

aids treatment update

1992 - 2002 ten years of atu

This issue of ATU is a very special one - it's our tenth anniversary this month. Reading over the first editions, the writer in me was immediately struck by the archive's power as a historical document. ATU was launched in the dark days of HIV therapy, when the muddled use of monotherapies amounted to our best guess, but ultimately a misguided attempt at decelerating what was already a global health disaster. Though the science has opened doors in a way few people could have predicted, we all know that for many people the developments didn't come fast enough. Early contributors Mark Crowther and Sean McAteer died long before the paradigm shift which brought about HAART, a success story which has made up the bulk of our content for the last six years.

After ten years there are many people to thank. Amongst them, Edward King, ATU's founding Editor who established a model for patient information provision which valued independence, didn't seek to airbrush over scientific uncertainties, and respected our readers' intelligence. This model hasn't changed. Our Medical Advisory Panel, in the main unaltered from the first issue, continue to support NAM's work in a voluntary capacity. We're also grateful to our funders, whose ongoing commitment allows NAM to provide ATU at no cost to most of our readers.

Ten year relationships rarely survive without a degree of introspection and a pledge to learn from each other. You're doing your bit already, but you could help us plan for the future by completing the readers survey which accompanies this issue. Tell us what you like and don't like about ATU, and we'll promise to try to keep you all happy. After ten years, ATU remains your newsletter.

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Ten years is a very long time by anyone's standards, and as Edwin J Bernard shows in his review of *ATU's* first decade in the next article, the period since 1992 has been enormously eventful for HIV medicine. No better is this illustrated than by the unfolding story of d4T, an anti-HIV drug which has seen all the highs and lows one normally associates with media darlings. Not long ago considered to be the therapy of choice by many an HIV physician, the drug began its fall from grace much more recently. Now new data are leading some in the HIV community to question whether d4T should lose its status as a suitable first-line treatment option. Here we review this new information, and consider the lessons we might learn about how to appraise new therapies.

Background

d4T is an anti-HIV drug from the family known as nucleoside analogue reverse transcriptase inhibitors (or NRTIs for short). This group also includes ddI, AZT, 3TC, abacavir and ddC. NRTIs work against HIV by targeting a part of HIV called reverse transcriptase, an enzyme involved in the production of new viruses.

d4T has been in use for some time. In May 1996 it was approved in Europe as a treatment for HIV following AZT treatment failure or intolerance. Then in August 1997, it received full approval as an initial therapy for the treatment of HIV-infected adults and children (over three months old) with progressive or advanced immunodeficiency. Like most anti-HIV drugs, it is licensed for use in combination with other anti-HIV drugs.

d4T is manufactured by Bristol-Myers Squibb. It is also known as stavudine, or by its

tradename *Zerit*. After *Combivir* (a tablet which combines two drugs, AZT and 3TC), d4T was the most widely prescribed NRTI in 2001/02 in the London region.

Though originally linked to HIV drugs from the protease inhibitor (PI) class, over time, research has shown that the lipodystrophy syndrome (a side-effect of HAART therapy) appears to have more complex causes. The syndrome has been seen most frequently in those taking a combination of PIs and NRTIs, suggesting an interaction between the two is at play. Circumstantial evidence has repeatedly suggested an association between d4T and lipodystrophy (or more specifically lipoatrophy, or fat loss), in excess of that seen with other NRTIs. Whilst many have maintained that the link has not been definitively proven, it seems clear that the weight of evidence is growing rather than declining.

New information on d4T

New research reviewed here has been presented at two recent HIV conferences; the Fourth International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, and the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), both held in San Diego in September.

ACTG 384: Fat loss sub-study

ACTG 384 is a large HIV treatment strategy trial which compared the effects of starting various three or four drug HAART combinations. The design, and the virological and immunological results, were reported in *ATU* 116.

Participants in ACTG 384 were randomised to one of two NRTI backbones, AZT/3TC or

d4T/ddI, and further randomised to add either nelfinavir, efavirenz or both to that backbone. If the first combination failed, individuals in the triple therapy arms switched to the alternative drugs (e.g. from ddI/d4T/nelfinavir to AZT/3TC/efavirenz).

One hundred and fifty six patients were randomly selected for a sub-study in which DEXA scans (a form of X-ray designed to assess body composition) were carried out at baseline and during the 80 week follow-up of the main study. This analysis found that ddI/d4T was associated with a significantly greater loss of fat in the arms and legs after 48 and 60 weeks on treatment, compared with AZT/3TC¹.

Individuals randomised to ddI/d4T had lost 7.5% of their baseline limb fat by week 48, despite an initial increase in fat during the first 16-32 weeks of treatment. In comparison, the AZT/3TC group still had median fat proportions above baseline (+4.7%). This difference increased by week 64 (-13% versus +2%).

The analysis also looked at trunk fat, but did not distinguish between subcutaneous and visceral fat. The percentage of trunk fat remained above baseline in both groups at week 64, but was significantly higher in the AZT/3TC group.

The study allowed participants who were unable to tolerate their therapy to switch to the other study drugs. However, even when data from the nine people who switched for toxicity were excluded, the results of the fat loss analysis were unchanged.

When presented at the Lipodystrophy Workshop, the findings led Dr. Judith Currier of the University of California to state that "ddI/d4T should be taken off the [US] list of nucleoside pairs that are recommended for initial therapy".

Perth Study: More fat loss with d4T

A second study at the Lipodystrophy Workshop provided further evidence that fat loss is greater in recipients of d4T compared with other NRTIs. This study, from a team in Perth, prospectively tracked 53 male treatment-naive

patients who received DEXA scans at baseline and during their treatment course. In this non-randomised study, all participants began treatment with regimens that contained AZT or d4T. The vast majority of patients also received 3TC².

At baseline, participants had approximately 22% fat content in their legs. During the first year of treatment, individuals tended to gain fat. But as time went on, leg fat declined in both treatment groups. After 24 months, fat loss was greater in d4T users; leg fat content fell to 13% in the d4T group and 19% in the AZT group. Analysing the results according to PI or NNRTI use made no difference to these results. Leg fat as a proportion of total body fat also declined more steeply in the d4T group.

Switch from d4T improves body fat

According to a study sponsored by GlaxoSmithKline (who manufacture the three NRTIs AZT, 3TC and abacavir), people who experienced fat loss or high lactate levels (a potentially dangerous build up of lactic acid in the blood) on d4T saw an improvement in their symptoms after switching d4T for either abacavir or AZT³.

TARHEEL is a 48-week, open-label study which enrolled 118 individuals. Eighty-six replaced d4T with abacavir (because they had already taken AZT), and the remaining 32 with AZT. All participants had viral load below 400 copies at the time of the switch, and at least six months of d4T experience. A major weakness of this study is that there is no control group of people who remained on d4T to compare the results of the switchers against.

DEXA scans taken 48 weeks after the treatment switch showed significant increases in body fat in both groups. Fat levels in the arms had increased by 35.3% from baseline, whilst trunk fat and leg fat had increased by 16.4% and 12% respectively. CT scans indicated that the total increase in subcutaneous fat was 4%, whilst visceral fat declined by 2%. Seventy nine per cent of participants experienced an increase in subcutaneous fat, and 54% experienced a decrease in visceral fat.

glossary

antiretroviral A substance that acts against retroviruses such as HIV.

CD4 A molecule on the surface of some cells onto which HIV can bind. The CD4 cell count roughly reflects the state of the immune system.

enzyme A protein which speeds up a chemical reaction.

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

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

mitochondria Cellular compartment involved in energy production.

NNRTI Non nucleoside reverse transcriptase inhibitor, the family of antiretrovirals which includes efavirenz, nevirapine and delavirdine.

nucleoside analogue Chemical which resembles a nucleoside. Family of antiretrovirals which includes AZT, ddI, 3TC, d4T, ddC and abacavir.

open-label A clinical trial where both the researcher and participants know who is taking the experimental treatment.

protease inhibitor Family of antiretrovirals which target the protease enzyme. Includes amprenavir, indinavir, lopinavir, ritonavir, saquinavir, nelfinavir.

randomisation The process of selecting by chance the treatment that a clinical trial participant will receive.

what to do with d4T continued

NRTIs and mitochondria

Several HIV researchers have argued that the cause of fat loss seen in people taking HAART (and a number of other drug side-effects) is related to the effect of NRTIs on cellular components called mitochondria. The role of mitochondria is to produce the energy which allows body cells to perform their function. If they are unable to do their job, cells start to produce lactate, which eventually enters the bloodstream. If lactate levels are persistently high, a symptomatic condition called lactic acidosis may develop, which, although rare in people taking HIV treatment, can be fatal.

People who inherit mutations in the genes which govern mitochondrial function (mitochondrial DNA, or mt-DNA for short) are at increased risk of a number of conditions: neuropathy (nerve damage), myopathy (muscle damage), hepatic steatosis (fatty liver), pancreatitis (inflammation of the pancreas), diabetes, and – as mentioned – lactic acidosis. All of these conditions have been reported in people taking NRTIs, suggesting a link between the two. Mitochondrial dysfunction is not just hereditary however – it can arise due to obesity, alcohol use, aging and drug toxicity. Indeed, NRTIs have been shown to inhibit an enzyme (called polymerase gamma) which is involved in mt-DNA replication, and animal studies have indicated that NRTIs produce mitochondrial changes.

This has led several research groups to investigate mt-DNA levels in people taking NRTIs, and a number of recent presentations on this subject are reviewed here. However, it's important to note that tests which measure mt-DNA levels are a very new development, and there is still a lot of debate about the meaning and accuracy of their results. Because mt-DNA depletion is tissue-specific, it is not clear that measuring mt-DNA levels in other body compartments is relevant to side-effects concerning fat cells. Further to this, mt-DNA

levels may not be an accurate marker of mt-DNA function.

NRTI switching and mt-DNA

The same GSK-sponsored group behind the TARHEEL study also reported on the effect on mt-DNA levels of a switch from d4T to abacavir or AZT. This small study enrolled sixteen people who had taken d4T for at least two years, and monitored changes in mt-DNA over 48 weeks after these patients switched to abacavir (fourteen people) or AZT (two people). DEXA scans on twelve people revealed increases in arm, leg and trunk fat of 23%, 12% and 18% respectively after the switch. At baseline, median mt-DNA levels were 174 copies/cell, compared to 863 copies/cell for 22 HIV-negative controls. Mt-DNA levels in peripheral blood mononuclear cells (a type of immune cell) and in muscle tissue did not differ between the switch group and control group at baseline⁴.

After 48 weeks, mt-DNA levels had risen to 453 copies/cell, and had also increased in muscle cells. However, a weakness of this study is that it did not distinguish between mt-DNA levels in different types of fat cell, and again, the results are not controlled by patients who remained on d4T.

Gilead 903 study

Gilead's 903 study compared their new NRTI tenofovir with d4T as first-line HIV therapy. We've previously reported the virological and immunological results of this trial in *ATU 118*. In brief, 903 found there was no difference in response to the two therapies (which were taken with efavirenz and 3TC) after 48 weeks.

Whilst the study reported no overall differences in the frequency of grade 3 or 4 (moderate to severe) side-effects between the two arms, d4T recipients were more likely to experience increases in triglycerides, total cholesterol and LDL cholesterol. These differences remained

regardless of whether fasted or non-fasted values were analysed.

North American participants in this international trial were entered into a sub-study which investigated the effects of the different treatments on mt-DNA, and compared these with an HIV-negative control group. Amongst the one hundred and thirteen tenofovir recipients, mt-DNA rose from an average of 239 copies/cell at baseline to 321 copies/cell at week 48. In comparison, the 114 d4T recipients gained less mt-DNA, rising from a baseline average of 256 copies/cell to 284 copies/cell at week 48. The average mt-DNA level was 321 copies/cell amongst the 49 control patients⁵.

Whether the difference in mt-DNA response between the two treatments is clinically significant is not clear. Whilst abnormal lactate levels were seen more frequently amongst d4T recipients (36% versus 7%), these changes were asymptomatic and did not require HIV treatment to be changed.

The frequency of any mitochondrial toxicity-related side-effects of the kind noted above was greater in the d4T arm than the tenofovir arm after 48 weeks (10% versus 3%). This difference was largely explained by the greater frequency of neuropathy amongst d4T users (7% versus 2%).

Further report of lactic acidosis on d4T

FTC-301 was a randomised, double-blinded study comparing an experimental 3TC-like NRTI, FTC (emtricitabine), with d4T in people new to HIV treatment. All participants received open-label, enteric-coated ddI plus efavirenz in addition to their allocated therapy. The study was closed early after a planned analysis at 24 weeks noted a clear benefit in those receiving FTC, a result we reported in *ATU* 117.

According to a presentation at ICAAC, clinical lactic acidosis occurred in three people receiving d4T in this trial. There were no cases in the FTC arm. Other than this, there were no differences in laboratory-measured toxicities between the two arms⁶.

Use of ddI/d4T with hep C treatment

A further report has raised concern about a possible increased risk of mitochondrial toxicity-related side-effects in people taking treatment for hepatitis C virus (HCV) alongside the NRTI combination ddI/d4T.

The French RIBAVIC study investigated the effects of pegylated versus standard interferon, plus ribavirin, in HIV/HCV co-infected individuals taking HAART. Analysis of 265 participants found that 22% of patients (9/41) receiving ddI/d4T and ribavirin (which is also an NRTI) developed high lactate levels or pancreatitis. The risk of mitochondrial toxicity-related side-effects was 24 times higher in those receiving ddI/d4T compared to other anti-HIV drugs⁷.

ddI/d4T in pregnancy

In January last year, the US Food and Drug Administration (FDA) issued a warning regarding the use of ddI with d4T during pregnancy. This followed a series of seven case reports of lactic acidosis in pregnant women receiving these two drugs. Three of the seven cases were fatal. Of the three women who died, one also had hepatic steatosis, and the other two had pancreatitis. As mentioned above, all of these conditions are recognised to occur in the presence of mitochondrial toxicity.

Soon after the FDA warning, drug manufacturers Bristol-Myers Squibb recommended that ddI/d4T should be avoided during pregnancy if other NRTIs could be used instead. In a public statement issued around the same time, the European Medicines Evaluation Agency (EMA) took a different line, finding insufficient evidence that the risk of lactic acidosis in pregnancy was greater in users of ddI/d4T compared to other NRTIs.

What does all this mean for d4T?

Speaking to members of *ATU's* Medical Advisory Panel, it's clear that Judith Currier is not alone in forecasting a reappraisal of d4T's strategic role in HIV therapy.

Professor Tony Pinching of the Royal Hospitals NHS Trust urged a thoughtful approach: "People on d4T who are having problems may

glossary continued
resistance A drug-resistant HIV strain is one which is less susceptible to the effects of one or more anti-HIV drugs because of its genotype.

subcutaneous Beneath or introduced beneath the skin, eg a subcutaneous injection is an injection beneath the skin.

viral load Measurement of the amount of virus in a sample. HIV viral load indicates the extent to which HIV is reproducing in the body..

visceral Of or pertrating to the internal organs.

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what to do with d4T continued

well need to consider changes on therapy with their doctors, where alternative options exist. There should not, however, be a rush to judgement, but rather a considered balancing of the risks and benefits of all therapies. It may be that d4T as an initial agent will need to be considered carefully, again on the balance of risks and benefits."

Professor Brian Gazzard, Chelsea and Westminster Hospital, agreed that d4T's problems must be viewed in relation to those of the alternatives: "The results of ACTG 384 certainly do suggest d4T-containing combinations are associated with more rapid development of fat loss, although long-term follow-up seemed to suggest this was also occurring with AZT combinations."

Professor Janet Darbyshire, Director of the Medical Research Council's HIV Clinical Trials Unit, saw these new data as a significant development. "I think the data in naïve people will change practice. Before, it was not clear if the excess fat problems with d4T were due to the drug or the fact that [patients] had already had a lot of NRTIs before they got d4T. It will probably move to second-line."

Dr Fiona Boag, Chelsea and Westminster Hospital, expects "that d4T will not be used as first-line therapy, and that patients taking it already will request treatment change. Where this is feasible I would imagine that it will

occur. d4T will remain, however, an essential option for many patients."

Dr Ray Brettle, of Lothian University Hospitals NHS Trust, forecast little change to his current practice. "Personally I have avoided the combination of d4T and ddI for some time if there were alternatives because of the increased risk of neuropathy. The increasing evidence will reinforce our practice of examining competing side-effects for all patients on long-term therapy. I will continue to use d4T but will be careful about what I put it with."

As ever, you should not make changes to any treatments you are taking without discussing your concerns with your doctor beforehand. The risks of taking d4T, or any other drug, must be balanced against the drug's benefits, and this balance needs to be considered on a case-by-case basis. If you are not experiencing side-effects from taking d4T and are responding well to your treatment, then any decision to switch is likely to be influenced by the alternatives available. Where mitochondrial toxicity-related side-effects are occurring, the data reviewed above suggest certain of these may improve by switching from d4T to AZT or abacavir.

Needless to say, other treatment options present established risks of their own. And if one thing above all others is clear from this report, it's that our understanding of the effects of medications is always subject to change.

key conclusions

- A number of HIV drugs have been linked to the lipodystrophy syndrome, a side-effect of treatment.
- New evidence suggests that d4T may cause more problems of this sort than other similar drugs.
- Substituting d4T with abacavir or AZT, if this is feasible, may improve these side-effects in some people.
- All treatment decisions should be considered carefully with your doctor.

ten years of atu

as this newsletter marks its tenth anniversary, we invite four doctors who've supported atu since its inception to reminisce a little interviews by edwin j bernard

When NAM began publishing *AIDS Treatment Update* a decade ago, the only approved HIV treatment was AZT, opportunistic infections (OIs) were frighteningly frequent, an HIV-positive or AIDS diagnosis meant coping with, at best, an uncertain future, and condoms and behaviour modification were the only tools available for HIV prevention.

"Ten years ago we told people that we couldn't do much to prolong their life, and we'd help them die in peace and dignity, with as little pain as possible," recalls British HIV Association Chairman Brian Gazzard, Professor of HIV Medicine, Imperial College School of Medicine, and HIV Research Director, Chelsea and Westminster Hospital.

Today we have more than a dozen antiretrovirals to choose from, AIDS-defining events have declined dramatically, people are living longer than anyone ever expected, and condoms and behaviour modification are still the only tools available for HIV prevention.

After unprecedented leaps ahead in drug development, immunology and virology Brian Gazzard, can now tell his UK patients "that I think they'll survive 30 or 40 years if they take the medicine adequately." But today he and other distinguished HIV experts spend much of their energy and expertise attempting to bring HAART to the developing world, where the vast majority of people benefit neither from HIV treatment nor from HIV prevention. Have we really advanced as far as we think?

1992-1995: The Dark Ages

Director of the Medical Research Council HIV Clinical Trials Centre, Professor Janet

Darbyshire, has overseen many of the clinical trials that got us from there to here. "I think it's been a very exciting time," she says. "Things have moved amazingly quickly."

The second issue of *AIDS Treatment Update* featured the results of the pan-European and Australian Alpha trial – one of the first multinational clinical studies of antiretrovirals – which hoped to compare the effectiveness of two doses of ddI with placebo in patients who were intolerant of AZT. The placebo arm had to be dropped when too few people enrolled, and the only difference detected between the high and low dose arm was in toxicity.

"Although the results of Alpha are less crucial now, it was important in informing study development," remarks Tony Pinching, Professor of Immunology, St. Bartholomew's Hospital Medical School, and Clinical Director, Infection and Immunity Clinical Group, Royal Hospitals NHS Trust. "It showed that scientists and clinicians needed to be more in tune with the needs of patients."

Months later, the devastating results of the Anglo-French-Irish Concorde trial were announced. Concorde found that there was no difference in survival between early and deferred treatment with AZT monotherapy. Professor Jonathan Weber, Head of Department, GU Medicine and Communicable Diseases, Imperial College School of Medicine at St. Mary's, London was on the Concorde steering committee, and recalls the moment the results were unblinded. "It was a shocking experience," he says. "No-one really expected such a negative result."

“Concorde was a crucial, if a rather depressing outcome,” concurs Pinching, “but it did change people’s approach to both clinical treatment, and to trials and their interpretation. It demonstrated that you simply can’t make biological and clinical assumptions that go way beyond the data.”

It would be another two years before convincing results from the pan-European-Australian Delta trial provided much-needed optimism. Here, for the first time, a combination of AZT with either ddI or ddC, showed a significant improvement in survival, and sounded the death knell for the concept of monotherapy.

Jonathan Weber was also present at the Delta unblinding. “It was the first really successful intervention in the natural history of HIV,” he says. “That was the turning point in the whole decade.”

1995-7: The Age of Enlightenment

Post-Delta, HIV science progressed rapidly, if not always straightforwardly. Two papers published in the journal *Nature*¹ in January 1995 broke new ground in understanding viral dynamics and the rapid turnover of both HIV and CD4 cells, setting the scene for clinical data announced at Vancouver eighteen months later.

“These were the most cited papers of the year,” recalls Jonathan Weber, “fundamental papers, truly transforming scientific perception.”

The International AIDS Conference in Vancouver in July 1996 announced the era of ‘Highly Active Antiretroviral Therapy’ (HAART). The excitement was palpable, as the promise of combination therapy with a new class of drugs, protease inhibitors (PIs), was unveiled by Dr David Ho. ‘Undetectable’ and ‘eradication’ were the new buzzwords signifying the hope that the AIDS epidemic might be over in a decade, and at the very least, HIV disease would be as manageable as diabetes.

“The Vancouver Conference was obviously a very big milestone, and was the beginning of the rest of our lives,” says Tony Pinching. “Having been in the field since the very beginning, that was certainly the event that changed everything in terms of therapies. It represented the beginning of a totally different level of

efficacy in our treatments, and a different understanding of how we should manage patients with this infection.”

Not everything lived up the hype, however. David Ho, the first scientist to be named Time Magazine’s ‘Man Of The Year’ since 1960, and his eradication theory led many clinicians down a dangerous path, advocating an aggressive ‘hit hard, hit early’ approach that has since been discredited².

“Vancouver was great in terms of the science, but the speculation over eradication was inappropriate,” adds Pinching. “We have recognised that that type of reasoning was neither wise nor justified.”

“One thing we have learned since Vancouver is that mathematical models are just that,” agrees Weber, “they’re not the real world. You can become unstuck drawing inferences from them.”

1997-2002: A Golden Age?

The effect of combining the new PIs with the existing and newer Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) in triple drug combinations had a tangible benefit in the real world within months of Vancouver.

“At a very simple level, people stopped dying,” notes Pinching. “Having buried so many of my patients in the earlier decade-and-a-half, the respite from those ravages, even for people with quite advanced disease, was quite astonishing, and very palpable. It was quite transforming.”

The glow of the Lazarus-like effect of HAART soon began to fade, however, when anecdotes of a new side-effect, initially termed ‘Crix Belly’ after the commonly-used PI, indinavir (*Crixivan*), began to appear within a year of the Vancouver conference. Five years on, despite the damage to self-esteem and HAART compliance caused by the psychological effects of facial and limb fat loss and trunk fat gain, we still know surprisingly little about the cause, treatment and long-term effects of lipodystrophy.

“Personally,” says Brian Gazzard, “I think that we shouldn’t get the toxicities out of proportion. I think the data that many people will develop toxicity are poor, which is good news. So, although we all worry about toxicities, perhaps

we over-worry in comparison to the tremendous improvements in survival in general."

"The gains have been enormous," agrees Pinching, "and obviously people's prospects have been transformed. That's not to say the disease is easy to manage. There's no question that these treatments can be hard to take, whether it be because of toxicities or the burden of taking regular treatment. I am staggered at the capacity of patients to manage toxicities or adherence issues over long periods. I think that shows resilience and extraordinary adaptability."

A milestone paper on the effects of HAART on the immune system was published in *Science* exactly a year after Vancouver. Here, Brigitte Autran and colleagues showed that when HIV is controlled by HAART, the immune system is able to slowly repair and regenerate³. This, along with the realisation that eradication was not an achievable goal, and the concern over the toxicity of long-term therapy, has led to a gradual move away from the 'hit hard, hit early approach' in the years following Vancouver.

"There are now studies that have demonstrated that you don't lose a great deal by deferring treatment intervention," states Pinching. "I think that is a significant change, and although it's been a gradual change, it's one of the most important milestones: a change of culture."

With more choices of drugs available, and advances in tests to help manage treatment, HAART is now individualised, providing more potent and potentially less toxic treatment than ever before.

"I think we're increasingly adjusting people's therapy to what they're prepared to take, what they're able to take, how old they are, what their lipid profile is, and what their lifestyle is like," says Brian Gazzard.

Prevention: Failure and aspirations

Treatment, however, is only half the story. For all the advances that have been made in the past decade, the latest UNAIDS statistics (as of December 2001) show that of the estimated 40 million people who are living with HIV/AIDS, five million were thought to have been newly infected with HIV during 2001 alone⁴.

"Some years before Vancouver, I wondered whether an effective treatment for HIV might create a serious adverse effect on prevention programmes," recalls Tony Pinching. "And I think that while some of my fears have not been realised, there is no question that the positive effect of treatment has, to some extent, been undermined by the perception that HIV is treatable and so people may be less careful."

As discussed in last month's *ATU*, HAART is no prevention panacea, but advances in prevention tools like microbicides and vaccines – if they can be called advances – have disappointingly lagged behind treatment.

"Part of the problem is that prevention is now seen mainly as a developing country activity," explains Janet Darbyshire. "Microbicides are an area where there really isn't much interest from big Pharma. The same is true for vaccines. You make more money from drugs and in many ways they are easier to develop, and so a lot of money has been spent on drug development."

The most studied microbicide candidate of the past ten years, nonoxynol-9, has since been found to cause damage to human tissue, leading to inflammation and ulceration. And far from protecting against HIV and other viral infections, nonoxynol-9 can leave users more susceptible to it.

Jonathan Weber, who has been studying microbicides since 1995, wasn't surprised by the nonoxynol-9 fiasco, but is optimistic about the handful of microbicide candidates currently entering phase III trials.

"They all promise to be safe, but critically we need to know if they're going to be effective with long-term use," he says. "I think we'll know by 2007 whether the second generation of microbicides will work or not. But we wouldn't be going down the microbicide route at all if we were confident that there would be a vaccine." It has been eighteen years since it was predicted by US researchers that an AIDS vaccine would enter clinical trials within two years.

"We're no closer now than we were then," admits Tony Pinching. "In fact, some of the immunological obstacles look as big, if not bigger than they did then. There's no question

editor's note

The four interviewees for this article, Janet Darbyshire, Brian Gazzard, Tony Pinching and Jonathan Weber, have been members of ATU's Medical Advisory Panel, which reviews content prior to publication, since the newsletter's first issue which appeared ten years ago this month. NAM thanks them, and all our Panel Members, for the unique contribution they make to our work.

Back issues of ATU are available in pdf format on NAM's website aidsmap.com to February 1999. The full ATU archive is held at NAM's offices.

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that it is an important scientific area for vigorous pursuit, but I think we have to be realistic that the answer may be that it still can't be done." He is equally despondent about immunotherapeutic vaccines and treatments, including IL-2.

"I think translating immunological knowledge into immunological therapies has been rather disappointing," he says.

Brian Gazzard is more hopeful. "I'm still moderately optimistic about a vaccine in ten years," he says.

"There is quite a lot of hope around vaccines that induce cellular immunity," adds Jonathan Weber. "There's also a lot of money now available, and I think that with enthusiasm there really will be progress."

"There are currently several large public/private partnerships for the development of both vaccines and microbicides," concludes Janet Darbyshire. "And if we make huge strides in vaccines and microbicides, we'll look back at condoms and think it was the Dark Ages for prevention. The hope of the next ten years is that microbicides and vaccines will begin to be effective and practicable."

Future prospects

Along with a search for a preventive vaccine, bringing antiretroviral therapy to developing nations is at the top of today's AIDS agenda, inspiring an unprecedented concerted effort between politicians, clinicians and drug companies. Brian Gazzard believes that a pilot study underway in Botswana shows that if it can be done on a small scale, then scaling-up is a real possibility.

"I'm very impressed by our experience in Botswana," he says. "With quite moderate sums of money you can make people adhere to therapy. Only four out of 800 have stopped therapy in the first six months of treatment, with a relatively low risk of side-effects. I think that was an amazing finding in terms of what

you potentially could do for very large numbers of people."

Meanwhile, Tony Pinching is looking closer to home – recent immigrants attending Barts and The London Trust in East London.

"It's all very well talking about the rest of the world, but we are seeing very large numbers of patients presenting with late disease," he says. "There are still enormous social, personal and cultural barriers to access to care here in East London. These people present enormous challenges, and are a reminder that access to these new therapies is incomplete, even within our own country."

As for the future of HIV treatment, all four experts agree that the gains seen in the past decade are unlikely to be repeated in the next ten years.

"Almost by definition, the next generation of changes is going to be small, unless the holy grail of eradication therapy comes about," asserts Brian Gazzard.

"I think the next ten years are going to be even more challenging for scientists," says Janet Darbyshire, "in that it's going to be more difficult to make as much improvement."

"The field is maturing and slowing," adds Jonathan Weber. "A lot of what we do these days is chronic disease management."

"I think that part of where we're going is that we will become more sophisticated in avoiding toxicities," notes Tony Pinching.

New classes of drugs and new viral targets appear to be very likely. Gene therapy, on the other hand, "would be a giant leap," says Janet Darbyshire.

"I would be very optimistic that there will be easier regimes to take," concludes Brian Gazzard, "combination pills once-a-day which will aid adherence, and I feel fairly confident that drug companies will develop drugs with fewer side-effects."

news in brief

New guidance on adherence

Draft recommendations on adherence to HIV treatments have been issued by the British HIV Association (BHIVA) and the Medical Society for Study of Venereal Diseases (MSSVD).

The new guidance is aimed primarily at those working in HIV treatment centres, and emphasises that a wide range of health care professionals have a part to play in what should be a structured, and adequately resourced response. High adherence is influenced by a great many factors, some of which are easier to modify than others. It's clear that everyone taking treatment is both a potential high and low adherer, and so it's important to provide tailored support to everyone taking HIV therapy, and to maintain this support so long as therapy is continued.

The draft document is now available on [aidsmap.com](http://www.aidsmap.com) and will be open for consultation until April next year. Comments on the guidelines can be submitted via an online discussion group. A new booklet on *Adherence* will soon be available from NAM.

Source:
http://www.aidsmap.com/about/bhiva/bhiva_adherence.asp

Controversy over IL-2 trial

Disagreement has broken out between trial investigators and the sponsoring company, Chiron, over the future of SILCAAT, a large international trial. SILCAAT is investigating the effects of the immune therapy interleukin-2 (IL-2) on the rate of disease progression in people with advanced disease, when added to HIV therapy. In late October, Chiron announced their intention to close SILCAAT, planned to last four years, citing the high cost of completion and the potential low frequency of clinical events as the reasons behind their decision. Chiron plan to file for IL-2's approval on the basis of data which have been gathered so far.

The following day, SILCAAT's scientific committee issued a statement criticising Chiron's decision, saying, "We understand the need for such difficult decisions on the part of a company. In this instance the decision seems

particularly tragic to us insofar as it terminates a study that is fully enrolled, and that at the last DSMB meeting [an independent safety assessment], was noted to be proceeding as planned with intact assumptions regarding sample size."

The investigators hoped to salvage the situation through discussion with Chiron.

Meanwhile, another large study of IL-2's clinical effects, ESPRIT, continues. The ESPRIT study is an international study, with twenty-four UK sites, which is similarly investigating the effects of adding IL-2 to anti-HIV therapy, though is aimed at people with a higher CD4 count (above 300) than SILCAAT. Though the UK contingent is almost fully enrolled, a few places remain open. If you'd like to find out more about ESPRIT, visit the Clinical Trials database on aidsmap.com, or speak to your clinic doctor.

Alpha defensins: Another route to stop HIV?

Chief proponent of the HIV eradication theory, David Ho, has reported the discovery of a group of immune system messengers which may be responsible for protecting against HIV disease progression. These substances, named alpha defensins-1, -2 and -3 are proteins produced by both neutrophils and CD8 T-cells. In the case of the former, they are known to defend against infections. Now Ho reports that these same proteins may be playing a similarly protective role against HIV when produced by CD8 cells.

CD8 cell response has long been considered pivotal to the occurrence of long-term non-progression of HIV infection. When Ho and colleagues removed alpha defensins from CD8 cell cultures from a group of HIV long-term non-progressors, the cell's anti-HIV activity was weakened. Adding synthetic forms of the defensins to HIV strains in the test tube halted viral replication, raising hope that this latest discovery may pave the way for new drugs.

Source: Zhang L et al. Science Express (online publication) 26 September, 2002.
<http://www.sciencemag.org/scienceexpress/recent.shtml>

nonoxynol-9 spermicide warning

The World Health Organisation have warned against the use of the spermicide nonoxynol-9, found on some condoms, during anal sex. Nonoxynol-9, which has been under investigation for its potential effect on HIV transmission, was in fact found to increase the risk of contracting HIV when used by women at high risk. This information, from a study involving female sex workers with a high number of partners, was published in the September 28th issue of *the Lancet*.

The World Health Organisation note that nonoxynol-9 has not been found to be effective in preventing acquisition of any sexually transmitted disease, and is no more effective in preventing pregnancy than condoms lubricated with silicone. Consequently, they advise that nonoxynol-9 lubricated condoms should no longer be promoted. The WHO report can be read online at <http://www.who.int/reproductive-health/rtis/nonoxynol9.html>

credits

editor

Anna Poppa

founded by Peter Scott

design

Alexander Boxill

layout

Thomas Paterson

printing

Cambrian Printers

ISSN

0969-4706

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charity number

1011220

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