Chapter 1.7

NEW CONCEPTS IN ANTI-HIV THERAPIES

J. STEBBING[1], M. BOWER[1] and B. GAZZARD[1]
[1] *The Chelsea and Westminster Hospital, 369 Fulham Road, London, UK*

Abstract: Fewer than one million HIV infected individuals are currently receiving anti-retroviral therapy. The limitations of such treatment have underscored the need to develop more effective strategies to control the spread and pathogenesis of infection. In 1996, the era of highly active anti-retroviral therapy (HAART) commenced in established market economies, causing a dramatic reduction in morbidity and mortality in those infected individuals who received these medicines. These agents target aspects of the viral life cycle and there are now 20 approved therapeutic agents for licensed for treatment of infection with the human immunodeficiency virus (HIV), a pathogen that in the 1980s was uniformly fatal. These advances have been associated with significant toxicities and drug resistance. Antiviral potency and durability causing suppression of viremia has been the cornerstone of the initial success of HAART regimens. Following this, the restoration of immune function, the prevention of the emergence of resistance, and ultimately the prevention of disease progression has been the focus of treatment. Future progress will allow greater choices for physicians and patients.

1. INTRODUCTION

The treatment of HIV infection has been revolutionised in developed countries as a result of the introduction of highly active anti-retroviral therapy (HAART), which has reduced short-term mortality and markedly increased quality of life by preventing opportunistic diseases. A major challenge has been linking the potency of HAART with the other desirable

E. Bogner and A. Holzenburg (eds.), New Concepts of Antiviral Therapy, 189–212.

aspects of a therapeutic regimen: low pill burden, excellent tolerability, absence of major drug interactions, absence of long-term toxic effects, and absence of cross-resistance to other agents (Hammer, 2002).

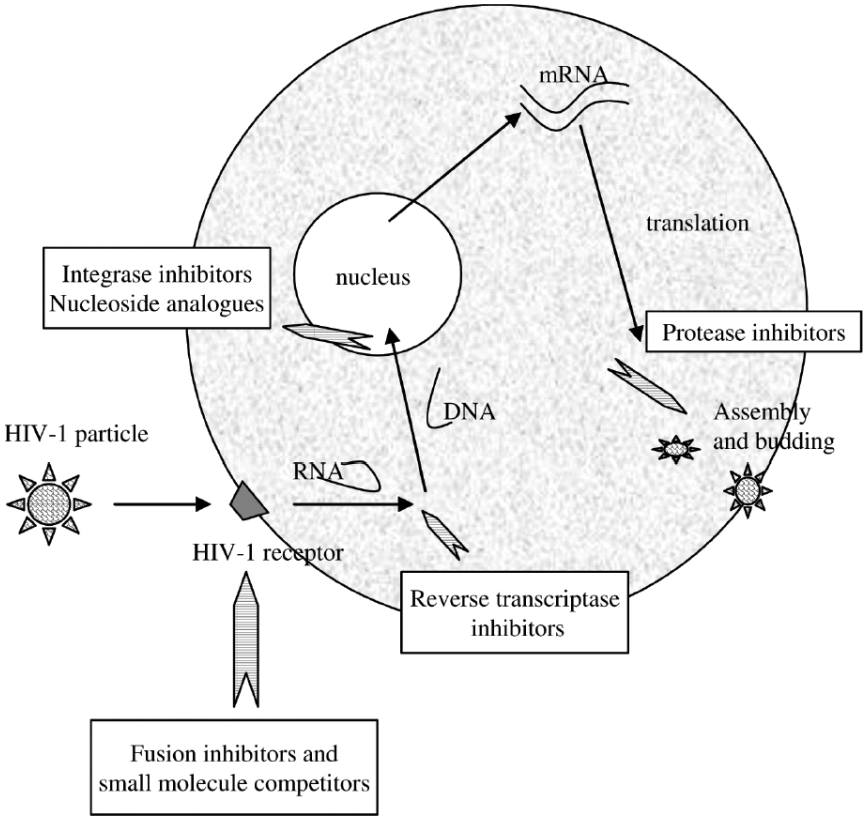

Figure 1. The HIV life cycle and drug targets.

While previous agents target the reverse transcriptase and viral protease, newer agents attack different stages of the HIV life cycle (figure 1).

2. NUCLEOSIDE ANALOGUES

The first drugs to be used clinically were the nucleoside analogues which act as chain terminators of HIV viral reverse transcriptase and require tri-phosphorylation within cells to become active. For most drugs the rate-limiting step involves the initial phosphorylation of Zidovudine (ZDV) during the conversion of ZDV monophosphate to diphosphate by thymidine kinase.

Zidovudine was the first drug to be used clinically. In short term studies there was a dramatic improvement in mortality and reduction in AIDS defining events in patients with symptomatic HIV disease (Fischl *et al.*, 1989; Fischl *et al.,* 1990a; Fischl *et al*., 1990b). Subsequently studies indicated that using ZDV as monotherapy in asymptomatic individuals offered no advantage over treating symptomatic disease only (Concorde, 1994). Subsequently two large randomised controlled trials with clinical end points demonstrated that using two nucleoside analogues together (Zidovudine and Didanosine or Zidovudine and Zalcitabine) produced a 33% survival advantage compared with use of ZDV monotherapy (Fischl *et al.*, 1995; Collier *et al.*, 1993). Subsequently a dual nucleoside analogue backbone has been the commonest component of the highly effective antiretroviral therapy regimes (HAART) currently used to treat HIV infection.

The drugs include

Zidovudine This drug produces a viral load drop of between 0.4 and 0.7 of a Log in HIV-1 RNA. Its major side effect is anaemia although a myopathy has also rarely been described. In the initial phases of therapy nausea, headache and sometimes diarrhoea occur. Initial studies used 1.2 g of Zidovudine spaced throughout the day but more recently, 250 mg and 300 mg of the drug twice a day are exclusively used following clinical studies suggesting that this dose was as effective as the larger dose but had fewer side effects.

Didanosine Monotherapy with this adenine nucleoside analogue used in the ACTG 175 trial was shown to be as effective as dual nucleoside combinations (Ragni *et al.*, 1995). The viral load drop produced in monotherapy studies is similar or greater than that seen with ZDV. A major side effect of this drug is pancreatitis which may be fatal and the drug is contra- indicated in those with pre-existing pancreatic damage. Peripheral neuropathy also probably occurs with didanosine, particularly in those who

are pre-disposed although some large trials have failed to show an increased incidence of this complication which is sometimes a direct effect of HIV infection (De la Monte *et al.,* 1988). The dose normally prescribed is 400 mg per day as one dose taken on an empty stomach. There is evidence that higher doses are associated with increased toxicity including hepatic damage.

Stavudine Like ZDV this is a thymidine analogue. *In vitro* studies indicate that stavudine may antagonize the effects of ZDV as it competes with the phosphorylation pathway mentioned above (Hoggard *et al.*, 1997; Fischl *et al.*, 1993a). This was confirmed in early clinical studies which showed a fall in CD4 count when AZT and stavudine were used together. A major side effect of stavudine is a peripheral neuropathy which may be irreversible as it produces axonal degeneration. The dose normally prescribed is 40 mg twice a day although an unlicensed extended release preparation was shown to have a similar effect on viral load given once a day. This preparation is likely to be licensed soon and there is a possibility that this may have fewer side effects as the peak level of drug in the plasma is lower.

Zalcitabine This drug is rarely used now because one unpublished study showed it to be less effective than ZDV as monotherapy and peripheral neuropathy is a major side effect (Fischl *et al.*, 1993b). It is given three times a day which can be inconvenient for patients.

Abacavir This guanidine analogue was introduced more recently than the other compounds and in monotherapy studies was shown to have a greater effect on plasma HIV viral load than some other nucleosides in short term studies with a viral load drop of more than 1.2 logs. A major side effect of this drug is an idiosyncratic hypersensitivity reaction which may be fatal if the patient is re-challenged following cessation of therapy. The hypersensitivity reaction is easy to recognize with prominent respiratory and gastrointestinal symptoms, a fever and usually a rash. Discontinuation of therapy results in rapid improvement in symptomatology but rechallenge is strongly contra-indicated. The CPK is often greatly raised during an attack. A widespread physician and patient educational programme has ensured that this condition is recognized. The hypersensitivity reaction is very strongly associated with the ancestral haplotype B5701 (Hetherington *et al.,* 2002). Whether this should be used as a screening test prior to introduction of therapy is unclear and the association is not sufficiently strong to use this as a test to diagnose a hypersensitivity reaction. This drug is prescribed twice a day but intracellular pharmacokinetics indicate that the triphosphate levels of the drug are maintained throughout a 24 hour period and as studies

comparing twice a day with once a day regimens indicated a similar drop in plasma HIV viral load, it may be licensed for once a day use in the future.

Lamivudine (an analogue of cytosine) This drug was almost not developed because although significant plasma viral load drops were seen in patients treated in monotherapy studies, these were evanescent. However, sustained viral load drops were subsequently shown when Lamivudine was combined with other nucleoside analogues, particularly ZDV (Randomised trial, 1997). It is relatively free of side effects. Although the licensed dose is 150 mg twice a day, the long intracellular half-life of the triphosphate component indicates it can probably be used once a day. Again studies indicate that once a day regimes produced similar viral load drops to those when the drug is given twice a day and it is likely to be licensed for this indication shortly.

There are a number of new nucleoside analogues in development to treat HIV infection. These are summarized in Table 1. A number of nucleoside analogues which have been in development over the last two or three years have fallen by the wayside because of toxicities or unexpected pharmacokinetic difficulties. DAPG is continuing its Phase 3 development programme. Like Tenofovir DAPG is also active against Hepatitis B.

As the mechanisms for resistance to nucleoside analogues becomes clarified, it is likely that medicinal chemistry will start to develop drugs which can either overcome the reduced sensitivity of the virus or avoid it. Two mechanisms of resistance development are now clearly understood. With some drugs like 3TC the development of resistance by the virus involves mutations which increase the affinities to the natural nucleoside substrates at the expense of the drug. For other drugs resistance involves conformational changes which encourage the removal of the chain terminating nucleoside analogue once it is attached. The process of reverse transcriptation and elongation of the DNA chain is a reversible process. The nucleoside is substituted for by a phosphorus molecule either donated from pyrophosphate (pyrophosphorylisis) or from ATP. This process of reversal of chain termination is exaggerated in resistant mutant viruses. Tenofovir still acts as a chain terminator with some AZT resistant viruses because this reversal process is inefficient, presumably because of the particular structure of tenofovir.

Table 1. New nucleoside analogs for HIV

Drug	Stage of development	Comment
Emtricitabine [(-)-FTC]	Approved in July 2003	Similar in many ways to lamivudine (cross resistant to M184V) with once daily dosing
Alovudine (MIV-310, FLT)	Phase II	*In vitro*, it has potent activity against NRTI-resistant viral strains of HIV-1, including zidovudine-resistant viruses
Amdoxovir (DAPD)	Phase II	A guanosine analogue NRTI that is active *in vitro* against both HIV-1 and HBV
Racivir [(±)-FTC]	Phase II	See below
Reverset (D-d4FC, DPC-817)	Phase II	A cytidine nucleoside analog with potent activity against both wild-type and NRTI-resistant HIV-1, including lamivudine- and zidovudine-associated mutants
SPD 754 (dOTC)	Phase II	An investigational cytosine analogue NRTI
Elvucitabine (L-d4FC	Phase Ia/IIb	A L-cytidine analog with activity against HIV resistant to several other nucleoside analogs, including zidovudine and lamivudine

3. PROTEASE INHIBITORS (PIS)

The development of the protease inhibitors was a major advance in the treatment of HIV infection. Following the formation of HIV DNA as a result of reverse transcription, this is incorporated into the host genome.

Subsequent host cell activation is associated with transcription of this HIV DNA and a polyprotein is produced which is cleaved into its active constituents by a virally encoded protease. As this is an aspartate protease, it is dissimilar to mammalian proteases and was an obvious drug target (Andreeva *et al.*, 1995). Clinical utility was rapidly confirmed by three clinical end point studies. One showed an improved outcome in late disease when ritonavir was added to otherwise failing therapy. A second showed a reduced frequency in clinical end points when a regimen of indinavir and two nucleoside analogues was compared with using the nucleoside analogues alone (Hammer *et al.,* 1997). Although protease inhibitors are potent drugs, they have a number of potential disadvantages. Most have short half-lives and have to be taken several times during the day. Absorption through the gut mucosa is often variable producing wide intra-patient and inter-patient variability in plasma levels. Most are metabolized by the microsomal enzyme system and some induce and others inhibit their own metabolism via cytochrome P450 which produces a wide variety of drug interactions.

For many protease inhibitors plasma levels can be enhanced by blockade of the cytochrome P450 system. This improves absorption, which is reduced in the gut as a result of the presence of cytochrome P450 and inhibits metabolism of these drugs. The most commonly used inhibitor of liver cytochrome P450 is ritonavir which, because of its side effect profile and its potent effects on cytochrome P450, is used in small doses which do not have an anti HIV effect per se. Few randomised trials are available to assess the effectiveness of boosted PIs although one study has demonstrated that lopinavir boosted by ritonavir produces superior surrogate marker results at 60 weeks when compared with nelfinavir therapy (Ruane *et al.*, 2001). Most guidelines now recommend the use of boosted PI regimens because of convenience of administration and high plasma levels. A number of different PIs are now licensed.

Saquinavir This was the first PI to be licensed and was in the form of a hard capsule where absorption was sub-optimal although this is significantly enhanced by Ritonavir. Although the soft-gel formulation of saquinavir has better absorption characteristics, it is mainly used clinically in conjunction with ritonavir in twice daily regimens.

Ritonavir This produces major gastrointestinal side effects when it is used as an anti HIV agent and so is little used other than as a pharmacokinetic (PK) booster.

Nelfinavir This is the only protease inhibitor which remains widely used without a PK enhancer. The drug can be administered twice a day, diarrhoea being the major side effect. Nelfinavir itself is an inhibitor if cytochrome P450 and can be used to boost the levels of saquinavir (Moyle *et al.*, 2000). This combination is rarely used in clinical practice. To maximise absorption nelfinavir is taken with a fatty meal. Nelfinavir has been shown to improve surrogate marker outcome at 48 weeks when compared with the use of dual nucleoside analogues alone (PENTA 5 trial, 2002) but to be inferior to lopinavir boosted with ritonavir over a similar period.

Indinavir As a single PI is taken three times a day on an empty stomach. The regime is inconvenient and is now little used to initiate therapy. Indinavir's major side effect is the development of renal damage, mainly because of the formation of Indinavir calculi in the collecting system. This side effect occurs in 10% to 15% of individuals and there have been reports of progressive renal damage. Indinavir's pharmacokinetics are improved by administration with ritonavir although in the doses first used, (100 mg Ritonavir and 800 mg of Indinavir twice a day) the instance of renal complications was unacceptably high at 20% at 24 weeks (Gatell *et al.*, 2000). Other unlicensed dosage regimes such as 400 mg twice a day + 100 mg of Ritonavir twice a day may be an effective anti HIV regimen and have fewer side effects.

Amprenavir This drug induces its own metabolism and thus if drug regimes are started with a standard dose, many patients suffer from gastrointestinal side effects during the initiation of therapy. Thus relatively few patients initiate treatment with amprenavir. Amprenavir boosted by ritonavir may have a role in treating patients who have failed previous protease inhibitor therapy.

Lopinavir Lopinavir is a potent drug *in vitro*. When used alone, because it is rapidly metabolised, plasma levels fall quickly. However, when boosted with ritonavir, high plasma levels can be maintained with twice daily treatment. For this reason many viruses with reduced sensitivity to other protease inhibitors remain susceptible to this drug combination. This was confirmed clinically in cohort studies of patients taking lopinavir and non nucleoside reverse transcriptase inhibitors (see below), although the relative importance of these two drugs in the favourable outcome is unclear. Recent data have supported the efficacy of the lopinavir-ritonavir combination (Walmsley *et al.*, 2002).

Atazanavir is an azapeptide which has potent inhibitory effects on HIV *in vitro* and because of its long plasma half life, can be given once daily. Phase

2 dose ranging studies in antiretroviral naïve patients indicates that at 48 weeks this agent is at least as potent as Nelfinavir (Cahn *et al.,* 2001). In individuals failing protease inhibitor containing regimes, using atazanavir is as effective in subsequent therapy as ritonavir/saquinavir combinations when combined with a new, nucleoside analogue regime (Haas *et al.*, 2001). Unfortunately this latter data set is relatively difficult to interpret as the majority of people failing the initial PI did not have resistant mutations to this class of drugs but presumably were failing because of poor adherence. Nevertheless atazanavir represents a potentially important new drug as 48 week studies have shown very little effect on triglyceride or cholesterol blood levels in treated individuals when compared with those treated with other PI containing regimens.

It may be that some individuals experiencing failure of protease inhibitor containing regimens who do have resistant mutations will remain sensitive to atazanavir particularly when plasma levels of this drug are boosted by additional ritonavir; doing this, however, is likely to reduce one of the major advantages of atazanavir which is its freedom from lipid abnormalities. This drug does now have a license for naïve patients in the US though it is used in conjunction with ritonavir boosting strategies in Europe.

TMC126 This drug which is in early development with Tibotec/Virco (as is TMC125) is active *in vitro* against a wide variety of viruses with reduced sensitivity to virtually all known PIs. Encouraging Phase 2 studies indicated a favourable pharmacokinetic profile when this drug is used with a small boosting dose of ritonavir (Erickson *et al.*, 2001).

Tipranavir Tipranavir is now widely available on compassionate release and has been developed as *in vitro*. This drug continues to be active against viruses with widespread mutations to the PIs. Recent studies have confirmed this *in vivo* although Fuzeon, the effects of Tipranavir are evanescent in that other drugs which are also active can be combined in the regime. Tipranavir is dosed twice a day with 200 mg of Ritonavir on each occasion because of its otherwise unfavourable pharmacokinetics.

TMC114 This drug is in phase 3 development. It has been developed again because of its ability *in vitro* to inhibit viruses which contain mutations to the presently available PIs. It is also dosed with ritonavir either once or twice a day and should be licensed in 2006 if all goes well.

Other new protease inhibitors for HIV include R944 (in phase 1; Roche) and TMC-114 (in phase 2, Johnson and Johnson).

4. NON NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIS)

The clinical utility of this class of compounds has been assessed by surrogate marker trials. Like Lamivudine their early development was hampered by the rapid development of resistance and the prototype compound, TIBO, only produced transient rises in CD4 count because of the rapid selection of resistant mutations (Larder *et al.,* 1993). The first important positive controlled trial of non nucleoside reverse transcriptase inhibitors was with nevirapine which demonstrated that in a regimen also containing zidovudine and didanosine, there was a superior surrogate marker outcome compared to the use of the two nucleosides alone. This study was followed by a comparison of zidovudine and lamivudine with efavirenz and indinavir with the same nucleoside analogues which showed an equivalent or superior surrogate marker response at 48 weeks for the NNRTI containing regimen (Staszewski *et al.*, 1999). Nevertheless both efavirenz and nevirapine have established an important role in the initial treatment of HIV infection because of their freedom from irritating toxicities associated with drug administration and their relatively long half life (efavirenz is taken once a day and nevirapine which is licensed for twice a day is often used once a day). This long plasma half-life also gives considerable latitude around the time of dosing to maintain an antiviral effect. Two drugs in this class are currently licensed in Europe and three in the United States.

Nevirapine This drug is administered twice a day in the dose of 200 mg although pharmacokinetic data confirms that it can be given in a single 400 mg dose and this is widely used. As the drug induces its own metabolism, the initial dose is 200 mg a day for two weeks followed by the full dose which is said to minimise toxicity. Rash affects 20% to 30% of individuals taking it and is occasionally serious with a Stevens-Johnson reaction (also known as erythema multiforme major). Another serious side effect is hepatotoxicity. Fulminant hepatic failure requiring liver transplantation has occurred in HIV negative individuals given this drug in an unlicensed indication as post exposure prophylaxis (Sha *et al.*, 2000). This effect appears to be much less common in HIV seropositive patients and the frequency appears to be inversely related to the CD4 count. Hepatotoxicity is commoner in those with pre-existing abnormal liver function tests, those with other forms of liver disease, particularly Hepatitis C and B, and in older patients. Fulminant hepatic failure may not be possible to predict even when liver function tests are frequently monitored.

Efavirenz This drug is administered once a day in a dose of 600 mg. Drug absorption is enhanced by food although it is usually taken on an empty stomach last thing at night which is thought to minimise the vivid dreams which are an early side effect of this drug. It is also associated with skin rash although this is less likely to be severe than that seen with Nevirapine and continuing treatment is usually associated with resolution of the rash. A major side effect of Efavirenz is the central nervous system disturbance which usually wanes with continuing use although it is sometime persistent. Discontinuation because of this side effect is rare. Efavirenz acts both as an inducer and inhibitor of the cytochrome P450 complex and has the potential to cause a number of drug-drug interactions.

Delavirdine This is the only NNRTI which acts as a pure inhibitor of cytochrome P450 and allows dose reduction of protease inhibitors when used in combination. Rash which is common shortly after administration of this drug, is very rarely serious and most patients continue therapy. Hepatotoxicity is unusual. The drug has to be taken three times a day. The few surrogate marker trials performed with Delavirdine have been relatively more difficult to interpret than studies with other NNRTIs which is why it was not licensed in Europe.

5. SURROGATE MARKERS

The era of comparative studies with clinical end points as the major outcome came to an end with the initial studies on protease inhibitors. Clinicians and patient groups felt that treatment had improved so much that further studies using death or major deterioration as an end point were unethical (ACTG 320, 1997).

Both the fall in plasma viral load and rise in CD4 count following the introduction of antiretroviral therapy fulfil many of the criteria of clinical outcome (Lagakos, 1993). Thus both the levels of HIV, RNA and CD4 count prior to treatment predict outcome. Changes in both of these markers have a biological plausibility that they would affect outcome and changes in these markers can explain most but not all of the treatment effects (Carosi *et al.*, 2001). All recent studies of antiretroviral therapy have used these surrogate markers to assess likely clinical effectiveness. Preventing HIV viral replication as completely as possible has always been regarded as important and, therefore, particular attention has been paid to the ability of drugs in combinations to reduce plasma levels of HIV below detectable limits of sensitive assays, (currently less than 50 copies per ml). Many clinicians thus

believe that the most important outcome of a clinical trial is the proportion of individuals who have a below 50 copy HIV-1 RNA assay using an intent to treat analysis at 48 weeks. This does not assess the durability of treatment and, therefore, time to treatment of virological failure is becoming an important yardstick for successful combinations. Monoclonal antibodies can be categorised according to type.

6. WHAT TREATMENT TO START WITH?

There have been no definitive controlled trials to demonstrate the clinical superiority of any one HAART regimen containing three active drugs used as initial therapy i.e. protease inhibitor first, NNRTI first or three nucleoside reverse transcriptase inhibitors first. For patients with very high viral loads there is some suggestion that more than three active drugs may result in a more rapid decline in viral load (Hoetelmans *et al.*, 1998). Studies are in progress to determine whether this will lead to better long term outcomes compared with standard, three drug HAART.

With currently available antiretroviral agents, eradication of HIV infection is not likely to be possible (Chun *et al.*, 1997). The aim of treatment is thus to prolong life and improve quality of life by maintaining suppression of virus replication for as long as possible.

The three groups of treatment naïve patients for whom treatment guidelines are required are: patients with primary HIV infection, patients with asymptomatic HIV infection and patients with symptomatic HIV disease or AIDS.

6.1 Primary HIV infection

There is one placebo-controlled study of zidovudine (ZDV) monotherapy in primary HIV infection (PHI) (Kinloch-de Loes *et al.*, 1995) and it showed short-term benefit only. As yet there is no evidence of long-term clinical benefit from any study of treatment of PHI compared with deferring treatment until later, however. If it is recognized clinically, the diagnosis of PHI may represent a unique opportunity for therapeutic intervention. It is likely that, at the time of PHI: (1) there is a narrowing of the genetic diversity of the infecting virus compared with the virus in the index case

(Zhang *et al.*, 1999); (2) viral ability to infect different cell types may be limited; and (3) the capacity to mount an immune response is usually greater than it is later on. Therefore, the treatment of PHI may preserve HIV specific immune responses.

6.2 Symptomatic HIV infection

All patients with late disease and/or symptomatic HIV infection with a CD4 lymphocyte count consistently <200 cells/mm^3, or who have been diagnosed with AIDS or severe/recurrent HIV related illnesses or tumour at any CD4 count, should start therapy. This is because of the high risk of further opportunistic infections which, although treatable, may cause irreversible damage or be life threatening.

6.3 Asymptomatic HIV infection

There are no ongoing or planned controlled studies that sufficiently address the optimum time to start therapy. Current guidelines are therefore based upon previous studies of monotherapy and data from large clinical cohorts. Since the quality of evidence is relatively poor, opinion is divided on this question. In the UK, patients are diagnosed with HIV infection at a late stage. Over 30% present with a CD4 count of <200 cells/mm^3 (Gupta *et al.*, 2000) and, consequently, the early vs. late debate is irrelevant to many.

The decision on when to start treatment will be influenced principally by two considerations: the short term risk of developing AIDS prior to treatment and the potential efficacy of starting treatment at various CD4 counts. Data from several cohort studies with short term follow-up have suggested that patients who initiate therapy when the CD4 count is <200 cells/mm^3 have an increased mortality (Hogg and Wood, 2001; Sterling *et al.*, 2001; Kaplan and Karon, 2001) compared with those above this level, but were unable to show any difference in those starting at any CD4 level >200 cells/mm^3. However, data from other cohort studies (Phillips *et al.*, 2000) suggest that patients who delay therapy until the CD4 lymphocyte count is <200 cells/mm^3 may have a similar virological and immunological response to those starting earlier. This is in contrast to data from prospective

clinical studies (Wood and Team, 2000; Opravil *et al.*, 2001), although the effect of baseline CD4 response on therapy may not be the same for all drugs (Nelson *et al.*, 2001). One study (Nelson *et al.*, 2001) has suggested that patients who commenced therapy with a CD4 count >350 cells/mm^3 were less likely than those who commenced later to experience disease progression or death.

These data suggest that, ideally, patients should start therapy earlier, before the CD4 count has fallen to <200 cells/mm^3. A number of factors need to be considered when making decisions with each individual patient. Patients with a rapidly falling CD4 count (e.g. falling >80 cells/mm^3 per year on repeated testing) have an increased risk of CD4 cell count decline to <200 cells/mm^3 in the next 6 months. This group many thus be considered for initiation of therapy relatively earlier within the CD4 count range 200-350 cells/mm^3. Previous guidelines have suggested starting therapy relatively early in patients with a high plasma viral load (Carpenter *et al.*, 2000). There are three reasons why viral load measurement should help guide decisions about when to start antiretroviral therapy. First, a viral load >55000 copies/ml (Mellors *et al.* (2000) predicts a faster rate of decline in CD4 cells. Second, this level of viral load is an independent risk factor for subsequent disease progression and death. However, these data are from an era before the introduction of highly active antiretroviral therapy (HAART), and may not be relevant. Furthermore, recent cohort studies (Sterling *et al.*, 2001; Kaplan *et al.*, 2001) have suggested that baseline viral load does not predict subsequent mortality independently of the baseline CD4 count after starting therapy. Third, some data have suggested that the baseline viral load adversely affects the virological response to treatment in some prospective studies (Staszewski *et al.*, 1999; Moyle and Opravil, 2000).

In asymptomatic patients with established chronic HIV infection and CD4 cell counts consistently above 350 cells/mm^3, few data support starting therapy.

6.4 Management of treatment failure

The possibility of using cyclical treatment using drugs before they become resistant to limit toxicity is an important concept and there have been recent successes with use of trizivir and tenofovir in this setting. Only a limited amount of clinical controlled trial data helps the clinician to decide what therapy to switch to following initial treatment. Many of the controlled

trials which do exist are relatively unhelpful because they have studied patients who received sub-optimal initial therapy. Nevertheless a number of important general points can be made (for more detail refer chapter 1.9).

Resistance to the NNRTI class of drugs is caused by mutations in a pocket of the reverse transcriptase enzyme adjacent to the catalytic site. Resistance to one of the NNRTIs produces cross resistance to other members of this class and so the currently available drugs are not used in sequence. Promising data with TMC-125, a diarylpyrimidine derivative, suggests that this NNRTI is able to overcome resistance to other NNRTIs.

It was initially thought that nucleoside analogues induced distinct mutational patterns in the viral reverse transcriptase associated with reduced sensitivity and that substitution of one nucleoside analogue for another would be successful. While this remains broadly true it is now appreciated that mutations reducing sensitivity to one nucleoside analogue also reduce the sensitivity to other members of this class. This is particularly true of the thymidine analogue mutations producing reduced sensitivity to zidovudine and also display reduced sensitivity to stavudine. Tenofovir is a nucleotide analogue closely related to the nucleosides with a similar mode of action. Most viruses with reduced sensitivity to the other nucleoside analogues remain sensitive to tenfovir *in vitro* and viral load drops in individuals who harbour such viruses have been demonstrated *in vivo*.

Proteinase Inhibitors Virological failure of initial therapies containing protease inhibitors is often associated with only a few mutations in the protease gene. With some mutations such as at codon 30 for nelfinavir, a good response to a subsequent proteinase inhibitor can be expected.

7. USE OF RESISTANCE TESTING

Development of rapid sequencing techniques which allow the demonstration of changes in the viral genome associated with reduced sensitivity to drugs has had major importance in our understanding of the way in which such drugs work and the causes of drug failure. However, resistance testing demonstrates which drugs are unlikely to be effective rather than those that will. When patients fail an initial regime, most clinicians would wish to change all components of that regime even if resistance testing indicated continuing sensitivity to some of them. The primary value of resistance testing at this stage is to ensure that all the

switches have a reasonable chance of working and, at this stage, may prove of value when trying to construct successful 3rd and 4th line regimens.

A failing NNRTI regime Trials to test optimum policies in this situation are difficult to undertake because failure of such regimes is normally associated with poor adherence rather than virological failure despite continued drug use. Nevertheless as NNRTI resistant mutations are likely to remain protease inhibitor sensitive, most clinicians would switch to two different nucleoside analogues and a boosted PI containing regimen. Clinical experience indicates that this is usually successful in completely suppressing plasma viral load.

A Failing PI containing regime The obvious drug class to use in this situation is an NNRTI. This will only be successful providing the total regimen is capable of stopping viral replication completely. Otherwise resistance to the NNRTI will develop rapidly. It is for this reason that most clinicians prescribe nucleosides and an NNRTI and add an alternative PI. This has been shown to be the most successful policy in individuals failing two nucleoside analogues (Deeks *et al.*, 2000). The second PI to be added will depend partly upon the resistance test and also on which PI has been used first. Probably the most successful PI to use in this situation is Lopinavir boosted with Ritonavir (Ruane *et al.*, 2001).

Subsequent therapies There is a growing number of patients who have become resistant to all the present medication. Even in these patients the death rate is low providing the CD4 count is maintained above 50 cells/mm^3. It is clear that continuing therapy is beneficial compared with discontinuing, presumably because viral mutations which are less sensitive to drugs are also less virulent and therefore have less effect on reducing the CD4 count. Thus in these individuals, there is a paradigm switch of treatment from trying to make the viral load undetectable (which is not possible) to one in which the CD4 count is kept as high as possible for as long as possible. In this situation some clinicians believe that the minimum number of drugs to continue to give those viruses which are resistant already in the circulation a continuing survival advantage, whereas others believe that large numbers of drugs, even though they may have little effect individually are beneficial overall. The disadvantage of this latter mega HAART approach is increased toxicity, a large pill burden and unexpected pharmacokinetic interactions. It is likely that this is the stage at which T20 would be prescribed but it only has an evanescent effect if it is the only active drug in the regime. Thus it is probably better to use T20 in the last regime at which undetectability is likely to be achieved. Alternatively T20 can be used so that the patient can be treated with new drugs as they come on stream.

8. NEW DRUGS

New drugs in development are of two sorts. There are a number of drugs which are developments of currently available classes which are developed because of improved pharmacokinetics, a reduced toxicity profile or are active against viruses which have resistance mutations to presently available drugs.

New drug classes acting against different parts of the life cycle of HIV are under development as well.

Attachment Inhibitors The viral attachment process has been very thoroughly elucidated and involves initially loose binding between the CD4 receptor of T cells and the B3 loop of the GP120 of the viral coat. Interestingly during this process constant regions of GP120 are exposed and although the exposure of these constant regions of GP120 are extremely evanescent the neutralising antibodies to this region might have a beneficial effect either as a vaccine or in HIV infected individuals. Bristol Myers Squibb have a drug in the early stages of development which inhibits this interaction although there is considerable intrinsic variability in the sensitivity of viruses to this class of compound. As they are active in molecule concentrations, this natural variability may not prevent further development.

The second part of the attachment process is tighter binding of the virus envelope to the cell surface by means of interaction with a chemokine receptor (see chapter 1.8). The commonest chemokine receptor utilised is CCR5 and a number of compounds capable of inhibiting this interaction are now in various stages of development, the most advanced of which is now in phase 3 study. Obviously only individuals who harbour viruses which is CCR5 trophic are likely to respond to this drug and the long term side effects of inhibiting one of the body's receptors is unknown although a large deletion within this receptor which renders it inactive is a common balanced polymorphism in European communities without major untoward effects. The virus also is capable of utilising the CXCR4 receptor present particularly on CD4 cells and such viruses are associated with a more rapid progression to AIDS. Although there have been worries that the use of CCR5 inhibitors may encourage the virus to mutate to become CXCR4 trophic, there is limited evidence in vivo as yet that this is the case. CXCR4 inhibitors are also being developed but these are at an earlier stage of evolution.

Table 2. New attachment inhibitors to treat HIV

Phase I	Phase I/II	Phase II
AMD-070 (CXCR4)	BMS-9043 (Anti-gp120)	Pro-542 (attachment inhibitor)
AMD-887 (CCR5)	SCH D (CCR5)	SP-01A
GSK-873140 (CCR5)	TNX335 (Anti-CD4)	UK-427/857 (CCR5)
CCR5mAb004 (CCR5)		

Fusion inhibitors represent an excellent example of where detailed knowledge of the processes involved in HIV replication have led to specific drug design. T20 represents the first of a new series of fusion inhibitors. This peptide was specifically designed to interact with helical portions of GP41 which contract during the process of fusion to draw the surface of GP120 into close proximity with the host cell, allowing interaction with the T cell receptor and the chemokine receptors. T20 is administered subcutaneously twice a day and is effective in salvage therapy. It was used as additional therapy to standard care in patients who failed all three classes of drugs where marked viral load drops (1 log) which persisted for up to 48 weeks were seen. Virological failure in patients taking T20 is associated with mutations in the relevants portions of GP41. A new form of this drug which can be administered once a day is also being developed. As often happens during drug development the optimum role for this drug which is likely to be licensed soon remains unclear. Most clinicians would like to combine T20 with other drugs which are also likely to be effective to reduce viral replication to undetectable levels eg tenofovir and lopinavir boosted with ritonavir in individuals following initial PI failure.

A variety of small molecules which inhibit various phases in the fusion process are also under development. Thus the interaction between the V3 loop of GP120 and the CCR5 receptor can be inhibited by a series of products made by Schering Plough. Product C which is in the most advanced stage of development was shown recently to produce viral load drops of nearly 1 log in short term human studies. Interestingly this occurred after a one to two day lag period following administration. As a result of experiments *in vitro*, worries have been expressed that the inhibition of the

interaction between the virus and CCR5 would encourage mutations to a more virulent form capable of interacting with the alternative chemokine receptor, CXCR4. More recent *in vitro* studies and limited human experiments have not indicated that this is likely to happen. Unfortunately the main drug which is being developed to inhibit the interaction between HIV and CXCR4, AMD310, which has to be administered intravenously, showed very little effect in Phase 1 human studies (Dameta *et al.*, 1996). Its future development must be in doubt.

As well as chemokine V3 loop interactions, fusion is brought about as a result of interactions with the TCR. During the process of fusion a normally hidden area of envelope is exposed by confirmational change which interacts with the TCR. This highly conserved area is an obvious target for the development of neutralising antibodies although it is only evanescently exposed to the environment. A number of drug molecules are being developed (Bristol Myers Squibb) which are capable of inhibiting this interaction and some quasi species of HIV are sensitive to these molecules while others are not. As these compounds are extremely potent, the relative insensitivity of some HIV variants may be dealt with by increasing the dose of such drugs.

New drugs in the NNRTI class are likely to be developed either to improve upon the pharmacokinetics of the present drugs (which would be difficult) or to reduce toxicity. Other important reasons for developing new NNRTIs would be that they would be active against HIV viruses with mutations rendering them insensitive to present members of the class.

BMS083 This drug was in development by duPont Pharma and its future progress will now be decided by Bristol Myers Squibb. Initial studies suggest that 083 is equally potent as Efavirenz when used in antiretroviral naïve patients with a relatively similar toxicity profile (Jeffrey *et al.*, 2000). Results in individuals who are resistant to efavirenz and then treated with 083 remain difficult to interpret and further studies in these patients will make it easier to define whether this drug has a future.

TMC120 This drug was specifically designed by Tibotec/Virco to have activity against viruses which contain mutations rendering them insensitive to the present NNRTIs. Eight day Phase 1 studies performed in Russia indicated that this drug was highly active *in vitro* (De Bethune *et al.*, 2001). A Proof of concept of Phase 1 study has also looked at viral activity in a group of individuals failing efavirenz and nevirapine containing regimens and has shown a viral load drop over 8 days of nearly 1 log in such individuals who all had very high levels of phenotypic and genotypic

resistance to both drugs. At present large numbers of pills must be given three times a day to produce these effects but the company is working to reduce the pill burden to an acceptable level.

Capavirene This drug is being developed for similar reasons to TMC120 (Hernandez *et al.*, 2000). It has activity against viruses with reduced sensitivity to the presently available NNRTI. It is likely to be given three times a day and will require ritonavir boosting to produce acceptable drug levels. Drug development was suspended until recently because of a vasculitis noticed at high dosages in dogs. However, in lower dosages comparable to those given to patients, no vasculitis was seen and so development has now been allowed to continue. The role of this drug which requires remains unclear but one obvious use would be in individuals failing initial NNRTIs in whom standard therapy at the moment would be a ritonavir boosted PI, and adding capavirene to this regime might increase potency.

Our understanding of the biochemical processes which take place in the cell during virus replication are increasing rapidly. Of particular importance is the role of many of the regulatory proteins produced by the virus which should, in the relatively near future, provide new targets to inhibit viral replication. Particularly important are the understandings of the role of Rev S and the clarification of the biochemical mechanism involved in the ability of tat to enable sufficient RNA transcriptation following activation of the LTR.

It is also likely that as the chemical process involved in viral assembly can more clearly understand a variety of inhibitors might be developed. However, in the short-term future, it is likely that two new targets to prevent HIV replication will receive most attention.

Two companies are developing Di Keto compounds which inhibit HIV replication *in vitro*. It is now clear that these compounds act as integrase inhibitors as viruses with reduced sensitivity to them have mutations in the integrase gene. Initial Phase 1 studies indicate that they have a favourable pharmacokinetic profile and Phase II dose ranging studies in HIV seropositive individuals are planned for the near future.

9. CONCLUSIONS

In recent years, the demand for new antiviral strategies has increased markedly. There are many contributing factors to this increased demand,

including the ever-increasing prevalence of chronic viral infections such as HIV and hepatitis B as well as the emergence of new viruses such as the SARS coronavirus. The weaknesses of current drugs in the treatment of HIV are being tackled with new targeted therapies. Because of their early stage of development, the question of improved tolerance remains largely unanswered for most of these compounds and many such drugs will undoubtedly fall by the wayside, however some, will become new and valuable treatments.

REFERENCES

Andreeva N.S., Bochkarev A., and Pechik I., 1995, A new way of looking at aspartic proteinase structures: a comparison of pepsin structure to other aspartic proteinases in the near active site region. *Advances in Experimental Medicine & Biology* **362**:19-3

ACTG 320: last of the body count trials? PI Perspect. 1997:7

Cahn P., Percival L., and Phanuphak P., 2001, Phase II 24-week data from study AI 424-008: comparative results of BMS 232-632, stavudine, lamivudine as HAART for treatment naïve HIV infected patients. Abstract 5. Program and abstracts of The 1st IAS Conference on HIV Pathogenesis and Treatment. Buenos Aires, Argentina

Carosi G., Castelli F., and Suter F., 2001, Antiviral potency of HAART regimens and clinical success are not strictly coupled in real life conditions: evidence from the MASTER-1 study. *HIV Clin Trials* **2**:399-407

Carpenter C., Cooper D., and Fischl M., 2000, Antiretroviral therapy in adults. Updated recommendations of the International AIDS Society-USA panel. *JAMA* **283**:381-390

Chun T.W., Carruth L., Finzi D., Shen X., DiGiuseppe J.A., Taylor H., Hermankova M., Chadwick K., Margolick J., Quinn T.C., Kuo Y.H., Brookmeyer R., Zeiger M.A., Barditch-Crovo P., and Siliciano R.F., 1997, Quantification of latent tissue reservoirs and total body viral load in HIV-1 infection [see comments]. *Nature* **387**:183-188

Collier A.C, Coombs R.W., Fischl M.A., Skolnik P.R., Northfelt D., Boutin P., Hooper C.J., Kaplan L.D., Volberding P.A., Davis L.G., et al., 1993, Combination therapy with zidovudine and didanosine compared with zidovudine alone in HIV-1 infection. *Annals of Internal Medicine* **119**:786-793

Comparison of dual nucleoside-analogue reverse-transcriptase inhibitor regimens with and without nelfinavir in children with HIV-1 who have not previously been treated: the PENTA 5 randomised trial. *The Lancet* 2002 **359**:733-740

Concorde: MRC/ANRS randomised double-blind controlled trial of immediate and deferred zidovudine in symptom-free HIV infection. Concorde Coordinating Committee. *The Lancet* 1994 **343**:871-881

Dameta R., Rabin L., and Hincenbergs M., 1996, Antiviral efficacy in vivo of the anti-human immunodeficiency virus bicyclam SDZ SID 791 (JM 3100), an inhibitor of infectious cell entry. *Antimicrob Agents Chemother.* **40**:750-754

Deeks S., Brum S., and Xu Y., 2000, ABT378/ritonavir (ABT378/r) suppresses HIV RNA to <400 copies per ml in 84% of PI experienced patients at 4 weeks. VII Conference on Retroviruses and Opportunistic Infections. San Francisco, CA

De Bethune M., Andries K., and Ludovici D., 2001, TMC120 (R147681), a next-generation NNRTI, has potent *in vitro* activity against NNRTI-resistant HIV variants. Program and abstracts of the 8th Conference on Retroviruses and Opportunistic Infections Abstract 304. Chicago, Illinois

De la Monte S.M., Gabuzda D.H., Ho D.D., Brown R.J., Hedley W.E., Schooley R.T., Hirsch M.S., and Bhan A.K., 1988, Peripheral neuropathy in the acquired immunodeficiency syndrome. *Annals of Neurology* **23**:485-492

Erickson J., Gulnik S., and Suvorov L., 2001, A femtomolar HIV-1 protease inhibitor with subnanomolar activity against multidrug resistant HIV-1 strains. Program and abstracts of the 8th Conference on Retroviruses and Opportunistic Infections Abstract 12. Chicago, Illinois

Fischl M.A., Richman D.D., Causey D.M., Grieco M.H., Bryson Y., Mildvan D., Laskin O.L., Groopman J.E., Volberding P.A., Schooley R.T., et al., 1989, Prolonged zidovudine therapy in patients with AIDS and advanced AIDS-related complex. AZT Collaborative Working Group. *JAMA* **262**:2405-2410

Fischl M.A., Parker C.B., Pettinelli C., Wulfsohn M., Hirsch M.S., Collier A.C., Antoniskis D., Ho M., Richman D.D., Fuchs E., et al., 1990, A randomized controlled trial of a reduced daily dose of zidovudine in patients with the acquired immunodeficiency syndrome. The AIDS Clinical Trials Group. *New England Journal of Medicine* **323**:1009-1014

Fischl M.A., Richman D.D., Hansen N., Collier A.C., Carey J.T., Para M.F., Hardy W.D., Dolin R., Powderly W.G., Allan J.D., et al., 1990, The safety and efficacy of zidovudine (AZT) in the treatment of subjects with mildly symptomatic human immunodeficiency virus type 1 (HIV) infection. A double-blind, placebo-controlled trial. The AIDS Clinical Trials Group [see comments]. *Annals of Internal Medicine* **112**:727-737

Fischl M.A., Stanley K., Collier A.C., Arduino J.M., Stein D.S., Feinberg J.E., Allan J.D., Goldsmith J.C., and Powderly W.G., 1995, Combination and monotherapy with zidovudine and zalcitabine in patients with advanced HIV disease. The NIAID AIDS Clinical Trials Group [see comments]. *Annals of Internal Medicine* **122**:24-32

Fischl M.A., 1993, Treatment of HIV disease in 1993/1994. [Review]. *Aids Clinical Review* **94**:167-187

Fischl M.A., Olson R.M., Follansbee S.E., Lalezari J.P., Henry D.H., Frame P.T., Remick S.C., Salgo M.P., Lin A.H., Nauss K.C., et al., 1993, Zalcitabine compared with zidovudine in patients with advanced HIV-1 infection who received previous zidovudine therapy [see comments]. *Annals of Internal Medicine* **118**:762-769

Gatell M.L., Arnaiz, J.A. et al., 2000, A randomized study comparing continued indinavir (800 mg tid) vs switching to indinavir/ritonavir (800/100 mg bid) in HIV patients having achieved viral load suppression with indinavir plus 2 nucleoside analogues: the BID Efficacy and Safety Trial (BEST). XIII International AIDS Conference. Durban, South Africa

Gupta S., Gilbert R., and Brady A., 2000, CD4 cell counts in adults with newly diagnosed HIV infection. results of surveillance in England and Wales, 1990-98. CD4 Surveillance Scheme Advisory Group. *AIDS* **14**:853-861

Hammer S.M., 2002, Increasing choices for HIV therapy. *N Engl J Med* **346**:2022-2023

Hammer S., Squires K., and Hughes M., 1997, A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. *N Engl J Med* **337**:725-733

Haas D., Zala C., and Schrader S., 2001, Once-daily atazanavir plus saquinavir favorably affects total cholesterol (TC) and fasting triglyceride (TG) profiles in patients failing prior

PI therapy (trial AI424-009, wk 24). Program and abstracts of the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago, Illinois Abstract LB-16

Hernandez J., Amador L., and Amantea M., 2000, Short-course monotherapy with AG1549, a novel nonnucleoside reverse transcriptase inhibitor (NNRTI), in antiretroviral naive patients. Program and abstracts of the 7th Conference on Retroviruses and Opportunistic Infections Abstract 669. San Francisco, CA

Hetherington S., Hughes A., and Mostellar M., 2002, Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. *The Lancet*. **359**:1121-1122

Hoetelmans R., Reijers M., and Weverling G., 1998, The effect of plasma drug concentrations on HIV-1 clearance rate during quadruple drug therapy. *AIDS* **12**:F111-F115

Hoggard P.G., Kewn S., Barry M.G., Khoo S.H., and Back D.J, 1997, Effects of drugs on 2',3'-dideoxy-2',3'-didehydrothymidine phosphorylation *in vitro*. *Antimicrobial Agents and Chemotherapy* **41**:1231-1236

Hogg R., Yip B., and Wood E, 2001, Diminished effectiveness of antiretroviral therapy among patients initiating therapy with CD4+ cell counts below 200/mm3. VIII Conference on Retroviruses and Opportunistic Infections. VIII Conference on Retroviruses and Opportunistic Infections Abstract 342. Chicago, IL

Jeffrey S., Logue K., and Garber S., 2000, New second generation NNRTIs: improved resistance and cross-resistance profiles. Program and abstracts of the XIII International AIDS Conference. Program and abstracts of the XIII International AIDS Conference Abstract TuPpA1145. Durban, South Africa

Kaplan J.H., and Karon, J, 2001, Late initiation of antiretroviral therapy (at CD4+ lymphocyte count <200 cells/L) is associated with increased risk of death. VIII Conference on Retroviruses and Opportunistic Infections. Chicaogo IL

Kinloch-de Loes S., Hirschel B.J., Hoen B., Cooper D.A,. Tindall B., Carr A., Saurat J.H., Clumeck N., Lazzarin A., Mathiesen L., et al., 1995, A controlled trial of zidovudine in primary human immunodeficiency virus infection. *N Engl J Med* **333**:408-413

Lagakos S.W., 1993 Surrogate markers in AIDS clinical trials: a conceptual basis, validation, and uncertainties. *Clinical Infectious Diseases*. **11**:22-25

Larder B.A. Kellam P., and Kemp S.D., 1993, Convergent combination therapy can select viable multidrug-resistant HIV-1 *in vitro*. *Nature* **365**:451-453

Moyle G.P, and Opravil, M., 2000, The SPICE study: 48-week activity of combinations of saquinavir soft gelatin and nelfinavir with and without nucleoside analogues. Study of Protease Inhibitor Combinations in Europe. *J Aquir Immune Defic Syndr*. **23**:128-137

Mellors J.W., Rinaldo C.R., Gutpa P., White R.M., Todd J.A., and Kingsley L.A., 1996, Prognosis of HIV-1 infection predicted by the quantity of virus in plasma. *Science* **272**:1167-1170

Nelson M., Staszewski S., and Morales-Ramirez J., 2001, Successful virologic suppression with efavirenz in HIV-infected patients with low baseline CD4 cell counts: post hoc results from Study 006. X European Conference of Clinical Microbiology and Infectious Diseases. Stockholm

Opravil M., Lederberger B., and Furrer H., 2001, Clinical benefit of early initiation of HAART in patients with asymptomatic HIV infection and CD4 counts >350/mm3. VIII Conference on Retroviruses and Opportunistic Infections. Chicago, IL

Palella F.J, Delaney K.M., Moorman A.C., Loveless M.O., Fuhrer J., Satten G.A., Aschman D.J., and Holmberg S.D., 1998, Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators [see comments]. *N Engl J Med.* **38**:853-860

Phillips A., Staszewski S., and Weber R., 2000, Viral load changes in response to antiretroviral therapy according to the baseline CD4 lymphocyte count and viral load. *AIDS*. **14**:S3

Ragni M.V., Amato D.A,. LoFaro M.L., DeGruttola V., van der Horst, C., Eyster M.E., Kessler C.M., Gjerset G.F., Ho M., Parenti D.M., et al., 1995, Randomized study of didanosine monotherapy and combination therapy with zidovudine in hemophilic and nonhemophilic subjects with asymptomatic human immunodeficiency virus-1 infection. AIDS Clinical Trial Groups. *Blood* **85**:2337-2346

Randomised trial of addition of lamivudine or lamivudine plus loviride to zidovudine-containing regimens for patients with HIV-1 infection: the CAESAR trial, 1997, *The Lancet* **349**:1413-1421

Ruane P., Mendonca J., and Timerman A., 2001, Kaletra vs. nelfinavir in antiretroviral-naive subjects: week 60 comparison in a phase III, blinded, randomized clinical trial. Program and abstracts of The 1st IAS Conference on HIV Pathogenesis and Treatment Abstract 6. Buenos Aires, Argentina

Sha B., Proia L., and Kessler H., 2000, Adverse effects associated with use of nevirapine in HIV postexposure prophylaxis for 2 health care workers. *JAMA* **248**:2723

Staszewski S., Morales-Ramirez J., and Tashima K., 1999, Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team. *N Engl J Med.* **341**:1865-1873

Staszewski S., Keiser P., and Giorgi J., 1999, Comparison of antiviral response with abacavir/Combivir to indinavir/Combivir in therapy-naive adults at 48 weeks (CNA3005) Abstract 505. XXXIX Interscience Conference on Antimicrobial Agents and Chemotherapy. San Francisco, CA

Sterling T., Chaisson R., and Bartlett J, 2001, CD4+ lymphocyte level is better than HIV-1 plasma viral load in determining when to initiate HAART. VIII Conference on Retroviruses and Opportunistic Infections Abstract 519. Chicago IL

Walmsley S., Bernstein B., King M., Arribas J., Beall G., Ruane P., Johnson M., Johnson D., Lalonde R., Japour A., Brun S., and Sun E., 2002, Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection. *N Engl J Med*. **346**:2039-2046.

Wood R., and Team T., 2000, Sustained efficacy of nevirapine (NVP) in combination with two nucleosides in advanced treatment-naive HIV infected patients with high viral loads: a B1090 substudy Abstract WeOrB604. XIII International AIDS Conference. Durban, South Africa

Zhang L., Ramratnam B., and Tenner-Racz K., 1999, Quantifying residual HIV-1 replication in patients receiving combination antiretroviral therapy. *N Engl J Med.* **340**:1605-1613