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A Risk-Benefit Assessment of HIV Protease Inhibitors

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Abstract

The use of triple therapy regimens, often called highly active antiretroviral therapy (HAART), generally involving 2 nucleoside analogues and an HIV protease inhibitor, have been endorsed as the standard of care for persons with HIV initiating therapy by a number of sets of international guidelines. The widespread availability of protease inhibitor–containing regimens has been associated with a dramatic drop in the incidence of new AIDS events and mortality throughout the developed world. Use of HAART regimens, particularly in treatment-naïve individuals, is also associated with dramatic reductions in HIV RNA load, rises in CD4+ cell numbers and improvements in some aspects of immune function.

However, protease inhibitor therapy is associated with a range of adverse effects, which varies between agents, and regimens frequently involve inconvenient administration schedules and disruption to patient's lives. Thus, the undoubted benefits of antiretroviral therapy come at some cost in terms of both physical and psychological morbidity to the recipient. In assessing an individual for therapy, consideration of the risk of disease events and the benefit of therapy

in reducing or preventing these events must be weighed against the potential of therapy to cause morbidity.

Using these criteria, we suggest that an individual with a 3 year risk of disease progression of less than 10% (based on CD4+ cell count and HIV RNA load) is more likely to a experience a morbidity if treated with HAART than if left untreated and monitored. For individuals with higher risks of HIV progression the risk versus benefit of initiating therapy may, in many cases, still be in favour of no therapy and continued observation. This will vary depending on the individuals risks (such as family and past medical history) and on the choice of agents in the regimen, some regimens having greater risks than others.

1. Treatment of HIV Infection

The history of the treatment of HIV infection has been punctuated by periods of enormous enthusiasm as new treatments produce promising results, followed by despair as the new treatments do not live up to expectations.[1-3] This wildly oscillating pendulum makes it difficult for both the prescribing physician and the patient to make clear objective decisions about treatment. Another such pendulum swing has occurred with regard to HIV protease inhibitors, from the excitement of their therapeutic potential during the 11th World AIDS conference in Vancouver in 1996 to the anxieties about emerging adverse effects during the 12th World Conference on AIDS in Geneva in 1998.

The widespread introduction of triple therapy regimens, often called highly active antiretroviral therapy (HAART), has been associated with a dramatic drop in the incidence of new AIDS events and mortality throughout the developed world (figs 1 and 2) and to lower hospital inpatient admissions.[4] However, these therapies continue to remain unavailable to most resource-poor countries that also face the highest burden of the AIDS epidemic. The cost-benefit of triple therapy, in terms

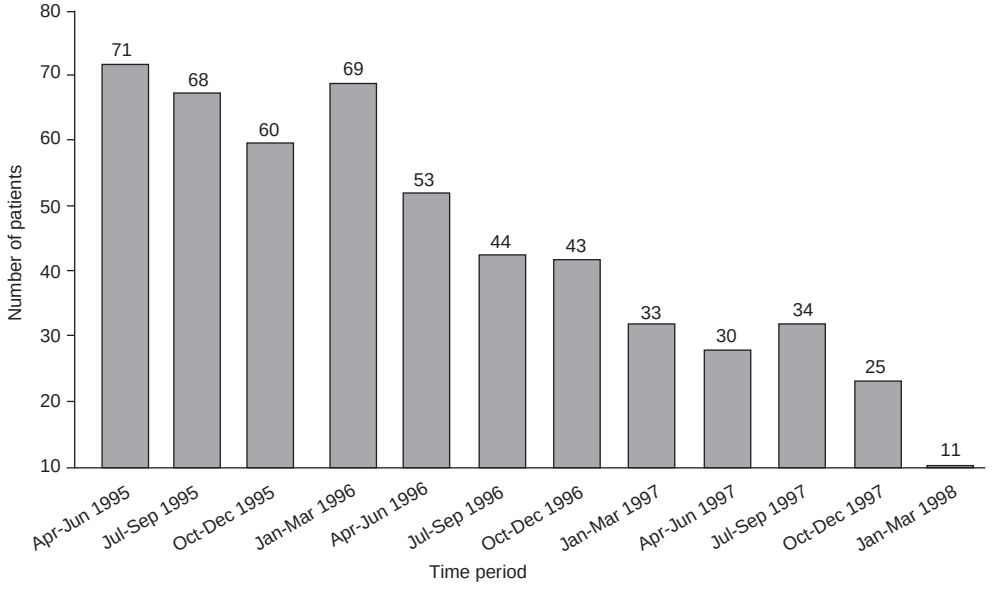


Fig. 1. Number of patients newly diagnosed with AIDS at Chelsea and Westminster Hospital, London, England, between April 1995 and March 1998.

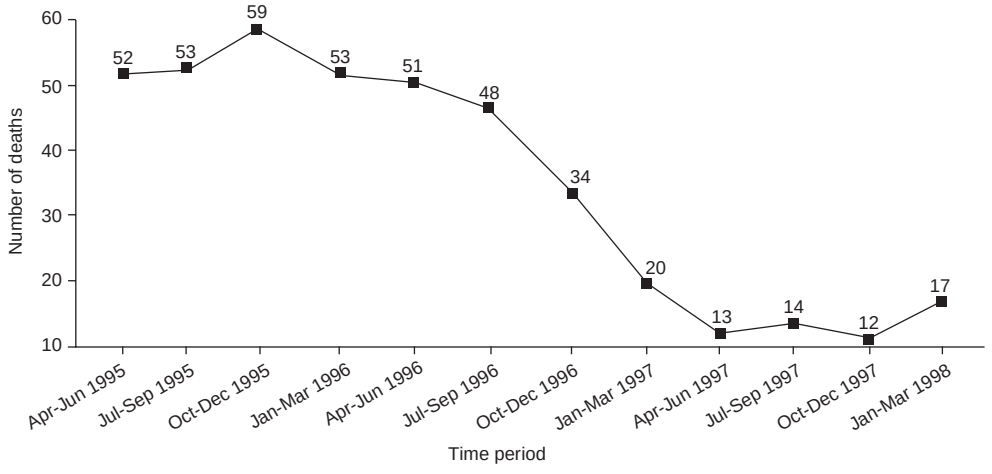


Fig. 2. Number of deaths in patients with HIV per month at Chelsea and Westminster Hospital, London, England, between April 1995 and March 1998.

of cost per year of life saved, in a developed world cost structure is increasingly well established.[5,6]

The use of triple therapy regimens, generally involving 2 nucleoside analogues and an HIV protease inhibitor, have been endorsed as the standard of care for persons with HIV initiating therapy by a number of sets of international guidelines.[7-9]

Recent debate has focused on the timing of initiation of antiretroviral therapy. International AIDS Society-US panel guidelines recommend treatment at any CD4+ cell level and viral loads ≥10 000 copies.[7] Others have advocated hitting HIV not only hard but also early, essentially at any detectable viral load. The draft guidelines from the US National Institutes of Health are available on the Internet at: www.hivatis.org. The British HIV Association agrees that the arguments for starting treatment are clear in persons with a CD4+ cell count below 350/mm^3 and viral loads in or above the range of 10 to 50 000 copies/ml. However, in persons with higher CD4+ cell counts and lower viral loads, the decision to treat or not to treat requires a weighing of the risks of therapy, both physical and psychological, against the potential benefits of therapy in terms of reduction in morbidity and mortality.[8,9]

Indeed, antiretroviral therapy is not without risk and only limited data on long term (>2 years) safety and efficacy are available. Additionally, in part due to the requirements of drug approval, most intervention studies have been conducted in persons with symptomatic disease, CD4+ cell counts <500/mm^3 and, more recently, viral loads >10 000 to 20 000. Thus, even short term safety data on antiretrovirals in persons with high CD4+ cell counts and asymptomatic disease are limited. However, a number of important adverse effects have been identified. Some of these adverse effects appear to be associated with all currently approved protease inhibitors, hence may be considered a 'class effect' (at least for the current peptidomimetic class), whereas other events appear unique to or most prominent with a single agent.

Protease inhibitors are amongst the most potent single agents available for the treatment of HIV infection. Treatment with these drugs has revolutionised HIV care in recent years and protease inhibitors are likely to remain an extremely important part of the therapeutic armamentarium for the foreseeable future. Randomised controlled trials with clinical end points attest to their value in relatively late and usually symptomatic disease. For example, using the combination of zidovudine, lamivudine and indinavir in treatment-experienced patients in the AIDS Clinical Trials Group (ACTG) 320 study was associated with a halving of clinical

events over 38 weeks follow-up compared with treatment with zidovudine and lamivudine.[10] A similar reduction in risk was reported for treatment-naïve persons commencing therapy with the combination of zidovudine, zalcitabine and saquinavir hard-gelatin capsules (HGC) [an old formulation of saquinavir no longer in widespread use] compared with zidovudine and zalcitabine.[11] Another study in advanced, nucleoside analogue pre-treated patients indicated that the addition of ritonavir to an established nucleoside analogue regimen (not a currently recommended treatment strategy) also resulted in dramatic improvements in survival and a delay in clinical events in patients with very advanced disease.[12]

The approved protease inhibitors, indinavir, nelfinavir, ritonavir and saquinavir soft-gelatin capsules (SGC) are all peptidomimetic agents with an identical mode of action against HIV protease. Whilst there are differences in pharmacology, the activity of the protease inhibitors when used in triple therapy regimens in treatment-naïve patients, based on several small studies, and cross study comparisons appears similar.[13] Therefore, the choice of HIV protease inhibitor will be based not only on activity but also on issues such as:

- safety profiles
- potential pharmacokinetic and metabolic interactions with concomitant medications [e.g. cytochrome P450 (CYP) enzyme system inhibition or induction]
- convenience of administration (including twice or thrice daily administration, need for administration with food or in a fasting state)
- resistance profile and the potential for salvage after resistance-associated treatment failure
- patient status and past and family history
- *in vitro* synergy or non-antagonism with other drugs
- compartmental penetration e.g. lymph nodes, CNS, genital tract.

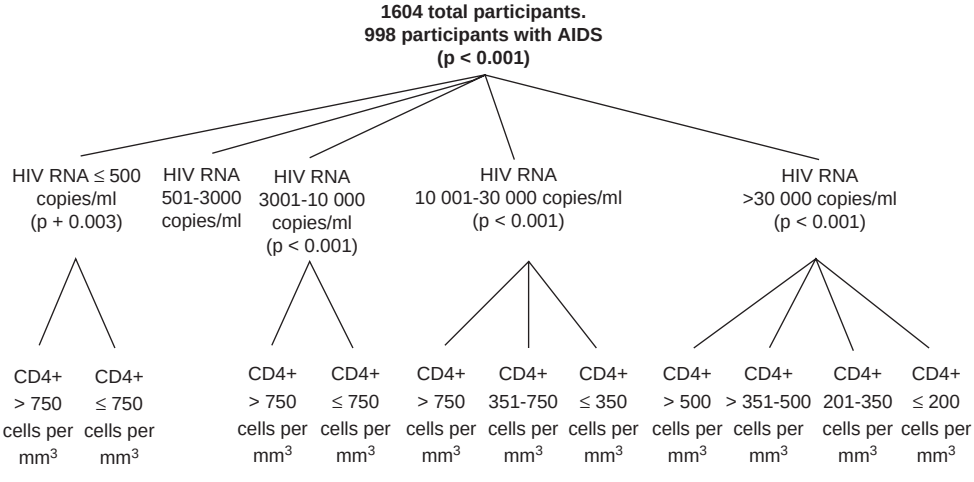
While decisions regarding therapy must be individualised, in this article we plan to review the available data regarding the risk of therapy balanced against established the risk of no therapy based primarily on the Multicentre AIDS Cohort Study (MACS) analysis.[17] Together, this should provide information on whether to treat or not to treat, which can then be used to make informed individual therapy decisions. Additionally, we will briefly discuss the choice of individual protease inhibitor and considerations for the use of protease-sparing HAART regimens.

2. Risks of No Treatment

Data from natural history studies suggest the future clinical course of HIV-1 infection may be determined soon after acquisition of the virus. Specifically, CD4+ cell count–matched persons with low viral loads (e.g. <3000 to 5000 copies/ml) at presentation have significantly fewer events in both the medium (3 to 5 years) and long (>10 years) term than those with higher initial viral loads.[14-17]

Data from the 1604 patient MACS have provided actuarial type assessment of risk of disease progression based on single or multiple CD4+ cell count and viral load results.[17] At the time this cohort study was initiated no antiretroviral treatments were available. Therefore, the study provides valuable insights into the natural history of untreated HIV infection. It is clear from this, and other studies,[14-18] that the risks of progression and/or death are mainly confined in the short (1 year) term to those with a CD4+ cell count <200/mm^3. However, measurement of viral load provides invaluable additional discriminatory data on both short and medium/long term risk of disease progression in persons across the full range CD4+ cell counts.

Use CD4+ cell count and viral load provides a powerful means of assessing risk or 'staging' HIV disease. Based on these data, a regression tree incorporating both HIV-1 RNA and CD4 measurements was designed to provide risk estimates for AIDS over 3, 6 and 9 years' follow-up. Viral load risk categories used in this study, as measured by the branched DNA (bDNA) assay version 2 (limit of detection 500 copies/ml), were ≤500, 501 to 3000, 3001 to 10 000, 10001 to 30 000 and >30 000 copies/ml (fig. 3).[17] Levels of HIV-RNA measured by reverse transcription polymerase chain re-



All participants (n) :												
	66	56	257	93	300	64	259	73	141	121	104	70
Participants with AIDS (n) :												
	3	13	90	39	179	42	194	63	105	111	92	67
Percentage of participants with AIDS (95% confidence intervals):												
By 3 years	0.0	3.7	2	3.2	8.1	9.5	16.1	40.1	32.6	47.9	64.4	85.5
	(0-0)	(0-4)	(0-7)	(0-7)	(5-11)	(3-18)	(12-21)	(29-52)	(25-40)	(39-57)	(56-74)	(77-93)
By 6 years	1.7	9.6	16.6	14.2	37.2	36.7	54.9	72.9	66.8	77.7	89.3	97.9
	(0-6)	(2-17)	(12-21)	(7-22)	(32-43)	(25-49)	(49-61)	(63-84)	(58-76)	(69-85)	(82-95)	(92-100)
By 9 years	3.6	22.3	35.4	40.4	59.7	62.4	76.3	86.2	76.3	94.4	92.9	100.0
	(0-9)	(12-35)	(29-41)	(30-52)	(54-66)	(49-75)	(71-82)	(77-94)	(69-83)	(90-99)	(87-98)	(100-100)

Fig. 3. Probability of developing AIDS according to HIV-1 concentration and CD4+ lymphocyte count. The P values are derived from the likelihood ratio test using Cox regression. Mean 95% confidence intervals were derived from 500 bootstrap samples using the percentile method (reproduced from Mellors et al.,[17] with permission).

action (RT-PCR) are approximately 2-fold higher than those measured by bDNA methods.[17]

Whilst immune activation markers, such as soluble tumour necrosis factor type II receptors (TNFRII)[18] or CCR5 allele status,[19] may provide some additional predictive value beyond using viral load and CD4+ cell count, they are not routinely available. Additionally, care in interpretation of individual viral load results must be taken due to the known variability of the assays (approximately 3-fold) and the potential for recent infections or vaccinations to transiently increase viral load. Therefore, decisions based on viral load measurements should be confirmed with a second sample.

Three-, 6- and 9-year probabilities of AIDS are summarised in figure 3.

3. Benefits of Protease Inhibitor–Based Highly Active Antiretroviral Therapy, and Considerations for a Risk-Benefit Analysis

In establishing a risk-benefit analysis we sought to considered several issues:

- the magnitude of benefit gained relative to no therapy and/or other available therapies
- the frequency of adverse events experienced, particularly at a moderate or more severe level, or those requiring drug discontinuation

- the impact of therapy on quality of life, both the physical and psychological aspects.

3.1 Benefits of Therapy

There is no question that regimens involving protease inhibitors significantly prolong life and delay progression to AIDS.[10-12] Reductions in the risk of progression of around 50% relative to dual nucleoside analogue regimens alone have been seen in several clinical endpoint studies with protease inhibitors, including both pre-treated and treatment-naïve patients.[10-12] These may represent underestimates of the true benefits of protease inhibitor–based triple therapy as these studies all included methodological differences (formulations and dosage sizes, addition of a single agent only, and inconvenient administration schedules) to current practice. Clinical endpoint data and follow-up data for >1 year are essentially only available in individuals with a high likelihood of developing clinical events in the near future. For example, the ACTG320 study was conducted in persons with a mean CD4+ cell count of 87/mm^3 and viral load of 5.0 log[10] (i.e. patients with a 3 year probability of progression in MACS of >85%).[17] Similarly, the Invirase International Phase III Trial (SV14604) included patients with median CD4+ cell count of 195 to 204/mm^3 and viral load of approximately 5.0 log.[11] In these circumstances, when the risk of no treatment is very high, the benefit of an effective therapy, even one with a considerable safety risk, is on balance, likely to strongly favour intervention.

Clinical outcome studies using protease inhibitors have not been conducted in persons with less advanced disease. However, in persons with less advanced HIV disease, studies of over 24 to 48 weeks of follow-up indicate that triple therapy regimens including a protease inhibitor result in a substantial proportion of patients who remain on therapy achieving and sustaining viral load levels at levels that are associated long term nonprogression. The proportion of patients achieving such responses is consistently better than the proportion of responders observed following treatment with 2 nucleoside analogues alone.

Additionally, substantial and sustained improvements in CD4+ cell numbers and function have been well documented with protease inhibitor–based regimens. Thus, protease inhibitor–based triple therapy in less advanced disease patients results in changes in established markers of HIV disease which suggest a substantial but incomplete reduction in risk of future disease progression. However, this benefit is only sustained in persons who are able to remain tolerant and adherent to therapy; what proportion of asymptomatic recipients this represents remains unclear.

However, in such patients, analyses such as quality-adjusted life-years (QALYs) saved or quality-adjusted time without symptoms and toxicity (Q-TWiST) are required. These types of analyses have not been performed with protease inhibitor–containing regimens. With zidovudine monotherapy in asymptomatic persons the reduction in quality of life caused by severe adverse effects approximately equals the increase in quality of life associated with a delay in disease progression.[20] While HAART regimens provide greater antiviral potency and clinical benefit than zidovudine monotherapy these regimens also include a greater number of potentially toxic agents.

Two quality-of-life analyses have been reported from protease inhibitor studies.[21,22] However, both analyses were conducted in settings that are not directly comparable to current practice: one involved a suboptimal and now superseded formulation of saquinavir and the second involved the addition of ritonavir alone to failing nucleoside therapy. Additionally, both were conducted in patients with advanced disease. In the first analysis of the study SV14604,[11] patients gained a quality-of-life benefit from 3-agent therapy relative to 2-agent therapy, the benefit being greatest in the physical function dimension.[21] In the second analysis, with ritonavir,[12] initial quality of life, as measured by the European Quality of Life (EuroQOL) questionnaire, but not the MOS-30 survey, deteriorated over the first 4 to 8 weeks of therapy before

it improved. Using the MOS-30 survey, after 3 months of therapy a range of function and well-being scores improved, or were better maintained in ritonavir recipients than in placebo recipients.[22]

Protease inhibitor-containing HAART regimens result in approximately 60 to 80% of therapy-naïve recipients achieving a viral load below standard assay quantification values (400 to 500 copies/ml) and 40 to 70% have a viral load of below 50 copies/ml by 24 weeks of therapy, suggesting that not all patients respond optimally to therapy. Many HAART recipients develop serious or severe and treatment-limiting drug-related adverse effects sooner than disease progression would have occurred. Failure to achieve or sustain antiviral effects and treatment limiting toxicities result in many patients commenced on protease inhibitor–based HAART still experiencing disease progression. For example in ACTG320, 33 (6%) of 577 patients randomised to zidovudine, lamivudine and indinavir developed AIDS or died over a median of 38 weeks of follow-up. In the sub-population of 219 patients entering the study with a CD4+ cell count of ≤50 CD4 cells/mm^3, disease progressed in 23 (11%) of patients.[10]

Therefore, the benefits of protease inhibitor therapy cannot be seen as absolute. Thus, when considering the benefits of HAART, it cannot be assumed that all patients commenced on therapy will have the risk of disease progression reduced to zero. We would suggest that this reduction in risk may be around 75% in patients with advanced disease relative to no therapy. This benefit may be greater in less advanced patients. This is based on benefits observed with monotherapy relative to no therapy, the relative reductions in risk observed in dual nucleoside therapy studies relative to monotherapy and triple therapy relative to dual therapy.[13]

3.2 Risks of Early Intervention

Asymptomatic patients commencing therapy may have substantial psychological morbidity associated with intervention and a perceived entry into the sick role. Additionally, asymptomatic patients appear to find it more difficult to adhere to therapy than those who have experienced significant symptoms.[23] Poor adherence is strongly associated with persistent measurable virus load on therapy, hence an increased risk of resistance.[24] Resistance to zidovudine, and potentially to other antiretrovirals, is an independent risk factor for accelerated disease progression relative to the presence of wild type virus.[25] Furthermore, cross-resistance within therapeutic classes appears common, hence failure on one regimen may reduce the chances of a prolonged therapeutic response to a subsequent regimen.[26]

Thus, in asymptomatic persons with higher CD4+ cell counts (for example >350 cells/mm^3) and low viral loads (certainly <10 000 copies/ml), where the 3 year probability of disease progression is <10%,[17] appreciation of whether the 3 year risk of treatment-associated morbidity is greater or less than 10% is required if therapeutic intervention is to be justified.

We currently believe that intervention is not justified in persons with a risk of disease progression of <10% over 3 years as intervention in these individuals will produce more episodes of moderate, severe or treatment limiting events than it will prevent disease progressions. Additionally, it may be possible by routine follow-up to identify many of the subset of patients within that population who will progress as their CD4+ cell count and viral load results are likely deteriorate moving them into a prognostic group where intervention is favoured. Patients with a 10 to 20% risk, such as those with a CD4+ cell count of 351 to 750 cells/mm^3 and viral load as measured by bDNA of 10 000 to 30 000 copies/ml may represent a 'grey zone' where therapy with a regimen with a low incidence of adverse effects may be justifiable.

3.3 Is There a Clear Rationale for Early Intervention?

There is a range of biologically plausible reasons why early intervention in an infectious disease with potent agents is a logical approach. With early intervention, the viral pool may be relatively

smaller and more homogeneous, the virus may be only able to infect a narrow range of cells and preventing viral replication at this stage prevents or diminishes progressive damage to the immune system which may be irreparable. Hopes that early therapy might also be associated with eradication of the virus after 3 or 4 years of intensive therapy have been reduced by the finding of a replication competent virus in long lived immunological cells (probably T memory cells).[27]

Data on immune restoration during HAART suggest that, over prolonged follow-up, improvements in numerical and functional measures of immunity occur and may be accelerated by immune-based interventions such as interleukin-2.[28,29] While restoration thus far appears incomplete,[30] it is sufficient for patients to stop a range of treatments or prophylaxes for opportunistic infections.[31,32] Unfortunately, as HIV-specific responses are not restored and a pool of HIV-infected cells remain, antiretroviral therapy cannot be stopped.[29] Additionally, restoration of lymph node germinal centres occurs over time,[33] suggesting that there is the potential to re-establish the critical connections between antigen presenting cells and CD4+ lymphocytes. Once seroconversion has occurred, critical aspects of immune function, that are not necessarily restored by HAART have occurred[34] and, in mathematical models, the extent of HIV replication prior to seroconversion appears more than sufficient to generate extensive heterogeneity in the viral population.[35] Intervention in, for example, the Delta study was associated with similar clinical benefits across a range of patients from those with asymptomatic disease to those with AIDS.[36] Therefore, outside of intervention during seroconversion illness, arguments in favour of early intervention do not necessarily stand up to closer scrutiny.

A pragmatic view would suggest that although AIDS is ultimately the endpoint of persistent HIV replication, the clinical manifestations of HIV infection, which cause symptoms and ultimately death, are those of a failing immune system. Opportunistic infections and tumours are relatively rare until a profound immune deficit has occurred and are certainly unusual when the CD4+ cell count is >300 cells/mm^3.

This suggests, that in the present state of knowledge, commencement of potentially lifelong intervention with substances with an undetermined long term safety record, such as protease inhibitors and nucleoside analogues, in persons with 'early' disease (as assessed by CD4+ cell count and viral load measurements) and a low risk of medium term (3 years) disease progression, should be undertaken only after informed consideration of the risks and benefits associated with such a strategy.

4. Protease-Sparing Regimens

A discussion of a risk-benefit analysis for protease inhibitor use is further complicated by the availability of so called 'protease-sparing' regimens, which also achieve optimal antiretroviral responses in a high proportion of recipients. The most well studied of these regimens involve 2 nucleoside analogues with a non-nucleoside reverse transcriptase inhibitor (NNRTI); however, triple nucleoside analogue regimens are also under evaluation. Three NNRTIs, efavirenz, delavirdine and nevirapine, are now widely available. In treatment-naïve patients, the combination of efavirenz plus 2 nucleoside analogues has shown similar effects on plasma viral load and similar rises in absolute CD4+ cell numbers as an indinavir-containing regimen over 24 weeks follow-up.[37] In this first direct comparison of these approaches, the efavirenz-containing combination showed better tolerability and a more convenient administration schedule.[37] Studies with the NNRTIs nevirapine and delavirdine and the nucleoside analogue abacavir with two nucleoside analogues in treatment-naïve patients have also demonstrated superior antiviral effects to dual nucleoside therapy and comparable rates of undetectabilty of viral load assays to protease inhibitor–based combinations in similar populations.[13] NNRTIs appear well tolerated with the majority of adverse events occurring within the first few weeks and rates of treatment discontinuation being generally <5% for drug related toxicity.[37]

The most common adverse events with NNRTIs are rash, which is generally self-limiting but can rarely be severe, and generally short-lived CNS disturbances with efavirenz.[37] Abacavir is associated with a hypersensitivity reaction in 2 to 5% of patients with is usually managed by drug discontinuation.[38] Specifically, rechallenge after interruption of abacavir may potentially result in a more severe or life-threatening reaction.

Both efavirenz and nevirapine can be administered once daily and delavirdine and abacavir can be administered twice daily without regard to food and few tablets are required. Thus, the impact of these drugs on daily life appears, in the absence of quality-of-life data, to be lower than may be the case with most protease inhibitors. A further attraction of NNRTI-based or triple nucleoside regimens, in part, lies in the potential use of protease inhibitors in salvage regimens after failure of an initial regimen. NNRTIs have not, for the most part, shown the impressive antiviral effects in nucleoside analogue–experienced patients that have been observed with protease inhibitor–containing regimens and hence may be less effective as salvage agents.

However, long term data (>1 year) with protease inhibitor–sparing regimens are currently sparse and NNRTIs are not without initial toxicity. Additionally, a number of adverse effects of protease inhibitors were not observed until after approval, and we do not currently have sufficient long term experience with protease inhibitor–sparing regimens to say they are as safe or safer than protease inhibitor–containing regimens in long term therapy. Furthermore, there remains debate as to whether single target regimens or regimens made up only of pre-transcriptional inhibitors may have disadvantages relative to multi-target, pre- and post-transcriptional inhibitor combinations. Additionally, resistance to the NNRTIs (but perhaps not with abacavir) generally requires only a single mutation whereas significant phenotypic resistance *in vitro* to protease inhibitors is only observed after accumulation of 3 or more mutations. It is therefore possible that NNRTI-containing regimens may be more 'brittle' than those containing protease inhibitors as accumulation of fewer mutations is required for failure. Furthermore, data on control of HIV replication in so called sanctuary sites, such as lymph nodes, the genital tract and CNS are not currently available and data on changes in immune function with NNRTI or triple nucleoside regimens are also currently sparse. Therefore, accumulation of comprehensive data over the long term comparing benefits of protease inhibitor–sparing *versus* protease inhibitor–containing regimens are essential.

In conclusion, NNRTI based triple therapy appears to have some advantages over protease inhibitor–based regimens hence there use may be justified in patients who lie in a zone where risk *versus* benefit for intervention with a protease inhibitor–based regimen may not clearly justify intervention.

5. Risks with Nucleoside Analogues

Data available on the long term (>2 years) safety of antiretroviral therapy are limited to studies with some nucleoside analogues. Partly because of the requirements of drug approval, most treatment intervention studies have been conducted in persons with symptomatic disease, CD4+ cell counts <500/mm^3 and, more recently, viral loads >10 000 to 20 000. Thus, even short term safety data on antiretrovirals in persons with high CD4+ cell counts and asymptomatic disease are limited.

Nucleoside analogues currently represent 2 of the 3 agents used in HAART regimens. They are frequent contributors to observed adverse effects during therapy and are likely to continue to be widely used. The adverse effects of these agents occur mostly as secondary effects to inhibition of human DNA polymerase γ. Overall, the incidence of severe or worse severity adverse events appears similar with zidovudine monotherapy or with combinations of zidovudine and zalcitabine or didanosine in asymptomatic patients.[1-3,36,37,39,40] Additionally, the incidence of adverse events with zidovudine plus lamivudine appears, in the only comparative study, similar to the combination of

zidovudine and zalcitabine in a relatively advanced population.[41]

Rates of peripheral neuropathy with stavudine, the principal dose limiting toxicity of this agent, were 15% (compared with 6% for zidovudine) in patients with CD4+ cell counts of 50 to 500/mm^3 (mean 235/mm^3) followed for a mean 115 weeks,[42] a figure that is in line with studies of zalcitabine in similar patient populations.[43] However, several studies have shown a clear association between peripheral neuropathy with nucleoside analogues and clinical status as assessed by US Centers for Disease Control category and CD4+ cell count.[43]

Thus, therapy with 1 or 2 nucleoside analogues, even in persons with asymptomatic disease and preserved CD4+ cell counts, appears to be associated with a low, but clinically important, frequency of adverse events of either grade 3 to 4 severity or of sufficient severity to requiring cessation of therapy. Overall, the rate of drug discontinuation or severe toxicity across these studies of 2 to 3 years follow-up is around 10%.

6. Risks with Protease Inhibitors

Limited data are available on the prolonged use of protease inhibitors, although these drugs are widely viewed as being generally well tolerated. However, a number of important adverse effects have been identified, many of which have come to light during the post drug-approval stage. Some of these adverse effects appear to be associated with all of the currently approved agents and hence may be considered a 'class effect' (at least for the current peptidomimetic class), whereas other events appear unique to or most prominent with a single agent.

While class effects clearly exist, the relative frequency of each adverse event, based on limited data, varies. Thus, while all protease inhibitors may have the potential to cause these events, the risk associated with each protease inhibitor is different. Given that the antiviral effects, hence presumably the clinical benefit of each protease inhibitor is similar (although differences in immunological benefits, which may also have a bearing on long term clinical benefit have not been adequately compared), there is likely to be a different risk-benefit ratio for each of the individual agents. Indeed, the risk-benefit ratio for any combination of agents may vary between individuals as the risk of some protease inhibitor–related adverse events in an individual may relate to issues such as family history (e.g. diabetes mellitus or hyperlipidaemia) past medical history (e.g. renal calculi) or current medical problems (e.g. diarrhoea, hepatitis B or C infection).

6.1 Class-Related Effects

6.1.1 Gastrointestinal

Gastrointestinal disturbances are commonly observed in the first weeks of protease inhibitor therapy. Therefore, many physicians now routinely provide antinausea and antidiarrhoeal agents at the start of therapy and counsel patients on the management and generally self-limiting nature of these effects. Additionally, as protease inhibitors are generally started concomitant with other agents, usually 2 nucleoside analogues, it is difficult to fully appreciate what proportion of these adverse gastrointestinal effects relate specifically to the protease inhibitor. Limited data are available on the need for medication to control diarrhoea or the duration of diarrhoea. A summary of gastrointestinal events derived from the European summary of product characteristics (SPC) for indinavir, saquinavir-SGC, nelfinavir and ritonavir is shown in table I.

In clinical practice, indinavir is associated with few gastrointestinal events that require treatment cessation. No differences in the frequency of severe or worse adverse events, including gastrointestinal events, were reported between the combination of zidovudine plus lamivudine plus indinavir and zidovudine plus lamivudine in the ACTG320 study.[10] Similar good tolerability was observed in the smaller Merck 035 study. In this study there was only 1 withdrawal from treatment due to nausea in the triple therapy group (zidovudine plus lamivudine plus indinavir).[44] However, both these studies were conducted in persons who

Table I. Incidence (% of patients) of gastrointestinal adverse events as summarised from the European summary of product characteristics

	Indinavir[a]	Saquinavir-SGC[b]	Nelfinavir[b]	Ritonavir[a]
Nausea	35.3	10.6	4.5	47.5
Vomiting	11.0	2.9		23.6
Diarrhoea	24.6	19.9	25.9	44.9
Dyspepsia	10.7	8.4		Frequently
Taste perversion	19.1	>2		11.4
Abdominal pain	14.6	2.3		11.6

a Assessed as at least possibly related to drug therapy.

b Adverse effects of moderate or severe intensity, considered possibly related to drug therapy.

SGC = soft-gelatin capsules.

had already been established on therapy with zidovudine. In therapy-naïve patients, treatment with the combination of zidovudine, lamivudine and indinavir, a higher incidence of adverse gastrointestinal events may occur. For example in the DMP-006 study, 22% of recipients experienced nausea and 14% experienced vomiting of grade 2 or higher and 15 of 148 (10%) discontinued this regimen due to gastrointestinal events.[37]

The most common reported gastrointestinal events in the ritonavir clinical endpoint study, using a liquid preparation of ritonavir, in persons with CD4+ cell counts of ≤100/mm^3 were nausea (52%), vomiting (29%), diarrhoea (50%), circumoral paraesthesia (28%), and altered taste (12%).[12] Nausea was responsible for over half (10.4%) of the withdrawals (21.1% of total) in the ritonavir group compared with 1.1% of the total 8.3% who withdrew while receiving placebo. Other gastrointestinal-related withdrawals from treatment (as a percentage of the total population *vs* placebo) were vomiting (4.8 *vs* 0.9%), diarrhoea (4.3 *vs* 0.9%), altered taste (1.7 *vs* 0.4%) and circumoral paraesthesia (1.7 *vs* 0%).[12] Initial tolerability of this agent appears better with the capsule formulation and the use of dosage escalation regimens; however, a substantial proportion of patients continue to experience initial nausea and diarrhoea with this agent (see section 6.2.2). These adverse experiences tend to resolve over the first 4 to 8 weeks of therapy.

Diarrhoea is a prominent initial adverse event with nelfinavir that persists in some patients. In a phase I/II study of an earlier formulation of nelfinavir, 70% of 10 patients receiving nelfinavir 1026 mg/day experienced grade 2 or worse diarrhoea over a 28-day treatment period. Seven of 22 patients in this dose-finding study required treatment with at least one dose of an antidiarrhoeal.[45] A retrospective chart review at a single centre found that 38 out of 42 nelfinavir recipients had ≥2 loose stools per day; the diarrhoea in 96% of these 38 patients responded to treatment with a proprietary antidiarrhoeal.[46] In a comparative study of 241 patients receiving nelfinavir administered thrice or twice daily in combination with stavudine and lamivudine over 36 weeks follow-up, the only moderate or worse adverse events occurring in >2% of persons were diarrhoea in 12.3 to 13.1% and nausea in 2.3 to 4.6%, with only 1 patient discontinuing therapy because of diarrhoea.[47]

Data from the Study of Protease Inhibitor Combination in Europe (SPICE) study[48] indicate that the majority of gastrointestinal adverse events with nelfinavir, saquinavir-SGC or the combination of these 2 protease inhibitors occur within the first 16 weeks; data presented as cumulative events by week 16 and 48 are shown in table II.

Similarly, in the Amsterdam Duration of Antiretroviral medication (ADAM) study using the combination of stavudine, lamivudine, nelfinavir and saquinavir (initially the HGC formulation) in treatment-naïve patients, 33 of 43 patients experienced loose or watery stools at least 2 to 3 times/day; 50% of these patients required treatment with

loperamide.[49] However, only 1 patient discontinued treatment because of diarrhoea.[49]

Additional data with saquinavir-SGC in 442 mostly nucleoside analogue experienced patients receiving this drug for up to 1 year, revealed that 8% of the study population discontinued treatment because of adverse events, of which most were related to the gastrointestinal tract.[50] Moderate severity or worse gastrointestinal disturbances that were at least possibly drug related included diarrhoea (20% of patients), nausea (11%), abdominal discomfort (9%), dyspepsia (8%) and flatulence (6%).[50]

6.1.2 Lipid Disturbances

A syndrome of hyperlipidaemia, insulin resistance and peripheral fat wasting (lipodystrophy) has recently been reported in patients receiving protease inhibitor therapy. Whilst causation and mechanisms of this syndrome have not been clearly established, most clinicians agree this syndrome was rare prior to the availability of protease inhibitors. The syndrome consists of fat loss from arms, legs and face, accumulation of truncal, including intra-abdominal fat, and gynaecomastia and is commonly associated with elevations in serum triglyceride, low density lipoprotein (LDL)-cholesterol and serum insulin levels, glucose intolerance and insulin resistance. Less commonly, localised accumulations of fat, such as in the dorso-cervical region (so called 'buffalo-hump') have been reported.[51-56] In the largest cross-sectional study reported to date, fat redistribution, as assessed by dual energy x-ray absorptiometry scanning, was present in 64% of protease inhibitor recipients after a mean of 13.9 months of therapy compared with only 3% of protease inhibitor–naïve persons.[51] Suggested risk factors for lipodystrophy in this study included longer duration of protease inhibitor therapy and use of the combination of ritonavir and saquinavir. However, the frequency of clinically significant problems remains unclear.

New-onset diabetes mellitus has been reported in 5.7% of mostly indinavir recipients in a study of an urban US cohort of patients and in this cohort a family history of diabetes mellitus was found to be a potential risk factor.[57] Other studies suggest the incidence of overt type 2 diabetes mellitus during HAART to be 0.5 to 2%. However, impaired glucose tolerance, as assessed by glucose tolerance tests may be present in 16% of protease inhibitor recipients.[58] In a chart review of 216 protease inhibitor recipients abnormal random serum glucose levels (actual levels not defined) were found with the following frequencies: indinavir (11.6%), nelfinavir (8.2%), ritonavir plus saquinavir (6.3%) and saquinavir (4.3%).[59]

Concomitant lipid level elevations influence levels of both LDL-cholesterol and triglycerides. Importantly, elevated triglyceride levels appear occasionally to be associated with potentially fatal pancreatitis.[60] Triglyceride levels were first noted to be elevated in studies of ritonavir: Cameron et al.[12] reported that 12.9% of ritonavir recipients (as compared with 0.4% of placebo recipients) had fasting serum triglyceride levels of above 16.9 mmol/L. A retrospective chart review of 232 patients receiving protease inhibitor therapy for >1 month indicated that elevations in triglyceride lev-

Table II. Cumulative adverse events[a] (% of patients) at weeks 16 and 48 in the Study of Protease Inhibitor Combination in Europe (SPICE) study[46] (by intention-to-treat)

Adverse effect	SQV + 2NAs		NFV + 2NAs		SQV + NFV + 2NAs		SQV + NFV	
	16wk	48wk	16wk	48wk	16wk	48wk	16wk	48wk
Diarrhoea	19	23	27	46	35	45	46	53
Nausea	19	19	8	19	8	8	0	4
Abdominal pain	8	12	4	4	2	4	7	7
Vomiting	8	8	4	4	4	4	2	6

a Includes only those adverse events that were considered to be moderate or worse in severity and to be at least possibly related to drug therapy or of unknown relationship to drug therapy.

NA = nucleoside analogue; **NFV** = nelfinavir; **SQV** = saquinavir.

els were most common in persons receiving ritonavir-containing regimens (with 57% of patients experiencing a doubling of random triglyceride values from baseline). However, levels were also significantly elevated in nelfinavir recipients.[62] Several additional studies have also suggested that different protease inhibitors may be associated with different risk of lipid disturbances, the risk being greatest with ritonavir, intermediate with indinavir and nelfinavir and lowest with saquinavir.[61-63]

The long term impact of hypertriglyceridaemia and elevated LDL-cholesterol levels on morbidity and mortality in persons with HIV infection are not known. Therapy with fibrates or HMG-CoA reductase inhibitors may be required by some patients. Therapy with HMG-CoA reductase inhibitors, other than pravastatin and atorvastatin, is relatively contraindicated because of the potential for drug interactions with protease inhibitors via the CYP enzyme system. Myocardial infarctions in relatively young persons receiving protease inhibitor therapy have been reported;[64] however, a clear cause and effect relationship has not been established.

Additionally, other symptoms potentially linked with the lipodystrophy syndrome and commonly observed during protease inhibitor therapy include dry skin and cracked lips, loss of body hair, in-grown toenails and gout. The hypothetical mechanism of this syndrome including inhibition of several proteins key to fat metabolism, has been recently proposed.[65] However, further data are required and it may be that if inhibition of several enzymes/transporter molecules by protease inhibitors is implicated in this syndrome, the expression of the syndrome may vary by protease inhibitor related to their effects on the different steps in the mechanism. For example, more lipid disturbance with 1 agent, greater risk of diabetes mellitus with another and a lower risk of CYP-related problems with a third. In addition, it is not known if nucleoside analogue therapy may further contribute to this syndrome, for example through chronic intracellular acidosis secondary to DNA polymerase γ inhibition.

6.1.3 Other Adverse Events

Other rare adverse events which appear class-related include haemolysis with one report being published. This involved an episode of haemolysis which occurred after the patient received 10 months of therapy with indinavir and resolved on withdrawal; the adverse effect recurred with fatal consequences on rechallenge.[66]

Increased bleeding in patients with haemophilia receiving protease inhibitors has also been described. In one series 10 out of 17 patients reported increased bleeding or changes in bleeding pattern, with increased need for blood products in 8 patients over 6 months of protease inhibitor therapy. No mechanism for these events has been reported.[67,68]

Hypersensitivity reactions may be more common in persons receiving protease inhibitors, possible secondary to improved immune function or CYP inhibition. One group reported that 13 out of 238 protease inhibitor–treated patients experienced hypersensitivity reactions, mostly maculopapular rashes.[69] Hypersensitivity reactions occurred in 4.5% of indinavir-recipients within 25 days of starting drug therapy and in 12.5% of ritonavir recipients within a mean of 16 days of starting therapy; none of the 50 saquinavir recipients experienced any such reactions. Nine out of 13 patients who experienced hypersensitivity reactions were already established on sulpha drug therapy.[69] Allergic reactions to protease inhibitors appear rare, although an episode of anaphylaxis with hypotension, fever, rash and raised liver enzyme levels occurred in a patient receiving stavudine, lamivudine and indinavir; the reaction recurred on rechallenge.[70]

6.1.4 Immune Restoration Syndromes

While the immune restoration observed with effective antiretroviral therapy is associated with a significant reduction in the risk of clinical events, a number of syndromes, particularly in individuals with late stage HIV disease, which are thought to be related to an improving immune system and re-

responsiveness to certain opportunistic diseases have recently been described. In some cases, immune reactivation results in intense inflammatory reactions such as around Kaposi's sarcoma lesions or molluscum contagiosum, which whilst initially painful may be associated with subsequent improvement in these conditions.[71,72] However, in some persons 'unmasking' of subclinical opportunistic disease has been associated with serious or severe clinical disease. For example, active vitritis of the eye in a proportion of patients with previous cytomegalovirus (CMV) disease, the appearance of localised tuberculosis or *Mycobacterium avium* complex disease (particularly abscesses and discharging sinuses) and flares in hepatitis have all been reported.[73-75] Patients with late stage HIV infection commencing protease inhibitor therapy may therefore need to consider, for example, the use of corticosteroids to dampen potentially serious inflammatory reactions in the first weeks after therapy commencement.

These events are not truly adverse effects of protease inhibitors but are likely to be related to a recovering immune system. It is unclear if protease inhibitor–containing therapy results in specific or more rapid improvements in immune function which make these events more likely or more severe than with protease inhibitor-sparing regimens. Whilst risk of these events does not represent an obstacle to therapy it does represent an additional cause of morbidity with therapy.

6.2 Adverse Events with Individual Agents

Data on other individual adverse effects, i.e. those not considered as class-related effects, as detailed in the European SPC are shown in table III. It should be noted that reporting of adverse events varies between products making direct comparison challenging. Additional information on more common, serious or severe events will now be discussed.

6.2.1 Indinavir

In a cohort of 240 patients (median CD4+ cell count of 472 cells/mm^3) indinavir was associated with a 3% incidence of renal calculi with a further 5% of patients who were treated for a mean 30 weeks experiencing dysuria, flank or back pain.[76] The annual incidence of urological symptoms is therefore likely to be higher. Furthermore, in this study there was a 20% incidence of crystalluria, often associated with ultrasonically detectable deposits in the renal cortex or medulla, the clinical significance of which is unclear. No association with CD4+ cell count, a range of risk factors for renal calculi or duration of therapy was observed. The mean time to symptoms was 18 weeks (range 1 to 47 weeks). Of 16 patients who interrupted and restarted indinavir therapy, 9 had recurrence of symptoms, all associated with recurrence of crystalluria.[76] Crystals of indinavir have been found in the urine although stones may be a mixture of indinavir and oxylates. Renal colic or nephrolithiasis was reported in 4% of triple therapy patients over a median 38 weeks in ACTG320.[10] The incidence of this adverse may be more common in warm climates[77] although the incidence is said to be lower if fluid intake is increased.[78] A syndrome of individuals developing (mostly) reversible obstructive nephropathy with renal dysfunction with crystaluria whilst taking indinavir has also been widely reported.[77,79-83]

In addition, hepatitis or more severe transaminitis with concomitant hepatitis A infection has been reported with indinavir.[84]

Overall, the incidence of all severe or worse adverse events was similar between the 2 treatment groups in ACTG320, a study of patients with advanced disease (CD4+ cell count of <200/mm^3) that compared the combination of zidovudine and lamivudine with zidovudine, lamivudine and indinavir. Patients receiving indinavir experienced a significantly lower incidence of neutropenia.[10]

Isolated asymptomatic hyperbilirubinaemia [total bilirubin level of 43 μmol/L (2.5 mg/dl)], reported predominantly as elevated indirect bilirubin levels and rarely associated with elevations in ALT, AST, or alkaline phosphatase, has been seen to occur in approximately 10% of patients treated with indinavir alone or in combination with other antiretroviral agents.[85] Most patients continue treat-

Table III. Incidence of adverse events (% of patients) as reported from the European summary of product characteristics

	Indinavir[a]	Saquinavir-SGC[b]	Nelfinavir[b]	Ritonavir[a]
Nausea	35.3	10.6	4.5	47.5
Vomiting	11	2.9		23.6
Diarrhoea	24.6	19.9	25.9	44.9
Dyspepsia	10.7	8.4		Frequently
Taste perversion	19.1	>2		11.4
Abdominal pain	14.6	2.3		11.6
Acid regurgitation	6.5			
Headache	25.2	5.0		15.5
Rash	19.1		3.0	Frequently
Fatigue/asthenia	24.3	4.7		22.3
Renal calculi	4.0			
Dry skin	16.2			
Flatulence	7.8	5.7	2.5	Occasionally
Insomnia	7.4			Occasionally
Pruritus	7.4			
Hyperaesthesia	7.1			Frequently
Dry mouth	6.8			Occasionally
Dysuria	6.5			
Paraesthesia	5.2			Peripheral 15.4 Perioral 26.6
Myalgia	5.2	>2		Occasionally
Dizziness	10.7			Frequently
Vasodilation				Frequently

a Assessed as at least possibly related to drug therapy.

b Adverse effect of moderate or severe intensity, considered possibly related to drug therapy.

SGC = soft-gelatin capsule.

ment with indinavir without the need for a dosage reduction and bilirubin values gradually decline toward baseline. Hyperbilirubinaemia occurred more frequently at dosages exceeding 2.4 g/day compared with dosages <2.4 g/day.[85]

6.2.2 Ritonavir

In patients with advanced immunodeficiency (CD4+ cell count ≤100/mm^3) the addition of a liquid preparation of ritonavir to established nucleoside therapy, resulted in 17% of patients stopping therapy because of adverse events compared with 6% of placebo recipients.[12] The most commonly reported adverse effects of ritonavir were nausea (52%), vomiting (29%), diarrhoea (50%), circumoral paraesthesia (28%), asthenia (25%) and altered taste (12%).[12] Nausea was responsible for withdrawal from treatment of 10.4% of all ritonavir recipients.[12] Laboratory abnormalities include raised hepatic transaminase levels (ALT level >215 IU/L in 9% of ritonavir recipients *vs* 4% of placebo recipients and γ-glutamyl transferase level >300 IU/L 21.1% *vs* 11.9%), raised creatinine phosphokinase levels (>800 IU/L 12.5% *vs* 8.2%) and raised blood lipids.[12]

Initial tolerability of this agent appears better with the capsule formulation and the use of dosage escalation regimens; however, a substantial proportion of patients continue to experience initial nausea and diarrhoea with this agent. These adverse experiences tend to resolve over the first 4 to 8 weeks of therapy and intolerance may be limited by dosage escalation over the first few weeks.[86] Comparing escalation to 600mg twice daily over 7 versus 14 days showed better results with the 14-day escalation. Data reported on 79 patients randomised 1 **:** 1 to 7 day (arm A) or 14 day (arm B) dosage escalation schedules are shown in table IV.[87]

Table IV. Adverse events with dose escalation regimens of ritonavir capsules[83]

Adverse event	No. of patients (%)	
	treatment arm A[a] (n = 39)	treatment arm B[b] (n = 40)
Nausea	19 (49)	12 (30)
Vomiting	7 (18)	5 (12.5)
Circumoral paraesthesia	26 (67)	13 (33)
Diarrhoea	17 (44)	24 (60)
Treatment discontinuation because of an adverse effect	15 (38)	9 (23)

a Arm A was a 7 day dosage escalation schedule.
b Arm B was a 14 day dosage escalation schedule.

Patients with a concomitant hepatitis B or C infection may have greater difficulty tolerating ritonavir, with some patients experiencing substantial elevations in hepatic transaminase levels in the weeks following therapy initiation. The incidence of this problem may be dosage related.[88]

6.2.3 Saquinavir

Saquinavir-HGC is the most well tolerated but least active available protease inhibitor preparation. Moderate or worse severity diarrhoea was observed in 3.8% of recipients with advanced disease receiving this drug in combination with zalcitabine, with liver function test and haematological abnormalities occurring in <1%.[89] However, this preparation cannot be recommended for use as the sole protease inhibitor due to lower potency than the new soft gel capsule or other protease inhibitors.

The soft-gel formulation of saquinavir, saquinavir-SGC, appears to be associated with a slightly higher incidence of adverse events than the HGC preparation. In the safety study NV15182 in 442 mostly nucleoside analogue treatment–experienced patients receiving this drug for up to 1 year, 8% discontinued treatment because of adverse events mostly related to the gastrointestinal tract.[50] Other moderate or worse severity events that were reported in more than 5% of patients were fatigue and headache. Shifts in hepatic transaminase levels (ALT or AST) of ≥2 grades occurred in 3 to 4% and <0.5% of patients discontinued treatment because of raised transaminase levels. In patients with a history of hepatitis B or C infection or unspecified hepatitis only 8/39 had ≥3 grade shifts in transaminases on study.[32]

6.2.4 Nelfinavir

The most common adverse event with nelfinavir is diarrhoea, although the incidence of dose-limiting diarrhoea is unclear from available data. Other adverse events have only infrequently been reported but include headache, asthenia, rash and myalgia and elevation of hepatic transaminase levels.[90] Limited published data on completed nelfinavir studies are available to provide informed opinion as to risk with this drug apart from gastrointestinal events. Many patients receiving long term nelfinavir treatment continue to report an altered stool consistency and less frequently diarrhoea which in some cases remains a problem for the patient. However, in the authors' experience few individuals with satisfactory treatment responses to nelfinavir wish to discontinue or modify therapy because of these effects.

7. Safety of Dual Protease Inhibitor Therapy

No unexpected adverse events have been reported with dual protease inhibitor therapy. However, some adverse events may be increased in frequency. Dosage reductions, particularly of ritonavir, enable therapy with this agent to be more readily tolerated in combination use.

Adverse events reported during treatment with ritonavir plus saquinavir are largely consistent with the safety profile of ritonavir.[12,91] Events include initial nausea, diarrhoea, taste disturbance and perioral paraesthesia. These effects generally resolve with continued therapy and can be reduced by following a dose-escalation regimen at the time of introduction of ritonavir. Lower dosages of ritonavir, such as 400mg twice daily, appear to be associated with improved tolerability of the ritonavir-saquinavir combination without loss of activity. Elevation of hepatic transaminase levels was observed in a small proportion of patients in the study of Cameron et al.,[91] most commonly in

Table V. Incidence (% of patients) of laboratory abnormalities as reported from European summary of product characteristics

	Indinavir[a]	Saquinavir-SGC[b]	Nelfinavir[c]	Ritonavir[d]
Raised ALT levels	≥10	5.7	<2	Frequently
Raised AST levels	≥10	4.1	<2	Occasionally
Raised GGT levels		5.7		12
Raised bilirubin levels	≥10	Reported		Occasionally
Raised CPK levels		7.8	3.9	Frequently
Raised glucose level				Occasionally
Low glucose level		6.4		
Raised potassium level		2.7		
Anaemia		Reported		Reported
Neutropenia	≥10	2.9	4.5	Reported, leucopenia 16
Low platelet count		Reported		
Haematuria	Reported			
Proteinuria	Reported			
Raised TG levels				Frequently
Raised cholesterol levels				Reported
Raised amylase levels		Reported		Occasionally Abnormal thyroid function

a At least possibly related to drug therapy over 24 weeks of follow-up.

b Marked change, grade 0 to ≥3, grade 1 to grade 4, up to 1 year follow-up.

c Marked change, grade 0 to ≥3, grade 1 to grade 4, 24 weeks follow-up.

d At least possibly related to drug therapy in phase II/III studies.

ALT = alanine amino transferase; **AST** = aspartate amino transferase; **CPK** = creatine phosphokinase; **GGT** = γ-glutamyl transferase; **SGC** = soft-gelatin capsule; **TG** = triglycerides.

patients receiving the highest dosages of each agent. Risk factors for an episode of grade 4 transaminase level elevation included a hepatitis B or C infection and elevated transaminase levels at baseline and escalation of either agent to a dosage of 600mg twice daily.

With the combination of saquinavir and nelfinavir, nausea and diarrhoea have been the most commonly reported adverse events but they are generally mild to moderate and self-limiting.[48] The frequency of diarrhoea appears greatest in the combination arms in the SPICE study,[48] with diarrhoea (all grades) being reported in over 50% of dual protease inhibitor recipients (see table II). Laboratory abnormalities have been infrequent in this study.[48]

In ADAM[49] mild increases in liver enzyme levels occurred in 10/43 patients, causing discontinuation of therapy in 3 patients by week 16. Other adverse events (all grades) occurring by week 26, but not causing treatment discontinuation, were fatigue (16/43 patients), raised triglyceride levels (15/43), headache (16/43) and abdominal discomfort (9/43).[49]

8. Laboratory Abnormalities

The frequency of laboratory abnormalities as reported in the European SPC for the protease inhibitors are shown in table V. Further details of glucose and lipid disturbance were discussed in the section on lipodystrophy (section 6.1.2).

9. Other Therapy Considerations

9.1 Adherence

The success of any therapeutic intervention is dependent upon the patient adhering to the prescribed therapy. Non-adherence among patients is more prevalent when the illness is chronic and in the absence of clinical symptoms where treatment recommendations may be considered prophylactic. Experiences with other chronic diseases such as

Table VI. Adult dosage requirements of approved protease inhibitors at recommended administration frequency.

	Approved dose	Frequency	Food relationship	Number of pills/day
Indinavir	800mg	tid	Fasted or low fat	6
Nelfinavir	750mg	tid	Preferably with food	9
Ritonavir	600mg	bid	Preferably with food	12
Saquinavir-HGC	600mg	tid	Within 2 hours of food	9
Saquinavir-SGC	1200mg	tid	Within 2 hours of food	18

bid = twice daily; **HGC** = hard-gelatin capsule; **SGC** = soft-gelatin capsule; **tid** = thrice daily.

diabetes mellitus, organ transplantation, renal failure, tuberculosis and hypertension indicate that patient adherence has a direct effect on clinical outcome. In these illnesses, adherence to treatment, that is taking >80% of prescribed doses, averages 40 to 60% of patients. Investigators have identified a number of factors consistently associated with poor adherence. These include:

- lack of knowledge about disease and medication
- anxiety about taking medication
- concerns about adverse effects
- health beliefs
- complexity of regimens
- poor clinician-patient relationships.

Additionally, patients may choose not to adhere to treatment as away of retaining control or of coping with their illness. As poor adherence generally has no immediate or overt negative consequences for the patient, and in some cases may result in diminution of adverse effects, the patient may be readily able to reassure themselves that missing doses is relatively harmless.

Frequency of administration appears critical to adherence. In patients with hypertension, compliance improved from 59% with 3 times daily administration to 84% with once daily administration. Compliance between once and twice daily administration may not differ. With antihypertensive drugs given twice daily, less than half the doses were taken within 12 ± 2 hours.[92,93] Timing of doses may be particularly important in persons receiving protease inhibitors, which have a close plasma to intracellular concentration relationship and relatively short plasma half-lives. Treatment recommendations should therefore be individualised based on the patients' expectations or beliefs regarding their ability to manage different administration regimens including twice or three times daily and the need to administer with or without food.

The approved administration requirements for protease inhibitors are shown in table VI. However, short term activity and safety data suggesting twice daily administration of both nelfinavir, saquinavir (and the unapproved protease inhibitor amprenavir) is feasible. Twice daily administration with indinavir, however, requires the inclusion of ritonavir 100 to 400mg twice daily to ensure adequate trough concentrations.

Data from our clinic in London suggest expectations of drug efficacy and safety, health beliefs, feedback of laboratory results and use of stimulant recreational drugs [such as methylenedioxymethamphetamine ('Ecstasy')] all impact on adherence in persons receiving protease inhibitors. Interestingly, pill burden was not noted to influence adherence; if patients were going to take their pills they would take the prescribed quantity.[94]

Thus, persons requiring therapy may accept a trade-off of a higher pill burden if it means receiving a better tolerated or more effective therapy.

9.2 Metabolism of Protease Inhibitors and Pharmacokinetic Interactions

The approved protease inhibitors are all primarily metabolised through the CYP3A4 isozyme of the CYP enzyme system although a small proportion of ritonavir, and possibly other agents, is metabolised through CYP2D6.[91] The CYP3A4 isoenzyme is found both in enterocytes in the gut wall and in hepatocytes. A normal distribution exists in the activity of CYP3A4 across populations hence substantial exposure differences occur between in-

dividuals with the fixed doses of protease inhibitors currently employed. This may represent a common reason for inadequate or poorly sustained response to protease inhibitor therapy. Additionally, transcellular transport (permeability) of some protease inhibitors may be influenced by p-glycoprotein, an efflux transporter protein thought responsible for failure of some cancer chemotherapy agents.

All protease inhibitors act as competitive inhibitors of CYP3A4. However, variability exists between the affinity of each agent to the enzyme and hence the extent of competitive inhibition. Ritonavir is the most potent inhibitor of CYP3A4 and may also inhibit other CYP isozymes such as CYP2C9, CYP2C19 and CYP2D6. Ritonavir induces its own metabolism through CYP3A4 and also induces glucuronosyl transferase and CYP1A2, thus some interactions may persist for a short period after therapy with this agent has been discontinued. Some autoinduction is also thought to occur during the initial weeks of nelfinavir use. Therefore, interactions between these agents and other pharmacological agents may differ from those with indinavir or saquinavir which appear to only inhibit CYP3A. Saquinavir is the weakest inhibitor of CYP3A4 and nelfinavir and indinavir are intermediate to this agent and ritonavir. Thus, ritonavir has the greatest effect on a co-administered CYP metabolised drugs (both legal and illegal) whereas saquinavir has the smallest effect.[91]

10. Conclusions: Individualising Risks and Benefits in Practice

While the risk-benefit ratio for the use of protease inhibitors as exceptionally potent remedies for the treatment of HIV disease was clearly in favour of their early use a year or so ago, emerging adverse effects have left the risk-benefit ratio for the treatment of early disease less clearly defined. It remains true that protease inhibitor-based HAART is the most well proven therapy for treatment of HIV-infected persons for whom a substantial risk (perhaps >10 to 20% over 3 years) of disease progression exists. In these circumstances, risks of protease inhibitor therapy appear to be outweighed by the benefits of therapy across a population. Similarly, in persons established on protease inhibitor therapy, who are achieving optimal therapeutic responses and who are not experiencing significant adverse effects, no change of therapy is indicated. However, in persons with a low risk of short to medium term (1 to 3 year) disease progression, monitoring rather than intervention may be associated with a lower overall morbidity. For example, intervention in 100 patients with a 10% 3-year risk of progression may prevent say, 8 or 9 of these progressions, but may cause say 15 persons to experience moderate or worse severity adverse effects or treatment-limiting drug-related toxicity. The remaining 75 patients gain no overt benefit or experience any significant toxicity. Most of the 10 patients who would have progressed would have been identified by monitoring as their markers of risk over time would have changed to indicate increasing risk, singling them out for intervention.

When the decision to use a protease inhibitor-containing regimen is clear, consideration should be given to the view that the risk associated with each protease inhibitor is different. Given that the antiviral effects of each protease inhibitor in therapy-naïve patients is similar there is likely to be a different risk-benefit ratio for each of the individual agents. Indeed, the risk-benefit ratio for any combination may vary from individual to individual as risk of some protease inhibitor-related adverse events in an individual may relate to issues such as family history (e.g. of diabetes mellitus or hyperlipidaemia), past history (e.g. of renal calculi) or current medical problems (e.g. diarrhoea, hepatitis B or C infection).

It is therefore not possible to provide a broad recommendation for any single protease inhibitor, suffice to say that all approved protease inhibitors have a role in clinical practice and further agents with improved tolerability and administration characteristics are required. Accumulation of additional data are required to further inform this decision, an issue which may require more robust encouragement or enforcement by regulatory bodies.

The problem with over-reliance on small short term activity marker studies to guide therapy is that long term adverse effects may be missed. It is too early yet to be certain where the new consensus will be found regarding therapy in early disease. However, we believe it is highly likely that protease-sparing regimens, with the use of potent NNRTIs and perhaps with triple combinations of nucleoside analogues involving abacavir, will become more widely used as the agents of first choice. This is particularly true if prolonged follow-up of ongoing comparative trials indicate similar antiviral activity and further underline the tolerability and administrative advantages of some NNRTIs. Protease inhibitor–based regimens should provide suitable second-line or 'salvage' regimens when and if these agents fail. This will, however, still mean a large number of persons receiving very long term protease inhibitor exposure.

Data are needed to identify those individuals for whom NNRTI-based HAART may not be ideal. The single codon mutation in the RT genome sufficient to produce high level resistance to most NNRTIs demands that these drugs should only be used in regimens which will completely suppress viral replication, when combined with agents of sufficient activity to ensure that the selection of pre-existing mutants to the NNRTIs cannot emerge. Protease inhibitors may have advantages in this regard as the development of significant phenotypic resistance may require a more complex set of mutational changes both within the protease genome and possibly also in the *gag* gene. However, it is not really clear whether this higher genetic barrier, as it is sometimes called, to protease inhibitors really exists, as there is usually one key resistance mutation which significantly affects the thermodynamic interactions between enzyme and inhibitor.

What is really required are head to head comparisons of the policies of starting treatment with an NNRTI-containing regimen followed by a protease inhibitor regimen for failure compared with starting the other way round. Such a trial is starting across Europe (called Initia) and a similar study is being carried out by the ACTG.

For the moment, however, the undoubted adverse effects of the protease inhibitors, the potency of non-protease inhibitor-containing regimens and the difficulties of adherence to certain protease inhibitor–containing therapies, mean that there is some caution in the previously perceived wisdom of using protease inhibitors in persons at low risk of HIV disease.

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