

Clinical issues

in HIV/AIDS

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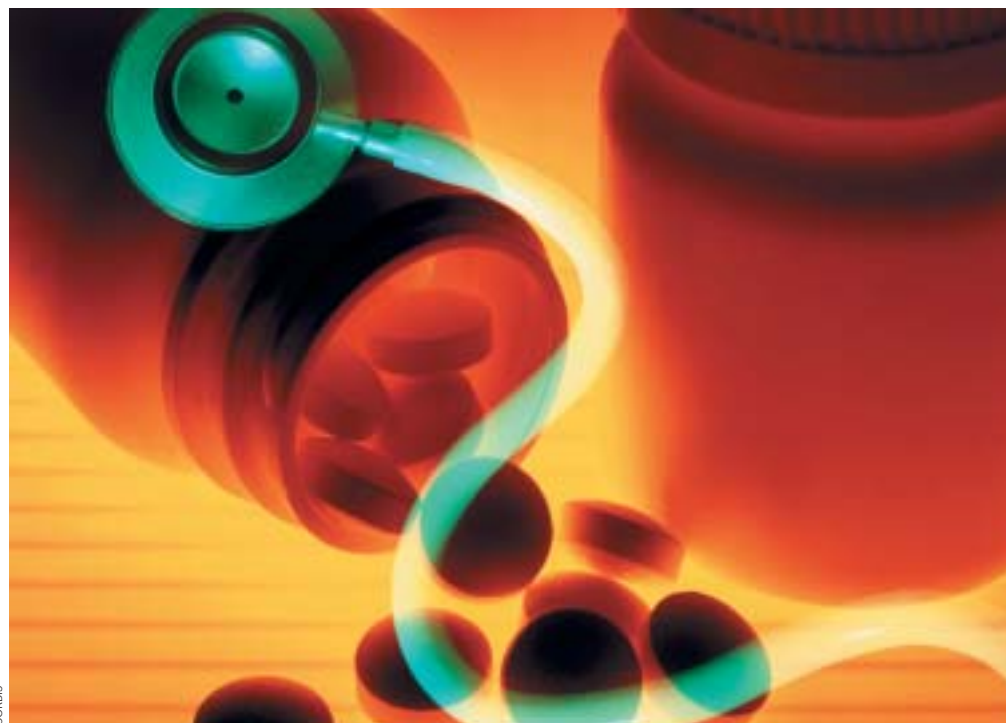
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This series focuses on advances in therapy for HIV/AIDS, particularly developments in triple therapy employing protease inhibitors.

The twelfth bulletin looks at the cost implications of combination therapy,

with particular emphasis on an indinavir/ritonavir regimen.

Also included is a retrospective of all editions of *Clinical issues in HIV/AIDS* published to date.



CORBIS

Commentary Enquiry highlights 'crisis' in sexual health

The old adage says that for some people the glass is always half-full; for others, half-empty. For those of the 'half-full' persuasion, the enormous clinical benefits of combination antiretroviral therapy, backed up by the publication of the first *National Strategy for Sexual Health and HIV*¹ in 2001 and then the *National Strategy for Sexual Health and HIV: Implementation Action Plan*² in 2002, might suggest that sexual health and HIV care is a priority in the UK.

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Commentary *continued*

If, on the other hand, you are the 'half-empty' type, you might point to the fact that neither sexual health nor HIV services has been given the status of a National Service Framework, that the National Institute for Clinical Excellence (NICE) has not prioritised a review of any related therapies and that a substantial number of primary care trusts (PCTs) have not identified commissioning leads for HIV or sexual health.³

Against a background of this spectrum of views about sexual health and HIV services in the UK, the House of Commons Health Committee's *Report on Sexual*

This will inevitably lead to an increased concentration on the cost-effectiveness of delivering treatment and care for HIV-infected individuals

Health was issued in May 2003.⁴ Their findings make stark reading and include a number of phrases subsequently highlighted by the media, such as: 'We have been appalled by the crisis in sexual health we have heard about and witnessed during our enquiry. We do not use the word "crisis" lightly, but in this case it is appropriate. This is a major public health issue and the problems identified in this report must be addressed immediately'. Everyone involved in the field

of sexual health and HIV in the NHS should read this report, which can be obtained by post from The Stationery Office or accessed via the Commons website (www.publications.parliament.uk/pa/cm/cmhealth.htm#reports).

An entire section of the Committee's work examines the issue of the funding of treatment and service provision for HIV and AIDS. The report recommends that NICE guidance for antiretroviral therapies should be prioritised and that PCTs should be required to include sexual health and HIV in Local Delivery Plans. This will inevitably lead to an increased concentration on the cost-effectiveness of delivering treatment and care for HIV-infected individuals. Issues to be addressed are both structural – such as the reorganisation of inpatient facilities – and therapeutic, especially the cost of diagnostic and monitoring tests, in addition to the cost-effectiveness of drug therapy itself. Thus, it is most pertinent that in this edition of *Clinical issues*, Gazzard and Johnson address the thorny question of whether we can reduce the cost of treating HIV/AIDS in the UK. Such debate is important, especially as antiviral drugs will reach generic status in the next few years, with the concomitant fall in costs. We must be critical as to whether or not newer drugs genuinely offer newer benefits, and we must ensure that rigorous NHS research continues.

For those individuals who wish to remain 'half-full' in their view of life, it should be emphasised that the whole modernisation agenda of the NHS fits closely with the philosophy of patient-centred care, which has been applied in the management of HIV and sexual health patients across the UK for many years. By aligning our delivery of these services to a concentrated view of cost-effectiveness, it should naturally lead to the prioritisation of our services to ensure that they lead the way in quality of care. In short, let's stay optimistic but get ever more realistic about the real cost of the services we provide.

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Can we reduce the cost of treating HIV/AIDS in the UK?

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Despite the public's apparent perception that the problem of HIV/AIDS is under control, increasing numbers of patients in the UK are being diagnosed with HIV infection. Latest data from the Health Protection Agency show that 5,542 new cases of HIV were diagnosed in 2002 – the highest ever number of new diagnoses in a single year (Figure 1).¹ Although the population at greatest risk of acquiring infection remains homosexual men, the number of heterosexual infections has risen. The majority of these new infections have been acquired abroad, predominantly in sub-Saharan Africa. This has resulted in a disproportionate burden of infection among minority ethnic communities, refugees and asylum seekers.²

The introduction in 1996 of combination therapy (highly active antiretroviral therapy [HAART]) has resulted in a considerable decrease in mortality rates – from 1,359 deaths in 1993 to 202 in 2002 (Figure 2).¹ Nearly 11% of people with AIDS are now aged 50 or over.³ The combination of the growing number of new cases and the lengthened lifespan of infected individuals means that the number of people living with HIV/AIDS is rising – estimates suggest an increase of 47% between 2000 and 2005.²

Growing prevalence, new drugs and growing costs

In 2000, the average lifetime treatment cost for a patient infected with HIV was calculated to be between £135,000 and £181,000.⁴ Such costs involve not only expenditure on drugs, but also the use of hospital services (both inpatient and outpatient). As patients live longer, the per-patient costs rise. As new and more expensive drugs are introduced, such rises are likely to be increasingly dramatic. As a consequence, the financial burden on the NHS from HIV/AIDS is increasing.

The cost of antiretroviral therapies and their impact on health budgets have been

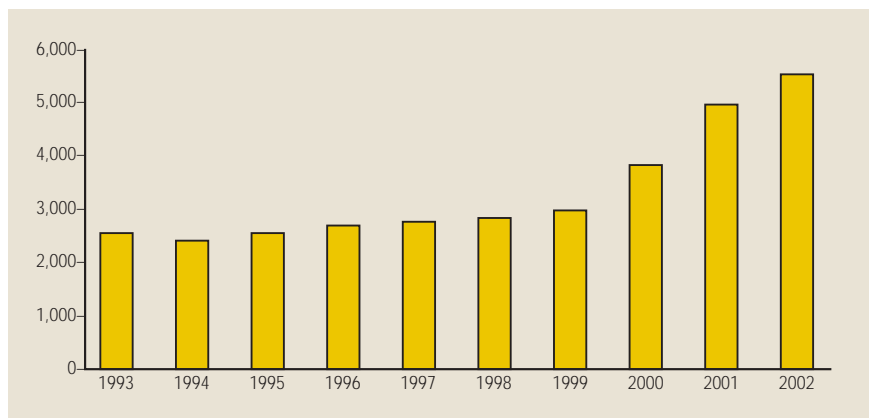


Figure 1. Number of new HIV diagnoses in the UK per year.¹

the subject of discussion for many years.⁵⁻⁸ A recent pharmacoeconomic analysis concluded that shifts in the balance between the use of outpatient and inpatient services – as a result of the introduction of HAART – had cancelled out any increase in expenditure on drugs.⁵ However, because of the increasing use of new drugs and regimens (such as salvage therapy and mega-HAART for patients with antiretroviral resistance), drug costs may increase further.^{5,9}

In the UK, these increasing costs present a problem for the NHS, which has limited resources available for the treatment of HIV/AIDS. This resource problem has been further compounded by the ending of ring-fenced funding for HIV treatment and changes to the commissioning of HIV services in 2002.¹⁰ Despite funding

increases promised to the NHS between 2002 and 2007, the amount of money that will be available for HIV treatment is uncertain, particularly as HIV services compete for budgets directly with other services and may not be viewed sympathetically due to the continuing stigma associated with the condition.¹⁰

Treatment of patients with HIV/AIDS

It is important that treatment for HIV/AIDS is targeted at each individual patient rather than the whole patient population. For HAART treatments, the interindividual variability is large, and an effective, tolerable drug combination for each specific patient must be determined.¹¹ HAART treatments can fail for a variety

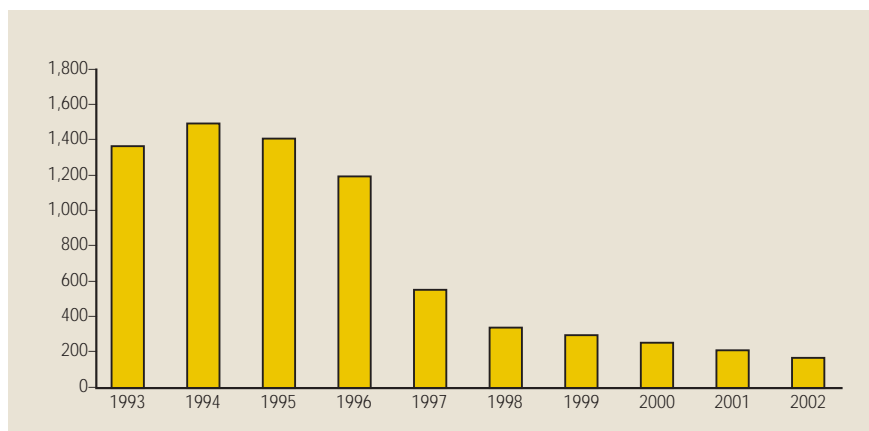


Figure 2. Number of AIDS deaths in the UK per year.¹ HAART was introduced in 1996.

of reasons, including poor adherence, insufficient drug potency, emergence of resistance, cellular factors and pharmacokinetic factors.¹² In addition, if a patient develops drug-related side-effects, their treatment may need to be changed. Treatments should also be chosen to avoid likely drug–drug interactions.¹¹

Choice of therapy

Two main classes of drug are available to treat patients with HIV:

- Reverse transcriptase inhibitors (in the form of nucleoside and non-nucleoside reverse transcriptase inhibitors [NRTIs/NNRTIs])
- Protease inhibitors (PIs).

Since 1996, the available drugs have been used in combination as HAART. Two types of HAART are available to clinicians: convergent and divergent. Convergent (or PI-sparing) therapy is so-called because it only involves the use of reverse transcriptase inhibitors. Divergent therapy involves the use of a PI and a reverse transcriptase inhibitor. Most divergent regimens also include ritonavir, a potent inhibitor of cytochrome P450 3A.¹³ This drug improves the pharmacokinetic profile of the PIs with which it is combined, either by increasing absorption of PIs or by extending their half-life. This may improve potency, reduce the risk of developing resistance and, by reducing the pill burden, improve adherence.¹¹ Convergent therapy may be perceived as having an advantage over divergent therapy in that it reserves PIs for possible later use,^{14–16} instead using combinations of NRTIs and/or NNRTIs.

The British HIV Association (BHIVA) has recently issued draft guidelines for treatment with antiretroviral therapies. These guidelines support the use of two NRTIs plus either a PI or an NNRTI for initial HIV therapy. NNRTIs are often suitable for use in once-daily regimens, have a lower pill burden and demonstrate fewer clinically important lipid abnormalities and a lower frequency of central fat accumulation than PIs.¹¹ However, PIs offer a highly durable therapeutic option – sustained suppression of plasma HIV-1 RNA levels for six years has been seen in most patients treated with a PI and two NRTIs within a recent clinical trial study.¹⁷ If a PI is to be used, the BHIVA guidelines recommend the use of a boosted PI combination (that is, a PI plus ritonavir).¹¹

Therapeutic drug monitoring

As discussed in the ninth issue of *Clinical issues in HIV/AIDS*, therapeutic drug monitoring (TDM) is becoming an important part of the management of patients with HIV/AIDS. It is used to measure plasma levels of specific drugs to check drug concentration and adherence, and to prevent toxicity. Inadequate drug levels, whatever their cause, are a reason for treatment failure; excessive levels may result in toxicity in the short or long term.¹² TDM is likely to be of little value

Evidence has suggested the existence of sanctuary sites, in which evolution of HIV may differ to that in plasma

for NRTIs as these agents require intracellular activation, and intracellular levels of active drug bear little relation to plasma levels of the parent compound.¹¹ It may, however, be particularly useful for PIs, as evidence confirms correlations between drug exposure and virological suppression and toxicity.¹¹ The link between virological suppression and exposure to NNRTIs is less clear.¹¹

Convergent versus divergent therapy

The Atlantic study by van Leeuwen *et al* aimed to compare convergent and divergent therapies with respect to suppression of HIV-1 virus replication and tolerability.¹⁶ Antiretroviral-naïve patients infected with HIV-1 were given didanosine 400 mg once daily and stavudine 40 mg twice daily as the ‘antiretroviral backbone’. They were then randomised to receive the PI indinavir 800 mg three times a day (a divergent regimen), or either the NNRTI nevirapine 400 mg once daily or the NRTI lamivudine 150 mg twice daily (convergent regimens). All doses were given orally. Patients were evaluated four and two weeks before treatment and then followed up at two, six and 12 weeks after treatment started, and then every subsequent 12 weeks with the intention of following up for up to 264 weeks.¹⁶

Long-term efficacy data for 139 of the 298 recruited patients up to 96 weeks after treatment have recently been published.¹⁶ A primary efficacy analysis failed to show statistically significant

differences between the three study arms. Viral suppression to a plasma HIV-1 RNA concentration (pVL) of <500 copies/ml at Week 48 was seen in 55–60% of patients, although patients taking lamivudine were less likely than those in the other treatment groups to achieve viral suppression to a pVL of <50 copies/ml (Table 1, opposite).¹⁶ When the probability of success was analysed with respect to baseline pVL, no statistically significant difference was seen between the strata.

Immune system recovery was measured by increase in number of CD4 T-lymphocytes from baseline. Increases adjusted for the baseline level were similar between the three groups: 238x10⁶ cells/l for indinavir, 139x10⁶ cells/l for nevirapine and 233x10⁶ cells/l for lamivudine. The differences did not reach statistical significance, even though patients who received nevirapine had a mean estimated increase of 100x10⁶ cells/l less than those who received lamivudine or indinavir. No significant difference in the incidence of serious adverse events was observed between the three groups.¹⁶

Sanctuary sites

The presence of latent viral pools has prevented the eradication of HIV from patients who have been successfully treated with antiretroviral therapy.¹⁸ There are many possible reasons for the failure of complete eradication, including circulating memory CD4 cells and viral evolution. In addition, evidence has suggested the existence of viral reservoirs, or sanctuary sites, in which evolution of HIV may differ to that in plasma.^{19–27} The main sanctuary sites are the central nervous system, lymphoid tissue and the genital tract. Therapeutic failure may be caused by insufficient drug penetration into these compartments, and variable diffusion of PIs in sanctuary sites may contribute to sustained HIV-1 replication, selection of resistance and subsequent failure to control the virus in plasma.^{28,29}

Lafeuillade *et al* studied the differences in detection of three PIs – indinavir, nelfinavir and lopinavir – in the cerebrospinal fluid (CSF), lymph nodes and semen of HIV-infected patients.³⁰ The results showed major differences in CSF diffusion between the three PIs, with only indinavir detectable in this compartment. However, HIV-1 RNA was undetectable in the CSF of all patients, regardless of the PI received. All three PIs studied were

Table 1. Treatment response in patients taking didanosine and stavudine plus one of indinavir, nevirapine or lamivudine. Adapted from van Leeuwen *et al*⁶

Panel*	Week 48			Week 96		
	No of patients	Response (%; 95% confidence interval)	p-value	No of patients	Response (%; 95% confidence interval)	p-value
<500 copies/ml						
Intention to treat						
Indinavir	100	57.0 (47.3–66.7)	0.965	100	50.0 (39.8–60.2)	0.120
Nevirapine	89	58.4 (48.2–68.7)		89	59.6 (48.6–69.8)	
Lamivudine	109	58.7 (49.5–68.0)		109	45.0 (35.5–54.8)	
On treatment						
Indinavir	66	81.8 (70.4–90.2)	0.390	38	86.8 (71.9–95.5)	0.491
Nevirapine	57	89.5 (78.5–96.0)		44	86.4 (72.7–94.8)	
Lamivudine	75	81.3 (70.7–89.4)		57	79.0 (66.2–88.7)	
<50 copies/ml						
Intention to treat						
Indinavir	100	55.0 (45.2–64.8)	0.353	100	44.0 (34.1–54.2)	<0.001
Nevirapine	89	53.9 (43.6–64.3)		89	55.1 (44.2–65.7)	
Lamivudine	109	45.9 (36.5–55.2)		109	28.4 (20.2–37.8)	
On treatment						
Indinavir	66	80.3 (68.7–89.1)	0.004	38	79.0 (62.7–90.5)	0.001
Nevirapine	57	80.7 (68.1–90.0)		44	81.8 (67.3–91.8)	
Lamivudine	75	58.7 (46.7–69.9)		57	50.9 (37.3–60.4)	

*All patients received didanosine and stavudine

detected in lymph nodes; however, there were wide differences in the lymph node/plasma ratio, with indinavir showing better penetration than the other PIs. The control of viral replication in genital fluids during HAART is of particular importance, as most HIV-1 infections are transmitted through sexual contact. The diffusion of PIs in semen was highly variable, with indinavir again showing the highest semen/plasma ratio. However, only three patients were identified with detectable HIV-1 RNA in semen, although this could be misleading as viral excretion in semen is sometimes intermittent and these patients were only investigated once.^{30,31}

Indinavir/ritonavir

Indinavir is a first-generation PI that was introduced before the importance of adherence was properly understood. Like its other class compounds, indinavir has an unfavourable pharmacokinetic profile, characterised by high peak levels that put patients at risk of adverse reactions, such as nephrolithiasis, and low trough levels that may induce viral resistance.^{32,33} Adherence to indinavir is of particular importance, therefore, in order to maintain viral suppression, but is made difficult by the side-effect profile of the drug.

The recommended dose for indinavir is 800 mg three times a day.³⁴ However, the need for a lunchtime dose makes it an inconvenient therapy option for some patients. The BEST study compared a twice-daily boosted indinavir regimen with the standard eight-hourly (q8h) regimen.³⁵ The study found that while a boosted twice-daily regimen was

Therapeutic drug monitoring of indinavir offers the ability to prevent or manage toxicity better

equivalent to indinavir q8h and provided a simpler and more forgiving dosing regimen in terms of adherence, the toxicity levels associated with the regimen were poorly tolerated by some patients.³⁵

The ATHENA Cohort Study Group evaluated TDM of indinavir to detect patients with drug concentrations outside the therapeutic range in an attempt to control toxicities by modifying doses. The authors found that TDM of indinavir offers the ability to prevent or manage toxicity better, particularly in patients

using indinavir 800 mg three times a day, or indinavir 800 mg plus ritonavir 100 mg twice daily.³⁶

To improve the tolerability of boosted indinavir regimens, Katlama *et al* recently presented data to evaluate the efficacy and tolerance of indinavir/ritonavir 400 mg/100 mg twice daily in combination with two nucleoside analogues (from didanosine, zidovudine, lamivudine and stavudine) in antiretroviral-naïve patients. In this pilot, single-arm study, 40 patients were recruited with a baseline viral load of >5,000 HIV RNA copies/ml (median viral load 230,957 copies/ml).³⁷

At Week 48, intention-to-treat analysis showed that 65% and 50% of patients achieved a viral load of 400 and 50 copies/ml, respectively. On-treatment analysis showed that 96% of patients had a viral load of <400 copies/ml and 74% of patients had a viral load of <50 copies/ml. Thirteen patients discontinued therapy: eight for drug-related adverse events (none of which was related to nephrotoxicity), one patient withdrew consent, one patient discontinued for simplification after 24 weeks and three patients were lost to follow-up. Pharmacokinetic analysis revealed that 31 of the 40 patients had

adequate plasma trough concentrations, with 96% of these achieving a viral load of <50 copies/ml at Week 48.³⁷

These data back up studies by Ghosn *et al* and Justesen *et al* that have evaluated the pharmacokinetics, efficacy and tolerability of an indinavir/ritonavir 400/100 mg twice daily regimen.^{38,39} Ghosn's crossover prospective study of 20 patients found this combination to have excellent convenience, good antiviral efficacy and excellent tolerability.³⁸ The single-centre retrospective study reported by Justesen considered the regimen to be efficacious for up to two years with no serious adverse events, cases of nephrolithiasis or elevated creatinine levels observed. However, low indinavir C_{min} values suggest that the regimen should be guided by pharmacokinetic evaluation, highlighting the importance of TDM in maintaining viral suppression and controlling toxicity during treatment.³⁹

The studies described here draw attention to both the simplicity and reduced cost of this regimen when compared with the standard indinavir regimen (approximately 50% less, Figure 3), although there are the further costs of monitoring and performing additional trials to be evaluated. However, any potentially cost-saving regimen must be considered in light of the growing crisis of funding for HIV treatments in the UK.

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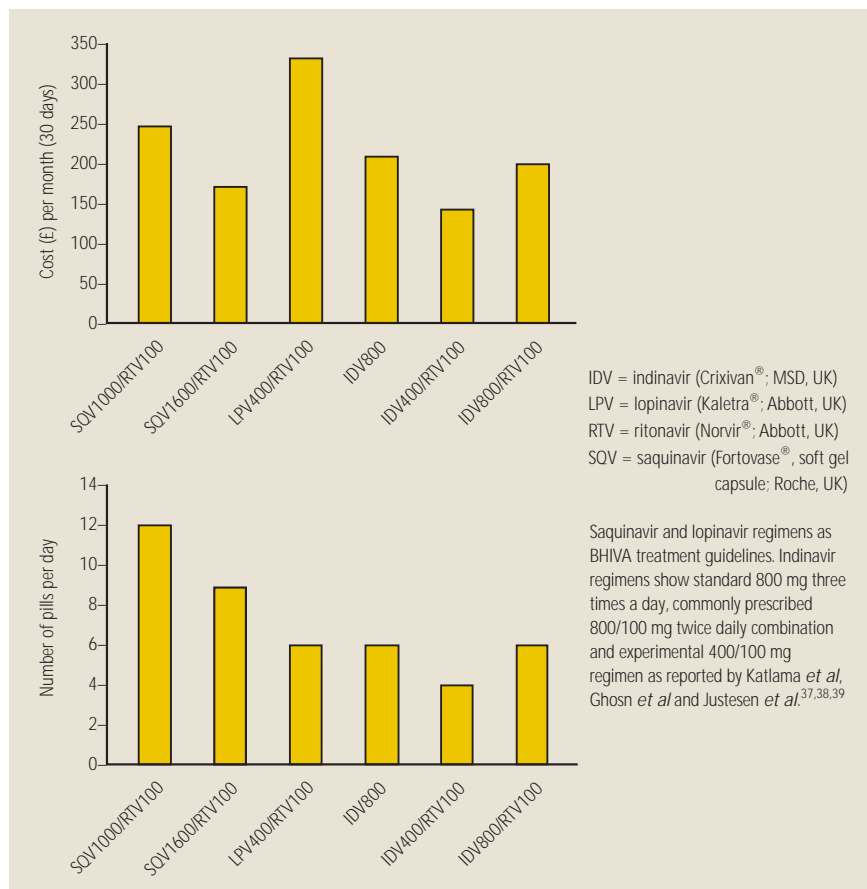


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Clinical issues – a retrospective

First published in December 1997, *Clinical issues in HIV/AIDS* is edited by Dr Simon Barton from the Chelsea & Westminster Hospital and Dr David Hicks from the Royal Hallamshire Hospital. This bulletin features practical, up-to-date and cogent research by key figures working in the field. It aims to provide a clear insight into the current scientific, therapeutic, clinical, economic and public health issues surrounding HIV/AIDS. Regular reviews of HIV/AIDS-related websites are also included. Topics covered to date are:

Issue 1

- **HIV infection and treatment – where are we now?** (Andrew Moore)
A summary of the knowledge gained about the virus and a look at protease inhibitors
- **HIV/AIDS interventions – an economic appraisal** (Ceri Phillips)
A look at the economic considerations related to HIV/AIDS, including reference to triple therapy
- **HIV/AIDS – a public health perspective** (Nicholas Hicks)
An overview of the questions that remain to be answered about protease inhibitors

Issue 2

- **HIV treatments can make a difference** (Andrew Moore)
An evaluation of the usefulness of randomised clinical trials in the treatment of HIV

Issue 3

- **Drug interactions in HIV infection** (David J Back, Michael G Barry & Sara E Gibbons)
The introduction of new therapies raises the risk of adverse interaction with other therapies, and the situation must be closely monitored

Issue 4

- **Clinical utilities of HIV drug resistance testing** (Deenan Pillay)
A look at how HIV drug resistance assays could be useful a) in patients failing therapy, b) prior to initiating therapy, c) to guide prophylaxis and d) during pregnancy
- **Update on drug interactions** (David J Back & Sara E Gibbons)
A follow-up to the main article in Issue 3, presenting key new data

Issue 5

- **Fat redistribution and metabolic abnormalities in HIV infection** (Graeme Moyle & Christine Baldwin)
A look at several new clinical and metabolic phenomena observed in individuals receiving combination antiretroviral therapy

Issue 6

- **Progress in setting standards and establishing networks for HIV care** (Will Huxter)
A review of the historical development of standards and service networks in the NHS and an examination of opportunities for further development and possible threats to progress

Issue 7

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