

aids treatment update

international AIDS conference 2002

This month's *ATU* is the first issue where we report back to you on new developments in HIV medicine following the Fourteenth International AIDS Conference held in Barcelona in July. If I tell you that the abstract books for Barcelona (where those presenting research provide a brief summary of their findings) weigh close to four kilos and run to 1,400 pages, you should get a sense of the discrimination this task involves.

Barcelona's remit is undeniably broad and it's clear that many stayed away because they anticipated a lack of focus. However, it's the sewing together of so many strands which makes these meetings important. For those involved in the field, it provides some context – a reminder about the bigger picture if you like.

Our main focus in this issue is on the clinical application of antiretroviral therapy, but there's also some important news on prevention issues, particularly on superinfection – whether it's possible to get HIV more than once. Next month we look at screening for anal cancer, one condition which seems to be *increasing* despite the use of HAART. And take a look at the news stories at our website [aidsmap](#). Here you'll find reports on lipodystrophy and other side-effects, new treatments, prevention technology, coinfections, treatment access and more.

the view from
barcelona 2

news in brief 10

the view from barcelona

2 fourteenth international aids conference meets in barcelona: highlights from the clinical sciences track by anna poppa with additional reporting by megan nicholson

Last month, Barcelona was host to over 10,000 visitors who were in town for the Fourteenth International AIDS Conference. Now divided into seven tracks (Basic Sciences, Clinical Sciences and Care, Epidemiology, Prevention Science, Social Sciences, Interventions and Program Implementation, and Advocacy and Policy), these biannual events are an ambitious attempt to focus the global response to AIDS.

Since the watershed meeting two years ago in Durban, the primary direction of this response has been to enable better access to treatment and care in what are now referred to as *resource-poor settings*, and popularly termed the developing world. NAM's daily news coverage from Barcelona (online at aidsmap.com) reviewed several key developments relating to this 'scaling-up' of health care provision, and you can read more on this subject at the new *Global Issues* section of [aidsmap](http://aidsmap.com). This issue of *AIDS Treatment Update* covers presentations likely to be of greatest immediate relevance to our core audience in the UK and other well-resourced settings. As more people in less well-resourced countries gain access to a better standard of HIV/AIDS care, it's hoped that this 'us-and-them' method of information provision will become a less important distinction.

New treatment guidelines from IAS

Timed to coincide with the Barcelona conference, recommendations from the International AIDS Society-USA Panel on use of antiretroviral therapy were published last month in the July 10th edition of the *Journal of the American Medical Association (JAMA)*.

This consensus statement, devised by eighteen eminent HIV physicians from the USA, Canada, Europe, Australia and Brazil, was last updated in 2000. The UK was represented by Professor Brian Gazzard, Research Director at the Chelsea and Westminster Hospital, London, and Chair of the British HIV Association (BHIVA). Whilst other similar guidelines exist, the IAS recommendations will have particular weight globally as the IAS itself has grown in stature amongst world health care institutions in recent years. Here we consider the key developments in the 2002 revision alongside new data from Barcelona.

The IAS panel approached their task via the identification of four fundamental issues in anti-HIV therapy: when to start, what to start with, when to change, and what to change to.

When to start

In line with UK treatment guidelines from BHIVA (available at aidsmap.com), the IAS panel recommend anti-HIV treatment for everyone with symptomatic HIV or a CD4 count below 200. This advice is based on observational cohort studies which (with just one exception) have all reported worse prognosis in people starting HAART below this immune threshold. Because these studies have not been able to pinpoint the best time to start at higher CD4 levels, people with CD4 counts above 200 are recommended to base their decision on the speed at which their CD4 count is falling, the level and rate of increase of their viral load, and their commitment to taking therapy.

Regardless of the CD4 count at which treatment is begun, adherent patients (those

who take their medicine as prescribed, without missing doses) who can tolerate their therapy, commonly gain substantial increases in CD4 cells so long as their HAART regimen keeps their viral load suppressed. Boosted CD4 counts (above the 200 level) protect people from the opportunistic infections which are diagnostic of AIDS. However, new research presented in Barcelona suggests that the capacity of this regained immunity is dependent on the CD4 count at which HAART is begun, rather than the absolute number of CD4 cells gained (LbOr09).

This small study assessed the immune response to various antigens (foreign molecules such as protein fragments from infecting micro-organisms) in 29 people taking HAART and nine HIV-negative control patients. The HAART patients had all had undetectable viral load for at least twelve months on treatment and CD4 counts above 450. Fifteen patients began HAART with a nadir (lowest ever) CD4 count below 250, and the remaining fourteen above 250. The former group had received HAART for a longer period and had fully suppressed viral load for longer duration. The CD4 nadir was found to predict the immune response to the antigen challenge, and the relationship between the two was linear, meaning there appeared to be no threshold above or below which the immune response was significantly better or worse.

Commenting on this study, Professor Anthony Pinching of Royal London and St Bart's Hospital said: "While these data suggest there is a gradual rather than a step-wise loss of immune responsiveness as CD4 cell numbers decline, it is not clear whether this means there is a need clinically to initiate treatment earlier. The large study [covered below] suggests that the clinical outcomes may not justify intervention at higher CD4 counts, as only subtle benefits can be seen."

Predicting response to HAART

In 1997, John Mellors and colleagues from the University of Pittsburgh reported data on the risk of HIV disease progression in untreated HIV-positive gay men who were participants in the Multicenter AIDS Cohort Study (MACS).

These provided an estimate of the risk of developing AIDS, or dying, within the next three years according to a range of CD4 and viral load levels, so long as the individual continued not to take anti-HIV treatment. These predictions (a tabulated summary of which appears in NAM's booklet *Viral load & CD4* at aidsmap.com) have since been commonly used in discussions between doctors and people with HIV regarding the risks and benefits of starting or delaying HAART.

Now a new cohort study, reported in Barcelona and published in the July 12th issue of the *Lancet*, has provided important additional information which will further inform this process (TuOrB1140). The ART Cohort Collaboration is a unique venture which has brought together data from thirteen cohorts of HIV-positive people using a statistical method called 'meta-analysis'. Those included were Europeans and Americans who began a HAART regimen of at least three drugs, having previously taken no antiretroviral therapy. Data on subsequent response to therapy were analysed using an intent to continue treatment approach. This means that people remained within the study regardless of any switches or interruptions in treatment, which probably most accurately reflects how treatment is taken in 'real-life' settings.

The analysis included 12,574 people, 79% of whom were men. Twenty-one per cent had HIV disease classified as CDC stage 3 (AIDS). Eighty per cent began therapy with a protease inhibitor and two nucleoside analogues. At baseline, the median CD4 count was 250 cells, and the median viral load was 4.9 log. After six months of treatment, the median CD4 count had increased to 343 cells, and 73% of the cohort had viral load below 400 copies.

During 24,310 person/years of follow-up there were 870 AIDS events and 344 deaths (which therefore makes a total of 1,094 events of either AIDS or death). The researchers calculated the risk of disease progression at one, two or three years after beginning treatment according to five key baseline variables: CD4 count, viral load, age, transmission category and CDC stage.

further reading

This article features new information presented at the 14th International AIDS Conference, Barcelona, July 7-12th, 2002. Conference abstract numbers are given in brackets e.g. (ThOrB1186). The official conference website carries all conference abstracts in a searchable database and can be found at <http://www.aids2002.org>.



the view from barcelona continued

Overall, the following baseline factors predicted a poorer prognosis:

- CD4 count less than 200.
- viral load above 5 log (100,000 copies); lower levels were not predictive of response.
- age above 50.
- being an injecting drug user.
- CDC stage 3.

Specific risk estimates can be viewed either in the *Lancet* or online at <http://www.art-cohort-collaboration.org>. This excellent facility includes a calculator where a risk estimate is provided based on input patient data.

Predicting six month risk of AIDS

Important though the MACS and ART Cohort Collaboration data are, their risk estimates focus on the medium-term when ideally, doctors and patients may also want to consider the more immediate risk of disease progression if treatment is delayed for several months, for example until the next clinic appointment.

To answer this question, Andrew Phillips of London's Royal Free University College Medical School analysed data from the CASCADE cohort of seroconverters, including participants who had not been diagnosed with AIDS and were either treatment naïve or had only received monotherapy (treatment with one drug alone) (TuPeC4709).

The analysis included 3,226 people with viral load and CD4 data before beginning treatment, or during the AZT monotherapy era (defined as pre-1995). This gave 5,126 person/years of follow-up, during which time 219 people developed AIDS. Table 1 shows the risk of developing AIDS within six months according to baseline CD4 and viral load (RNA) level.

When those exposed to monotherapy were excluded from the analysis, the results were similar. Phillips also presented six month risk estimates by age which indicated, in line with the ART Cohort Collaboration, that risk was higher in older patients.

Drawing a parallel between the MACS data and the current CASCADE analysis, Phillips highlighted that according to MACS, the three year risk of AIDS for a person with viral load above 55,000 copies and CD4 above 350 is 39.6%. Using data from CASCADE, the six month risk for someone with a CD4 count above 350 and viral load above 100,000 is only 2.2%. "Many might consider this risk acceptable and defer therapy at least until the next patient visit in three to six months when a further CD4 count and viral load are available" says Phillips.

While this breathing space may only be temporary, it may help ensure that starting treatment is well-planned and supported, allowing time to consider available treatment options fully and evaluate likely needs regarding adherence support. The availability of additional data may also prove beneficial.

Discontinuing HAART

Earlier treatment guidelines from both the IAS and the US Department of Health and Human

CD4 count	below 200	200-349	above 350
RNA below 10,000	4.9%	0.5%	0.2%
RNA 10,000-30,000	12.7%	1.6%	0.5%
RNA 30,000-100,000	17.7%	3.2%	0.9%
RNA above 100,000	22.4%	4.7%	2.2%

Table 1
The risk of developing AIDS within six months according to baseline CD4 and viral load (RNA) level (TuPeC4709).

Services (DHHS) have been less equivocal on the use of HAART by people with high CD4 counts (above 350 cells). Given that BHIVA, the IAS and the US DHHS now do not favour starting therapy this early, there is a question mark over whether people who began treatment with a high CD4 count might now be better off stopping. Two studies reported data on this issue in Barcelona, but they were relatively small and do not resolve the matter.

Joel Gallant from Johns Hopkins University reported observational data on 75 people who discontinued HAART after having responded successfully (ThOrB1439). Before starting treatment, median CD4 count in the group was 426 and median viral load was 27,000. So, these are people who would not be advised to start treatment under today's guidelines.

At the time of interrupting treatment, median CD4 had increased to 677 cells and median viral load was 263 copies. A third of the group (23 people) re-started HAART after their CD4 count fell and/or viral load rose. In this group, after an average break in treatment of 30 weeks, median CD4 had fallen to 258 and median viral load had risen to 160,500. Amongst the two thirds who remained off treatment, median CD4 was 508 and median viral load 22,151 after an average time off treatment of 69 weeks.

Those who had lower CD4 counts at the time of first HAART initiation were the most likely to resume treatment following an interruption, and the size of the fall in CD4 cells off treatment was associated with the extent of the viral load rebound when drugs were stopped.

One of the key factors which may motivate individuals to stop therapy in similar circumstances is side-effects. Though this information is based on physician report (not an objective measurement) and should therefore be treated with some caution, 17 of 31 people who had lipodystrophy were noted to improve off treatment. Of 34% who had lipid (blood fat) abnormalities, 23% improved.

In the second study, a group from Buenos Aires performed a randomised trial of stopping

versus continuing HAART in people who began treatment with CD4 counts above 350 and viral load below 60,000 (ThOrB1440). Participants had been on stable therapy for at least six months with viral load suppressed to undetectable levels.

Twenty people had been randomised to stop treatment and sixteen to continue. Average time on treatment was 36 and 30 months respectively, and median nadir CD4 was around 450 cells in both groups. At weeks 12 and 24, there was a significant difference in CD4 change between the two groups, though this was largely accounted for by the continued increase observed in those who remained on treatment. Those who stopped lost an average of twelve cells. Nobody in the discontinuation group experienced a rise in viral load to more than one log above baseline, or above 100,000 copies, and there were no HIV-related symptoms. Lipids were not significantly changed in either group after 24 weeks. However, two people who stopped treatment were reported to have developed lipodystrophy off therapy. Whilst this was a transient experience in one case, the other persisted to the 48 week study endpoint.

Taken together, these studies provide evidence that the short-term risks of stopping therapy if you had started with a CD4 count above 350 appear relatively benign. However, the risk will vary according to your CD4 nadir. An additional issue, not reviewed by either of these studies, is the risk of developing resistance when treatment is removed. This relates to the differing speeds at which drugs leave the body, and means that treatment should only be stopped with advice from your doctor.

What to start with: ACTG 384

A key change in the most recent revision of the UK's treatment guidelines was the preference for an NNRTI-based regimen for initial therapy. The IAS guidelines have not adopted this approach, though NNRTI-containing combinations are referred to as being "one of the preferred" options.

New data on first-line options from a large US-Italian strategy trial were presented in

glossary

adherence The act of taking a treatment exactly as prescribed.

antiretroviral A substance which acts against retroviruses such as HIV.

baseline Starting point or value.

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.

cohort A group of people who share at least one common factor (e.g. being HIV-positive) and are studied over a period of time.

double blind A clinical trial where neither the researchers nor participants know which assigned treatment an individual participant in the trial is taking.

endpoint An event used by a clinical trial to evaluate whether a trial therapy is working, e.g. developing AIDS or a rise in viral load above a certain level.

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

lipid A general term for fats in the blood.

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

the view from barcelona continued

Barcelona (LbOr20A, LbOr20B). Though this is just one trial amongst similar ongoing studies (including the UK's INITIO trial, see aidsmap.com), the size of the study, the length of follow-up, and its randomised design mean its findings will be viewed with strong interest.

ACTG 384 was designed to answer three key questions about how to start HAART:

- Is it better to begin with ddI/d4T or AZT/3TC as the nucleoside analogue backbone?
- Is it better to start with a protease inhibitor (in this case nelfinavir, NFV) or an NNRTI (efavirenz, EFV)?
- Is it better to use two sequential three drug combinations, or a single four drug combination?

To answer these questions, the researchers recruited 980 people who had taken no prior antiretroviral therapy, and randomised them into one of six study arms shown in Table 2.

Participants in arms A to D were therefore to begin a three drug regimen (Step 1) and switch to an alternative second regimen (Step 2) on the failure of their first regimen. The primary trial endpoint for these four arms was the failure of the second regimen. Time to first regimen failure or first virological failure were secondary endpoints.

Arm	Step 1	Step 2
A	ddI/d4T/EFV	AZT/3TC/NFV
B	ddI/d4T/NFV	AZT/3TC/EFV
C	AZT/3TC/EFV	ddI/d4T/NFV
D	AZT/3TC/NFV	ddI/d4T/EFV
E	ddI/d4T/NFV/EFV	(no Step 2)
F	AZT/3TC/NFV/EFV	(no Step 2)

Table 2
ACTG 384
treatment
arms
(LbOr20A,
LbOr20B).

Participants in arms E and F began a four drug regimen. Their primary endpoint was reached when this regimen failed. So, at the time of reaching the primary endpoint, all trial participants would have been exposed to drugs from all three major classes: nucleoside analogues, NNRTIS and protease inhibitors. However, those in Arms A to D would have taken six different drugs compared to four in Arms E and F.

Regimen failure was defined as regimen intolerance/toxicity; premature study treatment discontinuation (for any reason); or using the following virological criteria (based on two consecutive viral load tests):

- less than one log decrease and above 200 copies at week 8.
- greater than one log increase from nadir, and above 2,000 copies.
- above 200 copies after two viral loads below 200 copies.
- above 200 copies after week 24 of a regimen.

Nucleoside analogues were given open-label, but both efavirenz and nelfinavir were given blinded by placebo.

All participants had viral load above 500 copies on entry, the median value being 4.9 log. Median CD4 count was 278 cells. Participants were followed for a median of 28 months. During this time, there were 263 premature treatment discontinuations at Step 1 or 2 which resulted in a primary endpoint.

Regarding the comparison between the two nucleoside analogue backbones, there was a trend towards delaying the primary endpoint in favour of AZT/3TC versus ddI/d4T when taken with efavirenz, but not with nelfinavir. In relation to the secondary endpoints, AZT/3TC significantly delayed both first regimen failure and first virological failure when combined with efavirenz but not with nelfinavir.

Turning to the protease inhibitor versus NNRTI comparison, there was no difference in time to the primary endpoint, but efavirenz outperformed nelfinavir with regard to delayed first regimen failure and first virological failure

when combined with AZT/3TC, but not with ddI/d4T.

ACTG 384 has not provided evidence that beginning with four drugs is preferable to three (though participants were stratified at entry for viral load, and future analyses will presumably provide more data on responses in those with high viral load, the group this strategy is sometimes favoured for). Overall, there was no difference in time to the primary endpoint between those starting with a four drug combination and those who began with three drugs and switched to a second three drug regimen. However, the four drug regimens delayed time to first regimen failure and first virological failure compared to the nelfinavir-based three drug regimens, and compared to ddI/d4T/efavirenz, though they performed no better than AZT/3TC/efavirenz here.

There were no significant differences in CD4 response across study arms. The median increase was 168 cells at week 48, 251 cells at week 96, and 295 at week 144.

As overall toxicity and (unsurprisingly) peripheral neuropathy were greater in the ddI/d4T arms, the study group concluded in favour of AZT/3TC/efavirenz compared to the other regimens studied.

What to start with: the CLASS study

Antiretroviral sequencing was also evaluated in the CLASS study (TuOrB1189). This American study randomised naïve patients to receive abacavir/3TC with either efavirenz (an NNRTI), amprenavir/ritonavir (a boosted protease inhibitor), or d4T (a third nucleoside analogue). A second stage of the study switched people whose first combination had failed to receive AZT/ddI plus amprenavir/ritonavir for those who had been on either efavirenz or d4T, or plus efavirenz in place of amprenavir/ritonavir. There was a further randomisation to include abacavir as a fourth drug in the second-line regimen. So, this study again looked at changing drug classes after the failure of a first combination.

Current results are from a planned 48 week analysis and focus only on experience of the

first regimen. The results are shown in Table 3 (which appears over the page).

After 48 weeks, a similar proportion in each group had viral load below 400 copies (over 75%). However, using a more sensitive test with a cut-off of 50 copies, there was a significant difference in favour of the efavirenz arm by intent to treat missing=failure analysis. This advantage was also observed for reaching below both 400 and 50 copies in those who began with viral load above 100,000 copies.

Issues in salvage: Treatment interruptions

The best option for managing patients with experience of all three major antiretroviral classes is not clear. One approach, noted but rather less than heavily endorsed in both the BHIVA and IAS guidelines, is the use of multi-drug regimens containing six or more 'recycled' therapies. This is known as mega-HAART.

In Barcelona, doctors from Paris presented further data from the GIGHAART study which evaluates multi-drug salvage regimens begun with or without a prior treatment interruption (WePeB5887). Treatment interruptions have been in vogue for some time now in HIV medicine, but continue to be advised against by both BHIVA and the IAS unless conducted within a clinical trial (the ongoing UK OPTIMA study being an example, see aidsmap.com). However, these French data appear to support the concept even though the length of follow-up remains relatively short.

Seventy people with viral load above 50,000 copies, CD4 below 200, and prior experience of at least two protease inhibitors, two nucleoside analogues and one NNRTI were randomised to immediate or deferred mega-HAART therapy. The deferred group completed an eight week wash-out (off therapy) prior to the multi-drug regimen. The regimen consisted of three of four nucleoside analogues (either d4T, ddI, AZT, 3TC or abacavir), hydroxyurea (optional after April 2000), one NNRTI, and three protease inhibitors (ritonavir, amprenavir or lopinavir plus either indinavir, saquinavir or nelfinavir).

At baseline, median viral load was approximately 5.3 log, median CD4 was 27

glossary continued

log Short for logarithm, a scale of measurement often used when describing viral load. A one log change is a ten-fold change, such as from 100 to 10. A two log change is a one hundred-fold change.

median The central value of the distribution, so that half the values are less than or equal to it and half are greater than or equal to it.

nadir Lowest point out of a series of measurements.

naïve Never having taken anti-HIV treatments before.

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

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

observational study A clinical trial which reports on an unfolding situation.

peripheral neuropathy Damage to the nerves of the hands and/or feet, causing symptoms ranging from numbness to severe pain.

placebo A pill which looks and tastes exactly like a real drug, but contains no active substance.

protease inhibitors Family of antiretrovirals which includes lopinavir, indinavir, nelfinavir, ritonavir, saquinavir.

the view from barcelona continued

cells, and median duration of prior therapy was approximately 6.5 years. Typical of such an advanced patient group, participants has been exposed to an average of eleven antiretrovirals (five nucleoside analogues, one NNRTI and four protease inhibitors).

Twelve week efficacy data were presented at a European AIDS conference in Athens last year. These early results appeared to support the hypothesis that a period off treatment would allow the patients' HIV population to revert from one that is largely drug resistant to one that is drug sensitive.

Responses after twenty-four weeks continue to show a benefit in the deferred treatment group. A significantly greater proportion of those undergoing a treatment interruption had at least a one log drop in viral load after 24 weeks (50% versus 24% by intent to treat analysis). The fall in viral load after twenty-four weeks was -1.08 log in the deferred group compared with -0.29 in the immediate group.

Treatment interruptions are associated with a fall in CD4 count, which is of obvious concern in patients who begin with such low CD4 counts. The GIGHAART study, however, found no difference in HIV-related adverse events

between the two arms (three in the immediate group versus five in the deferred group).

Issues in salvage: New drugs

Treatment interruptions aside, one of the major question marks hanging over mega-HAART therapy is whether so many drugs are really necessary, particularly when new agents are beginning to appear in reach.

The recently-licensed nucleotide analogue tenofovir (from a new sub-group of the reverse transcriptase inhibitor class) is one such example. In Barcelona, Dr Anton Pozniak of London's Chelsea and Westminster Hospital, reported final 48 week results from Gilead's 907 study which added tenofovir to the stable background antiretroviral therapy of patients with heavy drug experience and virological failure (WeOrB1266). After 48 weeks, the time-weighted change in viral load was -0.57 log in the tenofovir group, and 41% had viral load below 400 copies. Response to tenofovir is affected by resistance to nucleoside analogues, (a subject which was reviewed in *AIDS Treatment Update* issue 109).

Two similar studies, presented in Barcelona, indicate that adding T-20 (now called enfuvirtide or *Fuzeon*) to a new salvage

Table 3
CLASS study:
Results at 48
weeks
(TuOrB1189).

First-line regimen	efavirenz arm	amprenavir/ritonavir arm	d4T arm
Number randomised	97	96	98
Average baseline viral load	4.90 log	4.85 log	4.81 log
Average baseline CD4	307	306	296
Met switch criteria at 48 weeks	6	10	12
switched for side-effects	5	5	4
switched for viral load failure	1	5	8

regimen can also provide significant virological benefit. Enfuvirtide is the newest anti-HIV drug to emerge from the treatment pipeline. It belongs to a novel class of drugs called fusion inhibitors. This class targets the bonding between immune cells and HIV which facilitates HIV entry into uninfected cells.

Dr Keith Henry presented TORO 2 (T-20 versus Optimised Regimen Only) which compared an optimised salvage regimen of currently available drugs with an optimised salvage regimen plus enfuvirtide (LbOr19B). Participants were highly treatment experienced, having taken multiple drugs from each of the three main drug classes. Baseline median CD4 cell count was 80 and median viral load was 5.2 log. Background regimens were selected considering resistance test results and previous drug history.

After 24 weeks of treatment, intention to treat analysis showed that 51% of 326 enfuvirtide recipients achieved at least a one log reduction in viral load compared to 29% of the control arm. Furthermore, 37% and 20% of people in the enfuvirtide arm had a viral load below 400 and 50 copies, respectively, compared to 16% and 7% in the control arm. Overall the average fall in viral load was -1.70 log versus -0.76 log.

A similar study, TORO 1, compared enfuvirtide plus optimised background therapy versus

optimised background therapy alone in 504 highly treatment experienced people (LbOr19A). In this study, median baseline viral load was 5.1 log and median CD4 cell count was 98. The average reduction in viral load at week 24 was -1.43 log in the enfuvirtide arm and -0.65 log in the control arm. Forty-three percent of participants achieved a one log reduction in the enfuvirtide arm versus 21% in the control arm. Viral load below 400 and 50 copies, respectively, was achieved by 28.4% and 12.2% of the enfuvirtide arm compared to 12.2% and 5.3% of the control arm.

Most people injecting enfuvirtide report some pain or discomfort at the injection site. In a majority of cases, this pain is deemed to be mild or moderate. Less than 10% of recipients in the two TORO studies had to take painkillers to ease this pain. About 3% stopped treatment with enfuvirtide due to injection site reactions. No other side-effects were reported as being significantly associated with the drug.

Enfuvirtide appears to be a particularly appealing salvage option as it is not affected by resistance to the existing antiretroviral agents. Developed by Trimeris and Roche, enfuvirtide is currently an experimental treatment with limited availability. However, Roche will soon submit the drug for licensing in both the European Union and the USA, and it could be approved by early 2003.

key conclusions

- Observational cohort studies continue to report that response to HAART is impaired if begun at CD4 counts below 200.
- New information on the short-term risk of developing AIDS if treatment is delayed, and the medium-term risk if HAART is begun are available and will aid discussions between doctors and people with HIV on when to start treatment.
- It appears that people who began HAART with a CD4 count or viral load at which treatment is no longer recommended may be able to stop without undue immediate harm. Longer-term effects are not known and treatment should only be stopped with your doctor's advice.
- Data favouring the use of efavirenz-containing first-line combinations continue to accumulate.
- People with extensive drug experience may benefit from a break in treatment before beginning a new multi-drug salvage regimen. However, the availability of new drugs with proven benefit in this setting present alternative options and the best approach is not clear.

glossary continued
randomisation The process of selecting by chance the treatment that a clinical trial participant will receive.
regimen A drug or treatment combination and the way it is taken.
resistance A drug-resistant HIV strain is one which is less susceptible to the effects of one or more anti-HIV drugs because of its genotype.
salvage therapy Any treatment regimen used after a number of earlier regimens have failed.
seroconversion The time at which a person's antibody status changes from negative to positive.
side-effect Unwanted effect of a drug.
toxicity The extent or ways in which a drug is poisonous to the body.
undetectable viral load A level of viral load that is too low to be picked up the particular viral load test being used.
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.

Superinfection cases cause concern for people with HIV

Persuasive evidence was presented to the Barcelona AIDS Conference that it is possible for an HIV-positive person to become re-infected, or 'superinfected', with a second strain of HIV. Superinfection has previously been demonstrated in test-tube experiments, and cases suggesting that it is possible in 'real-life' were presented to the annual conference of the UK's Public Health Laboratory Service last year and to the Retrovirus Conference in Seattle in February 2002.

Two separate cases demonstrating superinfection were presented to the Barcelona conference. Investigators from the University of Geneva, Switzerland, presented the case of a 38 year old man who was noted to have an acute retroviral syndrome (the flu-like illness which often develops when a person first develops antibodies to HIV after infection with the virus) following a number of unprotected sexual contacts. The man was already known to be HIV-positive and had been treated with a HAART combination including AZT, 3TC, abacavir and amprenavir for 25 months as part of the QUEST trial. At the end of the study, trial participants including this man, were given an investigational vaccine, followed by a treatment interruption.

The patient's viral load fell from over 1 million copies to below 200 copies whilst he was

receiving HAART. One month after stopping treatment and receiving the vaccine, his viral load increased to 80,000 copies before falling back to 20,000 copies. However, a second viral rebound was noted two weeks later, when his viral load increased to 200,000 copies, and then fluctuated at between 200,000 and 400,000 copies before HAART was restarted.

Investigators were curious about the second persistent viral rebound and so analysed the patient's HIV gene sequence. This showed that he had initially been infected with HIV subtype AE, but that when his viral load rebounded subtype B could be isolated.

The possibility that the man had always been infected with two different HIV subtypes was ruled out when a polymerase chain reaction (PCR) test was used to isolate AE and B subtypes. The PCR confirmed the absence of subtype B before the second viral rebound. In addition, the type of subtype B the patient was infected with was found to be closely related to subtypes found in Brazil, where the man had been on holiday and had several unprotected sexual contacts. Analysis also showed that the subtype B HIV was capable of reproducing at a much greater rate than the patient's initial AE subtype virus.

In a second, similar case, Dr Bruce Walker of the Harvard Medical School in the USA, presented evidence that a man was superinfected after having unprotected sex despite having a strong and effective response to his existing HIV.

Dr Walker reported that a man involved in a treatment interruption study had demonstrated that his immune system was able to control HIV after three cycles of treatment and interruption. When a viral rebound occurred a detailed analysis of the man's viral profile was conducted which found the man had been superinfected with a new strain of subtype B HIV. Despite originally having a strong CD8 cell HIV-specific immune response, the man's immune system was less able to recognise the new strain leading to uncontrolled viral replication.

"I think the public health message is that it is possible to become re-infected with a second version of HIV" Dr Walker told the conference.

The cases not only highlight the risks for people with HIV in having unprotected sex with other HIV-positive people, but also has implications for vaccine research, which had assumed that a strong CD8 response could prevent infection with a wide range of HIV variants.

Sources: Fourteenth International AIDS Conference, Barcelona, abstracts ThOrA1381, WeOrA197, 2002.

PREP: Using drugs to prevent HIV infection?

Attention at the Barcelona conference focused on the possibility of using existing anti-HIV drugs to prevent HIV-negative people from becoming infected with HIV. The idea is to use a single anti-HIV drug as a pre-exposure prophylaxis (PREP), in effect a type of 'vaccine-substitute'.

The use of a single drug (and in the case of nevirapine, just two doses) has been shown to prevent mother-to-baby transmission, but may not be effective against other modes. There are concerns about using nevirapine in this way as it only takes a single mutation to make the virus resistant to the drug, and because of the risk of side-effects. Safety fears were allayed somewhat by a study conducted by Johns Hopkins University. In a phase I/II trial

nineteen HIV-negative people were given 200mg of nevirapine either once or twice a week, or on alternate days, and were monitored for sixteen weeks for drug exposure and evidence of side-effects. Nobody in the study developed any side-effects, including the rash often seen with nevirapine, nor were there any significant changes in liver function, even in the three trial participants with hepatitis C and the trial member with hepatitis B. In addition, none of the study population became HIV-positive during the trial (although the study was not designed to test the effectiveness of nevirapine in preventing transmission and is unable to provide an answer to this question with so few participants).

In a separate presentation Dr Mark Wainberg, a Canadian AIDS researcher, looked at the possibility of using nucleoside or nucleotide analogues as pre-exposure prophylaxis. The two drugs most likely to be investigated for use in this way are enteric coated ddI and tenofovir. Both these drugs are taken once daily and achieve sustained high levels in people's bodies. In addition, both these drugs are possible trial candidates as there is little transmission of HIV which is resistant to them, particularly in South Africa, where the first trial investigating their safety and effectiveness is likely to be set up amongst sex workers at high risk of HIV.

Dr Wainberg is proposing that a double blind, placebo-controlled trial is now carried out, in which provision of one of these drugs (compared to placebo) is accompanied by intensive support and encouragement to use condoms. He suggests a six month interim analysis could give indicative results and that such a trial need last no more than a year.

A study is planned by Dr Mike Youle at the Royal Free Hospital to examine the possibility of using tenofovir as PREP. A small number of high-risk HIV-negative gay men will be given tenofovir to establish the safety of this drug before a larger study is undertaken.

Sources: Fourteenth International AIDS Conference, Barcelona, abstracts MoOrD1105, MoOr109, 2002.

NAM barcelona feedback tour

NAM is partnering with several UK HIV agencies to provide feedback from the Fourteenth International AIDS Conference held in Barcelona in June. For details see the flyer with this issue of *ATU* or visit aidsmap.com.

author credit

News reporting by Michael Carter.

editor's note

Thanks to Robert Fieldhouse, Michael Carter and Tom Patterson for looking after last month's *ATU* in my absence.

credits

editor
Anna Poppa

AIDS Treatment Update
founded by Peter Scott

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design
Alexander Boxill

printing
Cambrian Printers

ISSN
0969-4706

charity number
1011220

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

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Professional/organisational rate: £75/year.

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Overseas rate: within EU add £10/year; outside EU add £15/year.

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