

aids treatment update

which nucleoside analogues?

Nucleoside analogues were first used to treat people with HIV in the 1980s, pre-dating many of the fundamentals of HIV medicine we're familiar with today. They remain the often unsung foundation of successful anti-HIV drug combinations, and as we review this month, new information on NRTI resistance and toxicity has been a reminder that a full understanding of a drug and its effects is not something we acquire quickly.

Though here at NAM our affinity is always with fact over fiction, we couldn't let January pass without inviting a few predictions for the year ahead. Robert Fieldhouse's interviews with Martin Fisher and the Medical Research Council Clinical Trials Unit, unusually well-placed to forecast the future trends in HIV treatments, begin on page 6.

NAM begins the year with three newly updated publications: the HIV & AIDS Treatments Directory, the AIDS Reference Manual, and the third edition of our Anti-HIV Drugs booklet. Later on, we'll be publishing a Directory of Complementary Therapies, a new booklet on lipodystrophy and a training manual for HIV educators, as well as unveiling a new look for our website and bringing you the 100th issue of *AIDS Treatment Update*. Happy New Year.

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which nucleoside backbone?

2 choosing anti-HIV drugs from the NRTI class by anna poppa

The current recommendation for people starting anti-HIV treatment is to begin with a combination of three drugs, two of which should be from the nucleoside analogue, or 'NRTI' drug class. This article considers how these two drugs, which form the 'backbone' of HAART regimens, may be selected.

As was discussed last month, there is no clear proof that certain HIV drug regimens are better than others. Drug combinations are therefore selected on an individual basis, through consideration of their potency, their side-effects, their adherence requirements, and the extent to which they may affect the choice of a subsequent regimen, (see table opposite).

In general, drugs in this class do not have large pill burdens, are dosed either once or twice a day, and most can be taken with food. The exception is ddI, which must be taken on an empty stomach. While the newly arrived enteric-coated capsule formulation of ddI (*Videx-EC*) may have significantly improved tolerability of this drug in some respects, the current dosing recommendation (at least two hours before and at least two hours after food), presents adherence challenges.

Comparing efficacy of NRTIs

Several studies have compared dual NRTI combinations, with or without an additional drug, in people new to treatment. Generally, studies have found most dual NRTI regimens are comparable in terms of their ability to suppress viral load and raise CD4 counts.

The Ozcombo and START I and II trials investigated the use of dual NRTIs with indinavir. In the former, after 52 weeks on treatment there were no differences in viral

load or CD4 response amongst 109 people receiving indinavir with either AZT/3TC, d4T/3TC or d4T/ddI. Fifty-eight percent had viral loads below 50 copies after one year, from a baseline average over 100,000 copies¹.

START I compared d4T/3TC/indinavir with AZT/3TC/indinavir in 204 people and found no differences in viral load or CD4 response between the two at 48 weeks. 49% had viral load below 50 copies at this point in each arm².

START II compared d4T/ddI/indinavir with AZT/3TC/indinavir in 205 people. Participants had no previous exposure to 3TC or indinavir, and less than four weeks on any other NRTI. At 48 weeks, there was no significant difference in the virological response; 41% and 35% of the d4T/ddI and AZT/3TC arms respectively had viral loads below 50. However, those on d4T/ddI had a greater average increase in CD4 count (214 versus 142)³.

The French ALBI study (ANRS 070) of 151 people who received d4T/ddI or AZT/3TC for six months, or both regimens for three months each, did find a difference in response, though the follow-up period is short. Those receiving d4T/ddI had significantly greater viral load suppression and CD4 count rises compared to those receiving AZT/3TC or those who took sequential d4T/ddI and AZT/3TC⁴.

The DELTA study found AZT/ddI more effective than AZT/ddC both in the reduction of illness and death, and in lowering viral load, in people who were new to HIV treatment^{5,6}.

NRTIs & mitochondrial toxicity

As there is little evidence of substantial differences in potency, differences in side-

Nucleoside analogue choices						
Drug name	AZT	ddI	ddC	3TC	d4T	abacavir
Pill burden	1 capsule twice a day*	1 capsule once a day	1 tablet three times a day [§]	1 tablet twice a day*	1 capsule twice a day	1 tablet twice a day
Food restrictions	None, but taking with food may reduce nausea	Take at least 2 hours before & at least 2 hours after food	None, but taking with food may reduce nausea	None	None, but taking with food may reduce nausea	None
Key side-effects	Gastro-intestinal, anaemia, neutropenia	Pancreatitis, peripheral neuropathy	Peripheral neuropathy	Gastro-intestinal	Peripheral neuropathy	Gastro-intestinal, hypersensitivity
Key interactions	Other drugs which may cause anaemia, neutropenia; d4T	Don't take with ddC; ddI tablets can't be taken with PIs	Don't take with ddI	None significant	Don't take with AZT	None significant
Cross-resistant with	d4T	ddC	3TC	ddC	AZT	3TC

* AZT and 3TC are available in a combined form called *Combivir*. Dosage of *Combivir* is 1 tablet twice a day.

[§] Twice a day dosing under investigation.

effect profiles offer a means of choosing between drugs. When NRTI therapy is begun, a variety of side-effects may need to be managed over the short-term, for example nausea, vomiting, headache, fatigue. More often than not, these resolve within weeks, and because they tend not to be severe, they don't usually cause people to stop treatment.

Over the longer-term, anti-HIV drugs are associated with other side-effects, which can have more serious consequences. In the case of the NRTI drug class, these are thought to be due to the effects of NRTIs on mitochondria, a component of human cells. Mitochondria are involved in the production of energy.

Different NRTIs are associated with different effects of mitochondrial toxicity: damage to

muscle tissue (myopathy) in the case of AZT; nerve damage (neuropathy) in the case of d4T, ddI and ddC, (the risk being greater when d4T and ddI are taken together than when either drug is taken alone); and fatty liver (hepatic steatosis) and raised lactic acid levels (lactic acidemia) relating to ddI, d4T and AZT. It is also theorised that the loss of fat on the face and limbs (peripheral lipoatrophy) which forms part of the lipodystrophy syndrome may be due to mitochondrial damage, and may result from NRTI therapy. d4T has been linked to this problem most strongly amongst NRTIs, and there is some evidence of an improvement in fat loss on stopping d4T, but whether there is a clear causal relationship remains disputed. Pancreatitis (inflammation of the pancreas) may also be related to mitochondrial toxicity. It occurs in a proportion of ddI users.

regimens not used

Some combinations are never used because they present an increased risk of side-effects, e.g. ddI/ddC because both drugs can cause peripheral neuropathy. Also d4T/AZT is not used because both drugs compete for the same human enzyme, resulting in a weaker antiviral effect.

lactic acidosis

See NAM Factsheet 42: Lactic acidosis, April 2000 for more information.

pregnancy

For women who begin anti-HIV therapy during pregnancy, the combination of AZT/3TC may be the more common choice of NRTIs as there is more experience with these drugs than other NRTIs. A study at last year's Durban International AIDS Conference suggested ddI/d4T is another option.

methadone

Methadone increases AZT concentration, and decreases absorption of ddI and of d4T.

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which nucleoside backbone? continued

Most of these side-effects tend to resolve once the offending NRTI is stopped, though occasionally peripheral neuropathy may worsen off treatment before it improves and, as has been discussed previously, fat loss is not easily treated or well-understood at present. Pancreatitis can be fatal, as can lactic acidosis, though fortunately both are rare.

Lactic acidosis occurs when lactic acid reaches an excessive level, and tends to be accompanied by marked tiredness, gastro-intestinal side-effects and a swollen, tender liver. At present there is little consensus over whether people whose lactic acids levels are raised, but not excessively so (lactic acidemia), require intervention, and there is no well-established means of monitoring for this problem, or for other manifestations of mitochondrial damage. How much bearing the growing interest in this area should have on treatment choices is unclear at present. It's clear that some people have already decided to avoid or switch from d4T because of the possible link with fat loss. This may or may not prove to have been a wise choice in the future.

Hypersensitivity to abacavir

Abacavir's major serious side-effect is an allergic-type reaction termed hypersensitivity. It tends to occur within the first few weeks of treatment and to involve a build-up of symptoms, most often including rash and fever. Though uncommon (frequency 4%), the abacavir hypersensitivity reaction has led to a small number of deaths where the drug has been re-started (and so this should never be undertaken). Concern remains over potential difficulty in distinguishing abacavir hypersensitivity from the rash which can accompany initiation of the NNRTI nevirapine, or the PI amprenavir; an important issue because these are managed quite differently. For this reason, some doctors are not keen to use these combinations together where alternatives exist.

AZT & blood cell effects

Between 5 and 10% of people who take AZT will develop anaemia (shortage of red blood cells) or neutropenia (shortage of neutrophils, a type of immune cell) as a result. The risk is greater in people with later stage HIV disease.

Drug resistance & future options

In common with other anti-HIV drug classes, the NRTIs are affected by cross-class resistance, (though to a lesser extent than NNRTIs and probably PIs). Developing resistance to one NRTI may prevent individuals from gaining full benefit from other NRTIs taken within subsequent regimens.

Gaps remain between our ability to map mutational patterns and our knowledge of their clinical significance. Mutations which result in drug resistance may also impair HIV's ability to reproduce (its 'fitness'). This is true of the 3TC signature mutation M184V, and of the ddI resistance mutation L74V.

The M184V mutation has gained a somewhat enigmatic status. Resistance to 3TC develops rapidly whenever 3TC is used in a less than fully suppressive regimen, and the M184V mutation is often the only resistant mutant found in people with viral load rebound on 3TC-containing HAART regimens. However, 3TC's addition to the treatment regimens of NRTI-experienced people in the CAESAR study delayed disease progression and death. It's possible that this was at least in part due to the effect of M184V on AZT resistant mutants because there is some evidence that 3TC resistance reverses AZT resistance.

d4T resistance underestimated

Until quite recently it was thought that the development of resistance to d4T was a rare event. However, in 1999 three research teams reported finding mutations which have been associated with AZT resistance in people whose d4T-containing regimen had failed, and who had not taken AZT^{7,8,9}, and there were further reports of these 'thymidine analogue mutations' last year.

There is also clinical evidence from the ALTIS 2 and CHORUS studies that these two drugs

are cross-resistant – prior experience of AZT resulted in poorer response to d4T than in those without AZT experience and vice versa. In addition, both AZT use and d4T use have been associated with a mutation (Q151M) which causes resistance to all NRTIs. Overall, it seems that earlier attempts to position d4T as a preferable first-line choice to AZT on the grounds that it would allow future use of that drug, and that the reverse would not, cannot be justified at present.

Abacavir as a backbone NRTI

Abacavir has come to the HIV therapeutic marketplace much later than the other NRTIs and therefore has been much less well studied as a component within a dual NRTI backbone for HAART. Manufacturer Glaxo Wellcome has developed the drug as an addition to its other NRTIs AZT/3TC, and as the cornerstone of triple NRTI therapy.

The combination of abacavir/3TC as a backbone for indinavir/ritonavir is under investigation in the DIRECT study, though this is an uncontrolled pilot study. However, a European paediatric study, PENTA 5, has recently reported results on the use of three different dual NRTI regimens, with or without nelfinavir in 128 children who were new to treatment¹⁰. The NRTIs were AZT/3TC, abacavir/AZT and abacavir/3TC. While the differences between the number of children with viral load below 50 copies after 48 weeks of treatment were not significant, the average

fall in viral load at this point was greater amongst those who received abacavir. Given that there is cross-resistance between abacavir and 3TC, there may be some benefit in using the two together rather than trying to use one after the other has failed. Like AZT and d4T, abacavir is active against HIV in the brain.

Transmitted resistance increasing

Evidence that drug resistant HIV is being transmitted with increasing frequency in many countries where anti-HIV drugs have been in use has raised concern about the potential for this to narrow treatment options in those affected. Current advice on the use of resistance tests suggests that people who begin treatment within months of infection may benefit from testing for evidence of transmitted resistance before selecting a regimen (though there is no evidence from clinical trials that this is helpful at present). It is not recommended that people who begin treatment at a later stage of infection undergo resistance testing prior to treatment.

A recent report from the UK assessed the genotype of 69 people who seroconverted between 1994 and 2000¹¹. None had taken anti-HIV drugs, and they had all been infected with HIV in the previous eighteen months. Eight people (13%) had mutations in either the reverse transcriptase or protease gene of their HIV, and it appears the risk infection with resistant virus grew during the later years of the study period.

key conclusions

- Standard anti-HIV drug regimens usually contain two drugs from the NRTI class.
- Most NRTIs are dosed once or twice a day, and can be taken with food. ddI cannot.
- Several dual NRTI combinations appear as effective as each other in reducing viral load, though AZT/ddC has been found less effective. Some, e.g. ddI/3TC are less well studied than others.
- All NRTIs can cause side-effects, and these may be worsened when two drugs are taken together, e.g. ddI/ddC, ddI/d4T.
- There is conflicting evidence about the risk of fat loss on different NRTIs. All have been linked to this side-effect.
- Some combinations are not used because of harmful interactions, e.g. d4T/AZT.
- Resistance to one NRTI may prevent full benefit from other NRTIs which may be taken later.

glossary

adherence
The act of taking a treatment exactly as prescribed.

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.

cross resistance

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

HAART

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

mutation

A single change in gene sequence.

NRTI

Nucleoside analogue reverse transcriptase inhibitor.

nucleoside analogue

Chemical which resembles a nucleoside. Antiretroviral family which includes AZT, ddI, ddC, 3TC, d4T, abacavir.

regimen

A drug 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.

seroconversion

The time at which a person's antibody status changes from negative to positive.

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.

HIV treatment in 2001

6 how will the medical care of people with HIV change in the coming year?
dr martin fisher of royal sussex county hospital, brighton, interviewed by robert fieldhouse

AIDS Treatment Update (ATU): A better understanding of the need to balance risks and benefits has prompted discussion about when to start therapy. Which way do you think the pendulum will swing in the coming year? How do you think the revised British HIV Association (BHIVA) treatment guidelines, expected later this year, will reflect these tensions?

Martin Fisher (MF): Though I can't predict what the consensus BHIVA guidelines will contain, I think that recent information showing the apparent equal efficacy of antiretroviral therapies, as long as CD4 counts are greater than 200, alongside increasing concerns regarding long-term toxicities and sustainability of complex therapies, may lead

to the pendulum swinging towards a more conservative approach to therapy.

The discussions at the recent Glasgow meeting appear to suggest that many USA 'experts' are moving their goalposts towards the less aggressive stance of UK physicians. The immunological data similarly appear to suggest that early therapy – with the possible exception of primary infection – may not be superior to later treatment, as had previously been proposed by some.

Unfortunately, a large proportion of people in the UK continue to present later than elsewhere, and so for many people the early versus late argument becomes irrelevant. I think we need to concentrate increasingly on

identifying those who are HIV-positive but not aware of their status.

ATU: How do you see our understanding and management of the potential long-term side-effects of HAART improving?

MF: There's clearly a long way to go here. Mitochondrial toxicity has been the buzzword of 2000 where lipodystrophy was previously in 1999. Hopefully we'll begin to understand better the interaction between the various proposed mechanisms of the toxicities that are becoming all too commonplace in clinical practice. I hope that we'll shift away from trying to blame individual agents, and try to understand mechanisms and the complex interaction between the virus, drug therapies, and immune reconstitution. Without this, it's difficult to envisage proposing viable interventions for toxicities we don't understand.

The potential longer-term toxicities of non-nucleosides (and particularly central nervous system disturbances) will hopefully be more clearly defined. The role (or not) of structured treatment interruptions needs to be clarified –

of zidovudine, lamivudine and abacavir (*Trizivir*) will be licensed. Though its role in treatment naive patients has been hampered by concerns about effectiveness at high viral loads, I think that data on its role in simplification, and the possibility of a one-pill twice-daily regimen will prove attractive to many people.

It's highly likely that lopinavir/ritonavir will receive approval, though whether it will be used predominantly as a first-line protease inhibitor or within salvage regimens remains controversial [see News in brief]. The use of ritonavir as a protease-booster will probably increase, and many patients are already using such a strategy within their first-line protease regimen. The newly licensed protease inhibitor amprenavir may be increasingly used in this setting, as there's limited data to suggest a different resistance and toxicity profile to other protease inhibitors.

Newer classes of agents are likely to remain within the clinical trial setting, though may become available within expanded access programmes. These will include nucleotide

"It's difficult to envisage proposing viable interventions for toxicities we don't understand."

there's an assumption, currently unproven, that such a strategy will lead to a reduction in long-term toxicity. The relative merits need to be carefully balanced against the potential pitfalls, i.e. CD4 decline and drug resistance.

ATU: What new treatment options can we expect to be in clinic in 2001?

MF: There are likely to be several new options that may become available, although not all will reach the licensing stage, and many are merely new preparations or 'me-too' drugs. It's anticipated that the [triple NRTI] combination

analogues (tenofovir) and fusion inhibitors (T-20 and potentially T-1249). The difficulties in administration, production, and cost of the fusion inhibitors may limit their use. Newer nucleoside analogues with apparently promising resistance profiles (notably DAPD) wait further confirmation, whilst others (such as FTC and d4T slow release) may offer improved tolerability over existing preparations. Second and third generation non-nucleosides (such as capravirine and DMP 083) remain under investigation regarding their use in people who have already experienced non-nucleoside failure.

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HIV treatment in 2001 continued

ATU: How do you see use of resistance tests and therapeutic drug monitoring developing over the next year?

MF: I think they will be increasingly used, although I remain to be convinced that our understanding of exactly how to use them will advance considerably. Hopefully the Athena study from the Netherlands and the ERA study from the UK will improve our understanding, although recruitment to the latter has been disappointing.

The use of ritonavir to boost other PIs may mean that drug levels are used more to define toxicity rather than efficacy. Our understanding of cross-resistance between nucleosides (particularly AZT and d4T) and proteases (particularly lopinavir/ritonavir and 'first-line' proteases) may better define exactly how possible drug sequencing within classes is. The additional role of drug resistance testing over and above an accurate drug history, and the relative roles of genotyping and phenotyping may become clearer.

ATU: How do you see our understanding of the strategy of combining antiviral and immune therapies improving?

MF: The big studies combining antiviral and immune therapies are unlikely to reach major conclusions in the next year. The ESPRIT study of interleukin-2 therapy in people receiving HAART with high CD4 counts is likely to take much longer to provide the intended clinical end-points, and the comparable study in people with lower CD4 counts (SILCAAT) may well not produce results in the next twelve months.

The use of IL-2 without antiretroviral therapy

has yet to be accepted by many, though its role in the context of structured treatment interruptions warrants further study. The use of *Remune* as an adjunctive therapy either with HAART or in the context of treatment interruption will be further marked out. Overall I think it's unlikely that the next twelve months will see a major shift here, but potentially the year after will.

ATU: Having recently agreed to be involved in drafting the proposed BHIVA adherence guidelines, could you tell us why BHIVA have decided to publish them? What role do you hope they'll play in improving patient care?

MF: Previously BHIVA have been predominantly involved in proposing treatment guidelines regarding the use and monitoring of antiretroviral therapy. These have been successful in ensuring that a similar standard of treatment, and equity of access to drug therapy exists across the country.

As data increasingly emerge regarding the central role of adherence in treatment success, it's vital that treatment guidelines include an appropriate consideration of how adherence to such treatments is maximised. Unfortunately the evidence regarding how to intervene to improve adherence is limited, but I hope that the proposed guidelines will ensure that an evidence-based approach to adherence support, which makes use of the wide variety of available resources, can be recommended. This should ensure that not only are therapies available in an equitable manner, but also the appropriate resources to ensure their maximal acceptability and effectiveness. The guidelines should also stimulate future research into methods to improve adherence – for both patients and doctors.

AIDS Treatment Update (ATU): How is recruitment proceeding for each of the current MRC HIV-related clinical trials?

Medical Research Council Clinical Trials Unit (MRC): The INITIO trial is evaluating 'what to start with'. First line therapy compares two NRTIs (ddI and d4T), with either one NNRTI (efavirenz), or one protease inhibitor (nelfinavir), or both (efavirenz and nelfinavir). UK recruitment is running to plan and may be complete by the end of March 2001.

Recruitment to FORTE was 58 in December. The trial was amended [at this time] to concentrate on only two of the three original arms [see News in brief]. It is hoped recruitment of an additional 60 patients can be achieved by the end of March 2001.

Part A of the ERA study compares a genotypic resistance test to no test in 'early' treatment failure. Part B compares a genotypic resistance test to both a genotypic plus phenotypic resistance test in 'late' treatment failure. Recruitment to Part A was 48, and to Part B 221, by December 2000. The target for each part is 240. The ERA Steering Committee will meet in late January 2001 to discuss poor recruitment into Part A.

Over 400 patients have been recruited to the international ESPRIT trial since February 2000. Several UK sites opened to recruitment in the second half of December and while screening has taken place, no recruitment [was] expected until the first week of January. The UK/Ireland target is for 300 patients to be recruited by October 2001. ESPRIT will evaluate interleukin-2 (IL-2), an immune therapy, in patients with CD4 cell counts of 300 or more who are taking HIV therapy.

ATU: What are the MRC's plans for future HIV trials?

MRC: In collaboration with the US Veteran Administration and the Canadian HIV Trials Network, we're planning a trial (OPTIMA: Options in Management with Antiretrovirals) to determine the best management of patients

news from the medical research council interview by robert fieldhouse

with HIV infection for whom first and second line HAART have failed.

The proposed trial is to evaluate two strategies. The first is to give a large number of (five or more) antiretroviral drugs (mega-ART), in the hope that highly resistant viral strains, which escape the multiple drug pressure, will have less replicative fitness. Mega-ART will be compared to standard HAART. The second strategy is to introduce a drug free period of about three months in order to reduce toxicity and increase efficacy of resumed therapy at the end of the drug free period, possibly through re-population with sensitive 'wild-type' virus. Taking a drug free period will be compared to therapy without interruption. The trial plans to include 1,650 participants (375 from the UK) over a two year period, followed for at least one year. Decision on approval and funding is expected any time, and if approved, the trial should start in the Spring of 2001.

ATU: Has the MRC been involved in discussion about developing an international trial to look at the question of when to start therapy?

MRC: Janet Darbyshire [Head of the MRC CTU] has taken part in two meetings organised by the Division of AIDS in the US to explore the possibility of undertaking such a trial. We've also had several brainstorming sessions within the UK group and with individuals from the US to develop innovative approaches. There has been considerable interest from a lot of people as most people realise it's one of the most important questions to answer, but also appreciate the difficulties. We're planning to have further discussions in the New Year, including at the Retrovirus Meeting in Chicago.

thank you

This interview involved Janet Darbyshire, Abdel Babiker and Malcolm Hooker of the MRC CTU.



Rising HIV diagnoses

New estimates from the Public Health Laboratory Service (PHLS) indicate there will be a significant rise in the number of people living with HIV in the UK over the next three years. There were 20,800 people living with diagnosed HIV at the end of 1999 and this is expected to rise to 29,000 by the end of 2003. This increase represents a sustained rise in new diagnoses, and a decline in HIV-related deaths due to the introduction of effective anti-HIV therapy.

In a separate report by the Department of Health, the results of the Unlinked Anonymous Prevalence Monitoring Programme carried out annually by the PHLS, note that by 1999, 1 in 40 gay men under 25 in London who attended a GUM clinic was infected with HIV (see following story). According to Barry Evans of the PHLS, "Only about 63% of gay and bisexual men in 1999 who are HIV positive knew they were infected; amongst heterosexual men in London, this figure falls to just 48%."

Reference: The HIV projections are published on the PHLS website at <http://www.phls.co.uk/facts/HIV/Projections.htm>. The Anonymous Prevalence report is published by the Department of Health.

HIV rates in gay men

Anonymised HIV testing in gay men attending GUM clinics in England and Wales suggests that HIV transmission rates have not declined

over the past five years, according to a study published in November in the BMJ.

Around 5% of men with acute sexually transmitted infections attending London GUM clinics in 1998 were HIV-positive and unaware that they were infected. This level of undiagnosed HIV infection has remained stable since 1993, according to the Public Health Laboratory Service.

When men known to be HIV-positive were included, the proportion of acute sexually transmitted infections presenting in HIV-positive individuals was 9% in 1998 (a total of 123 individuals, of whom at least 64 had undiagnosed HIV infection). Although the proportion of individuals with acute sexually transmitted infections who are HIV-positive has declined since 1993, the researchers say that this change can be accounted for by changes in where HIV-positive individuals with an acute sexually transmitted infection go for treatment after an HIV diagnosis.

Acute sexually transmitted infections such as gonorrhoea and undiagnosed urethritis increase levels of HIV in semen, even in individuals with viral load suppressed to undetectable levels in blood.

Reference: Catchpole M et al. Serosurveillance of prevalence of undiagnosed HIV-1 infection in homosexual men with acute sexually transmitted infection. *British Medical Journal* 321:1319-20, 2000.

Lords ruling

The House of Lords select committee on Science and Technology has recommended a number of measures intended to regulate the provision of complementary therapy in the UK. Dedicated 'centres of excellence' should also be funded, the Lords advise, as a means of generating much-needed research into complementary medicine's effectiveness, and to introduce more rigorous training and accreditation schemes for practitioners.

The Lords' report, which can be read online at <http://www.parliament.uk>, points to the disarray which exists in some areas of complementary therapy, where large numbers of professional bodies compete for status. Except in the areas of osteopathy and chiropractic, it is currently legal for anyone to practise complementary medicine without any training; clearly not in the interests of patients' safety. According to a survey commissioned by the Department of Health, five million people consulted a complementary therapist in 1999.

Forte changes

The Medical Research Council Clinical Trials Unit (MRC CTU) has announced changes to their Forte trial. This trial was comparing three approaches when beginning HIV therapy: starting with a standard three-drug regimen, starting with a more intensive four-drug regimen, or starting with a four-drug regimen for six months and then dropping one drug to continue on three drugs (induction/maintenance), and comparing their success in suppressing viral load at least twelve months after starting treatment.

Due to slow recruitment, partly due to the unpopularity of taking four drugs beyond six months in one of the arms, the protocol has been changed to concentrate on the comparison between starting with a standard three-drug regimen and the induction/maintenance regimen. Recruitment to the arm using the intensive four-drug regimen throughout the trial has been stopped. For details see <http://www.ctu.mrc.ac.uk>.

Esprit opens in UK

As we reported overleaf, the international ESPRIT study is now open in nine sites across the UK, with a further fourteen expected to be open in the next few months. The purpose of the study is to compare the effects on disease progression and death of taking or not taking subcutaneous interleukin-2 over a five year follow-up period, in people with HIV whose CD4 cell count is equal to or greater than 300. Participants must also be taking combination antiretroviral therapy. Interleukin-2 is an immune therapy.

At the time of writing, an AIDS-defining illness is an exclusion criteria, but a revised version of the protocol has been submitted for approval, and agreement on this amendment is expected soon. The revision would allow people who have had an AIDS-defining illness but have had no evidence of active clinical disease for at least one year, in the judgement of the patient's doctor, to join the trial.

Details of this trial are at <http://www.espritstudy.org> and at the NAM/BHIVA site <http://www.aidsmap.com>.

Exercise & lipodystrophy

Exercise training is widely recommended for the treatment of blood fat (lipid) abnormalities in the general population, but it is unclear if lipid abnormalities seen in HIV-positive people with lipodystrophy will also respond well to exercise. A new study based at Body Positive North West in Manchester is investigating the issue further.

Participants perform two exercise sessions, the first of which is used to assess your exercise capacity. Blood samples will be taken before exercise, immediately after, and two, 24 and 48 hours after exercise. These will be analysed for various lipid levels. To take part, you must be on HAART, have a CD4 count above 50, have moderate to severe lipodystrophy, and should not have exercised regularly over the previous six months. For more information contact Allan at BP North West on 0161 873 8103.

ABT licensing

Abbott's boosted protease inhibitor *Kaletra* (lopinavir/ritonavir, ABT-378/r), received a positive opinion from the European Committee for Proprietary Medicinal Products (CPMP) in December. According to European Union bureaucracy, this move should allow the drug to become available on prescription a period of ninety days later. Last month's *AIDS Treatment Update* featured a review of the possible role of *Kaletra* in HIV therapy.

NAM forum

The topic of NAM's January information forum is *Which Anti-HIV Drugs First?*, which was the subject of a special issue of *AIDS Treatment Update* last month. Our guest speaker on Monday, 29th January will be Dr Barry Peters of St Thomas' Hospital, London. Barry will discuss practice at St Thomas' and answers questions from the audience.

The venue is the Palms Room, 4th Floor, University of London Union, Malet Street, London WC1, and the forum runs from 7-9pm. A sign language interpreter will be available, and everyone is welcome. NAM forums are free.



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any questions

For an introduction to HIV treatment issues
The booklets in NAM's Information Series for Positive People are free to people with HIV. This easy-to-read series covers six key topics: Viral Load, Clinical Trials, Nutrition, Anti-HIV Drugs, Resistance, and a Glossary.

The HIV & AIDS Treatments Directory
This 600 page book, published twice a year, is a comprehensive guide to the medical aspects of HIV. Available at only £9.95 to people with HIV, £57.50 to professionals.

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

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

AIDS Treatment Phonenumber 0845 9470 047
From Terrence Higgins Trust: Mon& Wed 3-9pm, Tue 3-6pm.

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



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