

Clinical issues

in HIV/AIDS

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

This scene-setting bulletin assesses the state of the art in such therapy

and presents analyses from the economic and public health perspectives.

Watch out for future update bulletins in 1998 to help keep you abreast of the latest work in this fast-moving therapeutic area.

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Introduction

When the definitive 'History of HIV/AIDS' is written in the first years of the next millennium, the last half of this final decade of the 20th century will be regarded as a crucial period. The efforts ranged against the transmission and effects of HIV will be rightly measured as immense. Countless quantities of man-hours and money have been directed towards countering the virus across a spectrum of fronts.

Now, although behaviour modification through education and barrier contraception remain our foundation for prevention, we are beginning to see these stupendous efforts in basic research bearing fruit and impacting on clinical aspects of the disease itself.

Three giant leaps forward can be recognised as having coincided in the recent past to effect this turning point.

Continued over

Introduction continued

The three giant leaps forward

The first giant leap forward concerns the development of viral load measurement. This accurately reflects prognosis in terms of risk progression to AIDS and/or death, and in this respect is clearly superior to CD4 cell count. We cannot yet, however, discard the latter measurement, since plasma HIV1 RNA, together with CD4 cell count, remains superior to the use of one marker alone. The value of plasma RNA measurement to help us decide when therapy needs to be changed is less certain but shows great promise. Its use in deciding when antiretroviral therapy should commence to maximise health gain is also under active scrutiny. Mathematical modelling of viral load and disease progression, with and without antiviral treatment, is an area of research from which we expect to hear more.

The second giant leap forward is reflected in advances in our understanding of the basic science of the virus, such as its genotypic variation and molecular epidemiology, which allow us to make projections about drug development (and resistance thereto) and the accuracy of screening assays and makes us rethink vaccine strategies. Our deeper knowledge of immunological dimensions is permitting a profound re-evaluation that will impact upon our understanding of transmission, genetic resistance and disease development.

The third giant leap forward is perhaps the most accessible and impressive advance for clinicians and patients – the development of new antiretroviral drugs, and in particular protease inhibitors. These chemical moieties are noted to be not only valuable in themselves but also more potent when used in combinations. Nucleoside reverse transcriptase inhibitors and protease inhibitors plus existing standard antivirals used together are seen to provide a total effect greater than that of the sum of their parts.

The purchasing perspective

Maybe the above is an over-optimistic account and the period we find ourselves in is a 'false dawn'. The virus may have yet more in its armamentarium to confound us if we allow it

time to do so. How unfortunate it would be then if these developments were not maximised to their full clinical and cost-effective benefit because we felt we could not afford them.

Such advances do not come cheaply, and yet we are all aware that finances are strictly limited in the NHS. It behoves us therefore to present to our purchasers a reasoned argument not only for the clinical use of such developments but for their financing. Current guidelines on prescribing and monitoring retroviral disease have developed organically. The seminal advances described above have occurred quickly and necessitated thinking 'on the hoof', so while we were busy assessing the impact of the drug costs of patients receiving two nucleoside analogues by reading the MRC Delta trial, the protease inhibitors were licensed, with a consequent change of focus.

A coherent evidence-based logic must be developed. If the initial financial cost of using the newer antiretroviral drugs is outweighed by savings from closing wards and avoiding expensive treatment (for CMV, for example), then we must be able to show this.

As busy clinicians ourselves we are well aware that time does not permit comprehensive dissection from the vast volumes of literature related to all of the above. In *Clinical Issues in HIV/AIDS* we hope to present a core of practical, up-to-date and cogent research by authors with a track record of user-friendliness to their readers. We hope, indeed, to clear some of the smoke of the present 'battles' and allow a clearer insight into current perspectives from the huge quantities of basic science, clinical, therapeutic, economic and public health literature. If we can save you a little time then we will have achieved our goal.

Please let us know should you feel that we have (or have not) done this, or that we have missed a contribution that you feel is important enough to be included in any future definitive 'History'.

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HIV infection and treatment – where are we now?

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The long, costly, tragic but deadly necessary fight against HIV continues. Now triple therapy employing protease inhibitors appears to promise a major push forward in the offensive. But how effective is it? And will the cost be acceptable? These are burning questions for healthcare purchasers working in the field, and answers are required. To address the questions, though, we must first go back to basics ...

Mode of action of HIV

When a human immunodeficiency virus enters a lymphocyte or macrophage, its RNA undergoes reverse transcription to produce double-stranded viral DNA. This is then integrated into the host DNA. The process of transcription and translation by host cellular enzymes produces large, non-functional, polypeptide chains called

polyproteins, which are assembled and packaged at the cell surface to produce immature virions that are then released into the plasma. These polyproteins are then cleaved into smaller, functional, proteins by HIV proteases, allowing the virions to mature into new active viruses. FIGURE 1 illustrates this process.

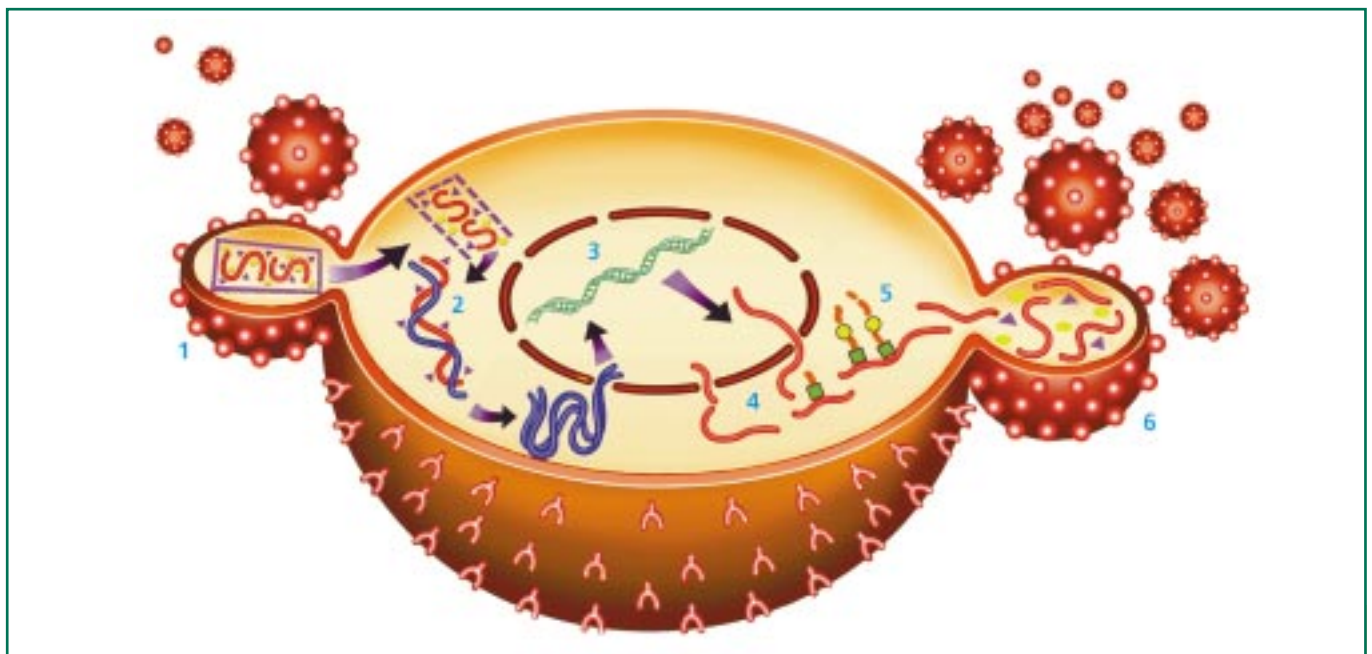


FIGURE 1. The HIV lifecycle

HIV cannot reproduce by itself. Like a parasite, HIV latches onto healthy immune system cells like CD4 lymphocytes. HIV then uses these cells as miniature factories to produce new HIV. It has been estimated that, each day, more than 1 billion new HIV particles are created in an average person with HIV/AIDS.

1. HIV particle binds to a T-lymphocyte CD4 receptor on the immune cell's surface. HIV genetic material is then injected into the cytoplasm of the cell.

2. HIV genetic material, which is RNA, is transcribed into DNA by the HIV enzyme reverse transcriptase.

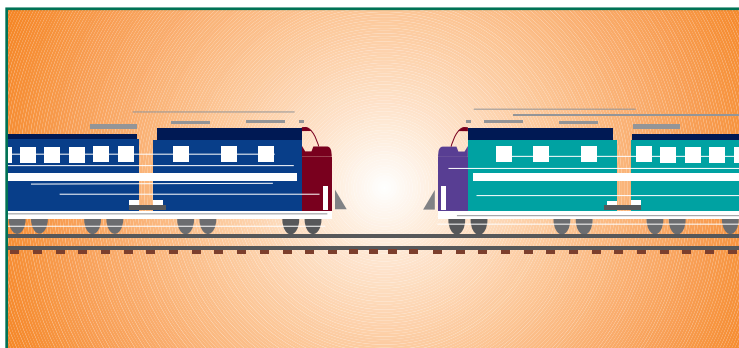
3. HIV DNA is integrated into the host immune cell chromosome and transcribed back into RNA. This may be rapid or follow a period of latency.

4. RNA is translated into long protein chains and enzymes.

5. The enzyme protease cuts the long protein chains to enable assembly of the components for the new virus particles.

6. Completed HIV particles bud away to infect new cells.

The interaction between CD4 T-cell count and viral load in the blood has been likened to an impending train crash, where the viral load indicates the speed of the train and the CD4 cell count the distance to the crash site



Therapy for HIV and AIDS has until recently concentrated on using nucleoside analogues to inhibit the production of double-stranded viral DNA. In 1988 the HIV-1 protease enzyme was crystallised and its three-dimensional structure determined. Computer models were then used to find chemicals that fit into the cleavage site to inhibit protease activity. Some of these inhibitors have been tested in humans and show exciting efficacy in reducing the number of HIV viruses produced.

Reductions in HIV viral load using protease inhibitors have been linked with significant improvements in HIV treatment when associated with the use of conventional nucleoside antiviral agents. Progression to AIDS and death is slowed. At least one randomised clinical trial comparing protease inhibitors with placebo in combination with nucleoside analogues has been halted because the benefits of the protease inhibitor were so great.

Protease inhibitors will pose important questions on the delivery of treatment to HIV patients. These will include the provision and use of surrogate end-points like HIV viral loads, choosing which patients to treat and when (and how), and assessing the costs and benefits to the health service. The preliminary information available does not yet allow these questions to be answered in full, and there remain huge ethical questions over what studies are to be permitted.

This publication aims to bring together some of the information pertinent to answering these questions. It will address first the issue of viral load tests and how viral load is linked to disease progression and outcome, and then examine the preliminary results from combination studies involving protease inhibitors.

HIV infection

HIV viruses infect T-helper lymphocytes and macrophages, gaining entry via the CD4 cell

surface receptor. CD4 T-cell counts are usually above 500/ μ L but show a transient fall during the months after initial infection, while the concentration of virus in blood rises dramatically and then falls to much lower levels. During this period seroconversion occurs, with antibodies to viral envelope protein appearing in the blood.

The average time between infection and development of AIDS in adults is about 11 years. There is wide variation: about 20% of infected individuals progress rapidly to AIDS within five years of infection, while 12% remain free of AIDS for up to 20 years. During this asymptomatic period there is a steady decline in CD4 T-cells and virus can be detected in blood. Viral load in blood rises and the CD4 count falls, which heralds advanced immunosuppression and AIDS. Viraemia is sustained by a continuous round of viral replication and reinfection of blood cells. Since viral replication in lymphocytes kills the host cells, high levels of virus in blood are associated with low CD4 T-cell levels. Perhaps the enormous turnover of HIV, some 100 million or so virus particles a day, is associated with the defeat of the immune system, associated with the development of conditions like cytomegalovirus infection of the retina, *Pneumocystis carinii* infection of the lungs, or tumours like Kaposi's sarcoma or non-Hodgkin's lymphoma.

HIV viral load

Various forms of viral nucleic acid can act as markers for disease progression or response to antiretroviral therapy. Viral RNA concentrations in plasma (also called viral load) are inversely proportional to the concentration of CD4 T-cells.^{1,2} Viral RNA in plasma can be detected and measured in plasma by several techniques, such as reverse transcription followed by polymerase chain reaction (PCR), branched-DNA (bDNA) signal amplification and nucleic acid sequence-based amplification (NASBA). These tests tend to give comparable results,¹ having detection limits

as low as 500 molecules of viral RNA per mL, but capable of measuring levels above one million molecules/mL. This covers the range of concentrations of viral RNA seen in patients with HIV and AIDS. The tests have acceptable reproducibility,¹⁻³ although they may have different specificities for different HIV-1 strains (known as clades).

Knowing levels of both viral load and CD4 cells is an essential tool in the management of HIV-infected patients. The interaction between CD4 T-cell count and viral load in the blood has been likened to an impending train crash, where the viral load indicates the speed of the train and the CD4 cell count the distance to the crash site.⁴

Viral load, CD4 and prognosis

REFERENCE 5 This important study demonstrated that viral load is an indicator of progression to AIDS and is a better predictor than the number of CD4 T-cells. It studied all 209 HIV-1 seropositive men enrolled in a Pittsburgh clinic in 1984 and 1985. Clinical status, CD4 T-cell count and blood samples for laboratory studies were obtained at baseline and every six months for up to 11 years; samples were then stored at -70°C. Samples from 180 men were subsequently available for testing. Individuals were followed up for progression to AIDS and death. Only 41% had received any antiretroviral therapy.

Viral load at entry (TABLE 1)

At entry, viral load levels ranged between undetectable (<500 molecules/mL) and 294,000 molecules/mL. The results demonstrated a clear relationship between viral load at entry and progression to AIDS and death. Those in the lowest quartile of viral load had the smallest chance of progressing to AIDS, with the median

time to progression or death (>10 years) limited by the duration of the study. Those in the highest quartile had the highest chance of developing AIDS (62% within five years), and half died within five years.

CD4 T-cell numbers were not prognostic. Only the quartile with the lowest CD4 count (<320 cells/ μ L) was associated with a shorter time to development of AIDS or death.

Viral load at entry with CD4 >500/mL

In patients with a CD4 T-cell count of >500 cells/ μ L (median about 780 cells/ μ L), and in whom therapy would not normally be indicated, plasma viral load was also prognostic of progression to AIDS or death. The median time to death of individuals in this category with a viral load above 10,000 molecules/mL was 6.8 years; 50% died within six years of study entry. In those with viral loads below 10,000 molecules/mL, the median time to death could not be estimated because only 30% had died within ten years; only 5% died within six years of study entry.

Consecutive viral load measurements

There was a worse prognosis for subjects with a persistently high viral load. Using mean values of viral load (at entry and at the six-month follow-up), a shorter time to death (median 3.9 years) was seen in those in the highest quartile than was found in those in the highest quartile with only a single viral load estimation at entry (median 5.1 years).

Extended study

REFERENCE 6 A more extensive study in 1,604 men infected with HIV-1 has emphasised the importance of this finding. In this multicentre study a wide range of markers were compared for their ability to predict

TABLE 1. Prognosis and viral load in 209 men⁵

Viral load quartiles (molecules/mL)	Progression to AIDS by 5 years (%)	Median time to development of AIDS (years)	Proportion who died within 5 years (%)	Median survival time (years)
<4,500	8	>10	5	>10
4,500–13,000	26	7.7	10	9.5
13,001–36,300	49	5.3	25	7.4
>36,300	62	3.5	49	5.1

TABLE 2. Prognosis and viral load in 1,604 men⁶

CD4 count (cells/ μ L)	Viral load category	N	AIDS-free survival (%)		
			3 years	6 years	9 years
>500	I	110	94	82	70
	II	180	96	81	56
	III	237	92	70	42
	IV	202	84	50	25
	V	141	66	28	14
351–500	II	47	96	74	40
	III	105	90	57	31
	IV	121	83	40	16
	V	121	50	20	5
201–350	II	27	93	74	59
	III	44	91	52	27
	IV	53	62	26	11
	V	104	34	9	6
\leq 200	IV	20	50	25	10
	V	70	14	1	0

Viral load category: I, \leq 500 molecules/mL; II, 501–3,000; III, 3,001–10,000; IV, 10,001–30,000; V, >30,000

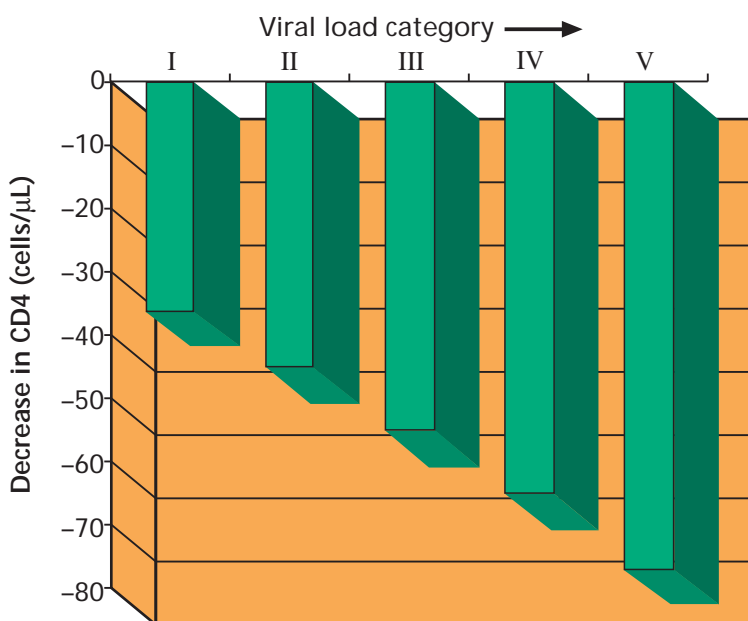


FIGURE 2. Annual fall in CD4 lymphocytes (cells/mL) by viral load⁶

progression to AIDS and death during a ten-year period. Plasma viral load was the single best predictor of progression. Five risk categories were defined by plasma viral load: \leq 500, 501–3,000, 3,001–10,000, 10,001–30,000 and >30,000 molecules/mL.

In progression to AIDS and death, those in the highest viral load categories progressed most rapidly (TABLE 2). Just as in the smaller, earlier study,⁵ there was a pronounced effect of viral load, and here also CD4 count, in determining disease progression.

The larger study⁶ also demonstrated clearly the effect of plasma viral load on the reduction in CD4 lymphocyte count over time (FIGURE 2). The higher the HIV-1 RNA concentration, the greater the rate of decline in the CD4 lymphocyte count. Together with the earlier data, this emphasises the importance of viral load in the development of AIDS in HIV-1 infected persons. It also emphasises the importance of having the test available to determine when to initiate treatment and when to switch therapies because of failing treatment.

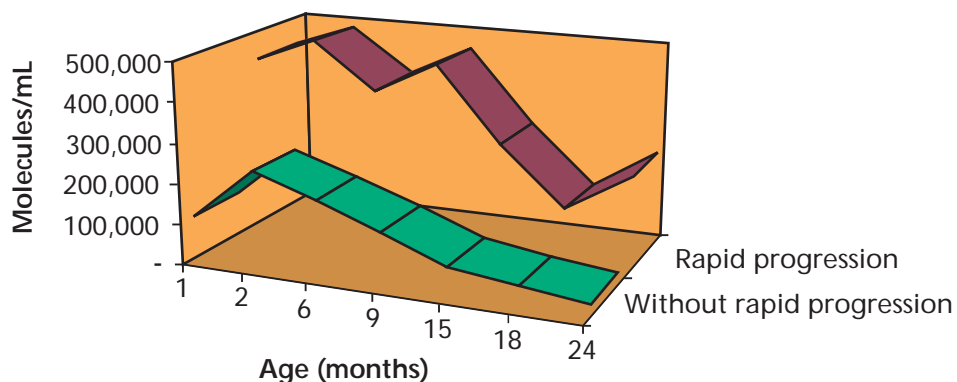


FIGURE 3.
Viral load and disease progression in infants⁷

Viral load and disease progression in infants

REFERENCE 7 Viral load has also been shown to be prognostic of disease progression in infants. Plasma viral load increased rapidly after birth (FIGURE 3) with median peak values at one and two months of 318,000 and 256,000 molecules/mL respectively. Levels then fell progressively to 34,000 molecules/mL by 24 months. Infants with a rapid progression of disease had a higher peak viral load (median 724,000 molecules/mL) in the first two months of life than those without a rapid progression (median 219,000 molecules/mL). Moreover, none of the infants with fewer than 70,000 molecules/mL at one, two and four months had rapidly progressing disease, though there was no threshold value above which rapid progression could be predicted.

REFERENCE 8 The association between viral load and mortality was confirmed by retrospective examination of viral load in the

serum of children entered into a randomised intravenous immunoglobulin trial. This showed not only an association of mortality with viral load, but that children with high viral loads and low CD4 T-cell counts had the worst prognosis (FIGURE 4). [Breastfeeding is discouraged in HIV-infected mothers, because of the possibility that virus may be transferred in breast milk.]

Viral load and mother-to-baby transmission

Three recent reports have indicated that high maternal viral load is associated with a higher rate of transmission to infants.⁹⁻¹¹

REFERENCE 9 A group of 67 HIV-infected mothers in Barcelona gave birth to 69 children. Infants were classified as infected on the basis of persistent HIV antibodies at 18 months, detection of virus or progression to AIDS before 18 months. The mean RNA load was 172,000 molecules/mL in transmitting mothers and 9,700 molecules/mL in

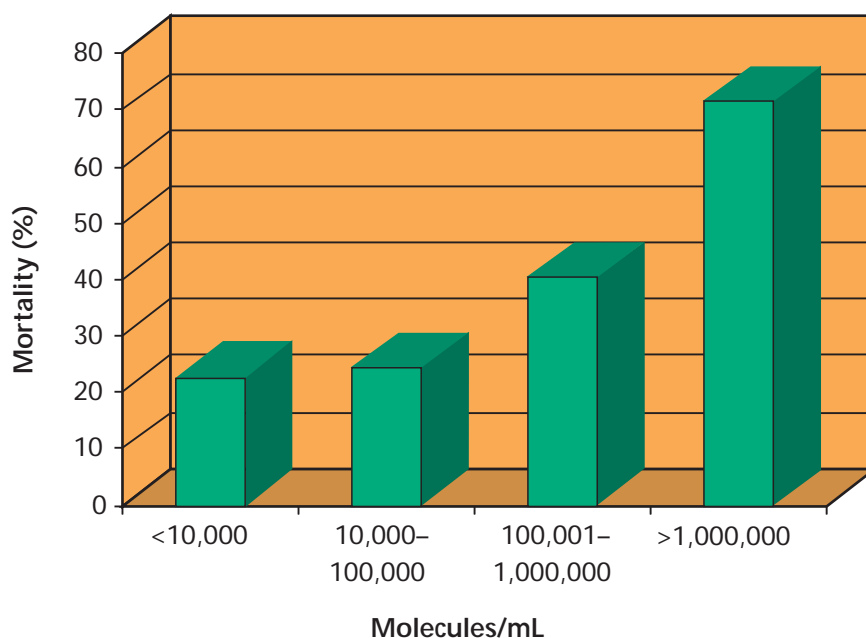


FIGURE 4.
Viral load at entry and mortality in intravenous immunoglobulin trial in children⁸

TABLE 3. Viral load and mother-to-child transmission⁹

Maternal factor	Infected children (%)	Odds ratio (95% confidence interval)	Likelihood ratio
<i>CD4 T-cell</i>			
<400/ μ L	11/27 (41)	4.1 (1.1–15.5)	2.1
>400/ μ L	6/42 (13)		0.5
<i>Viral load</i>			
>100,000 molecules/mL	11/15 (73)	22 (4.4–119)	8.4
<100,000 molecules/mL	6/54 (11)		0.4

non-transmitting mothers. Viral load was more predictive of HIV infection in infants than were CD4 T-cell counts (TABLE 3). The odds ratio and likelihood ratio of a maternal viral load of >100,000 molecules/mL were high. With a prevalence of 24%, a likelihood ratio of a positive test would predict a more than 55% chance of the infant being infected; a result of fewer than 100,000 molecules/mL would predict a less than 10% chance of the infant being infected.

REFERENCE 10 A cohort study in France examined maternal–infant transmission with respect to viral load in 236 children notified to a central register over a five-year period. The median viral load (two samples) was 10,600 molecules/mL in transmitting mothers and 3,600 molecules/mL in non-transmitting

mothers. Only maternal viral load was significantly related to the risk of transmission.

REFERENCE 11 Perhaps one of the most important studies in mother-to-infant transmission was the AIDS Clinical Trials Group (ACTG) protocol 076 study, which randomised mothers to either the antiviral zidovudine or placebo during pregnancy. This study of 402 maternal–infant pairs showed a transmission rate with placebo of 22.6% (95% confidence interval 17.0–29.0%), compared with the much lower rate of 7.6% (4.3–12.3%) with zidovudine.

REFERENCE 12 Evidence on mother-to-infant transmission related to maternal viral load continues to accumulate. In a study from the Bronx, in 160 women whose infants' HIV-1 infection outcome was known, the same association with maternal viral load was shown (FIGURE 5). This study was interesting because it had more detailed information on other maternal information that may affect transmission, such as drug abuse, unprotected vaginal intercourse during pregnancy, and duration of ruptured membranes, all of which were positively associated with transmission of infection to the infant. [Caesarean section protects against mother-to-infant transmission.]

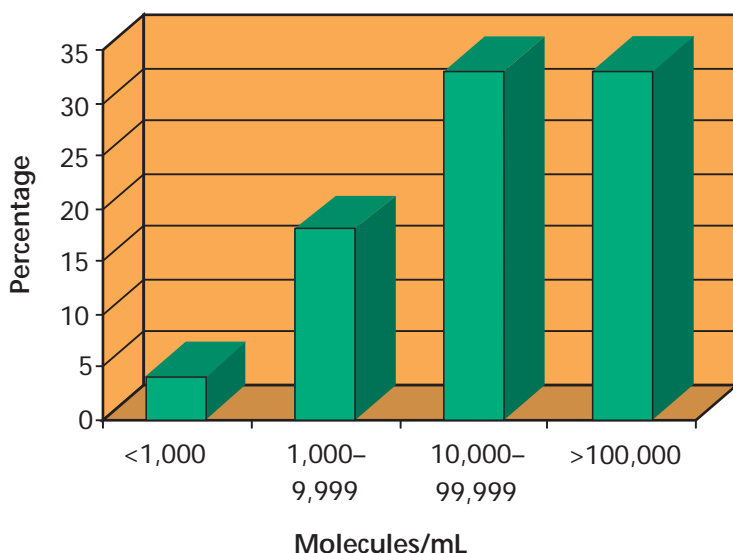


FIGURE 5. Mother-to-infant transmission¹²

Viral load and other infections

Transient increases in viral load have been observed in patients on constant antiretroviral therapy who have bacterial pneumonia¹³ and other opportunistic infections.¹⁴ Typically, viral load increased in all patients for samples taken during an episode of intercurrent illness compared with samples taken before or after the illness. In bacterial pneumonia, the median increase was 179,000 molecules/mL,¹³ and in a

mixture of opportunistic diseases the median level was 145,000 molecules/mL.¹⁴

Viral load predicts therapeutic response

Two publications have demonstrated the usefulness of viral load measurements, together with CD4 counts, in predicting success and failure with antiretroviral therapy.^{15,16} Both of these showed that in randomised trials a reduction in plasma viral load about eight weeks after starting antiretroviral treatment reduced the risk of disease progression by about half. By contrast, a return to baseline viral load within six months was associated with progression to AIDS.¹⁶

Viral load models

Mathematical modelling of viral load and disease progression has become possible. In the absence of antiretroviral treatment, patients with a viral

load of 100,000 molecules/mL are at risk for progression to AIDS in less than three years.¹⁷ Those with a viral load of about 300,000 molecules/mL are at risk in less than one year. But with lower viral load the time to progression to AIDS extends, so that at 10,000 molecules/mL patients have at least 2.8 years and up to 19 years.

HIV-1 protease inhibitors

The mode of action of these agents is illustrated in FIGURE 6.

A systematic review of peer-reviewed publications, abstracts from conferences and product registration information concerning HIV-1 protease inhibitors up to September 1996 has been published,¹⁸ as well as a review that puts protease inhibitors into perspective in HIV.¹⁹ There are some important practical points about the use of protease inhibitors, of which there are

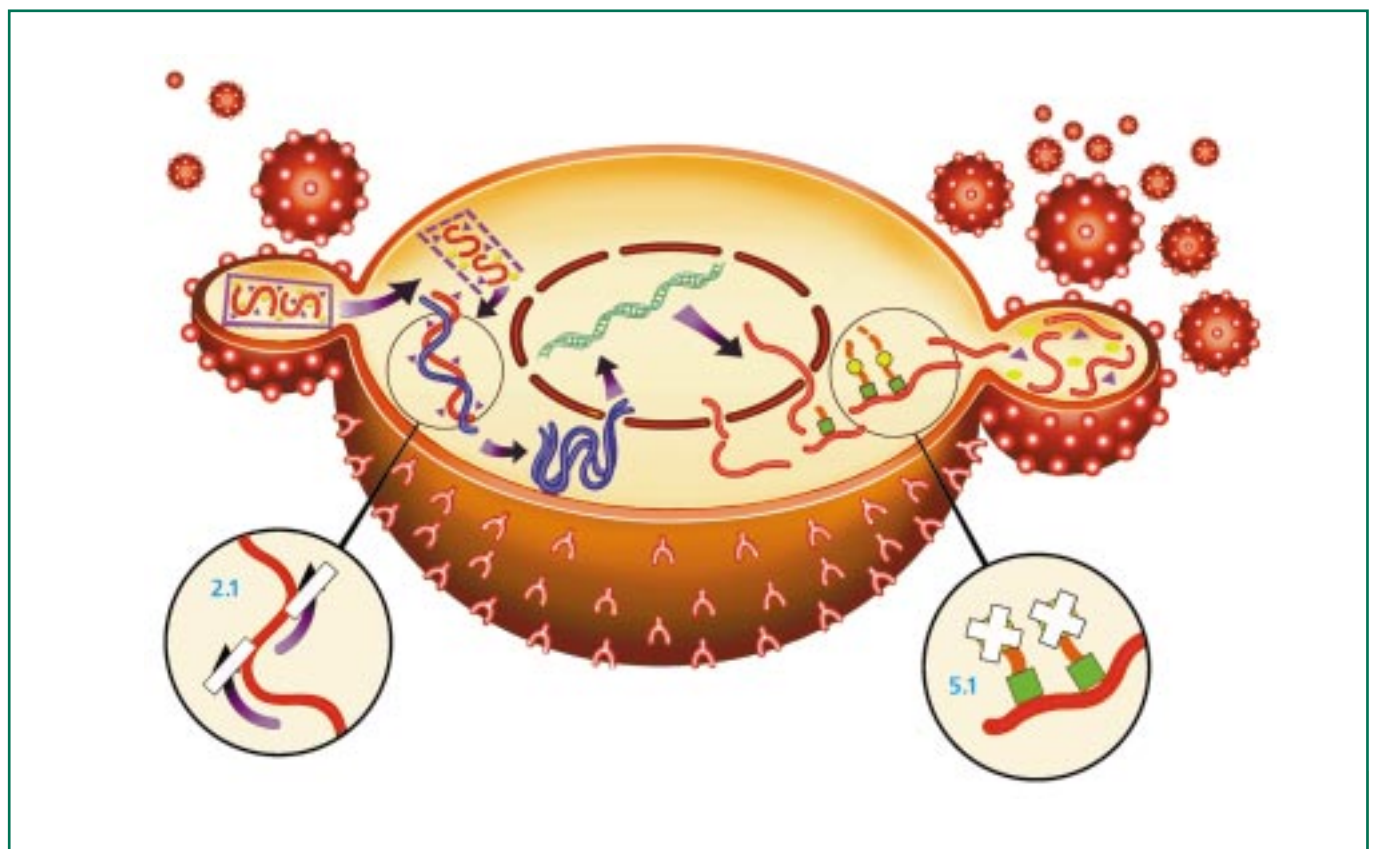


FIGURE 6. Mode of action of an HIV protease inhibitor

Protease inhibitors, the newest class of HIV/AIDS drugs to be developed in a decade, effectively inhibit the action of the critical protease enzyme used by HIV to reproduce.

They block the enzyme (at step 5.1; Step 5 in the scheme of things outlined in FIGURE 1), thereby interfering with the virus's ability to reproduce. Older drugs, reverse transcriptase inhibitors, target HIV at a different point in its lifecycle (step 2.1). However, these

agents have been less effective at reducing the level of HIV.

three available in the UK – saquinavir, ritonavir, and indinavir – but with others being made available through research programmes.

Efficacy of protease inhibitors

The role of protease inhibitors is as part of combination therapy with at least two nucleoside analogue reverse transcription inhibitors.

The problem is that many studies have been started with protease inhibitors used in combination therapy (with positive results, as, for example, in conference abstracts), though we have no head-to-head comparisons. But, as yet, few have appeared as full peer-reviewed papers to allow data abstraction. An additional complication is that some trials examine or report on surrogate markers like CD4 counts or viral load, while others examine clinical outcomes.

One trial that has attracted much media attention because it was stopped early owing to good results (it was considered unethical to continue with less effective treatment in patients receiving dual therapy alone – that is, the group receiving placebo protease inhibitor) was the ACTG 320 trial with indinavir.

ACTG 320 trial

REFERENCE 20 This was a randomised, double-blind, placebo-controlled trial in which people with HIV-1 infection and CD4 cell counts of no more than 200/μL received either a two-nucleoside regimen plus protease inhibitor (indinavir) or the same regimen plus placebo. Patients had over three months experience of AZT (21 months on average) and less than seven days experience of 3TC (another antiretroviral drug). The average viral load in these patients was 100,000 molecules/mL.

Stratification of outcomes was by CD4 count more or less than 50 cells/μL. Follow-up was at four, eight and 16 weeks, and every eight weeks thereafter up to 40 weeks.

1,156 people were randomised, and the median duration was 38 weeks. Patients lost to follow-up were few, at 5%. There were 227 (20%) premature discontinuations, of which a major portion was patients seeking open-label treatment with protease inhibitors. The main results are shown in TABLE 4.

AIDS or death

Addition of protease inhibitor halved the rate

About protease inhibitors ...

- They may have limited oral bioavailability. Saquinavir is only about 4% available in its present formulation, but others, like indinavir, are up to 60% available orally.
- Drugs that induce cytochrome P450 activity in the liver may reduce the blood level of some protease inhibitors by increasing first-pass metabolism. Drugs that inhibit P450 (eg, ritonavir) may increase blood levels.
- There will be complex drug interactions in HIV or AIDS patients between protease inhibitors and a variety of different drugs – not only antiretrovirals, but also other drugs to combat intercurrent disease.
- Protease inhibitors are associated with a number of adverse effects, including gastro-intestinal disturbances and rashes. These may be related to plasma concentration.
- Other adverse effects are more esoteric. For instance, indinavir precipitates in the renal collection system, leading to symptoms of renal colic, so increased fluid intake is recommended; nephrolithiasis caused by indinavir may be treated by hydration, pain relief and temporarily stopping therapy.

TABLE 4. Protease inhibitors and HIV: results from ACTG 320²⁰

Outcome	Nucleosides plus indinavir	Nucleosides plus placebo	Relative risk	Absolute risk reduction	NNT
All patients – main outcomes					
AIDS or death	33/577	63/579	0.53 (0.35–0.79)	0.05	19 (12–50)
Death	8/577	18/579	0.45 (0.20–1.03)*	0.02	58 (29–>1,000)
Plasma viral load <500 molecules/mL	52/577	347/579	6.7 (5.1–8.7)	0.51	2.0 (1.8–2.2)
All patients – adverse effects					
Neutropenia	29/577	87/579	0.33 (0.22–0.49)	0.10	10 (7.5–15)
Hyperbilirubinaemia	35/577	6/579	5.9 (2.5–14)	0.05	20 (14–34)
Renal colic	21/577	5/579	4.2 (1.6–11)	0.03	36 (22–93)
Outcomes stratified by CD4 count					
AIDS or death CD4 ≤50/mm ³	23/219	44/220	0.53 (0.33–0.85)	0.09	11 (6.2–35)
AIDS or death 51–200 CD4/mm ³	10/358	19/359	0.53 (0.25–1.12)	0.02	40 (18–∞)

*Statistically significant by hazard ratio calculation in original article.

of progression to AIDS or death from 11% to 6%, and of death from 3.1% to 1.4%. Overall the number-needed-to treat (NNT²¹) was 19, but in those patients with the lowest CD4 cell counts of ≤50/μL (that is, the most advanced disease) the same halving of the rate produced an NNT of 11 because of the higher progression rate.

Plasma viral load

The addition of the protease inhibitor indinavir was very effective in reducing the plasma viral load to levels below the sensitivity limit of the assay (500 molecules/mL). 60% of patients treated with protease inhibitor had such low values, compared with 9% in the placebo group. The NNT was 2.

CD4 cell count

CD4 cell counts rose substantially in patients given protease inhibitor, by nearly 150/μL over 40 weeks. Placebo-treated patients had increases that were below 50/μL.

Adverse effects

Neutropenia was much less common in patients on a protease inhibitor – one in ten fewer patients were affected. Both hyperbilirubinaemia and renal colic were more common with protease inhibitor, affecting an extra one in 20 and one in 36 patients respectively.

Other indinavir trials

Other randomised trials support the findings of ACTG 320.

REFERENCE 22

A randomised comparison of a dual combination of AZT and indinavir against indinavir alone and AZT alone in Brazil involved 996 antiretroviral-naïve patients with CD4 T-cell counts between 50 and 250/μL.

Interim analysis was of 224 patients, and preliminary results showed that after 24 weeks of treatment 70% of patients in indinavir

TABLE 5. Summary of randomised studies with protease inhibitors

Reference	Patients	Treatments	Outcomes
Collier <i>et al</i> 1996 ²³	302 patients with CD4 count 50–300/ μ L, AZT experienced	2 nucleosides, AZT + saquinavir, triple therapy for 24 weeks	Triple therapy had greatest decline in viral load by a peak of about 0.7 log
Lalezari <i>et al</i> 1996 ²⁴	904 patients with CD4 count 50–300/ μ L, AZT experienced	Zalcatabine, saquinavir, dual therapy for 74 weeks	Dual therapy had fewer AIDS events or deaths (15%) than saquinavir (24%) or zalcatabine (27%) alone. NNT for dual over zalcatabine was 8.2 (5.4–17)
Danner <i>et al</i> 1996 ²⁵	84 patients with CD4 count 50/ μ L	Different ritonavir doses for 32 weeks	In highest dose groups, peak decrease in viral load of 1.9 log, with increases in CD4 count
Cameron <i>et al</i> 1996 ²⁶	1,090 patients with CD4 count <100/ μ L	Ritonavir, placebo, on top of existing regimen, for 24 weeks	Decreased disease progression or death – 33% on placebo compared with 16% on ritonavir. Implied NNT of 6
Berry <i>et al</i> 1996 ²⁷	266 patients, AZT naïve, with CD4 count 50–500/ μ L	AZT, indinavir and dual combination for 24 weeks	Decrease in viral load was 1.2 log for dual combination, 1.0 log for indinavir alone and 0.3 log for AZT. Large increase in CD4 count for combination
Gulick <i>et al</i> 1996 ²⁸	97 patients, AZT experienced with CD4 count 50–400/ μ L and viral load \geq 20,000 molecules/mL	Two nucleosides, indinavir or triple therapy for 24 weeks	92% with undetectable viral load with triple therapy compared with 0% with transcriptase inhibitors and 38% with indinavir alone. NNT 1.1 (1.0–1.2)
Gathe <i>et al</i> 1996 ²⁹	33 patients with CD4 count \geq 200/ μ L and viral load \geq 15,000 molecules/mL	Nucleoside, same plus nelfinavir, for 22 weeks	By month 2, the mean decrease in viral load was >2 log
Brazilian study, 1996 ²²	996 patients with CD4 count of 50–250/ μ L	AZT, indinavir or both in combination for up to 58 weeks	Proportion with undetectable viral load was 9% with AZT alone, 34% with indinavir (NNT 4) and 42% with dual therapy (NNT 3). Disease progression or death was 18% with indinavir alone and 6% with dual therapy (NNT 11)

groups had CD4 counts of more than 50/μL, compared with only 20% treated with AZT alone. Viral load had decreased by 100-fold in 17% of patients on dual therapy. Also, 37% of patients in indinavir groups, as opposed to only 7% treated with AZT alone, had viral loads below the limit of detection. By 58 weeks, study of 996 patients showed that undetectable viral load in plasma was found in 42% on dual therapy, 34% on indinavir alone and only 9% on AZT. This implies an NNT for clearing HIV-1 virus from plasma over a year of 4 for indinavir alone compared with AZT and 3 for dual therapy compared with AZT alone.

Adverse clinical outcomes were reduced in patients treated with indinavir – from 18% with AZT to 8% on indinavir and 6% on dual therapy (AZT plus indinavir) by the mean follow-up of 58 weeks. The NNT of 8 for dual therapy implied by these figures is similar to that of 11 for triple therapy over 38 weeks in the ACTG 320 trial.

Other trials

Results of other randomised trials are shown in TABLE 5. There is a general picture of protease inhibitors, especially in combination with nucleoside inhibitors, being effective in reducing viral load, improving CD4 counts and delaying the interval to disease progression and/or death. Many of the results are preliminary, and it will be some time before the full results are published. Despite this **there is clear evidence of efficacy**.

Treatment guidelines

REFERENCE 30

A consensus statement by the British HIV Association has recently outlined some broad principles for HIV treatment in the UK. These were based on current available evidence and are:

- Treatment should be offered before substantial immunodeficiency ensues.
- Initial treatment should include combinations of at least two drugs.
- Switches in therapy should involve substitution or addition of at least two agents.
- Viral load and CD4 measurements are essential.
- Reduction in viral load to below the detection level of a sensitive assay represents optimal treatment response. Failure to achieve or sustain this control should prompt consideration of therapy modification.

TABLE 6. Summary of updated recommendations of the International AIDS Society – USA panel³³

Starting therapy

- Therapy is recommended for all patients with HIV RNA levels above 5,000–10,000 molecules/mL
- Therapy should be considered for all HIV-infected patients with detectable HIV in plasma
- For patients at low risk of progression (low viral load and high CD4 count) therapy may safely be deferred with re-evaluation every 3–6 months

Selected options

- Two nucleoside analogue reverse transcriptase inhibitors plus protease inhibitor
- Two nucleoside analogue reverse transcriptase inhibitors plus non-nucleoside inhibitor

Indications for changing therapy

- Treatment failure, rising viral load or failure to achieve low levels, rising CD4 count, progression
- Unacceptable toxicity, intolerance, non-adherence to regimen
- Current use of suboptimal therapy

REFERENCE 31

A recent *Drug and Therapeutics Bulletin* endorses this approach and also suggests approaches to needlestick injury. It reports that the risk of HIV transmission following needlestick injury of about 0.4% can be reduced by a further 80% by a four-week course of AZT, and reports on guidelines from the USA using prompt triple therapy with two nucleosides (AZT plus lamivudine) plus, possibly, indinavir for four weeks.

REFERENCE 32

Department of Health guidelines on post-exposure prophylaxis for healthcare workers occupationally exposed to HIV (June 1997) recommend a combination of zidovudine, lamivudine and indinavir.

REFERENCE 33

Even these recent guidelines may have to be updated. Due to the fact that new data have provided a stronger rationale for starting more aggressive therapy earlier, new recommendations from the

13-member panel of the International AIDS Society USA panel detail likely treatment regimens optimised for each patient for optimal long-term clinical benefit and adherence. They conclude that the plasma viral load measurement is a crucial element of clinical management. Other key points from the recommendations are shown in TABLE 6.

The latter guidelines are in major agreement with two other guideline documents recently released in the USA.^{34,35}

And yet more good news ...

The ability of combinations of nucleosides plus protease inhibitors to reduce plasma viral loads below detectable concentrations in plasma raises the question of how long such treatment should continue. Words like eradication have begun to appear in reports, with the suggestion that these new treatments may even herald hope of a cure. It is probably far too soon to contemplate this, but three new reports offer more good news.

REFERENCE 36 The issue is one of 'reservoirs' of HIV in the body outside blood cells, where latent infection of CD4 cells may occur despite apparently low viral loads as measured in blood, or apparent lack of symptoms in patients. Chun and colleagues examined lymph nodes of infected patients and concluded that infection is sustained by relatively few infected cells. They concluded that as few as five and seven cells per million may be infected in lymph nodes and blood respectively. The mean frequency of macrophages containing integrated HIV-1 DNA was 54 cells per million.

REFERENCE 37 So what happens when triple therapy apparently clears virus from the blood? Perelson and colleagues from the USA and Finland looked at viral load in eight patients starting treatment with zidovudine, lamivudine and nelfinavir. They found that HIV-1 in plasma drops by more than 99% in the first two weeks due to rapid elimination of the free virus (half-life less than six hours) and loss of productively infected cells (half-life of about 1.6 days). They propose that this rapid phase is followed by a second, slower phase of decay of plasma virus. Their mathematical model shows this loss of long-lived infected cells (with a half-life of up to four weeks). This

enables them to estimate that 2.3–3.1 years of treatment with a completely inhibitory regimen would be needed to completely eliminate HIV-1 from these longer-lived compartments. This, of course, could be longer if other reservoirs exist.

REFERENCE 38 Independent work by Cavert and colleagues from the USA, Holland and UK appears to agree. Serial tonsil biopsies from ten patients treated with zidovudine, lamivudine and ritonavir showed that the amount of HIV-1 virus trapped in follicular dendritic cells (another potential reservoir) and in infected cells dropped rapidly, initially with a half-life of about one day. After 24 weeks, even though some virus was still detectable, more than 99.9% of virus had been cleared from the lymphoid tissue reservoir.

All of this is exciting stuff but is still some way short of a cure. Indeed, there is a philosophical issue here of how 'cure' should be defined with a retrovirus – there are many examples of viral diseases that can become quiescent only to erupt again years later. There may be as yet undiscovered sanctuaries for the virus – in the central nervous system, for instance.

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Conclusion

If the fight against HIV and AIDS has seemed in the past to be like trench warfare, with every yard being hard fought, the new combination of effective tests for viral load and the advent of protease inhibitors seems like a cavalry charge. Ground is being gained, but the battle, let alone the war, is far from over. Many challenges remain. Some of those challenges will mean going back to the grind of doing high-quality clinical trials to test which combinations of the nucleosides and protease inhibitors give the best results in individuals with particular characteristics. Some will involve a wait to see whether these bright initial results work out in the longer term.

There are already problems. Deeks and colleagues¹⁸ point them out eloquently in their review, as does the BHIVA consensus statement.³⁰ Perhaps the most important is viral drug resistance and the need to ensure compliance with therapy. Adverse effects, and the complex pharmacokinetic and pharmacodynamic interactions of these complicated therapies, will challenge the clinical skills of those treating individuals with HIV and AIDS. But we also need to know which patients should be treated, how early in the asymptomatic period treatment should be started and which is the optimal sequence of available drugs to provide continued clinical benefit.

The delivery of healthcare will be challenged, particularly over issues of cost

and cost-effectiveness. The cost of treatment and tests associated with protease inhibitors has been estimated at \$10,000 a year. In the UK, going from no treatment to triple therapy would increase costs of drugs and tests by about £10,000 a year. So beginning therapy in seropositive individuals who are not immunocompromised would imply much more cost. Will the savings offset the costs? We have to wait for more information.

Triple therapy may mean that severe (and expensive) infections and complications related to AIDS are delayed or prevented (like cytomegalovirus infection of the retina). Cost avoidance for these conditions must also be considered. Moreover, the balance of costs to society of a young man or woman now in employment and paying taxes becoming unemployed, and therefore not paying taxes but consuming healthcare resources, is likely to favour keeping them healthy.

Then there is the public health perspective. Treating HIV-infected women in pregnancy can reduce transmission to infants. But will treatment to reduce viral load in infected individuals at risk of infecting others reduce the risk of transmission, or should we be thinking about post-coital protection with triple therapy for individuals at risk? Will any of the challenges be met, or can any drug costs be offset by savings in healthcare elsewhere?

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HIV/AIDS interventions – an economic appraisal

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The budgetary constraints facing all healthcare purchasing agencies highlight the need for new technologies and treatment strategies to be subjected to rigorous economic evaluation. The evidence that an intervention is effective must also be supported by evidence that it is cost-effective.

In other words, it must be demonstrated that either the same clinical benefits can be generated at lower cost than the next best alternative intervention (thereby releasing resources for purchasing other interventions), or that any additional resources required for the new intervention are more than offset by improvements in health status, which will secure reductions in the utilisation of services and release resources for use elsewhere.

The development of a new drug that appears from clinical trials to be effective but is also expensive is a prime example of the dilemma confronting purchasing authorities. Purchasers will wish to know the extent to which 'investment' in a new drug is likely to generate rewards in the form of, for example, resources that will not be required to provide care and treatment for patients later in the course of their disease.

Protease inhibitors

The advent of protease inhibitors alongside nucleoside antiretroviral agents in the treatment of HIV and AIDS presents a case in point. The review by Moore in this publication provides clear evidence for the efficacy of protease inhibitors in combination with other agents in reducing viral load, improving CD4 counts and slowing the progression of disease.

It has been suggested that protease inhibitors are the most promising agents developed in the ten years that antiretroviral therapy has existed, but that they may be the most difficult to use and have major cost implications.¹ The monthly costs of the three licensed protease inhibitors are compared in TABLE 1.

On the other hand, studies have also been

TABLE 1. Monthly costs of protease inhibitors (MIMS October 1997, 210-211)

Indinavir	£223.88
Ritonavir	£377.39
Saquinavir	£331.28

undertaken that suggest economic benefits can be generated which offset the additional drug expenditure resulting from the introduction of protease inhibitors.²⁻⁵ Reductions in the number and duration of hospital episodes and other forms of utilisation were recorded, although there was also evidence of changes in activity levels between inpatient and outpatient care, attributed possibly to an increase in individuals seeking care.⁴

Economic impact of HIV/AIDS

A number of studies across a number of countries have estimated the economic impact of HIV and AIDS. However, many of these have been restricted to hospital costs or costs to the acute sector and have failed to consider the impact on other health and social care agencies.

One study that provides a broader estimate of the costs of caring for people with HIV and AIDS in England and Wales,⁶ including the community and informal sectors, has estimated that the annual costs for a person with asymptomatic HIV disease are £4,515, for a person with symptomatic non-AIDS £8,836, and for a person with AIDS £15,268. These translate into an estimate of lifetime costs of £84,522 per patient. These costs were based on 1992/93 prices and therefore when brought into line with today's prices they become

£4,967, £9,720, £16,795 and £92,974 respectively (TABLE 2). The estimates did not include the indirect costs associated with the disease in terms of production losses or the intangibles such as pain and grief.

The study also forecast that the increase in the total cost of care would amount to nearly 40% during the five years from 1992, which in itself represents a major issue for purchasers at a time of severe financial restraint.

A study from the USA⁷ estimated that the prevention of an HIV infection would generate savings of between \$56,000 and \$80,000 (based on 1991/92 prices), which equates to between £35,000 and £50,000, or £41,000 and £59,000 at today's prices (£1=\$1.6). The study, which was based on the direct medical costs of HIV and AIDS only, showed that over 85% of the costs were incurred during the later stages of the disease (the AIDS-affected stage). If we adopt the thinking that '£1 in two years time will be worth less than £1 now', there are benefits to be gained from postponing the relatively high proportion of costs associated with the disease in its latter stages. In other words, slowing down the progression of disease and the move to higher-cost profiles produces lower costs in present value terms.

Cost comparisons

The issue in assessing the economic benefit from the introduction of protease inhibitors alongside other agents therefore amounts to a comparison of the costs associated with the introduction of the drug with the reduction in the costs of treatment and the costs of complications for patients brought about by reductions in viral load, improvements in CD4 and a slowing down in the progression of disease towards AIDS and death.

The probable cost of moving from dual therapy to triple therapy using indinavir is in the region

of £3,000 per patient-year. However, for every year a person is in the symptomatic non-AIDS category, as opposed to the AIDS category, the cost differential is £7,075. Given that the ACTG 320 study⁸ showed that the number of AIDS-defining illnesses and deaths was reduced by 50% for those patients receiving combination therapy compared with dual therapy, it is reasonable to expect that a similar proportion of patients will not progress to the higher cost category.

As a crude estimate, the saving from investing in triple therapy would be £538 (ie, 50% of £7,075 less £3,000) for every £3,000 extra cost incurred – that is, a net return of some 18%. In order for savings to be made, the percentage of patients receiving triple therapy who do not progress to the AIDS category would have to be 43%, which seems highly probable given the initial findings produced.

Such potential savings represent a very attractive return on investment, and, if they were to be realised, would release resources to enable other services to be purchased for other HIV/AIDS patients and in other areas of healthcare.

Further investigation

Obviously, a more detailed investigation is required along the lines of a study that modelled the implications of a slowing down in the progression of disease resulting from combination therapy of lamivudine and zidovudine compared with monotherapy,⁹ where the cost per life-year saved was estimated as £6,276 (95%CI £5,337–9,705). Of more relevance is an American study¹⁰ that produced incremental cost-effectiveness of between \$10,000 and \$18,000 per life-year gained for a combination of zidovudine, lamivudine plus the protease inhibitor indinavir as compared with zidovudine alone (depending on whether there are decreases in other healthcare costs to offset the additional pharmaceutical costs).

TABLE 2. Costs (£) of caring for people with HIV/AIDS in England and Wales

	1992/93	1997
Asymptomatic HIV	4,515	4,967
Symptomatic non-AIDS	8,836	9,720
Person with AIDS	15,268	16,795
Estimated lifetime costs per patient	84,522	92,974

The study also demonstrated that such ratios compare very favourably with other therapeutic interventions and concluded that: ***'Unless subsequent studies with longer term longitudinal clinical follow-up demonstrate that the improvement in HIV disease progression is of limited duration with combination therapy, not providing access to combination antiretroviral therapy may be shortsighted, leading both to greater subsequent costs of care, and an increased clinical burden of illness and early death that is now avoidable in patients with HIV infection.'***

The evidence provided for the effectiveness of protease inhibitors is also supported by evidence that investment in protease inhibitors is cost-effective in comparison with other healthcare interventions and will, in all probability, result in cost savings resulting from a slowing down in the progression of disease.

Conclusion

These calculations do not include the quality-of-life dimension that would enhance the findings in favour of protease inhibitors, since it is highly likely that a slowdown in the rate of progression

also adds quality as well as quantity of life to this particular group of patients. Such a slowdown would also add to the claim that, if the goal of therapy is maximal suppression of HIV replication for as long as possible,¹¹ practice guidelines need to reflect advances in the treatment of HIV/AIDS and purchasers need to be aware of the potential economic benefits of such treatment strategies.

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HIV/AIDS – a public health perspective

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Arguably, HIV/AIDS has been the leading global public health issue of the 1980s and 1990s. Progress, although frustratingly slow for the many thousands of people whose lives have been directly affected by the HIV virus, has in reality, and in comparison with responses to earlier global epidemics, been extremely rapid. The development of protease inhibitors marks the opening of a new chapter in this remarkable story.

In less than 20 years a new clinical syndrome has been recognised and characterised, the causative organism identified and its mode of spread determined. The public, patients, professionals and governments have responded to this epidemiological knowledge by coming together with advertisers, the media, industry and others to promote the necessary behavioural and attitudinal changes required to slow the spread of the disease. There are good reasons to believe that these public health campaigns have been surprisingly successful and have produced major changes in sexual attitudes and behaviour. Perhaps as a result, many countries are not experiencing the appalling death rates feared and predicted in the early years of the epidemic.

The importance of public health campaigns is highlighted by the dramatically different experiences of East Africa, Kenya and Uganda. In Uganda, where the government has, with others, promoted safer sex messages, condom use is widely accepted and AIDS death rates are relatively low. By contrast, in neighbouring Kenya, where safer sex messages have been less widely promoted, condoms are less frequently used and the rates of HIV infection and death from AIDS are considerably higher. The implication for developed countries, including the UK, is that well-conducted public health campaigns are, and should remain, an important part of every nation's fight against HIV/AIDS.

Combination therapy

As well as investing in epidemiological research and epidemiology-based public health

campaigns, companies have invested heavily in basic molecular, cellular and pharmaceutical research relating to the biology and treatment of HIV/AIDS. In recent years, this research has been bearing important fruit. Many of the more significant advances in knowledge and treatment are highlighted by Andrew Moore earlier in this publication.

It is interesting to note that one area so far absent from the list of successes has been the development of an effective HIV vaccine. However, the advent of protease inhibitors, with their ability to profoundly reduce HIV viral loads, to slow the progression of AIDS and death and, for some, even to offer the prospect of cure, has generated huge excitement and even euphoria. Undoubtedly there will be great demand for the widespread use of this new class of drug from those infected with HIV and from those who care for them.

The demand for protease inhibitors will present patients, the public, politicians and professionals with a number of difficult and important questions. They will find that, at the moment, many of the questions that require answers are unanswerable. The most important of these difficult questions are:

- **Defining the place of protease inhibitors in the treatment of HIV/AIDS.**
- **Defining the potential of protease inhibitors to slow the spread of HIV.**
- **The cost-effectiveness of protease inhibitors in different circumstances.**
- **The affordability of protease inhibitors and their relative priority in the competition for healthcare resources.**

The questions that need to be answered if these issues are to be resolved include the following:

? Defining the therapeutic role of protease inhibitors

- Can protease inhibitors in combination with other drugs eliminate HIV from the human body permanently or do they merely slow or halt viral replication?
- What is the optimal duration of treatment? Does it vary according to the stage of HIV/AIDS?
- At what stage of HIV/AIDS are protease inhibitors most effective?
- How reliable are the intermediate outcomes of changes in viral load and CD4 counts that are currently used to guide treatment decisions in predicting changes in important clinical outcomes of morbidity and mortality?
- What is the incidence and severity of any long-term adverse effects of protease inhibitors?
- How quickly and under what circumstances will protease inhibitor-resistant HIV strains develop?

? Defining the potential of protease inhibitors to reduce the spread of HIV

- Do protease inhibitors reduce sexual transmission rates of HIV between adults and, if so, by how much and under what circumstances?
- Do protease inhibitors reduce bloodborne (eg, needle-sharing and needlestick injury) transmission rates and, if so, by how much?
- Do protease inhibitors reduce mother-to-baby transmission rates of HIV and, if so, under what circumstances and by how much?

Answering these questions poses many challenges to those responsible for research design and data collection. But once the answers to these questions are known, it will be possible to determine the cost-effectiveness of protease inhibitors in different circumstances and their affordability in different countries. These judgements will be made according to the knowledge of the risks and benefits of treatments, the likely number of people who would benefit from treatment with protease inhibitors, and the cost per patient of treatment. Taken together, this information will allow the total population costs of protease inhibitors to be estimated. Assuming that protease inhibitors live up to their early promise, in judging cost-effectiveness and affordability it will be important to include

estimates of the value of healthcare savings (ie, the costs of caring for episodes of illness that are prevented by protease inhibitors) and broader societal savings (eg, the productive value of young adults working when otherwise they would be ill or dying) in these calculations.

Ability to pay

Inevitably, another important factor in determining the availability of particular forms of healthcare is society's ability and willingness to pay and governments' political determination to make the benefits of modern healthcare available to all.

Ability to pay will vary according to the wealth of countries. This raises two major public health issues. First, it is likely that there will be significant international variations in the availability and methods of use of protease inhibitors between and within countries. Indeed, there will probably be many parallels between HIV/AIDS and tuberculosis. For example, developing countries cannot afford effective antituberculous chemotherapy for the vast majority of those to whom it would be of benefit. And in many cases they also lack the healthcare infrastructure to ensure adequate professional supervision and follow-up. The consequences are inequity, maintenance of the global tuberculosis epidemic and the emergence of multidrug-resistant strains of tubercle.

While many in developed countries may not be concerned about the plight of those in developing countries, self-interest suggests they should be concerned at the way in which new drugs are used anywhere in the world, as the second major public health issue related to the ability to pay for adequate care is the risk that inadequate supervision and incomplete treatment will foster the emergence of protease inhibitor-resistant strains of HIV. The rise of multidrug strains of tuberculosis in the USA reminds us that this is an important public health issue for the developed world.

Affordability is unlikely to be an issue only for developing countries. The developed world is struggling to find the money to pay for healthcare. The arrival of effective, and often costly, new treatments for common serious conditions is forcing countries across the world to review the methods by which they identify and allocate healthcare resources. The politics of healthcare resource allocation, priority setting and rationing are rapidly becoming a visible and contentious public health issue in their own

right. There are no easy answers. The advent of protease inhibitors can only accelerate the debate and add to the difficulty of decision-making.

Conclusion

The use of combination therapies including protease inhibitors raises many public health issues. They offer the promise of an important advance in the global fight against HIV/AIDS. However, it is also important that they should be used in such a way that the potential benefits are not squandered by allowing resistance to develop prematurely and, as resources are scarce, that they are used in the most cost-efficient way possible.

However, it is clear from the information reviewed in this report, and from recently published guidelines from expert groups such as the British HIV Association¹ and from the International AIDS Society,² that there is inadequate information from randomised trials using morbidity and mortality as primary end-points to be certain how and in whom protease inhibitors should best be used. Where trial information is incomplete, information from other sources – for example, from short-term activity marker studies and mathematical modelling – must also be taken into account. When all the information is considered together by different groups of experts (eg, the British HIV Association and the International AIDS Society), similar conclusions have been reached about how to use drugs to maximise the benefit to individual patients and minimise the risk to the public from drug-resistant forms of HIV.

Important areas of consensus include agreement that:

- **The therapeutic aim of chemotherapy is to reduce viral load to below the detection level of a sensitive assay.**
- **Aggressive combination treatment should be started before a patient becomes substantially immunodeficient.**
- **Drug combinations should be selected so that patients are treated with drugs to which they have not been previously exposed.**
- **It is important that drugs are always used in optimum schedules and doses.**

Inevitably, this consensus reflects expert opinion and will need to be reviewed as new information becomes available. In the meantime, the challenge and responsibility for all those involved in prescribing for patients with HIV/AIDS is that drugs are used in such a way that relevant data can be collected to ensure that existing gaps in our knowledge are bridged as

quickly as possible. Only then will we be confident that the public is receiving the maximum benefit from important new advances such as the development of protease inhibitors. Even then, until HIV/AIDS is eradicated, the public health campaigns and familiar ‘safer sex’ messages will remain essential weapons in the war against AIDS.

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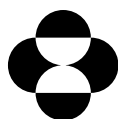
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