

Clinical issues in **HIV/AIDS**

This series focuses on advances in therapy for HIV/AIDS, particularly developments in triple therapy employing protease inhibitors.

The eighth bulletin addresses important questions that remain unanswered by clinical trial data to

date. These questions include when, and with what, to start treatment, and when to change treatment regimens.

The review section takes a look at two herpes websites with international outlooks on the topic, plus what may be the best virology site on the web.

In this issue ...

1 Commentary

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3 Combination therapy

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7 Website review

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Commentary

The publication of the UK government's national strategy for sexual health and HIV¹ in July clearly underlines the need for people with HIV infection to have equitable access to antiretroviral therapy and the expertise and laboratory support required to optimise the effectiveness of treatment.

However, even if this were to be fully funded and properly achieved, it is clear that there will still be major uncertainties for patients and their doctors to wrestle with, both now and in the future. These uncertainties are extremely well dissected in Margaret Johnson's excellent article in this edition of *Clinical Issues in HIV/AIDS*.

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Commentary continued

We should not become depressed by the existence of these uncertainties, but recognise that they are a long-standing feature in the history of medicine. For instance, sceptics of the ever-increasing use of multiple drugs in combination for patients with previous failure to antiretroviral therapy would easily associate with William Withering's quote from 1785 that, 'The ingenuity of man has ever been fond of exerting itself to varied forms and combinations of medicines'. However, with some combinations, more can mean less. For instance, combining two protease inhibitors can result in patients taking fewer capsules, with no food restrictions and apparently less discontinuation rate. Achieving such benefits without loss of efficacy and durability is a challenge that pharmacologists and physicians must rise to.

A further uncertainty relates to the timing of commencing treatment. In this debate, those who would advocate starting therapy in healthy individuals with normal CD4 counts and low viral loads might be cautioned by the words of Hippocrates in 400 BC when he asserted, 'First, do no harm'. This view can be supported with a quotation from one of the more interesting patient advocates of the last millennium, Napoleon Bonaparte, who stated to his over-eager physicians, 'I do not want two diseases – one nature made, one doctor made'.

So we continue to wrestle with these same dilemmas; wait and allow the condition to progress and cause ill-health, or treat and risk the side-effects being worse than the condition's effects. In HIV infection, of course, there is a further component relating to the potential for transmission of infection from the patient. Emerging data suggest that individuals with lower HIV polymerase chain reaction (PCR) RNA viral loads are less likely to transmit than those with high viral loads. The \$64,000 (or more contemporarily, million-pound) question is whether or not those with undetectable viral loads, in the absence of any concurrent sexually transmitted infection (STI) or inflammatory genital disorder, can transmit HIV infection. The answer to this latter question is a vexed one and has major implications for the advice which we

give to HIV-infected patients regarding their continued sexual activity.

Latest figures from the UK Public Health Laboratory Service monitoring suggest that there are increasing numbers of HIV infections being diagnosed both in gay men and especially in heterosexuals. A number of studies have identified that up to one-third of HIV-infected individuals continue to practise unsafe sex which opens them to the risk of acquiring concomitant STIs, passing the virus to an uninfected partner, and potentially acquiring a resistant virus from an HIV-infected partner who has previously had antiretroviral therapy failures.

These three facets require that we concentrate in a targeted way on the sexual health of HIV-infected individuals in order to understand it. It is important to explore the effects of antiretroviral therapy on sexual behaviour and make facilities available for patients to combine HIV-related outpatient visits with sexual health check-ups and reinforcements of safer sexual behaviour and, where appropriate, vaccinations (including hepatitis B).

This latter approach will be facilitated by the integrated national strategy for sexual health and HIV from the Department of Health, which has now been submitted for consultation. We very much hope that resources will be available in order to manage not only the treatment and care of HIV-infected individuals, but also to continue the efforts in terms of prevention that have been provided by the statutory and voluntary sector over the past 15 years. These efforts have maintained the UK's low sero-prevalence of HIV so far, but any complacency at either societal or governmental levels would seriously undermine this achievement.

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Over the last four to five years, the use of combination antiretroviral therapy for the treatment of HIV infection has led to very dramatic falls in HIV-related mortality and progression to AIDS-related clinical events.¹ These developments have occurred due to our increasing knowledge of using combinations of drugs in what is now known as highly active antiretroviral therapy (HAART) regimens. The choice of combinations has increased greatly. There are now 15 licensed antiretroviral therapies in the USA, with many other drugs in development and being investigated in clinical trials.

However, there are a number of very important questions that remain unanswered by clinical trial data to date: first, when to start treatment; second, what to start treatment with. There are now a number of choices for initial therapy but no definitive clinical trial data to say which HAART regimen is best. The other issues that require discussion are: when therapy should be changed on first virological failure; when therapy should be changed after more than one previous failure ('salvage therapy'); and what drug regimens should be used in these circumstances.

When to start treatment?

In patients with advanced symptomatic HIV infection there is universal agreement to advise the start of HAART treatment.²

Most clinicians would also consider treatment in patients with primary HIV infection – those patients who present within six months of seroconversion.³ It is essential to discuss the pros and cons of treatment with these patients and, although treatment at this stage will not be curative, as was initially hoped, the patient should be advised that it might provide possible benefit to the immune system by changing the viral load set point to a lower level. However, it is important that the patient is aware:

- That potential benefits should be balanced against potential long-term toxicity
- Of the difficulties of adhering to complicated therapy regimes for long periods of time
- Of the uncertainty as to how long treatment should be continued.

The third group is the most controversial – patients with asymptomatic HIV infection.

There have been no clinical trials that have compared earlier versus deferred therapy and certainly clinical guidelines from around the world differ in their recommendations. The British HIV Association (BHIVA) Guidelines² recommend therapy for patients with a CD4 count of <350 cells/ μ l and any viral load, and suggest considering treatment or deferring treatment and monitoring for patients with a CD4 count of between 350 and 500 cells/ μ l and a viral load >30,000 copies.

These recommendations are more conservative than other guidelines, in particular those from the International AIDS Society (IAS).⁴ However, it is important to recognise that there are little data showing that the immune consequences or outlook are worse for patients who start therapy at a CD4 count of 350 cells/ μ l than those who start early. It is also important to balance the potential benefits of therapy with the short- and long-term toxicities of these drugs and thus their potential to impair quality of life.

It has also been increasingly recognised that adherence^{5,6} is a very – if not the most – important parameter when it comes to long-term success of antiretroviral therapy. It is essential that patients are adequately prepared for starting antiretroviral therapy and that they understand the importance of adherence. They also need to be informed of the potential benefits, as well as the risks, of HAART and they need to be certain that they are ready to start treatment, before it is prescribed (Table 1, overleaf).

Which HAART regimen should be used for initial therapy?

It is clear that the use of HAART should include the use of at least three agents. The choices for initial therapy include:

- Two nucleoside analogues (NAs) plus two protease inhibitors (PIs) – the use of combined PIs improves the pharmacokinetic (PK) profile
- Two NAs plus a non-nucleoside reverse transcriptase inhibitor (NNRTI)
- Three NAs.

Two nucleoside analogues plus a protease inhibitor

The use of two NAs plus a PI has been shown in clinical trials to have both clinical and surrogate-marker efficacy.^{7,8} When looking at single PI regimens there has been no conclusive evidence of the superiority of one PI-containing combination over another, with very similar numbers of patients achieving adequate viral load suppression to below 50 copies at one year.

Increasingly, PIs are used in combination; for example, using a small dose of ritonavir to act as a PK booster for another PI – usually indinavir, saquinavir or lopinavir. PIs in combination have an improved PK profile, with higher trough levels and increased plasma concentration time curves (AUCs). This allows lower doses and longer dosage intervals and frees the patient from dietary restrictions. It is anticipated that these regimens, being more convenient, will improve adherence and, subsequently, efficacy. Studies are now in progress comparing the efficacy and toxicity of PK-boosted PIs. A recent study has shown a significant benefit of lopinavir when compared to the single PI nelfinavir – giving the first evidence

that PK-boosted PIs may be more effective when compared with single PIs used alone.⁹

The disadvantage of PI-containing regimens is the side-effect profile of these drugs, including gastro-intestinal disturbance with nausea and diarrhoea. Renal calculi have been reported in patients receiving indinavir alone and also in patients receiving ritonavir and indinavir in combination. Lipodystrophy and fat accumulation have also been reported. Lipid and other metabolic abnormalities have also been described. There are also a number of drug-drug interactions between PIs and other commonly used medication that complicate the use of PIs.

Two nucleoside analogues and a non-nucleoside reverse transcriptase inhibitor

The other frequent regimen for initial therapy is the use of two NAs with an NNRTI.

These combinations have not been as well evaluated as PI combinations in clinical trials using clinical end-points. However, there are now a number of studies showing surrogate marker efficacy. There is no published direct comparison of the NNRTIs, although studies are at present in progress. These data should be available in the near future. Only two NNRTIs, nevirapine and efavirenz, are licensed in Europe and these are the ones used in clinical practice.

Results from an open-label study comparing efavirenz with indinavir (both used with two NAs) showed superior surrogate marker end-points for the efavirenz-containing arm.¹⁰ However, there were very high discontinuation rates in both arms, which may have biased the results in favour of efavirenz. Efavirenz needs only to be taken once daily because of its long plasma half-life. Its main side-effects are central nervous system (CNS) symptoms – including depression, drowsiness and vivid dreams – and these may lead to discontinuation in some patients. In addition, a rash occurs. There are animal data to suggest that efavirenz may be teratogenic, so it should not be given to women at risk of pregnancy.

The other NNRTI is nevirapine and again there are only surrogate marker end-point data of its efficacy.^{11,12} Its most common side-effects are rash and hepatitis. The rash can be severe and even life-threatening.

The potential advantage of using two NAs with an NNRTI is that the regimens are simpler, with a lower pill burden and perhaps fewer side-effects. This is a major reason why many clinicians now choose these regimens for first-line therapy.

TABLE 1. Pros and cons of commencing combination therapy early

Pros

- HIV is a chronic, progressive viral infection resulting in immunodeficiency
- HAART clearly delays progression to AIDS and reduces mortality
- Early treatment may be associated with a lower incidence of drug-related side-effects
- Early treatment may reduce the risk of transmission from mother to child

Cons

- Understanding of HAART is developing rapidly and more effective drugs may become available in the future, when there may be a clearer understanding of what regimen to use first
- All HAART regimens have side-effects in the short term and also the potential for serious toxicities in the long term
- Early treatment may result in the earlier development of drug resistance
- Early treatment may result in the development of a drug-resistant virus and lead to the transmission of resistant viruses
- Early treatment may reduce future options

TABLE 2. Currently available antiretroviral agents

| Nucleoside reverse transcriptase inhibitors | Non-nucleoside reverse transcriptase inhibitors | Protease inhibitors |
|---|---|---------------------|
| ● Zidovudine (AZT) | ● Efavirenz | ● Nelfinavir |
| ● Lamivudine (3TC) | ● Nevirapine | ● Indinavir |
| ● Stavudine (D4T) | ● Delavirdine* | ● Ritonavir |
| ● Didanosine (DDI) | | ● Saquinavir |
| ● Abacavir | | ● Amprenavir |
| ● Zalcitabine (DDC) | | ● Lopinavir |

*Not yet licensed in Europe

However, the disadvantage of these regimens is that a single mutation in the reverse transcriptase gene can produce a virus with markedly reduced sensitivity and this extends to all members of the class. In addition, there are little long-term toxicity data available at present.

Three nucleoside analogues

The third strategy is the use of three NAs in combination. Surrogate marker data to 48 weeks have compared their use to the combination of two NAs plus one PI and have shown no significant difference. However, there was a suggestion that when patients with viral loads exceeding 100,000 copies/ml were compared in a subgroup analysis, the triple NA underperformed.¹³ However, in a recent open-label, randomised trial (CNAB3014),¹⁴ a higher proportion of patients receiving combivir/abacavir achieved a viral load <50 copies compared with combivir/indinavir. These three NAs are available in a single pill – AZT, 3TC and abacavir (known as trizivir) – and this may be advantageous in patients with adherence difficulties. A strategy using three NAs also enables PIs and NNRTIs to be available for future regimens. These regimens may be associated with fewer drug-drug interactions and are generally well tolerated. However, there is increasing recognition of mitochondrial toxicity associated with the use of NAs and thus the long-term toxicity of using three drugs in combination needs to be evaluated.

Conclusions

In all the regimens that have been discussed, two NAs are used as the backbone of initial therapy. The choice of which NAs to select should be

governed by the potential existence of primary drug resistance and overlapping toxicity. Zidovudine and D4T are contra-indicated for use together as they share a common phosphorylation pathway which has been shown to have a negative effect on CD4 counts when used in combination.

There remains controversy about which strategy to use in initiation of therapy, and without the results of head-to-head comparison the possible advantages and disadvantages of the different strategies should be discussed and the choice of therapy tailored to the individual patient. Table 2 shows the agents available.

Practical issues – starting initial therapy

Adherence has increasingly been shown in clinical trials to be an important parameter in determining the success of HAART treatment. It is important when patients start on therapy that they are adequately informed of the importance of adherence and the need for a very high level of adherence when compared with other medical treatments. They should be given precise instructions about when to take their drugs and warned about the potential side-effects. They should be given supplies of symptomatic therapies for commonly associated side-effects such as nausea and diarrhoea. They should also be clearly advised who to contact if they have any worries or problems after starting therapy.

Follow-up

Assessment of adherence should be monitored very regularly in the early stages of starting HAART and should be discussed at every appointment thereafter. It is essential to monitor

virological response and this should be carried out monthly, with a target of reducing the viral load to below 50 copies/ml. Clinical studies have shown a much higher virological relapse rate in patients achieving a viral load of <400 copies/ml and >50 copies/ml. Thus, complete viral suppression must be the goal of therapy.

Changing therapy on first virological failure

Patients should consider changing therapy if they have been started on HAART and their viraemia has not been suppressed to below 50 copies by 24 weeks.² Patients who have been on HAART and whose viraemia was initially suppressed but has again become detectable, with a rising viral load on two consecutive tests, should also be considered for treatment change.

If a patient appears to be failing on their initial therapy, it is essential to establish the reason why. Adherence should be assessed, and if this is identified as the problem, it should be optimised if possible. If the patient simply forgets to take their medication, identifying that this is a problem may be enough for the patient to improve adherence and again become virologically suppressed. However, if the regimen is proving difficult for the patient to adhere to, then identifying the component responsible and changing that drug is sometimes all that is required to regain control. It is also important to consider pharmacokinetics; and consider measuring drug levels if possible. If both factors have been excluded as a cause of failure, and it is felt that there is virological failure, then changing all drugs in the regimen may be necessary. Resistance testing should be undertaken before selecting the second-line regimen.

When patients virologically fail two NAs and an NNRTI, most clinicians would discontinue the NNRTI, change the two NAs and combine with either a single or dual PI. In patients failing two NAs with a PI the situation is less simple, as many studies have shown that failure may not be associated with PI-resistance, but may be related to poor adherence or poor pharmacokinetics. Change to a boosted PI may be needed to simplify the regimen and improve the PK profile. Another strategy would be to change the two NAs and add an NNRTI. Some clinicians would argue that there is a potentially high risk of virological failure and may want to keep a PI in the regimen and use drugs from all three classes.

Salvage therapy

Most patients requiring salvage therapy have had previous exposure to drugs of all three classes and may have a multiple-drug-resistant virus.

However, failure may also have been related to poor pharmacokinetics and poor adherence, and it is important not to prejudge the existence of a resistant virus. Resistance testing is vital and is recommended in all patients, with studies of both genotypic and phenotypic resistance predicting response to future regimens. Resistance tests should be carried out on specimens taken when the patient was still on antiviral therapy. Results of the resistance tests will be a guide to therapy.

It is always important to change as many drugs as possible and to introduce a new class if this is at all possible. In some patients it may be possible to delay change until there are new treatment options available.

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Website review

The International Herpes Alliance website (www.herpesalliance.org) is a site providing educational support to health professionals and patients. Its information includes regional support groups, educational materials and issues and events of interest to those with genital herpes and those who manage them. Its charter is probably well known to you but you may not be aware that its board includes patients, researchers, clinicians and advocacy group leaders from France, New Zealand, Canada, the Netherlands, Sweden, Australia and the USA.

The page design is rather bland and it is aimed much more towards the patient than the clinician.

However, I found the report on the second Patient Advocacy Workshop most valuable, and the perspective recognising the clinician as a 'partner' was useful. The 'how to work with the media' section could be used as a model for many situations and was a great deal of good common sense. The fact sheets are comprehensive and pragmatic if, perhaps, a little overlong at times, but their translation into three languages is much appreciated.

The recommended books list was particularly useful; however, the price appears in dollars and the publisher is not mentioned.

The 'shared experiences' area was informative, but at the time of my visit there was no individual who had experienced management of genital herpes through the NHS – although the themes were universal.

The website has a feedback page, but this is designed for patients rather than professionals who are only asked to complete three out of the 19 questions.

You will find the internet links particularly useful, I think, as well as comprehensive. Sites listed vary from individuals' experiences to scientific sites such as the University of Washington Virology Research Clinic and our own Medical Society for the Study of Venereal Diseases website.

The International Herpes Management Foundation (IHMF) has a website at www.IHMF.org and this is one for the clinician and researcher. It has a wide coverage of herpes viruses including cytomegalovirus, Epstein–Barr virus, human herpes virus and herpes simplex virus, and provides, for a trial period, the full text of every issue of *Herpes*, the journal of the IHMF, but you will need an Adobe Acrobat Reader™ to download this (free through this website).

The guidelines noted on the site cover the viruses mentioned above and there is the facility for commenting on some in draft. Recent additions include the management of herpes in pregnancy and an algorithm for managing herpes in primary care.

It is a huge site, with many useful features. I particularly appreciated the summaries of presentations at IHMF meetings and the library. The list of key papers was both up-to-date and impressive.

The site welcomes users to download and use any of the slides (the format is Powerpoint). The only request is an acknowledgement.

This is an attractive and comprehensive site and the word global comes readily to mind.

The list of external links is similarly huge, although some addresses are mentioned more than once.

www.tulane.edu/%7Edmsander/garryfavwebindex.html is seeking to be the best single site for virology on the internet. It is a bang up-to-date, visually appealing resource which includes the Big Picture Book of Viruses, a discounted virology bookshop, and virology and microbiology course notes for students. The latter includes diagrams, tutorials and video available online.

This is a must-see site and defies description, so my best advice is to visit and enjoy. Don't miss the page on 'weird virology'.

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