

# aids treatment update

rethinking treatment strategies

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# in this issue

There's a very good reason why current treatment guidelines recommend that we start anti-HIV treatment between 200 and 350 CD4 cells. Below 200, the short-term risk of becoming seriously ill or dying is relatively high. Above 350, the longer-term risks associated with anti-HIV drugs outweigh the benefits of treatment.

Some experts argue that the risk/benefit ratio has now changed and that people should start anti-HIV treatment at higher CD4 counts. It's an interesting debate and you can read more about it on page eight.

But why isn't there more debate over how and why people with dangerously low CD4 counts are not getting treatment? New data from the Health Protection Agency strongly suggest an inequality to HIV treatment access exists between UK regions, with 20% of people with CD4 counts below 200 not on anti-HIV treatment.

Is this because of cost issues? Are some doctors not reading or following treatment guidelines? Perhaps some people living with HIV are more afraid of anti-HIV treatment than HIV itself?

Whatever the reasons, they need to be addressed immediately. To know how to do this, we need an urgent investigation to discover exactly why one in five people who need anti-HIV treatment in the UK aren't getting it.

**page 3** This month's *Upfront* focuses on the disheartening news that the development of another promising anti-HIV drug has been discontinued due to an unacceptably high level of side-effects.

**page 4** In *Treatment for life?* Gus Cairns examines the fallout from the SMART study, which found that structured treatment interruptions are not a safe long-term treatment strategy, and asks whether this means that triple drug combination anti-HIV treatment is now a lifelong prospect.

**page 8** Some experts are arguing that it's time we started *Rethinking when to start* anti-HIV therapy, suggesting that earlier is better. Edwin J Bernard examines both sides of the evidence.

**page 12** Amongst the items in *News in Brief*, we learn that at least one out of every eleven HIV-positive people in the UK are also infected with the hepatitis C virus, and that there is uncertainty about whether combining ritonavir-boosted atazanavir (*Reyataz*) with certain acid-reducing drugs is as problematic as many think.

**page 14** Michael Carter talks to Dr Catherine Dodds of Sigma Research about how and why we got to the current state of affairs regarding the criminalisation of HIV transmission, and what the future might hold.



## aids treatment update

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# Reverset of fortune

another promising anti-HIV drug bites the dust, by Edwin J Bernard

Last month, development of DFC, the highly promising, much-needed next generation nucleoside reverse transcriptase inhibitor (NRTI), formerly known as D-d4FC or *Reverset*, was discontinued due to a 40% incidence of very high levels of an enzyme called lipase, which is associated with pancreas damage. Although this is very disappointing news, there are more options in the drug development pipeline for people with NRTI-resistant HIV.

## What went wrong?

Last July, when results from a 16-week, phase IIb study were reported at the Third International AIDS Society Conference in Rio de Janeiro, the investigators had concluded that their "data support the continued development of *Reverset*." Indeed, this looked like a very promising drug. Out of a group of 199 highly treatment-experienced individuals with a lot of NRTI resistance, those who added the highest (200mg once-daily) dose of DFC to their 'failing' regimen managed to sustain a very decent viral load drop that lasted for the four months of the study.

At the time, the investigators had only seen very high levels of lipase in participants who had taken 200mg of DFC alongside ddI (didanosine, *Videx/Videx EC*), and they concluded that these two drugs should not be taken together. They also found that combining DFC with either 3TC (lamivudine, *Epivir*, also in *Combivir*, *Kivexa* and *Trizivir*) or FTC (emtricitabine, *Emtriva*, also in *Truvada*) resulted in a less potent anti-HIV punch.

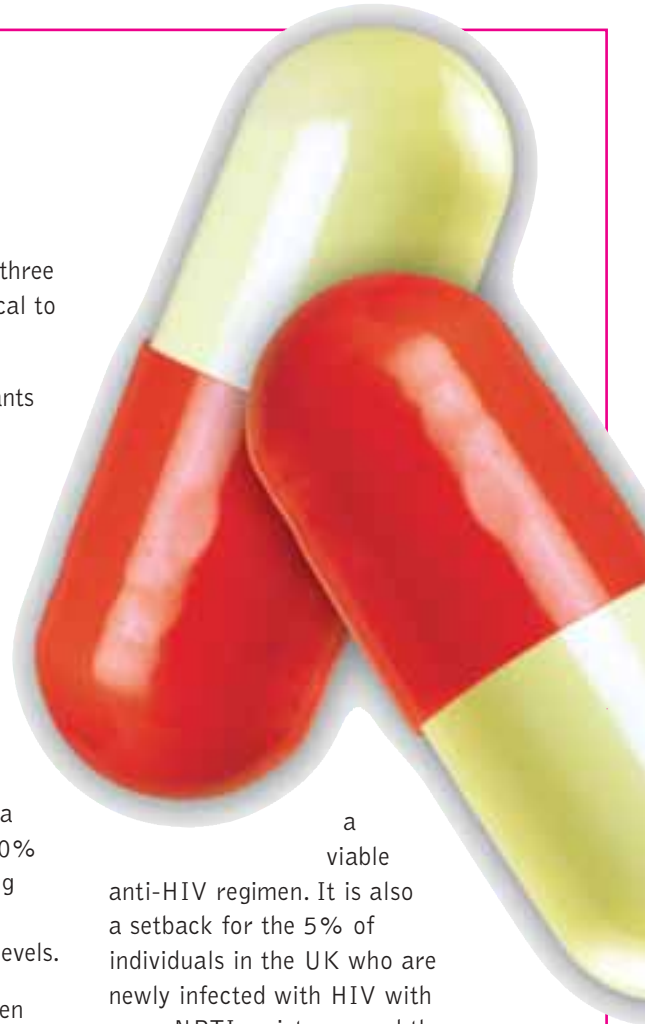
This wasn't so surprising, since all three drugs compete for the same chemical to become active within cells.

Many of the original trial participants continued taking DFC as part of their 'salvage' combination, and they were followed in a study extension called Study 901. About 70% were taking 100mg or 200mg of once-daily DFC on top of an anti-HIV regimen that also included 3TC or FTC and it took a while before enough people stopped taking these drugs for the investigators to see that there was a problem. In fact, they found that 40% of people who had taken the 200mg dose of DFC without 3TC or FTC experienced these very high lipase levels.

Since very few people had ever taken DFC without 3TC or FTC before, this particular side-effect had not been suspected with DFC alone. In the previous study, two (5%) of the 37 participants taking 200mg DFC without ddI did experience these very high lipase levels. But although there were also four cases of pancreatitis (a painful and serious inflammation of the pancreas, which can be life-threatening) in the study, these only occurred in individuals taking 100mg DFC, and so the investigators did not think they were necessarily linked to DFC.

## What does this mean?

The study was halted immediately, and the drug has now been shelved for good. This is bad news for people who urgently require new drugs to make up



a viable anti-HIV regimen. It is also a setback for the 5% of individuals in the UK who are newly infected with HIV with some NRTI resistance and the more than 55% of treatment-experienced individuals who have developed HIV with some NRTI resistance.

Fortunately, there are other drugs in development that are also active against HIV that is resistant to most current NRTIs, in particular HIV with the M184V mutation, which confers resistance to 3TC and FTC. The furthest along is AVX754, and results from a phase IIb study of 60 people with M184V resistance are expected by the summer. Both elvucitabine - which has the potential for once-weekly dosing - and racivir - developed by Pharmasset who partnered with Incyte on the chemically similar DFC - are also active against hepatitis B virus and are at earlier stages of development. ■

# treatment for life?

with treatment interruptions out of favour, is anti-HIV therapy now a lifelong prospect? asks Gus Cairns

Many treatment activists and others living with HIV were extremely disappointed with the termination of the SMART study, the largest HIV treatment strategy trial ever conducted. When the study began enrolling in 2003 hopes were high that this nine-year, 6000-person, multinational investigation would show that it was possible to spend a minority of your time on HIV treatment once your CD4 counts were restored to a reasonable level, reducing side-effects, saving money, and providing a break from having to remember to swallow pills once or twice a day.

SMART's aim was to reduce the time spent on antiretroviral therapy by discontinuing treatment when people's CD4 counts went over 350 cells/mm<sup>3</sup> and not restarting it until they went below 250 cells/mm<sup>3</sup>. Other, smaller studies of CD4-guided treatment interruptions had suggested this might indeed be possible. In one, the Italian BASTA study<sup>1</sup>, patients on treatment interruptions only spent twelve per cent of their time on treatment. In another, the Thai STACCATO trial<sup>2</sup>, participants were on treatment 38% of the time.

## What went wrong?

SMART wasn't due to produce its final results until 2012. But the fact that its investigators ended the study after a third of its planned duration shows how conclusive its results were - and how contrary they were compared to what was expected or hoped for.

Put simply, over twice as many participants randomised to treatment interruptions died or developed an AIDS-defining illness as did patients on continuous therapy (although in absolute terms this increase in risk was

small: doubling from 2% to 4%). This increased risk was only seen in people who had an undetectable viral load when they began their treatment interruption: those interrupting successful therapy were at the highest risk of HIV disease progression or death, no matter what their lowest-ever CD4 count was (a CD4 count below 200 cells/mm<sup>3</sup> was previously thought to be one of the major risks of interrupting therapy). The major lesson from SMART appeared to be that once you started there appeared to be no alternative other than staying on treatment for the rest of your life.

In the aftermath of the study, some experts argued that SMART had failed because it maintained people who interrupted therapy at CD4 counts between 250 cells/mm<sup>3</sup> and 350 cells/mm<sup>3</sup>, and they spent a longer time with lower average CD4 counts than the people in the study who didn't interrupt therapy. In contrast, the BASTA study stopped therapy when people had CD4 counts above 800 cells/mm<sup>3</sup> and then restarted them on therapy when they fell to 400



cells/mm<sup>3</sup>. Similarly, in the STACCATO trial, participants resumed their anti-HIV drugs when their CD4 counts reached 350 cells/mm<sup>3</sup>.

However, Dr Wafaa El-Sadr of Columbia University, New York, who presented the SMART study's findings at the recent Retroviruses Conference in Denver, recommended caution on concluding that keeping CD4 counts above 350 cells/mm<sup>3</sup> would be any safer. "To assume that interrupting treatment is safer at higher CD4 thresholds is premature," she argued, "because most of the studies [suggesting it may be safe] have included limited numbers of participants."

Besides, the other, smaller treatment interruption studies touted as successes at the Denver conference actually failed to show that treatment interruptions had any significant advantages over continuous treatment and often resulted in the acquisition of drug resistance.

### **Does coming off therapy improve quality of life?**

SMART dashed the assumption that the illness caused by drug side-effects was worse than that caused by HIV. But the other argument for treatment interruptions was that 'drug holidays' (as suggested by that phrase), would improve our quality of life.

A recent study<sup>3</sup> questions this assumption. Here, 46 participants with an average CD4 count of 715 cells/mm<sup>3</sup> were randomised to continuous treatment versus cycles of four weeks on and eight weeks off antiretrovirals. At the end of the study, there were no differences in physical health or 'symptom distress' between



the participants on continuous therapy and those on treatment interruptions.

However, mental health scores (a measure of depression, anxiety and other measures of quality of life) which had started off better in the treatment interruption group had declined to match those of the continuous therapy group by week 12 of the study. This effect was statistically significant and lasted until the end of the trial at week 40. The authors speculate that initial optimism about coming off anti-HIV therapy may have been tempered by the "additional effort" of stopping and starting drugs and worries about whether the drugs would still work when they were restarted.

### **The return of induction/maintenance**

Some experts were not surprised at the results of SMART. Dr Steven Deeks of the University of California, San Francisco has made a speciality out of studying what happens when you stay on anti-HIV therapy, even if you're 'failing' (i.e. have a detectable viral load.)

"We always knew that if you stop anti-HIV drugs you're more likely to get into trouble than if you stay on them," he says. "There is a risk to coming off



therapy at any CD4 count, though at high counts that's a difference between a small and a smaller risk. SMART was good science because it quantified those risks. The appropriate response is 'thanks for telling us exactly how bad HIV is for you'."

"However," he adds, "what SMART doesn't tell us is what to do for the patients who really do struggle to take their medication - and a lot of mine do." So, are there any strategies left which could reduce the drug burden - safely?

In the early years of the protease inhibitor (PI) era, there was much interest in an approach called induction/maintenance - starting with three or four drugs and stepping down to one or two after viral load had been controlled. Results were disappointing and the approach fell into disuse. The advent of ritonavir-boosted PIs - which are much more potent and much less likely to result in resistance than single PIs - has led several investigators to re-examine this strategy, but this time with a focus on maintenance solely with a boosted PI.

Most of the data on the new generation of studies examining induction/maintenance are on the use of ritonavir-boosted lopinavir (*Kaletra*)

although ritonavir-boosted saquinavir (*Invirase*) and ritonavir-boosted atazanavir (*Reyataz*) are also being studied.

The *Kaletra* studies have included people taking anti-HIV therapy for the first time<sup>4</sup>, as well as people switching after having successfully reduced viral load to undetectable levels on previous



therapy. The strategy has been successful for most participants, with one Spanish study<sup>5</sup> finding that more than 80% of people taking *Kaletra* alone kept their viral loads below 50 copies/ml for 72 weeks after switching to *Kaletra* monotherapy. However, there are still concerns about the long-term side-effects of most ritonavir-boosted PIs, particularly when they come with raised blood fats and the increased risk of heart attack and stroke.

Ritonavir-boosted atazanavir (*Reyataz*) is less strongly associated with raised blood fats and a small study presented in Denver in February<sup>6</sup> has found that this drug appears to work as well as *Kaletra* in people switching after having successfully got their viral loads below 50 copies/ml with convention triple-drug therapy. However, this study has only reported data to six months, which is too short a time to really know if the strategy will work over the longer-term.

### Good old monotherapy?

Using one drug to control HIV - monotherapy - has not been an

option since the mid-1990s, when the simultaneous use of three agents came to be the standard of care for the treatment of HIV infection. So, many people consider the notion of taking just a single drug from the start pretty radical in comparison to induction/maintenance. The concept was pioneered by Dr Joe Gathe, an HIV



doctor from Houston who treated 30 of his patients solely with *Kaletra* for a year in his IMANI-1 study<sup>4</sup>. It worked for most of his patients who stayed on the treatment, although some dropped out due to what Gathe called "situational non-adherence", meaning that they ran out of money to pay for their medication.

Gathe's radical treatment wasn't a way of making anti-HIV regimens more effective or tolerable: it was purely to save money for his largely poor, black and uninsured patients. "In a healthcare system like the USA - or indeed in Africa - why should you expose a patient to the cost of three drugs if one will work?" he asks. Gathe has now embarked on a second open-label study of *Kaletra* monotherapy in people who haven't taken anti-HIV drugs before. He argues that the concept of monotherapy requires serious and careful examination. One reason to consider monotherapy, he says, is drug conservation - not getting through your options too quickly.

### Making a success out of 'failure'

What choices are there for the 15% or so of individuals in the UK who *have* exhausted their options, and have multidrug-resistant HIV<sup>7</sup>? Are they doomed to clutch at the straws of whatever new drug trial comes along, and is increasing the number of drugs taken, known as mega-HAART - usually using fistfuls of up to eight recycled and experimental drugs - the only option?

Not according to some remarkable work Steve Deeks has done. "Deeks' discordants" are a group of his patients with detectable viral load and multi-drug-resistant HIV whose health he has managed to maintain with reasonably controlled viral loads and CD4 counts by giving them fewer drugs rather than more. "It takes about four years of continuous failure for people to lose all the CD4s they gained with their last regimen," explains Deeks. "With most patients we can afford to wait these days till several new drugs come along rather than putting them on some risky trial where they might end up on a placebo."

In one pivotal study<sup>8</sup> he found that by keeping his patients on NRTIs alone he was able to maintain viral loads at virtually the same level for six months. Deeks told the recent BHIVA Conference that he believed that this was not just due to the reduction in viral fitness caused by resistance mutations such as the 3TC-related M184V mutation - it was also because NRTIs continue to exert some direct antiviral effect, even against HIV that is supposed to be resistant to them. As evidence, he showed data suggesting that when someone stops taking 3TC their viral load starts going up *before* the M184V mutation disappears.

In a subsequent study<sup>9</sup> Deeks and colleagues also found that remaining on PIs after the emergence of resistance and increased viral load seems to help the immune system by reducing the number of activated CD4

and CD8 cells - a positive thing, since HIV-induced immune activation is the principal cause of the chronic immune decline that can lead to AIDS.

A small study from London's Chelsea & Westminster Hospital, reported at the recent BHIVA Conference<sup>10</sup>, suggests this can work for some people in the real world; more than 75% of the 35 people studied had CD4 increases a year after switching from standard multi-drug antiretroviral therapy to *Kaletra* monotherapy.

These individuals had not been controlling their viral loads with their current regimen, had taken a median of five previous regimens, and had a median CD4 cell count of 248 cells/mm<sup>3</sup> and a median viral load of just under 55,000 copies/ml before the switch.

Not surprisingly, CD4 cell counts increased by an average of 115 cells/mm<sup>3</sup> in the 14 (40%) who achieved an undetectable viral load, but even the six people whose viral load decreased by 1 log but remained detectable had an average CD4 cell increase of 73 cells/mm<sup>3</sup> after a year.

However, this didn't work for everyone: 15 (43%) didn't last the twelve months. Five switched away from *Kaletra* monotherapy because it wasn't keeping their virus under control, two because of side-effects and another because their CD4 cell count continued to fall. Another five were lost to follow-up and two switched for unknown reasons.

### Future strategies: therapeutic vaccines

Deeks' view is that the ideal goal of HIV treatment is eradication. Short of that ideal outcome, the goal of treatment should be to reduce the virus below the level that causes ongoing damage to the immune system or clinical harm. What this level actually is has not been defined, and may vary from person to person. For most people, the goal of 'undetectability' is reasonable, as this will ensure that drug resistance is unlikely to emerge over time.

But for people who already have some drug resistance, the number of drugs necessary to achieve an 'undetectable' viral load may result in more harm than benefit. Could a future strategy involve keeping drug resistant patients on just the right combination of drugs to render their HIV essentially harmless?

Another future possibility utilises therapeutic vaccines, which aim to control HIV and potentially provide a prolonged respite from having to take drugs by boosting our natural immune response to HIV. So far there have only been two really successful attempts to do this.

In 2004, a Brazilian/French team<sup>11</sup> re-injected HIV-positive volunteers with their own dendritic cells (immune cells that ferry foreign invaders to the T-cells for recognition and destruction) which had been induced to display particularly provocative bits of HIV on their surface. The result was a ten-fold

drop in viral load that lasted over a year, a similar rise in CD4 count, and a year off therapy.

And more recently another French team<sup>12</sup> tried a complex combination of therapeutic vaccines, the immune booster interleukin-2 (IL-2), and viral-load-guided treatment interruptions to produce a situation in which the participants who received therapeutic vaccination stayed off drugs for an average of 43% of the time while non-vaccinated patients were drug-free for 27% of the time.

However, there are potential drawbacks to both approaches: the dendritic-cells vaccine was as expensive to produce as a year's worth of anti-HIV drugs, and it seems unlikely that many people would want to subject themselves to the severe flu-like side-effects of IL-2 just to have a few months off drugs.

There are also potential drawbacks to the experimental monoclonal-antibody drugs, TNX 355 and PRO 140 currently in development. Although these anti-HIV drugs may only have to be taken once every two weeks, in their current formulation this involves being on an intravenous drip. Since these drugs will still have to be taken in combination with more conventional daily anti-HIV drugs, how many people - other than those with no other options - will be motivated enough to be willing to spend a morning at the HIV clinic every fortnight just to cut one pill out of their regimen?

### Treatment for life?

In the end, the results of SMART have really reminded us that HIV is toxic and life-threatening - even more so than the daily anti-HIV drugs we have come to both love and loathe. Perhaps there are worse things than popping a few pills every day. Maybe 'treatment for life' is just what it sounds like - a good thing.





# rethinking when to start

why do some experts think again that it's time to 'hit hard, hit early'? asks Edwin J Bernard

## Summary

- Current treatment guidelines recommend starting anti-HIV therapy when CD4 counts are between 200-350 cells/mm<sup>3</sup>.
- Some experts think that therapy should be started at higher CD4 counts in the light of recent studies.
- One of these studies contradicts itself, another provides no new information, and the SMART study was not about when to start anti-HIV therapy.
- In the real world, many people are not starting therapy according to current guidelines.
- This is because around one third of people with HIV in the UK are being diagnosed too late.
- However, some are not on therapy for other reasons, suggesting treatment guidelines aren't being followed uniformly at clinics around the UK.

**When highly active antiretroviral therapy (HAART) first became available a decade ago, experts behind treatment guidelines in the United States (US) adopted what was known as a 'hit hard, hit early' approach, recommending the aggressive treatment of HIV in individuals with CD4 cell counts as high as 500 cells/mm<sup>3</sup>.**

Although the idea behind this approach was well-intentioned – to prevent damage to the immune system and the illnesses that follow – what drove this strategy was the belief (rather than knowledge) that HIV could be eradicated by HAART after a few years on therapy; however, this was proven wrong several years later.

HIV treatment guidelines in the United Kingdom (UK), US and Europe currently recommend that, in the absence of HIV-related illness, HAART should be started after someone's CD4 cell count has fallen below 350 cells/mm<sup>3</sup> but before it falls below 200 cells/mm<sup>3</sup>.

In January, the SMART treatment interruption study was stopped early after they found that the people who interrupted their therapy and kept their CD4 counts between 200 and 350 cells/mm<sup>3</sup> had a 2.5 higher risk of disease progression and death than those who stayed on therapy and kept their CD4 counts higher<sup>1</sup>.

At the Retroviruses Conference, held in Boston in February, some experts felt that these results – as well those of two other studies presented at the conference, one of which received a lot of mainstream press coverage – suggest that it's time to seriously reconsider starting people on anti-HIV therapy at higher CD4 cell counts.

However, not everyone is convinced that it's again time to 'hit hard, hit early', and, as you will discover, nothing in HIV treatment is ever that straightforward.

**Has the pendulum swung too far?**

Renewed arguments for starting treatment earlier are not new: two

years ago, a group of US experts, including Dr Scott Holmberg of the US Centers for Disease Control (CDC), and senior HIV consultants Frank Palella, Kenneth Lichtenstein and Diane Havlir, argued in a respected HIV journal that "the therapy initiation pendulum has swung too far in the direction of later initiation - at a CD4 cell count near 200 cells/mm<sup>3</sup> - rather than earlier initiation at a CD4 cell count of above 350 cells/mm<sup>3</sup>."<sup>2</sup>

They argued that some studies had shown a clear survival benefit to starting at CD4 counts higher than 350 cells/mm<sup>3</sup>; that the risk of HIV-related opportunistic infections is smaller if you start treatment above 350 cells/mm<sup>3</sup>; and that starting HAART at higher CD4 cell counts increases the chances of getting and keeping viral loads undetectable.

They also said that arguments in favour of delaying HAART due to concerns over side-effects are no longer valid now that better-tolerated anti-HIV drugs are available. They argued that resistance is also less of a concern because there are now many anti-HIV drugs to choose from, including new classes, and that once-daily therapy is making adherence easier, so resistance is less likely to develop.

They also made both economic and public health arguments for earlier HAART initiation, and claimed that earlier HAART was cost-effective since it reduced the costs of caring for people who became ill at lower CD4 counts. They added that with more people on treatment, viral loads would be lower, reducing the likelihood of onward transmission of HIV.

However, their arguments may seem to some to be overly optimistic, and their public health arguments wouldn't affect the infectiousness of the 33% of HIV-infected people who don't know that they are HIV-positive. Besides, research has since shown that even on HAART some people with undetectable viral loads in their blood can still have potentially infectious sexual and rectal fluids.

**A need for caution?**

Many of the arguments against starting earlier were advanced in the same journal by a pair of US expert clinicians, Cal Cohen and Brian Boyle.<sup>3</sup> They said that although there are uncertainties about the best time to start HAART, studies have shown that people who commence anti-HIV therapy with low CD4 cell counts experience "significant immunologic recovery" and they noted the "impressive ability of the recovered immune system to restore control of pre-existing opportunistic infections."

In addition, anti-HIV therapy now packs such a powerful punch that regardless of CD4 counts viral loads can be brought down to undetectable levels and kept there.

They also argued that concerns about side-effects remain, particularly the longer-term risk of increased chances of heart attacks and strokes – which have since been associated with most ritonavir-boosted protease inhibitors (PIs) – and noted "reductions in bone density, increases in insulin resistance, and a small but still present risk of lipodystrophy" even with the newer less toxic drugs and regimens.

Resistance also remains a significant concern, they added, because most people start HAART today comprising either efavirenz (*Sustiva*) or nevirapine (*Viramune*). These non-nucleoside reverse transcriptase inhibitors (NNRTIs) require just one mutation to 'fail', and the failure of an NNRTI-based regimen is likely to leave an individual with resistance to all NNRTIs, as well as to some of the nucleoside reverse transcriptase inhibitors (NRTIs) used in their HAART combination.

Cohen and Boyle concluded that, despite the availability of new anti-HIV drugs, there is no strong evidence that HAART should be started earlier. "There remain potential disadvantages to doing so," they wrote, "including risks of antiretroviral toxicity and emergence of resistance, and, in a field anchored by evidence-based medicine, there is limited evidence of its advantages."

## is early treatment always better?

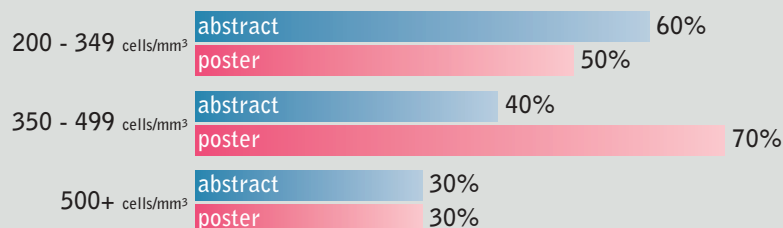
The chart below shows the differences between Lichtenstein's abstract and poster for three HIV and/ or drug-related symptoms based on starting anti-HIV therapy according to CD4 count.

Each bar shows the percentage reduction in risk compared to starting anti-HIV therapy when CD4 (lower is better) counts are below 200 cells/mm<sup>3</sup>

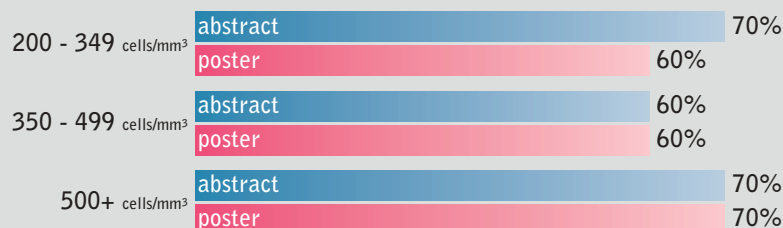
The abstract suggested starting at higher counts was better; the poster supports current guidelines.



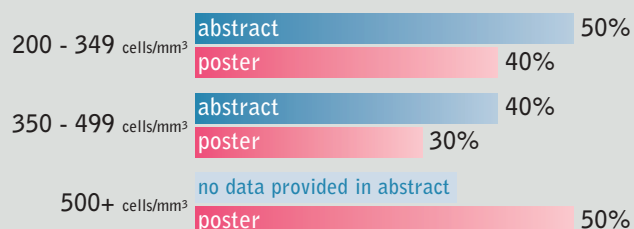
### renal insufficiency (kidney problems)



### neuropathy (painful nerves in feet/ hands)



### lipoatrophy (fat loss)



## Has anything really changed?

If you had read the popular press in February, you might have seen headlines that announced: 'AIDS study suggests: start medicines early'<sup>4</sup> and 'Early treatment always better for HIV, study finds'<sup>5</sup> This study<sup>6</sup>, whose lead author was pro-'hit hard, hit early' campaigner, Kenneth Lichtenstein, was presented as just one of 930 posters at the Retroviruses Conference, and yet it managed to achieve more mainstream press coverage than the much-discussed SMART study or the impressive results of a brand new class of drugs, integrase inhibitors, which were considered to be the two biggest stories of the conference.

This PR coup would be fine if the Lichtenstein study's conclusions actually agreed with the headlines. In fact, it would be fine if the poster as presented at the conference actually agreed with the abstract (a synopsis of the study that is submitted to the conference organisers months before the conference, and often the only evidence of a study once it is over – unless it is published in a peer-reviewed journal).

Why does this matter? The abstract – and the mainstream stories – suggests that far from being toxic, starting anti-HIV drugs at CD4 counts between 350 and 500 cells/mm<sup>3</sup> actually *reduces* the chances of having kidney problems, neuropathy (tingling in the hands and feet) and fat loss. But the poster that Lichtenstein actually presented at the conference contradicts these 'findings' and concludes that starting treatment according to current guidelines is better than waiting until your CD4 count has fallen to below 200 cells/mm<sup>3</sup>. Even though the abstract and news stories made it look like starting even earlier was better, this was definitely not the case.

Another poster presented in Denver<sup>7</sup> found that people who started HAART when their CD4 counts were lower than 200 cells/mm<sup>3</sup> had a 330% higher risk of becoming sick or dying of AIDS than people who started HAART when their CD4 counts were between 201

and 350 cells/mm<sup>3</sup>. They also found that people who started HAART according to current treatment guidelines, when their CD4 counts were between 201 to 350 cells/mm<sup>3</sup>, had a 46% higher risk of becoming sick or dying of AIDS compared with people who started HAART when their CD4 counts were between 351 to 500 cells/mm<sup>3</sup>: however, some people in the study actually did better if they waited until their CD4 counts were between 201 and 350 cells/mm<sup>3</sup>.

This isn't news: several previous studies have found similar risks, and the authors of the current UK treatment guidelines (due to be revised next year), were aware of these studies and felt that on balance, realistic concerns over long-term drug side-effects and the development of resistance needed to be balanced with the relatively small risk of disease progression at CD4 counts above 350 cells/mm<sup>3</sup>.

## What about SMART?

The surprising results of the SMART study – which found that more people who interrupted their therapy were getting sick and dying at any CD4 count (although most had CD4 counts well below 350 cells/mm<sup>3</sup>) than people on continuous HAART with the same CD4 counts – have led some experts to argue that being on HAART at any CD4 count might be better than not being on therapy. But SMART's primary objective was to see if it was safer to remain on HAART continuously or whether you could reduce the periods of time spent on therapy, and the conclusion drawn by most experts was that, as far as anti-HIV drugs are concerned, (like Pringles) 'once you pop, you can't stop'.

As Roy Gulick of Cornell University, New York, recently told Medscape: "One way of putting it is to say that the best way to decrease the amount of time on antiretroviral therapy is to delay starting it in the first place. I think this reinforces the point that we need to use medications when they're needed, and perhaps not start too early, because the bulk of the evidence here is that once a

person starts, they should continue on antiretrovirals, both for the benefits in terms of HIV disease, and again, as suggested by the SMART study, the benefits in terms of reducing other end-organ complications, such as cardiovascular, renal [kidney], and hepatic [liver] toxicities."

Adrian Palfreeman, the leading SMART investigator in the UK, recently told the BHIVA conference, that we shouldn't over-interpret the SMART results. "Only 5% of patients in SMART were [treatment] naive," he said. "I don't think we can necessarily be sure that the CD4 counts [in treatment experienced people] are of the same quality as CD4 cells that we see in [treatment] naive [people]. So, I would hesitate to use any of these data to make any conclusions about when to start therapy."

## The real world

Treatment guidelines are important, and set the standard for HIV care, but in the real world many people are not being diagnosed HIV-positive until their CD4 counts have fallen below 200 cells/mm<sup>3</sup>, making the debate about whether to start earlier something of a moot point.

A study by the Health Protection Agency (HPA) published last year in the *British Medical Journal* (BMJ)<sup>8</sup> found that one in three of new HIV diagnoses in the UK and Ireland were made when people's CD4 cell counts were already below 200 cells/mm<sup>3</sup>. They found that late diagnosis was significantly more likely to occur in black Africans and people who were older.

Although the BMJ study found that late diagnosis was less frequent amongst gay men, irrespective of their age or ethnicity, another study, published in the journal *AIDS* two months earlier<sup>9</sup>, found that one in four gay men in England and Wales were being diagnosed with HIV after their CD4 cell count had fallen below 200 cells/mm<sup>3</sup>, resulting in a tenfold greater risk of death within one year. The study's authors estimated that diagnosis of

these men before their CD4 cell counts had fallen to below 200 cells/mm<sup>3</sup> would have had a dramatic effect on death rates. "Early diagnosis of all [gay and bisexual men] in 2001 could have reduced short-term mortality by 84% and all mortality in that year by 22%," they concluded.

Last year, a BHIVA audit<sup>10</sup> found that 62% of people attending HIV treatment centres across the UK had started HAART after their CD4 count had fallen below 200 cells/mm<sup>3</sup>; this included 22% whose CD4 counts had fallen below 50 cells/mm<sup>3</sup> before starting HAART. Again, late diagnosis was identified as the problem.

And at this year's BHIVA conference, the HPA presented sobering data<sup>11</sup> which found that one in five of all people with CD4 counts below 200 cells/mm<sup>3</sup> who attended HIV clinics in the UK in 2004 – almost 1000 individuals – were not taking anti-HIV therapy. This varied by region suggesting that a postcode lottery-type variation in the following of treatment guidelines at different HIV clinics could at least be partially to blame.

## Falling between the cracks

The experts behind the current treatment guidelines have worked hard to find a consensus which finely balances the toxicity of drugs and the toxicity of HIV itself.

However, it seems that a significant number of people living with HIV in the UK either don't know they are infected, or aren't on anti-HIV therapy despite clear guidelines recommending that they should be on HAART.

Perhaps more time, money and effort should be spent trying to overcome the many obstacles that prevent people from testing for HIV in the first place, and making sure that treatment guidelines are followed uniformly across the UK. After all, what's the point of life-saving treatment, and guidelines for their use, if so many people are falling between the cracks? ■

## hepatitis

## One in eleven with HIV also have hepatitis C

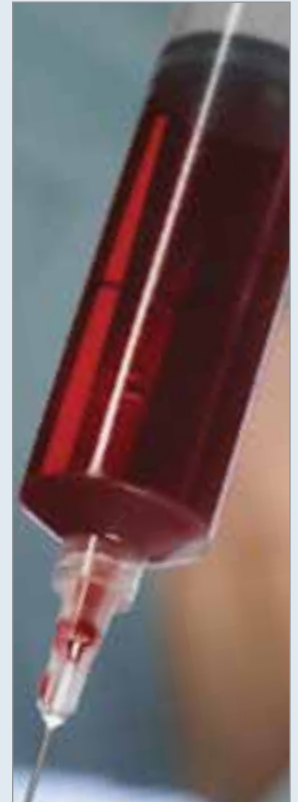
At least 9% of HIV-positive people in the UK are coinfecting with the hepatitis C virus, according to data presented to the British HIV Association (BHIVA) conference last month from the UK Collaborative HIV Cohort (UK CHIC), which includes 21,250 patients from seven UK HIV clinics.

However, although BHIVA guidelines have recommended since 2003 that all HIV-positive individuals are tested for hepatitis C soon after their HIV is diagnosed and at intervals thereafter if they have ongoing risk factors for the acquisition of hepatitis C, at least one-in-four weren't tested.

The UK CHIC study found that people most at risk of being coinfecting with HIV and hepatitis C are current or past injecting drug users and people from countries with a high prevalence of HIV and hepatitis C. Although this study - which included data until 2004 - found that gay men were not at an increased risk of testing positive for hepatitis C antibodies, more recent data from London and Brighton have found that sexual transmission of hepatitis C is occurring, and that it is associated with unprotected traumatic sex (like rough anal sex and fisting), group sex, drug use, and frequent partner change.

Another study presented to the BHIVA conference, which examined survival in people with limited anti-HIV treatment options due to acquired drug resistance and/or intolerance to most currently approved anti-HIV drugs, found that HIV-positive individuals who are coinfecting with hepatitis C appear to have a slightly worse prognosis than people who are infected with HIV alone.

The investigators concluded that "coinfection with hepatitis C appears to increase the risk of mortality, but this effect might be partly explained by a shorter time to switching/stopping antiretroviral therapy. One possible reason could be that hepatitis C virus-infected patients are less able to tolerate antiretrovirals."



## hepatitis

## Experts uncertain about atazanavir interactions

Some experts are concerned that people on atazanavir (*Reyataz*) who also take acid-reducing drugs may not absorb enough atazanavir, risking drug resistance and treatment failure. A few small studies have examined atazanavir's interactions with proton pump inhibitors such as omeprazole (*Losec/Nexium/Zanprol*) and histamine-2 blockers like ranitidine (*Zantac/Pylorid*). As a result of these studies, atazanavir's manufacturer, Bristol-Myers Squibb, currently recommend that proton pump inhibitors should not be used if you are taking atazanavir and that histamine-2 blockers should be taken twelve hours apart from atazanavir.

Last month, two teams of doctors and pharmacists called these recommendations into question for people taking

ritonavir-boosted atazanavir. Both teams have found that the patients who had taken proton pump inhibitors - either omeprazole or rabeprazole (*Pariet*) - alongside ritonavir-boosted atazanavir neither had significantly reduced blood levels of atazanavir, nor were more likely to 'fail' anti-HIV treatment.

It's clear that more studies are needed to find out once and for all if there is a significant interaction, but until those results are available, people taking ritonavir-boosted atazanavir together with proton pump inhibitors should either have therapeutic drug-level monitoring (TDM) done in order to make sure atazanavir blood levels are adequate, or continue to follow the current recommendation and use alternative acid-reducing drugs.

## hiv and the law



### First successful gay HIV transmission prosecution

Last month, a 47 year-old gay man became the seventh person in England and Wales to be successfully prosecuted for "recklessly inflicting grievous bodily harm" under the Offences Against the Person Act 1861, Section 20 by transmitting HIV to his 37 year-old partner. The man, who cannot be named, is the first to be successfully prosecuted for reckless transmission of HIV to another man. Last year, a young Welsh woman became the first female to be convicted of reckless transmission.

The man pleaded guilty at Isleworth crown court, West London, and will be sentenced at a later date. He faces a maximum prison sentence of five years.

This is the fifth time that someone has pleaded guilty to charges of reckless transmission in England and Wales, with only two cases - those of Mohammed Dica and Feston Konzani - actually going to trial. The judgements in these cases have established the principles that apply in England and Wales to those charged in cases involving reckless HIV transmission.

Put simply, the judgements confirm that if someone knows they are HIV-positive, is aware of the risk of transmission, and takes an unjustifiable risk that results in the transmission of HIV, they could potentially be accused of "recklessly inflicting grievous bodily harm".

Although a valid defence is to claim that the person who became infected with HIV consented to the risk of transmission, the kind of consent needed to avoid prosecution is informed consent. In most cases informed consent will be established if there has been disclosure by the HIV-positive person of their HIV status, but it is unclear whether disclosure is absolutely necessary to avoid prosecution.

It is also unclear whether transmission of HIV under any circumstances is considered reckless - such as when a condom fails, or through oral sex - or whether it only applies to when condoms are not used in vaginal or anal intercourse.

In addition, the cases do not make clear the relationship between nondisclosure and recklessness.

People in Scotland can also be prosecuted for transmitting HIV, although the legal system is different.

For more on how and why the law regarding the criminalisation of HIV transmission has changed, see the implications of criminalisation on page 14.

## policy news



### HIV treatment and care costs £16,000 a year

The cost of providing both highly active antiretroviral therapy (HAART) and NHS care to an individual living with HIV in the UK averages at just over £16,000 a year for someone on a first combination, and slightly more for second- and third-line HAART, at an annual cost of around £16,500 and £16,666, respectively, according to data presented to last month's BHIVA conference.

The researchers, who used data from 27 UK HIV clinics treating over 22,000 HIV-positive people between 1996 and 2002, also found that it wasn't resistance but intolerance to side-effects that was the major cause of treatment failure. Intolerance to side-effects was also cited as major problem in a recent pan-European study, and the study's authors write that there is "potential for continued improvement in future years with simpler, less toxic regimens and increasingly effective clinical care."

On Thursday May 25th NAM will be presenting a one day symposium in central London designed to deepen understanding of the complex changes now taking place in NHS provision of HIV care, as well as provide an update on the key advances in HIV medicine that are likely to have an effect on UK clinical practice in 2006-07.

For more information, and to download a registration form, visit: [www.aidsmap.com/en/events/symposium.asp](http://www.aidsmap.com/en/events/symposium.asp)

# the implications of criminalisation

Dr Catherine Dodds of Sigma Research explains to Michael Carter



catherine dodds

**In the autumn of 2003 many people with HIV and their representative organisations were shocked to learn that a man had been convicted by an English court and sent to prison after infecting his sexual partners with HIV. Several other prosecutions quickly followed, all resulting in conviction, with all but one of the cases involving men, three of whom were African.**

The prosecutions have been brought using Section 20 of the 1861 Offences Against the Person Act, with the individuals convicted of grievous bodily harm after 'recklessly' transmitting HIV during unprotected sex.

## The past

Until the first conviction it had been thought that it was highly unlikely for a prosecution for the reckless transmission of HIV to be brought under English law. Dr Catherine Dodds a research fellow at Sigma Research who has raised concerns about the impact of the criminalisation of HIV transmission on the communities most affected by HIV in the United Kingdom explained why. "The reasons date back to the 1890s and the so-called 'Clarence' case. Clarence was convicted in the lower courts under the Offences Against the Persons Act of grievous bodily harm after infecting his wife with gonorrhoea. The Court of Appeal overturned this verdict. It had reasoned that, because they were married, Mrs Clarence could not withhold her consent to sexual intercourse. This meant that because she "consented" there was no assault, even if the transmission of disease could be treated as assault (which, at the time, it could not).

Dr Dodds added that the Law Commission, which makes recommendations for new laws in England and is independent from the government, recommended in 1993 that both the deliberate and reckless transmission of disease should be a criminal offence. The Home Office rejected this in a 1998 White Paper which stated that only the intentional transmission of serious disease (including HIV) should be a criminal

offence, a position supported by HIV organisations such as the Terrence Higgins Trust and the National AIDS Trust. The Government's proposals were, however, never implemented.

## The present

Five years later, everyone was caught napping. The conviction of a man for infecting his partner with HIV in Scotland passed with little more than a ripple of concern in England as advocacy organisations and HIV-positive individuals assured themselves that it was a one-off case, brought under a legal system fundamentally different from that of England.

Indeed, so off the ball were HIV organisations, that the first time many knew that a man was in court charged with grievous bodily harm after infecting some of his sexual partners with HIV was when they read about it in the newspapers. This case involved Mohammed Dica, who in November 2003 was sentenced to eight years in prison after being convicted of infecting two women with HIV. "It set off the alarm bells. For the first few weeks following the conviction, nobody knew how to respond", explained Dr Dodds. Mr Dica eventually won the right to a retrial on appeal, but was later convicted of recklessly transmitting HIV to one woman and sentenced to four and a half years in prison.

Over the next few months a pattern emerged as other successful

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prosecutions were brought. "They were in three different locations, and all three involved African men", said Dr Dodds, who along with academic and HIV sector colleagues immediately started to question, "why are these prosecutions being brought now, and why do they involve African men?"

Dr Dodds feels that there is some merit in the notion that prosecutors took on cases against HIV-positive African asylum seekers or refugees accused of infecting their female sexual partners with HIV as these might be situations where a jury would be persuaded to convict. This would establish case law for later cases to be brought forward (including cases where white, gay, British men make complaints against their sexual partners).

The convictions had an immediate impact. Dr Dodds recalls the panic that she encountered in many HIV-positive people, particularly, but not exclusively in African men, in the immediate aftermath of the few cases. "There was a real worry amongst people with HIV that these cases could mean a visit from the police and prison", said Dr Dodds.

Advice was sought by HIV-positive people about their risk of prosecution. Prosecution guidelines that are currently being drafted by the Crown Prosecution Service (CPS) with the help of HIV and sexual health experts make it likely that even if HIV

transmission did occur, if the person had used a condom each time they had penetrative sex for the entire duration of sex, then a prosecution would not be brought. However, such guidelines will only be voluntary prosecution policy, and it will be difficult to provide definitive evidence about condom use in the face of conflicting statements. The existing judgments also make it likely that in the event of unprotected sex and HIV transmission occurring, disclosure of HIV status before sex would provide the basis for a successful defence.

There have also been implications for the doctor-patient relationship. It appears that some HIV-positive patients have lost confidence in the confidentiality of their medical records, as these have been used in court. "Adults attending sexual health clinics used to think that their records were absolutely sacrosanct and confidential," said Dr Dodds. "These prosecutions show that they aren't."

## The future

The professional body that represents UK HIV doctors, the British HIV Association (BHIVA), is preparing new guidelines for its members about how to respond to the prosecutions.

HIV, sexual health and gay rights organisations have met with the CPS to discuss draft guidelines for the bringing of prosecutions for the

transmission of HIV and other sexually transmitted infections. The draft guidelines recommend that very strong biological evidence of transmission between two individuals is now needed before a prosecution can be considered. But it's important to remember that these guidelines will only be voluntary.

In the meantime the prosecutions will continue. So far there have been seven successful prosecutions (including the recent guilty plea by a gay man, see *News in Brief*), all but one of which involved men, and as many as 15 further cases are in preparation.

The first full court case involving two gay men will be watched with particular interest by Dr Dodds who wants to see "how the police and CPS went about compiling evidence and if juries look at disclosure differently in cases involving gay men. If the defence team is on the ball, it should point out how much HIV health promotion has been targeted at gay men in the gay media and commercial venues. The instruction from the judge to the jury will be interesting – will it be different from the other cases? Will there be an acknowledgement that gay men have greater proximity to the HIV epidemic than UK heterosexuals?"

Sadly, more prosecutions will be needed to answer these questions. ■

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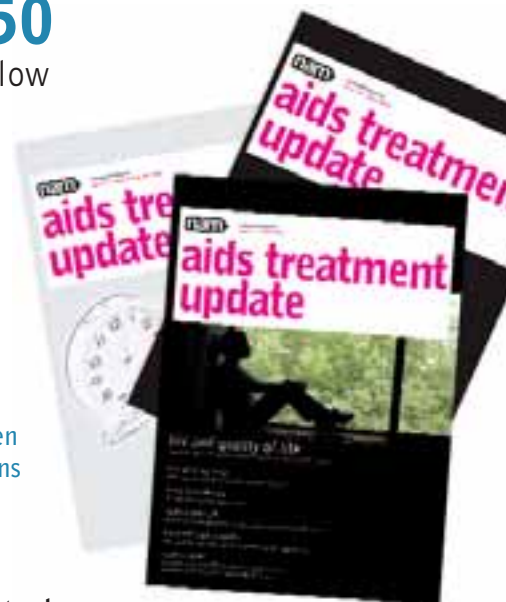
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