

Clinical issues

in HIV/AIDS

This is the second in a series of bulletins focusing on advances in therapy for HIV/AIDS, particularly developments in triple therapy employing protease inhibitors.

This bulletin looks at the encouraging evidence of reductions in

AIDS-related deaths and opportunistic infections in four countries using combination therapies, and reviews websites which should be of interest to those working in the HIV/AIDS field.

Watch out for future update bulletins in the coming months.

Commentary

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Simon Barton BSc MD MRCP HIV/GUM
Consultant, Chelsea & Westminster
Hospital, London

David Hicks FRCOG MFFP DipVen HIV/GUM
Consultant Physician, Department of
Genitourinary Medicine
Royal Hallamshire Hospital, Sheffield

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David Hicks FRCOG MFFP DipVen HIV/GUM
Consultant Physician, Department of
Genitourinary Medicine
Royal Hallamshire Hospital, Sheffield

This edition of *Clinical Issues* features a review by Andrew Moore, which those involved in the care of people with HIV/AIDS should find heartening as well as challenging. The cited figures illustrate the reversals in the number of individuals dying from AIDS, and the significant reductions in progression to AIDS diagnoses. This clearly supports the belief that reductions in plasma viraemia and rises in CD4 counts seen with different antiretroviral combinations are producing real benefits for patients. However, despite a potential for euphoria, there is a need for care and caution to be exhibited by patients, clinicians and health planners.

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Commentary continued

First, there is an urgent need for the introduction of specific protocols for clinical decision-making in the choice of antiretroviral therapies. Clinicians need to collaborate and undertake careful audits to ensure that patients do not receive sub-optimal regimes on the basis of the currently rapidly changing knowledge base. The introduction of new drugs – available on compassionate or named-patient release schemes – needs to be carefully integrated into the decision-making for doctors and patients whether they be attending large or small treatment centres.

Second, it is essential that research projects are instigated to examine the value of viral resistance testing in clinical decision-making. It is essential that individual patient's access to antivirograms or, indeed, to ultrasensitive assays of plasma viraemia, does not lead to hype and hope which forces patients to search out newer technologies from different units and even private laboratories. Statements such as the PACTS or BHIVA Guidelines on antiretroviral therapies concerning the usefulness of ultrasensitive viral assays and the value of viral resistance tests would be most useful to ensure as common an approach as possible.

Third, the increase in longevity of patients with HIV infection receiving combinations of antiretroviral therapy results in an entirely different profile of side-effects, not just with protease inhibitors and NNRTIs, but also with nucleoside analogues such as AZT, ddI and ddC which have not been used for such lengthy periods in so many patients before. We need to thoroughly investigate novel syndromes such as atypical skin eruptions, lipodystrophy and other metabolic changes to examine whether they are truly features associated with drug therapy or with the new longevity of HIV-infected individuals. The possibilities for amending drug therapy in patients with successfully achieved undetectable viral loads and CD4 immunorestitution need to be adequately examined in a rigorously randomised fashion to determine whether or not fewer side-effects can be achieved by drug switching without any loss of virological control.

Fourth, attention needs to be given to the new problems experienced by HIV-infected individuals receiving antiretroviral therapy, with undetectable viral load and rising CD4 counts.

These range from social issues around returning to work and potential loss of social and financial benefits for those who have been previously categorised as terminally ill, to issues concerning the potential for infecting new sexual partners and assurances that the benefits of long-term antiretroviral therapy are not translated into greater sexual risk taking.

Finally, we need to be alert to the possibility that not all AIDS diagnoses will diminish in incidence. Although CMV and MAI have declined, along with new diagnoses of Kaposi's sarcoma in patients treated with effective antiretroviral therapeutic regimes, there have been reports that non-Hodgkin's lymphomas are not showing such a reduction. Clinicians need to be especially alert for new syndromes and new presentations and they need to report such cases openly and rapidly.

The trend in many units towards ignoring the need for post-mortems in patients dying of AIDS-related conditions, once the common syndromes associated with advanced HIV were well described, may need to be reversed in order for us to properly understand why some patients are still dying despite adequate antiretroviral regimes.

Before the health planners close the wards, day care units and hospices and before the pharmaceutical companies call a halt to research into opportunistic infections such as MAI we must ensure that we remain reactive to potential future changes in the epidemiology of HIV's natural history and the long-term side-effects of antiretroviral therapies.

The need to prevent new HIV infection needs a redoubling of effort to reduce morbidity and mortality of other sexually transmitted infections on a worldwide basis. Furthermore, the provision of HIV care must be provided with as high a standard of equity as possible, a challenge that will continue to demand the full efforts of clinicians, health planners and politicians in order to make a difference.

Simon Barton BSc MD MRCP HIV/GUM Consultant, Chelsea & Westminster Hospital, London

David Hicks FRCOG MFFP DipVen HIV/GUM Consultant Physician, Department of Genitourinary Medicine, Royal Hallamshire Hospital, Sheffield

HIV treatments can make a difference

Andrew Moore MA DPhil CChem FRSC DSc Editor, *Bandolier*

It was reputedly Gertrude Stein who said: 'For a difference to be a difference it has to make a difference.' Perhaps that puts in a rather terse way a criticism that is made of the randomised clinical trial – that the results may not be replicated in the real world because trials are somehow 'unnatural', or because the patients are different, or for some less well-defined reason. The treatment of HIV/AIDS is one circumstance in which the transfer of knowledge gained from clinical trials has been used with wisdom in the treatment of individual patients, and it has made a difference.

Up to now the news has been in the form of headlines, abstracts of conference proceedings, or rumours. But now hard evidence is becoming available which shows that new treatments are making big differences to the lives of people infected with HIV. Presaging these publications has been information from the Centers for Disease Control and Prevention charting the fall in AIDS deaths in the United States (Figure 1).¹

A number of preliminary communications suggest that the first ever US national fall in AIDS deaths (in 1996) has been followed by further reductions in 1997. In Britain AIDS deaths are also falling: UK Communicable Disease Surveillance Centre figures show that in 1997 there were 450 AIDS deaths, down from 802 in 1996.² Several publications now clearly associate the fall in AIDS deaths and opportunistic infections, with the use of more aggressive treatment strategies using

combinations of antiretroviral drugs and protease inhibitors. The following reports from Europe and the USA all show the success of new antiviral combination therapies.

France

Information from 7,749 patients in ten centres³ showed that the introduction of highly active antiretroviral therapy and the treatment of more patients with antiretroviral therapy reduced the amount of time patients spent in hospital and had neutral or beneficial effects on overall costs. The study looked at monthly data over the year from September 1995 and particularly the difference in outcomes between September and October 1995 and September and October 1996.

The proportion of patients receiving antiretrovirals went up from 36% to 53%, and those receiving highly active antiretroviral therapy (which included a protease inhibitor) increased from 0.3% to 18%. There was an overall drop in hospital days of 35%, of AIDS-defining events by 35%, and in AIDS deaths of 46%. Centres that began using protease inhibitors earliest had a drop in hospital days of 41%, of AIDS-defining events by 41% and in AIDS deaths of 69%.

There was also a cost analysis which showed, in broad terms, that increases in costs of prescribed drugs were offset by the lower in-patient care costs, with an overall neutral effect on total costs.

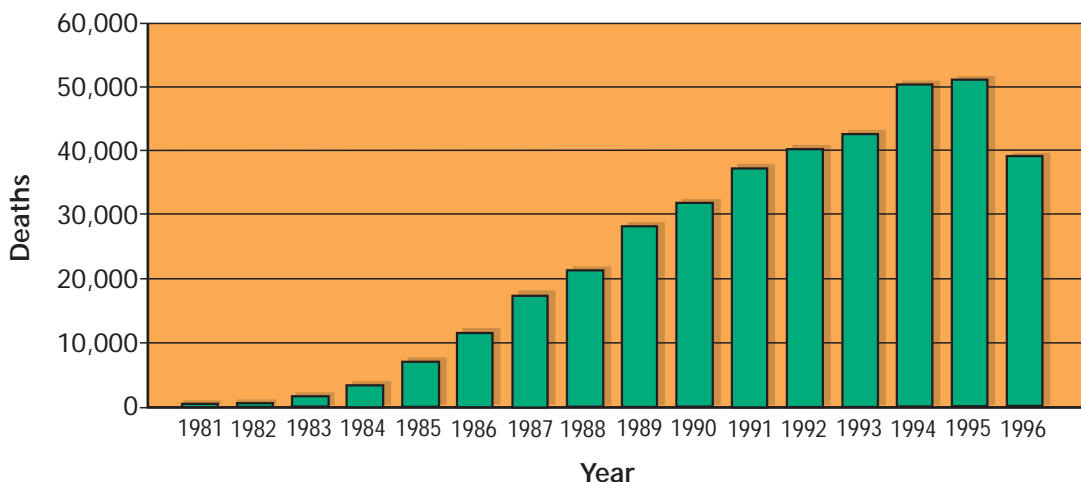


FIGURE 1. CDC report of US AIDS deaths¹

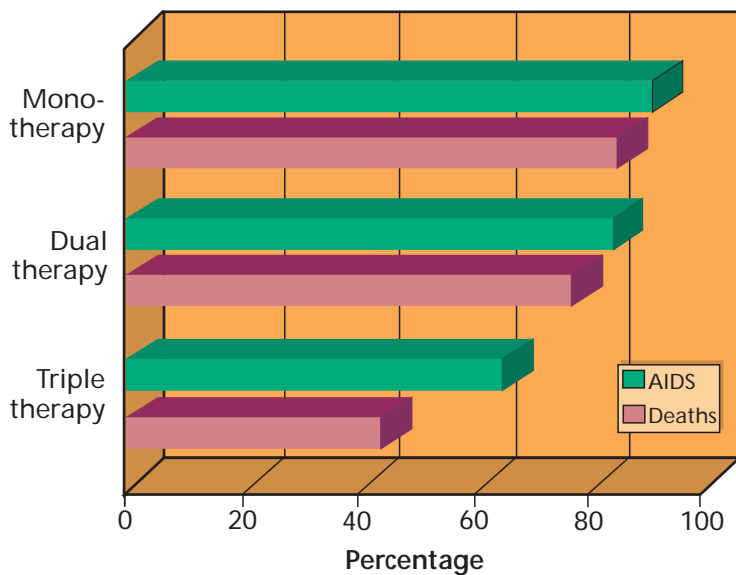


FIGURE 2.
Risk of progression to AIDS or death compared with no therapy⁴

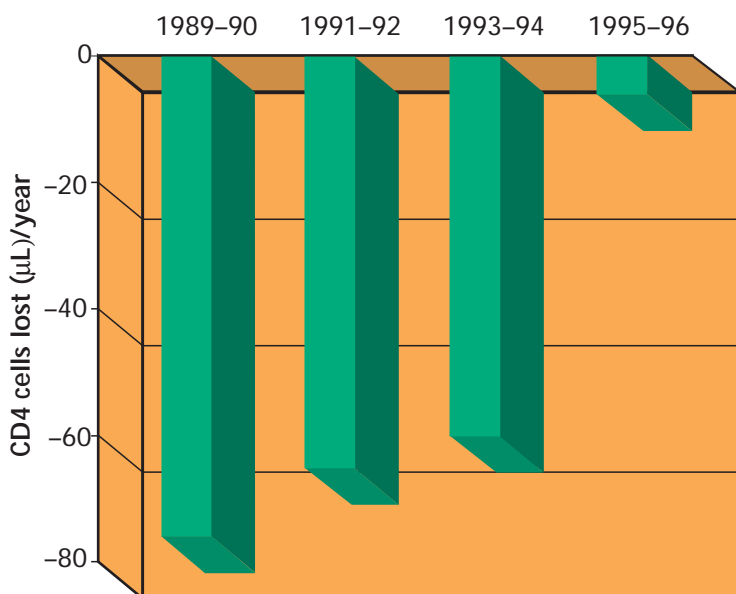
Switzerland

An observational prospective study that includes a large proportion of HIV-infected patients in Switzerland⁴ indicates that, for HIV treatments, inclusion in everyday practice produces startlingly good results. The study involved 5,176 participants enrolled since 1988.

Between 1988 and 1996 the proportion of patients having no treatment fell from 38% to 24%, and there were significant increases in patients having dual therapy (up from 17% to 60%) or triple therapy (up from 5% to 22%). The results (Figure 2) show that the use of more aggressive therapies led to reduced risk of progressing to AIDS and death. The results were particularly pronounced for triple therapy.

FIGURE 3.
Number of cells lost

Patients whose CD4 count first fell below 200 cells/ μ L before 1995 had a 40% chance of



progressing to AIDS within two years, and those whose CD4 count first fell below 50 cells/ μ L had an 80% chance of progressing to AIDS within two years. The introduction of newer therapies has cut the chance of progression in half for those whose first low CD4 count occurred in 1995-96. This was reflected in the mean number of cells lost per year (Figure 3), which was reduced dramatically in the most recent time period, coinciding with the biggest increase in most aggressive therapies.

Canada

In 1992 therapeutic guidelines in British Columbia recommended double therapy with antiretrovirals for HIV patients with CD4 cell counts >350 cells/ μ L. The introduction of this more aggressive therapy has been monitored in a prospective, population-based cohort study⁵ with death and progression to AIDS as the main markers.

Out of a population of 1,178 patients (951 had monotherapy and 227 had dual therapy) there were 390 deaths. Monotherapy patients were almost twice as likely to die over 15 months of follow-up (17.1%) than dual-therapy patients (10%). In the 877 patients who were AIDS-free at the beginning of treatment, progression to death or AIDS over 15 months occurred in 23.8% of those given monotherapy, compared with only 10.1% of those on dual therapy.

USA

As part of the HIV Outpatients Study in eight US cities, records of 1,255 patients with CD4 counts of below 100 cells/ μ L were studied from January 1994 to June 1997.⁶ Each clinic provides care for at least 150 HIV-infected patients per year.

During the study the pattern of antiretroviral therapy in this population changed dramatically. The proportion for whom any antiretroviral therapy was prescribed increased from 72% to 95%, and regimens that included protease inhibitors increased from 2% to 82% (Figure 4).

Mortality, which was between 25 and 35 per 100 person-years up to the first quarter of 1996 fell to 17 per 100 person-years in 1996 and 8.8 per 100 person-years in the second quarter of 1997 (Figure 4). This pattern of reduced mortality was seen in patients with different demographics, but there was a consistent pattern in which more aggressive therapies produced lower mortality.

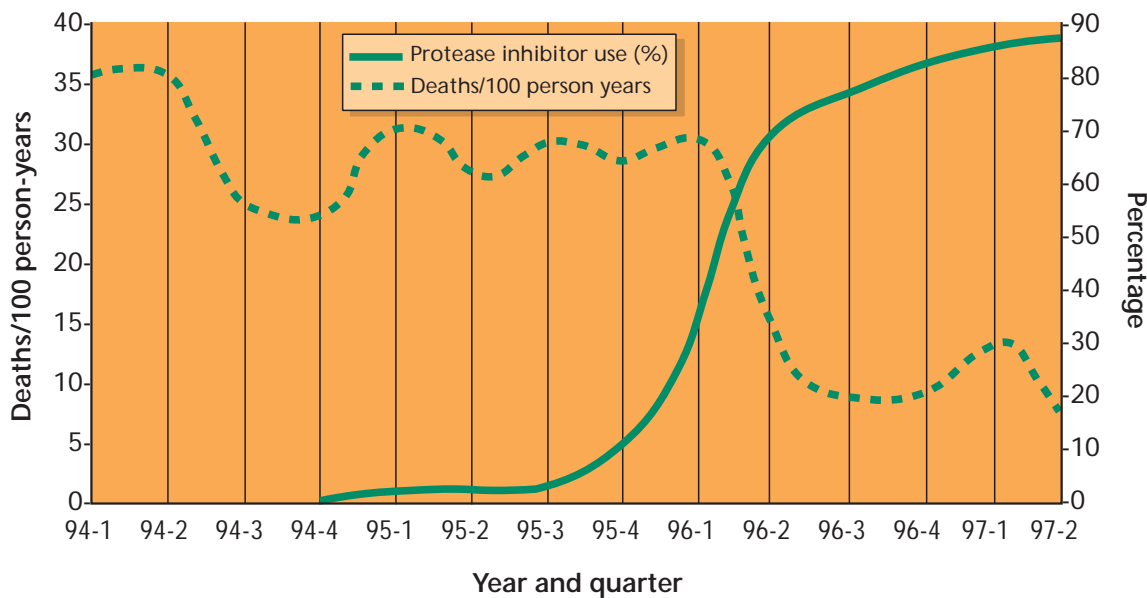


FIGURE 4. Mortality and protease inhibitors in the USA⁶

Morbidity (defined by the incidence of serious opportunistic infections) also declined at the same time and to about the same extent. The incidence of AIDS-defining diagnosis decreased from about 50 per 100 person-years in 1994 and 1995, to 29 per 100 person-years in 1996. From mid-1996 to mid-1997 the rate was 13 per 100 person-years. For three common opportunistic infections – *Pneumocystis carinii pneumonia* (PCP), *Mycoplasmata avium complex* (MAC) disease and *cytomegalovirus retinitis* (CMV) – the incidence fell from 22 per 100 person-years at the beginning of 1994, to 3.7 per 100 person-years by mid-1997.

Conclusion

Most healthcare professionals would agree that definitive evidence regarding the relative efficacy of various treatment strategies can only be gathered from randomised clinical trials. However, most would also have a concern that such trials might, for a variety of reasons, recruit patients who are in some way different from the population that may benefit. Extrapolating data from the randomised trial to use in real life situations may not be easy.

We now have accumulating evidence that the newer, more aggressive combination therapies are effective in many people with HIV infections, and lead to significant improvements in both mortality and morbidity. It is particularly impressive that these new studies from four countries show broadly similar results, whether they refer to a whole population^{3,4} or just to those with more advanced infections.^{5,6}

The implications for healthcare in the UK are focused on the following areas:

- The availability of the right therapeutic approach for all HIV-infected people who need it, with equity being a principal issue.
- How money is moved between budgets as higher drug treatment costs for more aggressive therapies are balanced with reduced needs for in-patient beds or perhaps specialist services.
- The total level of service provision and where that service can most appropriately be provided – large specialist centres versus broader dissemination of treatment.

But there is still the question about what happens in the longer term, since it is likely that many of those infected with HIV and on aggressive therapies will need to maintain that therapy for many years. Clearly some health economic modelling should be undertaken to help us in the development of services for HIV infection in the future, in the knowledge that treatment of HIV infection is a rapidly changing, but successful, part of a modern health service. The new HIV treatments are making a difference – the issue is now that of controlling the changes rather than wondering what the results might be.

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Website review

A round-up of internet sites of interest to those working in the HIV and AIDS field.

● An enormous site with seemingly endless links, **www.thebody.com** has a front page that is colourful and inviting, with a very user-friendly layout. The information is up to date and even includes a 'fact of the day'.

Sections on conferences, politics, quality of life and treatment are directed towards patients but links can lead the specialist to technical and diverse sources of information. The conference digest was particularly easy to read.

The site contains an interactive page where AIDS specialists can take questions live, but the timing could prove difficult for contributors from the UK.

This is an extremely useful, very attractive, bang up-to-date site with something for everyone and it is easy to see why it was the winner of the 1997 Global Information Infrastructure Award.

The text is available in several languages.

● The main contributions to the Fifth Conference on Retroviruses and Opportunistic Infections held in Chicago, USA on 1-5

February 1998 can be accessed after registering at **www.retroconference.org/signup/password**

This is a comprehensive programme and, with the right kit, you can hear the speakers and even download their slides. The site will remain on the Net for one year after the conference and is a valuable resource for referencing. It is not quite as good as being in the Windy City, but it is a good second best.

● For a good, comprehensive site use **aegis.com**. Its front page is a little bland but with perseverance some interesting information can be obtained.

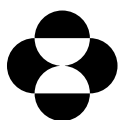
This is really a site for the non-medic, but it does have a useful updating service of global news items about HIV and AIDS. A word of warning, however: if you do register, expect to receive a lot of emails (sometimes several per day). To read them all takes some time and to keep and retrieve them uses up your disk space.

David Hicks FRCOG MFFP DipVen HIV/AIDS Consultant
Physician, Department of Genitourinary Medicine,
Royal Hallamshire Hospital, Sheffield

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Tel: (0171) 240 4493. Fax: (0171) 240 4479. email: edit@hayward.co.uk
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