side-effect profile
- resistance profile
- potential for interactions with other medicines.

## Comparing efficacy of older regimens

Historically, several studies have compared dual NRTI combinations (with or without an additional drug) in people new to treatment; the setting where drugs are likely to perform best. Generally, studies have found most dual NRTI combinations are comparable in terms of ability to suppress HIV. Key trials are reviewed here.

The Ozcombo and START I and II trials investigated the use of dual NRTIs with

indinavir (a protease inhibitor). In Ozcombo, after 52 weeks on treatment, there were no differences in viral load or CD4 response amongst 109 people receiving indinavir with either AZT/3TC, d4T/3TC or d4T/ddI. Fifty-eight per cent had viral loads below 50 copies after one year, from a baseline average over 100,000 copies<sup>1</sup>.

START I compared d4T/3TC/indinavir with AZT/3TC/indinavir in 204 people, and found no differences in virological or immunological response after 48 weeks. In both arms, 49% had viral load below 50 copies at this point<sup>2</sup>.

START II compared d4T/ddI/indinavir with AZT/3TC/indinavir in 205 people. After 48 weeks, there was no significant difference in the virological response; 41% and 35% of the d4T/ddI and AZT/3TC arms respectively had viral loads below 50. However, those on d4T/ddI had a greater CD4 count response; an average rise of 214 versus 142 cells<sup>3</sup>.

The French ALBI study (ANRS 070) of 151 people who received d4T/ddI or AZT/3TC for six months, or both combinations sequentially for three months, reported a difference in potency. Those receiving d4T/ddI had significantly greater viral load suppression and CD4 count rises compared to those receiving AZT/3TC or those who took sequential d4T/ddI and AZT/3TC<sup>4</sup>.

A more recent trial, ACTG 384, reported quite different results (see *ATU 116*, available on [aidsmap.com](http://aidsmap.com)). Briefly, this strategy trial compared the NRTI backbones AZT/3TC with d4T/ddI, when taken alongside efavirenz,

nelfinavir, or both these drugs. AZT/3TC was found to be superior to d4T/ddI in delaying regimen/virological failure when taken with efavirenz. There was no difference in the performance of the regimens when nelfinavir was used. This study reported that side-effects were more common in d4T/ddI recipients<sup>5</sup>.

Comparatively few studies have investigated the role of ddC within dual NRTI combinations, largely because the Delta study (a trial which was very important in establishing combination therapy as the way forward in HIV therapeutics) found that treatment-naïve recipients of AZT/ddI survived longer than recipients of AZT/ddC<sup>6</sup>.

### CNS penetration

Of all the currently licensed NRTIs, AZT penetrates the central nervous system (CNS) most effectively, and has been linked to a substantially reduced risk of developing HIV brain disease such as dementia. Small studies have suggested that d4T, 3TC and ddI also cross the blood-brain barrier to some extent, but their effectiveness against dementia has not been evaluated.

Abacavir crosses the blood-barrier barrier about as well as AZT. In study CNAB 3001, abacavir was added to the background anti-HIV therapy of 99 people with mild to moderate AIDS Dementia Complex. Over 12 weeks, both those who received abacavir and those who did not, experienced improvement in neuropsychological performance. The vast majority of participants were found to have NRTI resistance mutations in their virus at the time abacavir was added, which is known now to have an important influence on the success of abacavir therapy<sup>7</sup>.

### Resistance between NRTIs

Our understanding of the evolution of resistance patterns in people taking NRTIs continues to grow. Despite cross-resistance between drugs in this class, people who switch from a first dual NRTI combination to a second usually gain some benefit unless they have a high level of resistance to their first combination. However, d4T and AZT are now regarded as 'fully' cross resistant, so it's

unlikely that one of these drugs could be successfully replaced by the other if resistance has emerged.

Relationships between other NRTIs are less clear, though our understanding is evolving. Of late, Gilead Sciences have been praised for their attempts to categorise responses to their new NRTI tenofovir, based on the presence of NRTI resistance mutations in recipients of the drug (see *ATU* issue 109).

More recently, Pozniak and colleagues from the Chelsea and Westminster Hospital, London, reported new information on clinical cross resistance between 3TC and ddI<sup>8</sup>. Resistance to 3TC has been suspected of causing resistance to ddI (because the 3TC 'signature mutation', M184V, has been shown in test-tube studies to contribute to ddI resistance). Pozniak reported data from 281 people who switched from a 3TC-containing regimen to one including ddI. Viral load response on the new regimen was not affected by the presence of the 3TC resistance mutation at the time of switching.

Response to abacavir is impaired by the presence of the main 3TC mutation (M184V), particularly when three or more AZT resistance mutations are also present. In practice, this means that people who took AZT as a single treatment, then later added 3TC to their regimen, would not be expected to respond well to abacavir.

Mutations associated with multi-NRTI resistance occur relatively infrequently. One type (insertion mutations at position 69) has been found in approximately 2% of heavily treatment-experienced patients, and are associated with low-level resistance to all NRTIs. In the presence of key AZT mutations, the 69 insertions cause high-level resistance to all NRTIs.

Up to 5% of people who took dual NRTI therapy involving ddI with either AZT or d4T have been shown to harbour the Q151M mutation. This mutation is associated with resistance to all NRTIs, though less so in the case of 3TC or tenofovir.

### glossary

See also page 10

**antiretroviral A** substance which acts against retroviruses such as HIV.

**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 and used to produce steroid hormones.

**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.

**cross resistance** The mechanism by which HIV that has developed resistance to one drug may also be resistant to other, similar drugs.

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

**lipodystrophy A** disruption to the way the body produces, uses and distributes fat.

**mutation A** single change in gene sequence.

**NNRTI** Non nucleoside reverse transcriptase inhibitors, a family of antiretrovirals that includes efavirenz and nevirapine.

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

**nucleotide analogue** Family of antiretrovirals which includes tenofovir.

## new nrti backbones continued

As HIV drug resistance becomes an ever-more specialist subject, the need for expert interpretation of resistance test results grows. Space does not allow for a thorough review of this subject here, but more information is available at NAM's website [aidsmap.com](http://aidsmap.com). Several online sources provide tabulated reference guides on this subject, including the excellent Stanford HIV RT and Protease Sequence Database at <http://hivdb.stanford.edu/>

### Comparing side-effects

All drugs vary in the extent to which they cause side-effects, and the type of problems they may be expected to cause. In general, 3TC appears to be better tolerated than the other nucleoside analogues, and this partly accounts for its inclusion in many regimens. Nausea and vomiting are common side-effects which can usually be controlled with medication that can be prescribed before you start treatment. AZT, ddI and abacavir are more strongly associated with nausea and vomiting than other NRTIs.

Other longer-term side-effects can be more serious and may require you to stop taking the drug which is causing the problem.

Peripheral neuropathy (nerve damage) has been more strongly linked with d4T (15-21%), ddC (17-31%) and ddI (22%) in large randomised studies (AZT, 3TC and abacavir have not been implicated). If peripheral neuropathy develops on one of these three drugs, it is likely that it could be made worse by any of the remaining 'd' drugs. The risk of peripheral neuropathy is increased when d4T/ddI are taken together, and that risk is further raised by the addition of hydroxyurea. This combination has lost favour as a result.

Pancreatitis is most strongly associated with ddI, particularly when used with hydroxyurea, but has been associated with ddC less frequently, and with 3TC occasionally. Pancreatitis occurred in around 5% of those who received ddI through an early expanded access programme.

Drug	Approved dosing regimen
3TC	Two tablets once a day, or one tablet twice a day
abacavir	One tablet twice a day
AZT	One capsule twice a day
d4T	One capsule twice a day
ddC	One tablet three times a day
ddI	One capsule once a day ( <i>Videx-EC</i> <sup>TM</sup> ), or two/three tablets once a day depending on body weight
tenofovir	One tablet once a day
<i>Combivir</i> <sup>TM</sup> (AZT/3TC)	One tablet twice a day
<i>Trizivir</i> <sup>TM</sup> (AZT/3TC/abacavir)	One tablet twice a day

### Table: Approved dosing regimens for NRTIs

Note: Information provided for guidance only. Check the correct dosage with your doctor or HIV pharmacist.

A potentially very serious hypersensitivity (allergic) reaction occurs in 3-5% of individuals who start abacavir treatment. Those who restart the drug after such an episode must be carefully monitored by their doctor, as some people experience a further, more severe hypersensitivity reaction at this time. After a number of deaths, GlaxoSmithKline have implemented an educational programme for both doctors and recipients of abacavir which should ensure that everyone who takes this drug is familiar with the syndrome's symptoms.

Lactic acidosis is a life-threatening, though very rare side-effect of NRTI therapy, occurring in approximately 1% of individuals taking drugs from this class. The term lactic acidosis is used to describe high levels of a substance called lactate in the blood. Lactate is a by-product of the processing of sugar within the body. Tests to monitor lactate levels are available, but are used in diagnosis rather than to monitor for risk prospectively – their usefulness here has not been proven.

The precise role of NRTIs in the development of body fat changes (termed the lipodystrophy syndrome) during therapy is still unclear, though it's generally accepted that drugs from this class *do* contribute to the syndrome, particularly when taken with protease inhibitors. Whilst it's commonly suggested that some NRTIs are more to blame than others, this is not proven. A detailed review of this subject is available at [aidsmap.com](http://aidsmap.com).

### Dosing considerations

All the NRTIs are taken once or twice a day, which most people find easier to manage than regimens taken more frequently (see tabulated summary to left). The other relative advantage of the NRTIs is what's described as their 'low pill burden'. This means you only need to take a small number of tablets or pills each day. In addition, GlaxoSmithKline manufacture their NRTIs in combined formulations to reduce the pill burden further, and Bristol-Myers Squibb's enteric-coated capsule version of ddI (*Videx-EC*<sup>TM</sup>) has provided an alternative to the original crushable tablet formulation, which was a less-than-easy option.

Several pharmaceutical companies are working on ways of simplifying dosing schedules for their antiretrovirals, either through new formulations or less frequent daily dosing (see *ATU* issue 117).

### New NRTI combinations

The availability of several new anti-HIV therapies over recent years has provided additional options for HAART's NRTI backbone. How best to place these drugs within an HIV treatment strategy presents something of a dilemma. Abacavir and tenofovir, the most recently licensed drugs in this class, have been considered as candidates for HAART's 'third drug' slot, as well as part of the NRTI backbone. They've also been established as an effective means of 'intensifying' a HAART combination when added as a single drug (even in heavily treatment-experienced patients in the case of tenofovir). Clearly one drug cannot fulfill all of these roles.

Further to this are a number of experimental NRTIs which have become available through participation in clinical trials. Some six NRTIs are in human study at present, though it's not uncommon for drugs to fail this process, and indeed several of these candidates have been dogged by toxicity problems.

Data on some of the more novel dual NRTI combinations are reviewed below.

### Abacavir/3TC

As reported in *ATU* 116, the CLASS study evaluated the use of abacavir/3TC with either d4T, amprenavir/ritonavir or efavirenz in people new to treatment. After 48 weeks, an intent to treat missing=failure analysis found that more efavirenz recipients had viral load below 50 copies than those in other arms. This arm also performed better in those who began treatment with viral load over 100,000 copies<sup>9</sup>.

Whilst this study provides no conclusive information on the performance of abacavir/3TC relative to other dual NRTI backbones, the virological and immunological responses observed in all three treatment arms are at least comparable to those observed in other

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- 12 Molina J-M. 8th CROI, Chicago, 2001, abs 321



HAART trials. Around 13% of individuals in each arm developed serious side-effects on study treatment, forcing drugs to be stopped in three efavirenz, two amprenavir/ritonavir and two d4T recipients (a difference which is not significant). The abacavir hypersensitivity reaction was reported somewhat more frequently than seen in other trials; in 7%, 7% and 6% respectively. Six people receiving d4T experienced a symptomatic increase in lactate levels (compared to no cases in other arms). These were all managed either by switching d4T for AZT (in five cases), or by a complete regimen change.

Both abacavir and 3TC can be taken without regard to food.

### Tenofovir/3TC

According to recently reported data from Gilead's 903 study, the nucleotide analogue, tenofovir appears to be as effective as d4T at suppressing viral load and boosting CD4 count when taken in combination with 3TC and efavirenz, and appears to cause relatively few side-effects<sup>10</sup>.

Six hundred people who were new to HIV treatment were randomised into two study arms to receive either tenofovir/3TC/efavirenz or d4T/3TC/efavirenz. At the start of the trial, the average viral load in the two groups was approximately 90,000 copies, and average CD4 count was 279 cells.

After 48 weeks of treatment, 87% of those who began the study had viral load below 400 copies; and 95% by on treatment analysis (where data from participants who left the trial early are excluded). About 82% had viral load below 50 copies. Similar increases in CD4 count, of around 170 cells, were observed in each arm.

Overall, 9% of study participants withdrew because of side-effects. Similar levels of moderately serious, or serious side-effects were reported in the two study groups: 19% for those receiving tenofovir and 17% for the d4T arm. Moderately serious or serious lab abnormalities were seen in 28% of those receiving tenofovir and 31% of people

receiving d4T. Smaller increases in cholesterol were noted in the tenofovir arm than in the d4T arm (average increase 0.64mmol/L versus 1.37mmol/L). There was no increase in triglycerides amongst tenofovir recipients, but an average 1.91mmol/L increase in those treated with d4T.

Both tenofovir and 3TC can be dosed once daily, and taken at the same time with food.

### Tenofovir/ddI

As noted earlier, observations on the frequency of clinically important drug resistance suggest that this combination may be a good second-line NRTI choice, since both drugs are active against 3TC resistant HIV, and are less compromised by the presence of AZT and d4T-associated mutations.

Though both drugs can be taken once a day, taking them concurrently rather than at spaced intervals requires careful monitoring for ddI side-effects – tenofovir increases ddI levels if the two drugs are taken together with a light meal.

### FTC/ddI

FTC is an experimental nucleoside analogue with a similar structure to 3TC. A study comparing the use of FTC or d4T in combination with ddI/efavirenz was unblinded after an interim analysis showed that people receiving FTC were significantly less likely to stop treatment due to side-effects, and were significantly more likely to have viral load below 50 copies after 24 weeks (see *ATU* 117). FTC treatment is also associated with a reduced risk of developing the 3TC resistance mutation (M184V) if viral load rebounds, when compared with 3TC<sup>11</sup>.

An open label study of FTC/ddI/efavirenz showed very high rates of viral suppression: after 64 weeks, 90% of participants had viral load below 50 copies<sup>12</sup>.

FTC is not currently licensed in Europe or the United States.

#### **glossary**

See also page 7

**pancreatitis** A condition of the pancreas causing severe abdominal pain, shock and collapse, which can be fatal.

**plasma** Fluid portion of the blood.

**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.

**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.

## AIDS cases fall in European Union

According to new information from Eurostat, the statistical office of the European Union (EU), the number of new AIDS diagnoses reported within EU member states fell during 2001 compared to the previous year. 8,210 cases were reported in 2001, a fall of 11%.

The total number of AIDS cases reported within the EU has now reached 235,000. Year on year, the estimated incidence rate was 21.8 cases per million people in 2001, and 24.4 cases per million in 2000. Rates vary widely within member states, however. While in most states the incidence rate has fallen since 1990, the rate in Portugal has increased substantially to 105.8 cases per million in 2001. Alongside Spain, Italy and France, Portugal is one of the four worst affected European states.

In line with the changing epidemic, the proportion of European AIDS cases seen in gay and bisexual men is now lower than prior to 1995. The proportion due to injecting drug use is also lower. Whilst national epidemics vary, overall 39.4% of AIDS cases in Europe have been seen in injecting drug users; 32.6% in gay and bisexual men; and 17.6% in people whose transmission route is considered to be heterosexual sex.

Two thirds of AIDS cases have been reported in people aged 25 to 39, and the average age at the time of diagnosis has increased from below 30 years in 1998 to 38.7 years in 2001.

In the UK, 666 AIDS cases were reported in 2001, a fall from 793 in 2000. Incidence rates also fell here: from 13.3 per million in 2000 to 11.3 per million in 2001.

While falls in AIDS diagnoses most likely reflect the widespread introduction of HAART in the late 1990s, variations in the incidence of HIV infection present a clearer picture of how the epidemic is spreading in Europe today. According to a new report from UNICEF, the rate of HIV transmission in Central and Eastern Europe is alarming. By the end of 2001, there were an estimated one million people with HIV or AIDS in the region, up from 420,000 in 1998. Whilst Russia and Ukraine between them account for 90% of the region's estimated cases, the highest rate of new HIV infections is found in Estonia, where more than one in every 1,000 people were infected in 2001. This rate is twenty times the EU average.

## Continued smoking after a heart attack

A study in the *Annals of Internal Medicine* has reported further proof of the health benefits of stopping smoking. Comparing non-smokers, ex-smokers and active smokers, the risk of a second heart attack in those who had stopped smoking before their first attack, was the same as those who had never smoked. The period of follow-up was three years.

Whilst those who quit after their first heart attack faced a similarly increased risk of a second cardiac event as active smokers (about 1.5 times the risk faced by non-smokers), their risk gradually fell over the study period. At 36 months, it was the same as that faced by non-smokers.

People who smoke are more likely to develop blockages in the blood vessels which lead to the heart, causing a heart attack. Stopping smoking reduces this risk to that of a non-smoker within two to three years of stopping.

### **nam forum on children & adolescents**

The next NAM Information Forum takes place on Monday October 28th and the subject is *Children & Adolescents & HIV*. Our guest speakers are Dr Hermione Lyall and Stephen Head from the Family HIV Team at St Marys Hospital, London. The event runs from 7-9pm and is at University of London Union, 4th Floor, Palms Room, Malet Street, London W1. Entry is free and both refreshments and a sign language interpreter are available.

### **references**

European HIV/AIDS statistics from Eurostat. UNICEF report available at <http://www.unicef.org/programme/highlights/cee/>  
Smoking article: Rea TD. *Ann Intern Med* 2002;137:494-500.

# news in brief

### credits

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Anna Poppa

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## any questions

For an introduction to HIV treatment issues Booklets in NAM's Information Series for Positive People are free to people with HIV. This easy-to-read series includes: Anti-HIV Drugs, Clinical Trials, Glossary, HIV Therapy, Lipodystrophy, Nutrition, Resistance, and Viral Load & CD4.

### The HIV & AIDS Treatments Directory

This 600 page book, published twice a year, is a comprehensive guide to the medical aspects of HIV. Available at only £12.95 to people with HIV, £64.95 to professionals.

<http://www.aidsmap.com>

NAM's resources are also available online at [aidsmap.com](http://www.aidsmap.com). These include our extensive and searchable treatments database, the latest news on treatment developments, our online directory of AIDS service organisations, hundreds of links to recommended HIV-related sites, and free downloadable resources.

### Monthly NAM information forums in London

Each month an expert speaker discusses a treatment-related topic. Entry is free. Future forums are advertised inside this newsletter.

THT Living Well Phonenumber 0845 9470047 Mon-Thu 6-9pm  
i-Base Treatment Phonenumber 0808 8006013 Mon-Wed 12-4pm

NAM recommends that you discuss all your treatment decisions with your doctor.



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