

# aids treatment update

## Undetectable $\neq$ uninfected

This month's lead article, '*Undetectable' But Infectious?*', reports on several recent studies which have concluded that a significant number of people with HIV think that having a very low viral load means they are less infectious. These findings highlight a major problem: HIV doctors and their patients are often not communicating well enough with each other.

One of our peer panellists, Paul Clift, the HIV Patients' Representative at Brighton's Lawson Unit, says that, "A healthy doctor/patient relationship would ideally be a non-patronising model of information exchange and shared decision-making."

This would mean, he believes, not only that such misunderstandings would be less likely, but also that the patient would have "a clearer awareness of his/her health situation and of the way it can impact on people with whom they come into contact. In addition, the doctor would gain a clearer picture of the patient's understanding and experience of their illness."

In our other main article, '*Is Less More?*', Gus Cairns discovers that though there are many ways to simplify a HAART regimen, we are still struggling to find the ideal regimen – one that is both potent and easy-to-take.

'undetectable' but  
infectious? 2

is less more? 6

news in brief 10

# 'undetectable' but infectious?

## 2 what the difference between HIV levels in blood and sexual fluids means for infectiousness, by edwin j bernard

Last month, a study<sup>1</sup> in the respected journal *AIDS* added to the growing body of evidence that increasing numbers of HIV-positive, -negative and -untested people are using viral load test results as a tool to make decisions around safer sex choices.

In this particular study, HIV-positive gay men in Amsterdam who thought they had an 'undetectable' viral load were found to be significantly more likely to have unprotected sex with regular partners who were HIV-negative or of unknown HIV status.

In reality, however, almost a third of these men had detectable viral loads and were, therefore, potentially infectious; statistics that the investigators found "alarming".

However even 'undetectable' viral load does not eliminate the risk of HIV transmission.

### How widespread is this decision-making process?

The recent Dutch study is the latest of several that show how people with HIV in well-resourced countries are becoming increasingly more sophisticated with regard to making choices around safer sex.

A study<sup>2</sup> conducted in Sydney, Australia, and presented at the Fifteenth International AIDS Conference in Bangkok last July, found that, just as in the Netherlands, gay couples where one partner was HIV-positive and the other HIV-negative were more likely to have unprotected anal sex if it was thought that the HIV-positive partner had an 'undetectable' viral load.

In fact, a recent review<sup>3</sup> of all the previous studies that have looked at the association

between HIV treatment and sexual risk-taking found that both HIV-positive and HIV-negative individuals who believed that HAART or an 'undetectable' viral load made an individual with HIV less infectious were more likely to engage in unprotected anal sex.

Ten different studies looked at this relationship, and a consistent, significant, pattern emerged. The likelihood of unprotected sex was significantly higher in people who believed that HAART reduced the risk of HIV transmission. The association was significant in both US and non-US studies, in large and small studies, and in studies that included gay men and those that did not.

The authors of the review speculated that individuals reporting that they believed HAART reduced the risk of HIV transmission may be engaging in "self-justifying thinking" to reduce the guilt after an unprotected sexual encounter. However, even if this were the case, the belief that a low viral load or HAART reduces the risk of HIV transmission "may still serve to sustain risky behaviour in the future".

They concluded that prevention messages should emphasise that an 'undetectable' viral load and the use of HAART does not eliminate the risk of HIV transmission.

### Why HAART doesn't eliminate infectiousness

The idea that taking Highly Active Antiretroviral Therapy (HAART) can reduce infectiousness is not new, and was the subject of an *ATU* article two years ago (Issue 118, October 2002<sup>4</sup>).

In the past few years, scientists have discovered that levels of HIV measured in the blood –

which is what we know as viral load testing – are not always the same as levels of HIV measured in sexual fluids. These include cum and pre-cum (semen) in men, sex fluids produced by women, both as lubrication for sex and as 'ejaculation' at orgasm, and the coating (mucous membrane) that lines the arse (rectum).

Although many people on HAART with 'undetectable' viral loads in their blood also have an 'undetectable' viral load in their sexual fluids, and therefore seem less likely to transmit HIV, this is not always the case. Some people with 'undetectable' viral loads in their blood have quite high viral load in their sexual fluids, which could be high enough to infect somebody else.

The relationship between levels of HIV in the blood and in sexual fluids is quite complex, and it is thought to be governed by two major issues: the levels of anti-HIV drugs that penetrate into the genital tract, and the presence of inflammation, including, but not limited to, STIs in the genitals.

## genital tracts, semen and HIV

Genital tracts are the tubes inside the male and female sex organs. The male genital tract is generally considered to be a 'sanctuary site' for HIV (a place separate from the rest of the body where HIV can hide). This is due to the presence of something called the 'blood-testis barrier', which is a layer of cells connected by specialised 'tight junctions' that prevent drugs from passing between the blood and areas of the testicles where sperm develops and matures. It is currently thought that HIV found in semen comes from the blood, the prostate gland and/or the lining of the genital tract.

### Viral loads in the genital tracts of men

Although most studies show that the majority of men treated with antiretroviral drugs experience parallel declines in viral load in both the blood and semen, all studies have shown considerable individual variation in responses. This means that some men may still have infectious HIV in their semen after their viral

load tests indicate that HIV is undetectable in the blood. The following patterns have been observed:

- Viral load becomes undetectable in blood weeks, months or even years before doing so in semen
- Viral load becomes undetectable in blood but not in semen
- Viral load becomes undetectable in semen but not in blood
- Blood viral load rebounds after a period of undetectability but viral load in semen remains undetectable

In the first case, prolonged HIV production in the genital tract may be explained by the fact that long-lived cells that have been infected by HIV continue to pump out virus copies because anti-HIV drugs cannot adequately penetrate these particular cells.

Another explanation might be that virus production continues because latently infected cells are triggered into virus production by the presence of infections or inflammation.

Dr Tariq Sadiq, Senior Lecturer and Honorary Consultant in HIV and genitourinary medicine at St. George's Hospital Medical School, offers this explanation: "Many studies have shown that patients on protease inhibitor- or efavirenz-containing regimes have suppressed semen viral loads although there is poor penetration of these drugs into semen. This is probably because penetration [of these drugs] into the tissues of the genital tract, where it is likely to matter most, is not poor," he explains. "However, another explanation is that the nucleoside analogue components of the regimens, which are often at high levels in the semen, may be adequate to suppress genital tract virus."

### Drug levels are different in the blood and semen

A very recent study<sup>5</sup> has found that many anti-HIV drugs are not reaching high enough levels in semen to prevent HIV from replicating. This, many experts argue, increases the chances that an 'undetectable' viral load in the blood may not be providing a full picture of how well the drugs are controlling HIV in the genitals. This

## defining 'undetectable'

'Undetectable' viral load is one of the aims of anti-HIV therapy. However, the definition of 'undetectable' viral load is constantly changing as the technology used to measure viral load improves.

An 'undetectable' viral load result indicates that a specific viral load test cannot find any HIV in a given blood sample. An 'undetectable' result does not mean that the blood is free of HIV. In fact, most people with 'undetectable' viral load have HIV in their blood, as well as in blood cells, tissue and bodily fluids.

For each viral load test, there is a lower limit of detection – a limit below which it is not possible to measure the amount of HIV present. Samples with very low levels of HIV, for example below 50 copies/ml, are described as having a viral load that is 'undetectable', or 'below the level of detection'.

This lower threshold depends on the sensitivity of the test. The older, standard tests, which may still be in use in some UK clinics, measure down to 400 or 500 copies/ml. Consequently, an 'undetectable' result with a standard test may not mean an 'undetectable' result using an ultra-sensitive test, which can measure down to 20 or 50 copies/ml.

## references

1 Stolte IG et al. Perceived viral load, but not actual HIV-1-RNA load, is associated with sexual risk behaviour among HIV-infected homosexual men. *AIDS* 18: 1943-1949, 2004.



could result in higher levels of HIV in sexual fluids than in the blood, even when the viral load is 'undetectable' in the blood.

This particular study found that levels of the two most commonly-prescribed drugs in the UK – the non-nucleoside, efavirenz (*Sustiva*), and the boosted protease inhibitor, lopinavir (*Kaletra*) – do not reach high enough concentrations to reduce viral load in the male genital tract to 'undetectable' levels. The same was found for the ritonavir-boosted protease inhibitors amprenavir (*Agenerase*), and saquinavir (*Invirase*, *Fortovase*), as well as the recently-approved fusion inhibitor, T-20 (enfuvirtide, *Fuzeon*).

With the exception of indinavir, protease inhibitors (PIs) appear to have poor penetration into the genital tract. This is probably due to the protein binding of protease inhibitors and the

## drug levels in the male genital tract

Anti-HIV drug	Reach adequate levels?
AZT	Yes
DDI	Yes
D4T	Yes
3TC	Yes
ABACAVIR	Yes
TENOFOVIR	Yes
EFAVIRENZ	Conflicting evidence
NEVIRAPINE	Yes
RITONAVIR	No
INDINAVIR	Yes (alone and when boosted)
SAQUINAVIR	No (even when boosted)
NELFINAVIR	No (even when boosted)
AMPRENAVIR	No (conflicting evidence when boosted)
LOPINAVIR/r	No
T-20	No

high protein content of semen, or to the low levels of polyglycoprotein (Pgp), a substance which pumps protease inhibitor molecules out of cells. Pgp is present at very low levels in cells of the brain and testes.

## Viral loads in the genital tracts of women

Several large studies have found a strong association between the level of viral load in blood and the level of viral load in women's sex fluids. However, there is some evidence that antiretroviral therapy may not always result in an undetectable viral load in both blood and vaginal fluid, especially when a genital infection, like urethritis, is present.

In addition, viral load in the female genital tract varies during the course of a menstrual cycle, even among women on anti-HIV treatment. A recent study<sup>6</sup> of viral load changes during the menstrual cycle found that viral load levels in vaginal fluid tended to peak at the time of menstruation and fell to the lowest level just prior to ovulation.

## HIV in the rectum

Several studies have shown that detectable levels of HIV may persist in the tissue that lines the rectum even after HIV becomes 'undetectable' in the blood. A very recent study<sup>7</sup> that compared levels of viral load in the blood, semen and the coating of the rectal lining (mucous membrane) in men taking HAART found that viral load was, on average, five times higher in semen and 20 times higher in the rectal lining than in the blood.

These findings imply that men who believe themselves to have an 'undetectable' viral load and who are the receptive partner in unprotected anal intercourse may have a much higher risk of transmitting HIV than previously thought.

## Sexually transmitted infections

Sexually transmitted infections (STIs) are important co-factors in the transmission of HIV. Not only can STIs enhance the sexual transmission of HIV by increasing the rate of viral shedding, but HIV infection can also increase susceptibility to STIs.

Dr Sadiq and his colleagues have shown that even where viral load in semen is 'undetectable' on HAART, sexually transmitted infections can cause viral load rebound in semen<sup>8</sup>. Conversely, even when viral load is rising in blood, viral load in semen can be

brought under control if a sexually transmitted infection is treated, reinforcing the view that the blood and the genital tract are largely independent compartments.

However, Dr Sadiq points out that "the role of genital inflammation may not necessarily be critical. In the work we have done in the UK<sup>9</sup>, a minority of men negative for urethritis and sexually transmitted infections had viral loads considerably higher in semen compared to blood.

"Although it is true that the role of the genital tract as a separate compartment is often exaggerated, more work needs to be done to investigate non-inflammatory factors associated with apparent 'independent' genital HIV-1 replication."

### Is it sensible to make choices about safer sex based on viral load results?

A recent health education campaign by GMFA (a London-based, volunteer-led gay men's health organisation), which was aimed at gay men who choose to have anal sex without condoms, included information that suggested that a lower viral load could reduce the risk of HIV transmission.

Although studies in heterosexuals have shown that there is a link between higher viral loads and greater sexual infectiousness, and it does seem logical to assume that a lower viral load would mean a lower risk, the reality is much more complicated.

On the one hand, more information is appearing that suggests many anti-HIV drugs don't reach high enough levels in sexual fluids to suppress HIV levels in the same way that they do in the blood.

On the other, there is still uncertainty regarding how important anti-HIV drug levels are in sexual fluids, and other experts point the finger at sexually transmitted infections (STIs) as the cause of higher HIV levels in sexual fluids.

What is certain is that a viral load test is simply a 'snapshot' of levels of HIV in the blood at the time the test was taken, and that since your viral load can rise and fall at any moment, it could have changed since your last blood sample was taken.

Of course, if you are not taking HAART then you are likely to be more infectious than someone taking HAART.

It is also important to remember that 'lower risk' is a relative term, and does not mean low risk or no risk at all.

Given the uncertainties surrounding the effects of HAART on sexual infectiousness, is it really sensible to make choices about safer sex based on viral load results?

### key conclusions

- An 'undetectable' viral load and the use of HAART does not eliminate the risk of HIV transmission.
- Levels of some anti-HIV drugs are lower in sexual fluids, and this could mean that there is higher chance of HIV transmission even when viral load is 'undetectable' in the blood.
- Men with 'undetectable' viral loads who are the receptive partner in unprotected anal intercourse may have a much higher risk of transmitting HIV than previously thought.
- Levels of HIV in women's sexual fluids are also affected by their periods.
- It is important to remember that 'lower risk' is a relative term, and does not mean low risk or no risk at all.
- Sexually transmitted infections can increase levels of HIV in sexual fluids, whether you are on anti-HIV drugs or not.
- Making informed choices about safer sex requires taking on board a lot of information, which can change over time.
- The best way to protect your partners from HIV and yourself from STIs is to use condoms for anal and vaginal sex, gloves for fisting, and latex barriers like dental dams for sexual contact that is oral-genital (oral sex) and oral-anal (rimming) sex.

2 Van de Ven P et al. Undetectable viral load associated with more unprotected anal intercourse in serodiscordant gay couples in Sydney. XV International AIDS Conference, Bangkok. Poster presentation, abstract TuPeD5160, 2004.

3 Crepez N et al. Highly active antiretroviral therapy and sexual risk behavior. JAMA 292: 224-236, 2004.

4 <http://www.aidsmap.com/en/docs/pdf/atu118.pdf>

5 Ghosen J et al. Penetration of enfuvirtide, tenofovir, efavirenz, and protease inhibitors in the genital tract of HIV-1-infected men. AIDS 18: 1958-1961, 2004.

6 Benki S et al. Cyclic shedding of HIV-1 RNA in cervical secretions during the menstrual cycle. J Infect Dis 189(12):2192-201, 2004.

7 Zuckerman R A et al. Higher concentrations of HIV RNA in rectal mucosa secretions than in blood and seminal plasma, among men who have sex with men, independent of antiretroviral therapy. J Infect Dis 189: 156-161, 2004.

8 Sadiq ST et al. The effects of antiretroviral therapy on HIV-1 RNA loads in HIV-positive patients with and without urethritis. AIDS 16: 219-225, 2002.

9 Sadiq ST et al. The Effects of Gonococcal, Chlamydial and Non-specific Urethritis on Seminal Plasma HIV-1 RNA Loads in the United Kingdom. Eleventh Conference on Retroviruses and Opportunistic Infections, San Francisco, abstract 458, 2004.

# is less more?

## 6 are simpler HAART regimens always better? asks gus cairns

When Highly Active Antiretroviral Therapy (HAART) first became the standard of care, in 1996, a typical regimen, for example AZT/3TC/indinavir, involved taking a total of 16 pills three times a day. Initially, indinavir was also supposed to be taken an hour before, or two hours after food, but by 1997 it was conceded that this was not always possible and so the treatment was 'simplified' so that a low-fat or non-fat snack could be eaten at the same time.

Today, the most commonly prescribed initial HAART regimen, *Combivir* (AZT/3TC) plus efavirenz, involves taking just one pill in the morning and two pills at night, with or without food.

Currently, three drug companies – Bristol-Myers Squibb, Gilead and Merck – are in talks to produce an anti-HIV treatment in a once-daily pill. It might be an easy treatment to take, but we won't know how good it is until a clinical trial proves its potency and discovers its side-effect profile.

Until then, we are faced with a bewildering array of simplification options, some of which could be simpler even than one pill, once a day.

However, at the recent IAPAC (International Association of Physicians in AIDS Care) Symposium in London, Canadian clinician Dr Sharon Walmsley wondered whether it had now become a case of seeking "simplicity at all costs".

She pointed out that the distance yet to be travelled to a universally tolerable and convenient anti-HIV treatment was epitomised by the M97-720 study<sup>1</sup> of ritonavir-boosted lopinavir (*Kaletra*), which has now been going

on for five years. The latest results show that 99% of patients remaining on a triple-combination therapy of *Kaletra*, d4T and 3TC maintained a viral load under 400 copies/ml for five years.

But 'remaining' is an important word, Dr Walmsley emphasised. Only 66% of the patients had actually been able to take the combination for the full five years. The others were regarded as 'treatment failures', not because the regimen failed to control their HIV, but because it was not tolerable – they had to drop out either because they were tired of taking ten pills a day (which is known as 'adherence fatigue') or because of the side-effects of the drugs.

"The object of simplification is to close that 33% gap," said Walmsley.

### The aims of simplification

Simplification aims to improve adherence by making doses "less frequent, less large, and less restrictive". It can do this in several ways:

- By increasing the active drug content in individual pills. For example, the forthcoming saquinavir 500mg pill will reduce the twice-daily dose of that drug from five capsules to two pills, plus one ritonavir capsule.
- By co-formulating drugs into combination pills. Examples include *Combivir* (AZT/3TC) and *Trizivir* (AZT/3TC abacavir), the recently approved *Truvada* (tenofovir/FTC) and *Kivexa* (abacavir/3TC) as well as fixed-dose combinations manufactured for resource-limited countries, such as *Triomune* (d4T/3TC/nevirapine).

- By boosting blood levels of a protease inhibitor (PI) using ritonavir to slow clearance of the drug. The latest PI, atazanavir, was the first PI to be approved as a once-daily drug, thanks to the addition of one 100mg ritonavir capsule.
- By studying whether it is possible to reduce the number of drugs or pills people can take once their viral load is controlled (so-called 'induction-maintenance' therapy).
- By studies to see if HIV can be controlled by on-off (intermittent) therapy, rather than constant therapy.
- And ultimately – although these are further off – by investigating different drug-delivery systems such as long-lasting injections, implants or patches.

## Less drugs, less often

How often one has to take drugs (dosing frequency) does appear to affect adherence. For example, a 2001 study<sup>2</sup> of drug regimens (not just anti-HIV ones) found that the average adherence level to a once-a-day regimen was 79%, and only 69% to two doses a day. However, it has been established that adherence to even the most potent anti-HIV regimens needs to be above 95% to maximise treatment success.

The number of pills in a combination (the pill burden) also affects adherence. A review of the relative success of different drug regimens<sup>3</sup> found that pill count was the only predictor of achieving an undetectable viral load or a CD4 rise – it was more important than the actual choice of drugs.

A more recent Spanish study<sup>4</sup> compared once-daily and twice-daily anti-HIV regimens. Patients switching to once-daily regimens when they became available achieved 'undetectable' viral loads 91.4% of the time versus 83.4% of patients on twice-daily regimens. Again, it was pill count that was the sole determining factor of success.

A once-daily regimen is not as simple as it can get. As you will see, there are several options for slimming down anti-HIV regimens even further.

### once-daily drugs licensed in the EU/UK

NRTIs	3TC (lamivudine) ddI (didanosine)
	FTC (emtricitabine)
NtRTIs	tenofovir
NNRTIs	efavirenz
PIs	atazanavir

### potential once-daily drugs not yet licensed in the EU/UK

NRTIs	abacavir d4T(stavudine) <i>Zerit PRC</i> has been approved since 2002 but is not yet available
NNRTIs	nevirapine
PIs	<i>Kaletra</i> ritonavir-boosted saquinavir ritonavir-boosted fosamprenavir

## *Kaletra* monotherapy

The enhanced potency of some of the newer anti-HIV drugs, especially *Kaletra* (lopinavir co-formulated with a small 'boosting' amount of ritonavir), has made the previously impossible conceivable: controlling HIV with just one active drug.

Two recent studies have demonstrated pretty good control of HIV by using *Kaletra* alone (this is known as 'monotherapy').

Texas clinician Dr Joe Gathe<sup>5</sup> gave *Kaletra* monotherapy to 28 of his patients who were starting anti-HIV therapy for the first time. By the end of the 48-week study, all of the 20 patients who had managed to remain on *Kaletra* had viral loads under 400 copies/ml (18 of them had viral loads below 50 copies/ml). This was a group of patients who had started with an unusually high initial viral load (an average of 262,000 copies/ml), and

## references

- 1 Hicks C et al. Long-term safety and durable antiretroviral activity of lopinavir/ritonavir in treatment-naive patients. *AIDS*.18(5):775-9, 2004.
- 2 Claxton AJ et al. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther*. 23(8):1296-310, 2001.
- 3 Bartlett, John A et al. Overview of the effectiveness of triple combination therapy in antiretroviral-naive HIV-1 infected adults. *AIDS* 15(11):1369-1377, 2001.
- 4 La Paz, H et al. Adherence, treatment satisfaction and effectiveness of once-daily versus twice-daily antiretroviral therapy in a large prospective observational cohort. *XV Int AIDS Conf, Bangkok, abs WePeB5780*, 2004.
- 5 Gathe JC et al. IMANI-1 TC3WP single drug HAART- proof of concept study. *XV Int AIDS Conf, Bangkok, abs MoOrB1057*, 2004.



Dr Gathe said that most of the drop-outs had not been due to treatment failure, but to what he called 'situational adherence' issues. This referred to things that neither patient nor doctor had control over, such as loss of health insurance and, in one case, being deported to Africa. Indeed, Gathe said that one reason he had tried the concept of *Kaletra* monotherapy was his increasing concern at the number of patients who could not afford combination therapy – another, albeit non-clinical, reason for simplification.

In another study, Dr José Arribas<sup>6</sup> from Madrid simplified the therapy of 21 patients already on HAART by changing from *Kaletra* plus two NRTIs to *Kaletra* alone. Then he compared them with 21 patients who remained on the previous regimen. Three patients on *Kaletra*-monotherapy began to have detectable HIV, but when their blood was tested for resistance, they were not found to have any resistance mutations to lopinavir, the active PI in *Kaletra*. To date, the few people who have developed HIV mutations with resistance to lopinavir do not appear to be cross-resistant to other protease inhibitors. This, at least, preserves future treatment options.

### Induction-maintenance

The Madrid simplification study is an example of another approach to simplification, called induction-maintenance. Here, patients start with a potent HAART combination and then, when they reach viral undetectability, reduce the combination by using less drugs or fewer classes of drugs. Three studies presented at the International AIDS Conference in Bangkok earlier this year showed some success with this approach.

In one<sup>7</sup>, 77% of patients who had been on a year of a quadruple therapy of efavirenz plus abacavir/AZT/3TC (*Trizivir*) and who had maintained viral loads under 50 copies/ml for the previous three months, remained 'undetectable' when they simplified to *Trizivir* alone. This was considered to be equal to the 79% of patients who remained 'undetectable' on the four-drug regimen after two years.

In another, Dutch, study<sup>9</sup> simplifying from *Kaletra/Trizivir* to *Trizivir* alone had even better results – of patients reaching a viral load

under 50 copies/ml, 95% maintained this 'undetectable' viral load on *Trizivir*, although this study<sup>9</sup> only lasted for 36 weeks.

Another induction-maintenance study<sup>9</sup> was the French COOL trial. Here, the investigators started 140 patients on efavirenz, 3TC and tenofovir. Then, when their viral load had been under 50 copies/ml for six months, the regimen was simplified to just efavirenz and tenofovir. The full results are not yet available, but there have been no virological 'failures' so far in any patient.

### Treatment breaks

Another approach to simplification is the use of treatment breaks, also known as 'drug holidays'. Importantly, several ways of doing this have been found *not* to work, and the concept is still experimental. It was initially hoped that regular treatment breaks, by 'showing' the immune system a little HIV, would educate it to recognise the virus and produce permanently lower viral loads (the so-called 'auto-immunisation' theory). This appears not to work, probably because HIV is a paradoxical disease – increasing the body's immunity to HIV also increases the number of cells for HIV to replicate in.

Another approach that was found not to work was 'week-on, week-off' therapy, which also had a high 'failure' rate.

The idea of 'CD4-guided' treatment breaks, is, however, still being studied. This was covered in detail in a recent issue of *AIDS Treatment Update* (138, July 2004).

### Some drawbacks

A major drawback of once-daily therapy is the danger that if a dose is missed and a further dose is not taken until 24 hours after the missed dose, drug levels will have fallen far lower than they would if one out of two daily doses had been missed. This is likely to be particularly problematic when drugs are used which fail after the development of one mutation – drugs such as 3TC, FTC, efavirenz and nevirapine. These drugs are strongly represented among the current candidates for use in once-daily therapy.

And while simpler regimens have obvious advantages, there have turned out to be unexpected booby-traps in some of the approaches tried. In the quest for simplification, Dr Walmsley warned the IAPAC Symposium audience, doctors and patients "must not make up their own combinations without clinical trials".

In some of the induction-maintenance trials, for instance, patients who reached 'undetectable' viral loads did fine, but there were worrying drop-out rates before they ever got to that point. In the ESS 40013 study<sup>7</sup>, for instance, 50% of patients on *Trizivir*/efavirenz dropped out before they could ever get below 50 copies/ml. In the CD4-guided treatment interruption study, STACCATO, 25% of patients have so far not reached the 350 CD4 count they need to start taking a therapy break.

It is only possible to simplify therapy if you first respond: and patients with pre-existing resistance may need tough PI-based regimens to do that.

It's also only possible to simplify if your initial therapy hasn't made you ill, and if you manage to adhere to it; and a quest for 'simplification' that ignores drug toxicity and the importance of social support and education in adherence will fail.

Other examples of simplification failure are when people in resource-limited countries took fixed-dose combinations like *Triomune* from the start, and experienced nevirapine toxicity because they took the full dose immediately – not a half dose for the first eight weeks, as clinically indicated.

Finally, a quest for 'simplification' may turn up completely unexpected results. Last year several studies<sup>10, 11, 12</sup> examined whether NNRTI- and PI-sparing regimens, like the triple-nucleoside combinations of tenofovir/abacavir/3TC and tenofovir/ddI/3TC, could successfully preserve future treatment options, and avoid certain side-effects like lipodystrophy. On paper, they seemed a very good idea. However, there were some pretty disastrous failures, which surprised everyone involved. The two studies studying the first regimen observed 'failure' rates of 52% and 33% respectively, and the second regimen 'failed' in virtually all patients.

After eliminating several other explanations, the scientists eventually found that taking these drugs resulted in regimens which all 'pushed' HIV in the same direction – to developing a mutation called K65R (which conveys resistance to abacavir, tenofovir and ddI) and the anti-3TC mutation M184V. This is avoided when taking AZT at the same time. This was pretty bad luck for the trial patients, who were left with AZT as the only NRTI that might work for them.

Similar unexpected surprises may await clinicians – and patients – who try to 'simplify' too much, too soon.

## key conclusions

- Taking less pills, less often can help people stick to a drug-taking routine
- There are several anti-HIV drugs already available that can be taken once a day, and more should become available soon.
- Other experimental ways of simplifying treatment are being examined.
- One experimental method is to reduce the number of pills in a combination by taking less than the currently – recommended minimum of three drugs.
- Another experimental idea is to take a drug holidays based on how well your immune system is doing.
- However, there are some real drawbacks to simpler treatment regimens that have not yet been resolved.
- The most important of these is that simpler regimens may not be so effective at keeping HIV at bay.
- The number of side-effects, which make people not want to take the pills, is also an issue.
- Sometimes unexpected results happen when experiments take place, and so, before changing or stopping your regimen, always consult your doctor.

6. Arribas JR et al. Simplification to Lopinavir/r single-drug HAART. XV Int AIDS Conf, Bangkok, abs TuPeB4486, 2004.
7. Markowitz M et al. Maintenance with Trizivir (TZV) or TZV + efavirenz (EFV) for 48 weeks following a 48-week induction with TZV + EFV in antiretroviral-naïve HIV-1 infected subjects. XV Int AIDS Conf, Bangkok, abs LbOrB14, 2004.
8. van Raalte R et al. Induction-maintenance strategy re-evaluated: initial boosted-PI in combination with triple NRTI, followed by triple NRTI maintenance. XV Int AIDS Conf, Bangkok, abs TuPeB4597, 2004.
9. Girard PM et al. EFV/TDF vs EFV/3TC/TDF as maintenance regimen in virologically controlled patients under HAART: a 6-month analysis of the COOL Trial. XV Int AIDS Conf, abs TuPeB4493, 2004.
10. Farthing C et al. Early virologic failure in a pilot study evaluating the efficacy of abacavir, lamivudine and tenofovir in the treatment naïve HIV-infected patients. 2nd IAS Conf, Paris, abs 43, 2004.
11. Landman R et al. Low Genetic Barrier to Resistance Is a Possible Cause of Early Virologic Failures in Once-Daily Regimen of Abacavir, Lamivudine, and Tenofovir: The Tonus Study. 11th CROI, San Francisco, abs 52, 2004.
12. Jemsek J et al. Poor Virologic Responses and Early Emergence of Resistance in Treatment Naïve, HIV-infected Patients Receiving a Once Daily Triple Nucleoside Regimen of Didanosine, Lamivudine, and Tenofovir DF. 11th CROI, San Francisco, abs 51, 2004.

## Potentially life-threatening antibiotic interaction discovered

The commonly used antibiotic erythromycin increases the risk of sudden cardiac death, particularly when taken at the same time as protease inhibitors (especially ritonavir), antifungals (including fluconazole, ketoconazole, and itraconazole) and antidepressants.

Erythromycin is a broad-spectrum antibiotic used to treat a wide range of problems, from chest infections to sexually transmitted infections. Until now, the drug has been considered to have a good safety profile – the most widely reported side-effects being stomach cramps, nausea and diarrhoea.

However, there have been case reports of sudden cardiac deaths in patients treated with both oral and intravenous doses of erythromycin.

Erythromycin is metabolised in the liver using the cytochrome P-450 3A (CYP3A) pathway, which is also used by PIs, some antifungals and certain antidepressants, all of which can increase concentrations of erythromycin. The study found that the risk of sudden cardiac death in people taking erythromycin with other medications that inhibited CYP3A was five times higher than in those not taking these other medications.

Ray WA et al. Oral erythromycin and the risk of sudden death from cardiac causes. *N Engl J Med* 351: 1089-1096, 2004.

## Faster CD4 drop seen in those with higher immune system activation prior to infection

Individuals with a history of high immune system activation before HIV infection experience faster declines in CD4 cell counts, according to a Dutch study. The results suggest that people who experienced more infections during their lives before they became infected with HIV, and those who are genetically predisposed to greater immune stimulation in response to infection, progress to AIDS more rapidly than those with less immune activation.

van Asten L et al. Pre-seroconversion immune status predicts the rate of CD4 T-cell decline following HIV infection. *AIDS* 18: 1885-1893, 2004.

## Unusual STI seen in a cluster of HIV-positive men

A form of the sexually transmitted infection (STI) chlamydia, rarely seen in Europe and America since antibiotics became available, has been diagnosed in a cluster of Dutch gay men involved in a Europe-wide sexual network. The outbreak of rectal infection with Lymphogranuloma venereum (LGV) has been

found in 15 men, of whom 13 were HIV-positive. Symptoms, which include mucous discharge from the rectum, constipation and bleeding, can resemble Crohn's disease. All the men had rectal infections with LGV and the men reported both insertive and receptive anal sex without condoms. The investigators speculate that 'fisting' may have a role to play in the transmission of LGV, noting that this was a widespread sexual activity for this group of men. The treatment for LGV is 100mg doxycycline for 21 days.

Nieuwenhuis RF et al. Resurgence of Lymphogranuloma venereum in western Europe: an outbreak of Chlamydia trachomatis serovar L2 proctitis in the Netherlands among men who have sex with men. *Clin Infect Dis* 39: 996-1003, 2004.

## Rare Kaletra resistance reported

A rare case of resistance to the protease inhibitor (PI) lopinavir (which is combined with a small dose of ritonavir and marketed as *Kaletra*) has been reported. The investigators suggest that although resistance to lopinavir is difficult to generate during treatment, it is not impossible. The preferred pathway for lopinavir resistance may involve mutations at codons 47 and 32. However, this pathway appears to preserve other PI treatment options.

Friend J et al. Isolated lopinavir resistance after virological rebound of a ritonavir/lopinavir-based regimen. *AIDS* 18: 1965-1970, 2004.

## Does long-term HAART lead to CD4 count decline?

An unexpected increase in immune activation has been seen in a long-term study of 20 individuals who have remained on continuous HAART for between four-and-a-half and six years. This coincides with a surprising drop in CD4 cell counts in eleven individuals between year 5 and year 6. Remarkably, 17 of the 20 (85%) have remained on their original HAART regimen of AZT, 3TC and ritonavir. Of the three who changed their therapy, one was now taking AZT, 3TC and indinavir, another AZT, 3TC and

boosted saquinavir, and the third, d4T, nevirapine and boosted saquinavir.

The average increase in CD4 cells from year 3 to year 6 was 126 cells/mm<sup>3</sup>, or 42 cells/mm<sup>3</sup> a year. Surprisingly, however, 11 of the 20 (55%) experienced declines in CD4 counts after year 5, ranging from -20 to -178 cells/mm<sup>3</sup>.

When the researchers looked at the quality and type of CD4 cells in these individuals, they found an unexpected increase in the percentages of activated CD4 and CD8 cells from year 3 to year 6 in most of the group; 75% experienced an increase in activated CD4 cells and 85% experienced an increase in activated CD8 cells.

Although it is unclear why this persistent immune activation occurs, the researchers suggest that it is possible that the CD4 increases seen on HAART provide new targets for viral replication, and that low-level increases in viral replication could be driving this heightened immune activation. However, a more sensitive viral load assay would be needed to detect this low-level replication.

These 20 individuals will now have their HAART regimen intensified, and follow-up will continue.

Smith K et al. Long-term changes in circulated CD4 T lymphocytes in virologically suppressed patients after 6 years of highly active antiretroviral therapy. *AIDS* 18: 1953-1956, 2004.

## Abacavir/3TC once-daily pill gets EU scientific approval

GlaxoSmithKline's once-daily fixed dose combination of abacavir and 3TC (lamivudine) has received scientific approval from the European Medicines Agency. It is already licensed in the US as *Epzicom* but will be prescribed under the trade name *Kivexa* in Europe. *Kivexa* is likely to receive marketing approval from the EU by early 2005 and will then be available for prescription. The pill is already available on a named-patient basis, if doctors think that a once daily fixed dose combination of abacavir and 3TC may promote better adherence to treatment for an individual patient.

### news from

#### nam wins more awards

Two booklets from NAM have won 2004 BMA Medical Book Competition Patient Information Awards. 'HIV & Hepatitis' has been highly commended and 'Clinical Trials' has been commended.

#### nam forum

The last forum of the year will take place on Monday 29th November. The forum will start at 7pm at the University of London Union, Palms Room, 4th Floor, Malet Street, London, WC1. See <http://www.aidsmap.com/en/events/forums.asp> for more details.

#### write for atu

If you are already a published writer/journalist and have knowledge of HIV treatment issues, then *AIDS Treatment Update* is interested in hearing from you. Please send a short email and examples of your work to: [edwin@nam.org.uk](mailto:edwin@nam.org.uk) or write to Edwin J Bernard, Editor (*AIDS Treatment Update*), Lincoln House, 1 Brixton Road, London SW9 6DE. No phone calls, please.

## credits

founded by Peter Scott

### editor

Edwin J Bernard

### sub-editing & proofreading

Carolyn Partrick

### production

Joe Kaler

### design

Alexander Boxill

### printing

Cambrian Printers

### ISSN

0969-4706

### copyright

©NAM Publications 2004

All rights reserved

## medical advisory panel

Dr Fiona Boag

Dr Ray Brettle

Professor Janet Darbyshire

Dr Martin Fisher

Professor Brian Gazzard

Professor Frances Gotch

Dr Margaret Johnson

Dr Graeme Moyle

Dr Barry Peters

Dr Kholoud Porter PhD

Dr Gareth Tudor-Williams

Professor Jonathan Weber

Dr Ian Williams

Dr Mike Youle

## about NAM

NAM is a charity that exists to support the fight against HIV and AIDS with independent, accurate, up-to-date and accessible information for affected communities, and those working to support them.

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).

### disclaimer

The publishers have taken all such care as they consider reasonable in preparing this newsletter. But they will not be held responsible for any inaccuracies or mis-statements of fact contained herein. Inclusion in this newsletter of information on any drug or clinical trial in no way represents an endorsement of that drug or trial. This newsletter should always be used in conjunction with professional medical advice.

## thanks to our funders

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

Abbott Laboratories International & UK, Access 4, Miss Agnes H Hunter's Trust, Ajahma Charitable Trust, Allan & Nesta Ferguson Charitable Trust, International HIV/AIDS Alliance, Bolton PCT, Bristol-Myers Squibb International, Bristol-Myers Squibb UK HIV & Hepatitis British HIV Association (BHIVA), Birmingham PCTs, Boehringer Ingelheim International & UK, Derek Butler Trust, Cleopatra Trust, Crusaid, East Sussex, Brighton & Hove area PCTs, Gilead International & UK, GlaxoSmithKline, Government of the United Kingdom Department of Health, Hugh Fraser Foundation, Lloyds TSB Foundations for England & Wales and Northern Ireland, London HIV & GUM Commissioning Consortium, Lyndhurst Settlement, MAC AIDS Fund, North Manchester PCTs, Merck Sharp and Dohme UK & International, Newcastle PCT, Norfolk PCTs, Peter Moores Foundation, Positive Action (GSK), Russell Trust, Roche Products UK Hep C, Roche Products International & UK, Salford PCT, Shire Pharmaceuticals, South East Essex PCTs, South West Essex PCTs, St. Stephen's AIDS Trust, Stockport Social Services, Thomas Sivewright Catto Charitable Settlement, West Sussex PCTs, Worcestershire PCTs. NAM would also like to acknowledge the generous support of individual donors, and in particular Gavin Hay and Tim Cohen.

## order form

**Please set up my subscription to AIDS Treatment Update at the following rate:**

**free** (for personally affected individuals)

£75 (professional rate)

£55 (voluntary organisations rate)

### format required

(please tick the format you require):

paper

email (pdf)

audio tape

### overseas postage costs

(for paper and audio subscriptions only)

within EU please add £10/year

outside EU please add £15/year

name \_\_\_\_\_

address \_\_\_\_\_

postcode \_\_\_\_\_

email address (if applicable) \_\_\_\_\_

signature \_\_\_\_\_

**total payment due: £ \_\_\_\_\_ (if applicable)**

Payment can be made by cheque (payable to NAM), or call +44 (0) 20 7840 0050 with your credit card details.

NAM publishes a complete range of information resources about HIV and AIDS. Please tick this box if you would **not** like to receive information about them.

NAM occasionally undertakes fundraising campaigns to help support its work. Please tick this box if you would **not** like to receive information about them.

## subscriptions

### free subscriptions for individuals

AIDS Treatment Update is available free to individuals in the UK affected by HIV or AIDS. We ask individuals from overseas to contribute to postage costs.

### costs to professionals and organisations

professional/organisational rate:

£75/year

voluntary organisation rate:

£55/year

To begin your subscription simply complete the form opposite and return it to NAM, or call or email us.

**AIDS Treatment Update is also available on audio tape, and can be emailed to you as a pdf file. Call NAM on +44 (0)20 7840 0050 for details.**

## any questions

### for an introduction to HIV treatment issues

NAM's information booklets are free to people with HIV. Titles include: **adherence, anti-HIV drugs, clinical trials, glossary, HIV & hepatitis, HIV therapy, lipodystrophy, nutrition, resistance, and viral load & CD4**. Please contact NAM for your copies.

### HIV & AIDS Treatments Directory

This is a comprehensive guide to the medical aspects of HIV. Available at only £12.95 to people with HIV and £64.95 to professionals. Please contact us to order your copy.

### www.aidsmap.com

Visit our website for the latest news and conference reports, a fully searchable treatments database, and The Wheel – your personal pill planer.

### information forums in London

Each month an expert speaker discusses an HIV treatment-related topic. Entry is free. Future forums are advertised inside this newsletter and on our website.

### THT Direct Phoneline

0845 1221 200

Mon-Fri 10am-10pm Sat-Sun 12-6pm

### i-Base Treatment Phoneline

0808 8006013

Mon-Wed 12-4pm

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