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Antiretroviral Therapy for HIV Infection

A Knowledge-Based Approach to Drug Selection and Use

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Summary

In the absence of evidence that eradication of HIV from an infected individual is feasible, the established goal of antiretroviral therapy is to reduce viral load to as low as possible for as long as possible. Achieving this with the currently available antiretroviral agents involves appropriate selection of components of combination regimens to obtain an optimal antiviral response. In addition, consideration of a plan for a salvage or second-line regimen is required if initial therapy fails to achieve an optimal response or should loss of virological control occur despite effective initial therapy. Such a planned approach, based on consideration of the likely modes of therapeutic failure (viral resistance, cellular resistance, toxicity) could be called rational sequencing.

Choice of therapy should never involve compromise in terms of activity. However, the choice of drug should also be guided by tolerability profiles and considerations of coverage of the widest range of infected cells, compartmental penetration, pharmacokinetic interactions and, importantly, the ability of an agent or combination to limit future therapeutic options through selection of cross-resistant virus. Available clinical end-point data clearly indicate that combination

therapy is superior to monotherapy, with clinical and surrogate marker data supporting the use of triple drug (or double protease inhibitor) combinations over double nucleoside analogue combinations. Thus, 3-drug therapy should represent current standard practice in a nontrials setting.

Treatment should be considered as early as practical, and may be best guided by measurement of viral load, with a range of other markers having potential utility in individualising treatment decisions. Therapeutic failure may be defined clinically, immunologically or, ideally, virologically, and should prompt substitution of at least 2, and preferably all, components of the treatment regimen. Drug intolerance may also be best managed by rational substitution.

Evidence of massive viral replication during all stages of HIV infection strongly supports the view that immunological decline and subsequent clinical progression to AIDS are driven by HIV.[1,2] Therefore, to prolong length and quality of life in patients with HIV, therapeutic intervention should achieve substantial, preferably complete and prolonged, suppression of viral replication, prevent infection of additional cells and, at least, create an environment in which immune regeneration may occur.

Recognition of a reservoir of latently-infected CD4 lymphocytes with a long decay half-life has underlined the difficulties of viral eradication from chronically infected individuals.[3] Clinicians who still believe viral eradication is possible also believe that it is crucial to 'hit hard, hit early'; to commence aggressive therapy at the time of presentation. However, this approach ignores the potential for drug-related morbidity associated with all antiviral agents. In an individual with a low, short or medium term risk of HIV-related illness, therapy may be associated with a higher incidence of adverse events than no intervention.

In particular, the incidence and long term consequences of problems recently identified during prolonged protease inhibitor therapy, e.g. diabetes mellitus, bleeding and haemolysis, renal crystals and calculi, hyperlipidaemia and truncal obesity, require further investigation before widespread use of these agents can be recommended in patients with early disease and low short term risk of significant clinical or immunological progression. Additionally, asymptomatic individuals are less likely to adhere to therapy and thus their treatment may fail earlier than those who are motivated by symptoms to commence therapy. Clinical trials of intervention versus observation in early disease are therefore urgently required.

Many virologists and clinicians continue to believe that, in due course, the virus is likely to evade drug pressure. While achieving a virological response to below-assay detection, the optimal response may be associated with a more durable treatment response and delayed resistance compared with less complete reductions, resistance and loss of virological control, which are increasingly observed over prolonged follow-up.[4,5] This may be due to persistent viral replication below the detection levels of standard plasma viral load assays or in separate tissue compartments. Indeed, separate compartmental turnover of HIV beyond the plasma/lymphoid compartment has been documented in the genital tract[6] and CNS,[7] compartments which may not be well penetrated by all antiretroviral agents, and which may represent a potential source of resistant virus.

Acquisition of virus resistant to zidovudine and other antiretroviral drugs is well documented and increasingly common in urban seroconverter cohorts and may be contributory to poor treatment responses or early failure. Additionally, drug interactions, poor tolerability, intercurrent illnesses and episodic adherence failure (a well documented problem, particularly with complex regimens in a range of disease states) are all likely contributors to the circumstances which will enable viral escape. Furthermore, many recipients of antiretroviral therapy do not experience optimal responses, necessitating early treatment modification.[8] Thus,

in the absence of clinical evidence that viral eradication from HIV-infected individuals is possible, gaining optimum benefit from antiretroviral therapy will involve:

- strategic planning of drug therapy, to achieve the best virological responses with each therapy; and
- the avoidance of initial and subsequent therapies that squander future drug therapy options through, principally, cross-resistance.

In vitro and *in vivo* data demonstrate that arresting viral replication cannot be achieved in a sustainable manner through single agent therapy. Variants in the viral swarm that are resistant to antiretrovirals exist before initiation of therapy[9-11] and may be rapidly selected for during treatment to become the dominant quasispecies. This often coincides with virological failure.[12,13] Furthermore, clinical, immunological and virological responses observed during combination therapy appear to be consistently superior in both magnitude and duration to those seen with antiretroviral monotherapy. A number of 2- and 3-drug combinations have been observed to reduce viral replication to below the lower level of test detectability (as measured by plasma viral load assays) in the majority of recipients. These responses are associated with an apparent delay in the development of resistance, relative to poorer responders,[5] as well as a substantial rise in CD4 cell counts.

Achieving sustained viral suppression with the currently available antiretroviral agents involves individualised selection of components of the combination therapy to obtain an optimal antiviral response with a well tolerated and convenient regimen. Initial therapy should never be compromised in terms of activity since magnitude and duration of response appear to be greatest at the beginning of treatment. However, consideration of salvage therapy in case a patient does not respond to initial treatment appears to be an appropriate therapeutic strategy.

When considering a salvage or second-line therapy, knowledge of the resistance/cross-resistance profiles of the initial therapy is crucial, as viral resistance appears to be critical to the failure of most regimens. Some increasingly used combinations such as stavudine (d4T)/didanosine (ddI) [d4T/ddI] may, however, fail due to slowed intracellular activation, an issue on which more data are needed. It is not known how long cellular kinases take to return to normal after slowing during prolonged nucleoside analogue use. However, some physicians are now considering giving patients who have not responded to one regimen a short treatment 'holiday' before starting a new regimen. This may also be necessary when discontinuing an inducer of cytochrome P450 enzymes, as immediate initiation of another P450-metabolised drug may lead to diminished response due to increased first-pass metabolism.

A number of factors have been identified which diminish the chances of achieving an optimal or durable response to potent therapy. These include low baseline CD4 cell count, high initial viral load, prior prolonged therapy with nucleoside analogues or another protease inhibitor, and a history of poor treatment adherence.[14] Patients with these poor prognostic characteristics may therefore require more aggressive therapy, for example the use of 4 or more agents.

In addition to evidence from randomised clinical studies, rational choice of therapy may also take into account biologically plausible data from sources such as *in vitro* and mathematical models. Appropriately chosen combination regimens may not only provide the possibility of synergistic suppression of viral replication, but should also include agents with nonoverlapping resistance profiles, provide therapy against established resistant strains and cover a wide range of infected cell lines (e.g. monocyte-macrophages and lymphocytes, acutely and chronically infected cells), viral phenotypes [such as syncytium-inducing (SI)] and body compartments (e.g. CSF and lymph nodes).

In order to ensure the most rational and strategic use of the available agents, decisions regarding therapy should include consideration for a variety of other factors including:

- Tolerability profiles and potential interactions with concomitant medications.

- Clinical history (e.g. a history of peripheral neuropathy or pancreatitis).
- Current clinical status.
- Potential of a given agent or regimen to limit future therapeutic options or activity due to selection of cross-resistant or multi–drug-resistant virus.
- Pharmacokinetic and metabolic interactions (e.g. liver enzyme system inhibition or induction).
- Intracellular metabolic interactions.
- *In vitro* synergy or nonantagonism.
- Activity in different cell lines.
- Convenience of administration.

This article addresses the principles guiding initial choice of antiretroviral regimens in patients commencing therapy, and potential salvage for those experienced with antiretroviral therapy as well as how to manage drug intolerance. It is not intended to be used as a treatment 'cookbook', but rather to establish guidelines for best current practice which can then be applied to individual clinical situations. The choice of agents used in this discussion is based on the availability of clinical or surrogate marker data and a stage of clinical development that suggests likely availability in clinical practice within the next 1 to 3 years. These include:

- the nucleoside reverse transcriptase inhibitors (NRTIs) zidovudine, didanosine, lamivudine, stavudine, zalcitabine, and abacavir (1592U89);
- the non-nucleoside reverse transcriptase inhibitors (NNRTIs) nevirapine, delavirdine mesylate (delavirdine) and efavirez (DMP-266); and
- the protease inhibitors indinavir, nelfinavir, ritonavir, saquinavir-soft gel and VX-478 (141W94).

The hard gel capsule formulation of saquinavir as a mesylate salt is currently being withdrawn from use and cannot routinely be recommended for use as the sole protease inhibitor in a regimen due to demonstrated lower activity compared with the soft gel capsule formulation of this drug.[15] (see also review by Perry and Noble on page 461 of this issue). The issues of timing of therapy intervention and cost benefit are beyond the scope of this article and have recently been discussed in the British HIV Association guidelines[16] and several US-based guidelines.[17]

1. Goal of Therapy

Management of any medical condition aims to extend both length and quality of life. Ultimately, in HIV disease this aim should include eradication of the virus and renormalisation of the immune system. In the absence of evidence that eradication is feasible, extension of life and prevention of disease progression appears to be best achieved by arresting viral replication in all sites where HIV-infected cells are present, thus preventing infection of further cells and establishing the circumstances in which immune regeneration can occur. In practical terms, this means reducing plasma viral load to below the detection levels of standard assays (<400 HIV RNA copies/ml), and in the longer term, below detection limits of ultrasensitive assays (<40 copies/ml). However, treatment goals must be realistic so as not to create psychological morbidity in individuals who cannot achieve the optimal response. Indeed, over short periods of follow-up, reductions in viral load to <5000 copies/ml appears to be associated with a very low risk of progression and the lower the viral load achieved with therapy the lower the risk of a disease event.[18]

2. Antiretroviral-Naïve Patients

A number of studies have demonstrated the superiority of zidovudine monotherapy over placebo on the clinical end-points of disease progression and survival in treatment-naïve patients with AIDS and AIDS-related complex (ARC).[19,20] Earlier intervention with zidovudine monotherapy in individuals with asymptomatic disease or CD4 counts above 300/mm^3 may provide a delay in disease progression over 1 to 2 years compared with intervention at the onset of symptoms or at lower CD4 counts,[21-24] but it does not provide any additional survival or quality-of-life benefit.[22-28] Zidovudine monotherapy has been shown to be clinically superior to zalcitabine[28] in previously untreated patients with CD4 cell counts below 300/mm^3.

However, the efficacy of didanosine may be similar to that of zidovudine.[27,29,30]

Monotherapy with the protease inhibitors has been shown to produce initial activity marker responses greater than those typically observed during nucleoside analogue monotherapy.[31-40] However, these, or indeed any, antiretroviral agents should not be used as monotherapy.

Clinical end-point data from the ACTG 175[29] and Delta 1[41] studies have shown that combination therapy with zidovudine plus zalcitabine or didanosine is a superior first-line choice to zidovudine monotherapy, with no additional toxicity. Surrogate marker data from both studies demonstrated a correlation between improved clinical outcome and superior CD4 and viral load responses in the combination therapy arms. Data from the CAESAR study,[42] which included 16% treatment-naïve patients, also support this view, with recent data from Merck study 028 providing clinical evidence for the superiority of zidovudine/indinavir (or indinavir alone) over zidovudine monotherapy.[43]

Multiple surrogate marker studies and clinical end-point studies assessing combinations of reverse transcriptase inhibitors or nucleoside analogues with a protease inhibitor suggest that 3-drug combinations have greater antiviral activity than 2 nucleoside analogues. In small clinical studies, 70 to 90% of treatment-naïve patients on triple therapy regimens achieve viral load responses to below the detection limits of current assays, compared with 20 to 30% on 2 nucleoside analogues. Only those patients commencing therapy with viral loads of less than 5 to 10 000 copies/ml reliably and sustainably achieve viral load reductions to below assay quantification with 2 nucleoside analogues.[44,45] Therefore, dual nucleoside analogue therapy can no longer be considered a standard of care in countries where triple drug therapy is affordable and feasible.

Several small comparative studies of protease inhibitor–based triple therapy in mostly naïve patients suggest that similar treatment responses are observed between different regimens regardless of the choice of protease inhibitor[46,47] or nucleoside analogue combination.[48-50] Cross-study comparison of other reported trials supports this view. Although the studies do not have identical designs and baseline characteristics, comparison of responses illustrates that similar CD4 and viral load changes are observed in treatment-naïve patients with each of the leading nucleoside combination regimens and that inclusion of a protease inhibitor or an NNRTI as the third agent or using a double protease inhibitor regimen provides substantial additional antiviral effect (table I).[15,51-55]

In the absence of prospective comparative data, combinations of the approved NNRTIs with nucleoside analogues are perceived as yielding responses which are less impressive and may be less durable than protease inhibitor-based triple therapy combinations.[63] However, triple combination with zidovudine/didanosine/nevirapine in treatment-naïve patients has demonstrated greater antiviral effect over 1 year than the zidovudine/didanosine combination,[64] with a high proportion of triple therapy recipients achieving reductions in viral load to below 200 copies/ml. Patients with high initial viral loads were less likely to achieve this response, and hence the role of this regimen may lie in persons for whom protease inhibitor–based therapy is contraindicated or refused, and who have relatively low (<50 000 copies/ml) initial viral loads. Recent data on efavirenz in combination with zidovudine/lamivudine indicate that this is a highly potent agent worthy of consideration for use in initial regimens.[53] Additionally, the 2-drug regimen of efavirenz plus a protease inhibitor achieves short term virological responses similar to those obtained with standard triple therapy regimens,[65] and may in the future be considered for persons in whom nucleoside analogues are not preferred. Efavirenz has the additional advantage of convenient, once-daily administration.

Most clinicians would now consider triple therapy with 2 nucleoside analogues and a third agent to represent the current standard of care. Given similar activity across a range of triple combinations, the choice of combination will not be primarily driven by activity. There is, therefore, clearly a need for strategic consideration of other factors

Table I. Immunological and virological efficacy of antiretroviral combinations

Reference	No. of pts	Treatment arms	Baseline CD4 cell count (cells/mm^3)	Prior therapy	Peak mean rise in CD4 cell count (cells/mm^3)	Mean change in CD4 cell count from baseline to week 24 (cells/mm^3)	Duration of ↑ CD4[a] (week no.)	Peak mean decrease in viral load (log ↓ RNA copies/ml)	Mean decrease in viral load at week 24 (log ↓ RNA copies/ml)	Proportion of patients (%) below limit of HIV RNA quantification (<400 copies/ml) at week 24
Antiretroviral-naïve										
NV15355 (16wk data) [Conway[15]]	81	SQV-HGC + 2RTIs	447 (mean)	None	+115 (week 16)	+115 (week 16)	16	NA	–1.6	43 (week 16)
	90	SQV-SGC + 2 RTIs	401 (mean)		+97 (week 16)	+97 (week 16)	16	NA	–2.0	80 (week 16)[‡]
INCAS (6mo data) [Conway et al.[51]; Murphy & Montaner[52]]	51	ZDV/NVP/ddI	200-600 (376 mean)	None	NA	+120	NA	NA	–1.7	57
	52	ZDV/ddI			NA	+75	NA	NA	–1.3	35
	47	ZDV/NVP			NA	+10	NA	NA	–0.5	0
Hicks et al.[53]	137	ZDV/3TC/ EFZ 200	370 (mean)	None	NA	NA	NA	NA	NA	NA
		ZDV/3TC/ EFZ 400			NA	NA	NA	NA	NA	NA
		ZDV/3TC/ EFZ 600			NA	157 (week 16)	16	NA	–1.9 (week 16)	88 (week 16)
Mathez et al.[54]	29	ZDV/RTV/ddC	173 (mean)	None	+141	+130	36	–2.36 (week 20)	–2.13	
Nelfinavir AG1343 511 (Saag et al.[55])	99	NFV750/ZDV/3TC	No CD4 limit to entry	None	NA	+155	52 (+180)	NA	–2.3	80[b]
	96	NFV500/ZDV/3TC			NA	+160	24 (+180)	NA	–2.2	70[b]
	101	ZDV/3TC			NA	+104	24	NA	–1.3	≈20[b]
Antiretroviral-experienced										
Cameron et al.[56]; Heath-Chiozzi et al.[57]	1090	Existing ART +								
		RTV *or*	<101	>9mo prior ART	+47.5[†]	NA	NA	–1.29[†b]	NA	NA
		placebo			NA	NA	NA	NA	NA	NA
ACTG320 [Hammer et al.[58]]	577	IDV/ZDV/3TC		≥3mo prior ZDV (21mo median); all PI-, 3TC-naïve	+121 (week 40)**	91**	40	–2.8 (week 24)	–2.8	60[b]
	579	ZDV/3TC			+40 (week 40)	18	40	–1.0 (week 40)	–0.6	9[b]

CAESAR[42]		Existing ART +								
	462	3TC/LOV	25-250	ZDV only (62), ZDV + ddC (23), ZDV + ddI (15)	+74 (week 4)[b]	+22 (28wk)[b]	28	–0.79 (week 2)[b]	–0.25 (week 28)[b]	NA
	907	3TC			+43 (week 4)[b]	+23 (28wk)[b]	28	–0.67 (week 2)[b]	–0.1 (week 28)[b]	NA
	471	Placebo			+20 (week 4)[b]	Below baseline	Below baseline at week 28	NA	NA	NA
SPICE [Posniak[47]]	26	SQV-SGC/ 2 NRTIs	307 (mean)	46% treatment-experienced, all able to start ≥1 new NRTI	NA	NA	16	NA	–1.9 (week 16)	76
	26	NFV/2 NRTIs			NA	NA	16	NA	–1.7 (week 16)	50
	51	SQV-SGC/ NFV/2 NRTIs			NA	NA	16	NA	–1.9 (week 16)	84
	54	SQV-SGC/NFV			NA	NA	16	NA	–1.6 (week 16)	57
Merck 035 [Gulick et al.[59]]	33	IDV/ZDV/3TC	50-400 (median 144)	≥6mo prior ZDV (median 30mo)	NA	+86*	52	NA	–1.8 **,[#]	90[b]
	31	IDV			NA	+101	52	NA	–1.2	43[b]
	33	ZDV/3TC			NA	+46	52	NA	–0.8	0[b]
Mayers et al.[60] (24wk data)	59	IDV/EFZ[c]	284 (mean)	71% NRTI-experienced; all PI-, NNRTI-naïve	NA	+199	24	NA	–2.7	94
	42	IDV[d]			NA	+108	24	NA	–1.7	47
Pedneault et al.[61]	22	NFV750/ddI/d4T	70-709 (median 35)	50% ART experienced (all PI-, d4T and ddI-naïve)	NA	+218 (week 8)[b]	8	NA	–2.1 (week 8)	
Merck 039 [Hirsch et al.[62]]	320	IDV/ZDV/3TC	<50 (median 15)	≥6mo prior ZDV (all PI- and 3TC-naïve)	NA	+86[b]	24	NA	–2.2[b]	
		IDV			NA	+61[b]	24	NA	–0.17[b]	
		ZDV/3TC			NA	0[b]	24	NA	–0.16[b]	
ACTG 241 [Murphy & Montaner[52]]	398	NVP/ZDV/ddI	<350 (median 138)	≥6mo prior RTI	+34	NA	48	–1.2[b]	–0.10[b]	
		ZDV/ddI			+11	NA	Below baseline by week 24	–0.45[b]	+0.16[b]	

a CD4 cell count above baseline at stated week.

b Median.

c 200 increased to 600 after ≥36wk.

d Could add EFZ/d4T after 12wk.

Abbreviations and symbols: 3TC = lamivudine; ART = antiretroviral therapy; ddC = zalcitabine; ddI = didanosine; d4T = stavudine; EFZ 200, 400 and 600 = efavirenz 200, 400 and 600mg, respectively; HGC = hard gel capsule; IDV = indinavir; LOV = loviride; NA = not available; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitors; NRTI = nucleoside reverse transcriptase inhibitors; NVP = nevirapine; PI = protease inhibitor; pts = patients; RTI = reverse transcriptase inhibitors; RTV = ritonavir; SGC = soft gel capsule; SQV = saquinavir; ZDV = zidovudine; ↑ = increase; ↓ = decrease; * $p < 0.01$, ** $p < 0.001$ compared with ZDV/3TC; [†] $p < 0.001$ compared with placebo; [‡] $p < 0.001$ compared with HGC; [#] = $p < 0.001$ compared with IDV.

guiding choice in initial therapy. Such factors would include:

- convenience of administration;
- frequency and type of adverse events (including diabetes and hyperlipidaemia);
- the effects on CD4 and CD8 cells;
- the potential to limit future therapeutic options;
- the observed benefits of different agents in initial versus subsequent therapy regimens.

Additionally, novel approaches, such as the inclusion of hydroxycarbamide (hydroxyurea), which appears to substantially improve the virological activity of didanosine and zalcitabine *in vitro*[66] and at least didanosine *in vivo*,[67,68] probably by affecting intracellular deoxynucleoside triphosphate pools, warrant further investigation as a means of maximising the potential of nucleoside analogues.

3. Patients Who Do Not Achieve Optimal Responses

A significant proportion of treatment-naïve individuals who are started on triple therapy do not achieve a below–assay detection limits response by 12 to 16 weeks of therapy. This may be due to poor adherence, prior acquisition of virus resistant to one or more components of the regimen, pharmacokinetic issues such as variability in the cytochrome P450 system or insufficient potency of the regimen. Patients with high baseline viral loads (e.g. >100 000 copies/ml) or low CD4 cell counts (<200 cells/mm^3) appear to be most at risk. Strategies for managing these patients should be individualised on the basis of the assessment of the likely mechanism of incomplete response and the extent of residual viral replication. However, 2 approaches may be reasonable to consider: switching the entire regimen possibly to a regimen with more agents, or treatment intensification, i.e. adding one or more agents to the established therapy. For example, most patients who achieve an incomplete response to the combination of ritonavir/saquinavir have subsequently achieved a below-detectable viral load with the addition of 2 nucleoside analogues.[69] However, no clinical studies have examined treatment intensification and this strategy cannot be routinely recommended at present.

4. Antiretroviral-Experienced Patients

Studies in the early 1990s demonstrated that switching to an alternative agent as monotherapy or addition of a second agent is associated with clinical or surrogate marker benefits compared with continuing monotherapy. Clinical data suggest that the earlier such changes are initiated, the greater the associated therapeutic benefits. Only limited data are available on switching from or adding to combination regimens. However, many physicians now believe the best benefits are gained by switching at least two, and preferably all, components of a treatment regimen, with some recent data supporting this view.[43,70,71] This view is also endorsed by recent guidelines published by British and US groups.

4.1 Historical Data

Data from studies using suboptimal regimens and single drug switches may provide useful guidance regarding the likely activity of new agents in an appropriately modified optimum regimen. In patients with CD4 counts below 500/mm^3, significant delay in clinical progression has been gained by switching to didanosine following prior treatment with zidovudine,[29,72] although the presence of the zidovudine resistance–associated mutation at codon 215 may diminish the response to didanosine.[73] The value of switching to zalcitabine monotherapy is less clear, although a subset of patients has been shown to benefit,[74] and the only comparative study showed at least equivalence with didanosine.[75] Switching to stavudine 40mg twice daily in patients with at least 6 months prior zidovudine experience and CD4 cell counts between 50 and 500/mm^3 has been shown to be superior to continued zidovudine, significantly delaying disease progression, death or immunological decline.[76] The benefit of switching therapy appears to be independent of the duration of prior zidovudine therapy.[72,74,76,77]

In general, better responses are observed with the addition of agents to an ongoing regimen than with switching to a second monotherapy. Clinical benefits have been reported for the addition of didanosine, zalcitabine and lamivudine to established zidovudine therapy[29,30,31,42,74] and for ritonavir in severely immunodeficient patients experienced with and mostly still receiving a range of nucleoside analogues both as mono- and combination therapy.[56] Additionally, clinical benefit has been reported with adding lamivudine to established zidovudine/zalcitabine or zidovudine/didanosine therapy.[42] Data from surrogate marker studies also support the strategy of adding an additional therapy (table I)[42,47,52,56-62] with 24-week response data suggesting similar benefits with a range of agents.

5. Current Best Practice

To regain control of viral replication, and control viral resistance to initial therapy, it is widely considered prudent that switches in therapy should involve at least 2 new agents, preferably all new agents, and include at least one agent from a different therapeutic class. For example, after failure on 2 nucleoside analogues and an NNRTI, the best salvage therapy is likely to include 2 new nucleoside analogues and at least one, perhaps two, protease inhibitors. Using protease inhibitors as one of the salvage agents appears to provide a better response than NNRTIs in nucleoside analogue–experienced patients, with clinical benefit reported for protease inhibitor–based regimens.[58,78] This provides an argument for consideration of the use of NNRTIs in initial regimens, 'saving' the protease inhibitors for later use. However, as yet this approach has not been tested in clinical studies.

After failure of an initial protease inhibitor–based triple therapy, combinations of agents including new nucleosides, an NNRTI and dual protease inhibitors may provide the best responses. Salvage studies after protease inhibitor regimens, while mostly anecdotal and retrospective, suggest that changes are best initiated promptly after loss of virological control, and that the chances of response may in part relate to the number of accumulated mutations in the protease gene (table II).

While the benefit of switching or adding therapies appears to be independent of the duration of prior zidovudine, the presence of zidovudine-

Table II. Virological response after switching to a second-line protease inhibitor (PI) regimen

Reference	No. of pts	Duration of prior PI therapy	New therapy	Mean change in HIV-1 RNA (log_{10} copies/ml) after switch	Proportion of patients with HIV RNA below assay quantification (400 copies/ml) after switch (%)
ACTG333 (Para et al.[85])	72	112wk SQV-HGC	IDV	0.58 at week 8	43
Schapiro et al.[86]	10	58wk SQV-HGC	IDV. After 4wk, ZDV + 3TC also added	1.2 at week 4 (IDV added) 1.94 at week 24 (ZDV + 3TC added)	66 at week 24
Dulioust et al.[87]	22	9mo SQV-HGC	IDV	NA	NA (45% had HIV RNA <3.5 log_{10} copies/ml)
Lawrence et al.[88]	16	11mo SQV-HGC	NFV	0.56 at week 4	19 at week 4
	7	11mo SQV-HGC, 12wk NFV	IDV, NVP added	1.8 at week 4	NA
Pym et al.[89]	12	4.9y SQV-HGC	RTV added	0.97 at week 4, 0.03 at week 16	NA
Walmsley et al.[90]	16	14wk SQV-HGC	IDV	1.3 at weeks 8-12	25 (<500 copies/ml) after 2-3mo
Miller et al.[91]	20	IDV	SQV/RTV ± RTIs	–3.15 to +0.9 at week 4	NA (only 6 pts ≥1 log reduction at week 4)

Abbreviations and symbol: 3TC = lamivudine; HGC = hard gel capsule; IDV = indinavir; NA = not available; NFV = nelfinavir; NVP = nevirapine; pts = patients; RTI = reverse transcriptase inhibitors; RTV = ritonavir; SQV = saquinavir; ZDV = zidovudine.

resistant virus may make virological response to the addition of either zalcitabine, didanosine or delavirdine mesylate less likely.[73,79,80] This suggests that these therapies are best commenced with zidovudine. Some of these agents (e.g. zalcitabine, didanosine) may be subsequently re-used or recycled in a future regimen as failure during combination with zidovudine appears to be driven by zidovudine resistance.[81] Withdrawal of zidovudine in an *in vitro* system results in reversion of virus to a phenotype with sensitivity to these agents.[82]

No studies have yet examined treatment responses to second-line nucleoside analogues after initial therapy with stavudine. However, as no consistent genotypic mutations are observed with this agent, cross-resistance is likely to be less of a problem. Nevertheless, multi-nucleoside-analogue–resistant virus has occasionally been reported from patients heavily treated with a range of these agents,[83,84] suggesting that in some circumstances switching within this class may not be of value. Cross-class resistance appears to be a problem with NNRTIs and has been observed with all available protease inhibitors. However, limited (mostly non-prospective) data suggest that modest short term treatment responses are observed in some patients switched promptly from an initial protease inhibitor to subsequent single or double protease inhibitor therapy (table II).

6. Nucleoside Analogue–Intolerant Patients

Data on the comparative efficacy of the available antiretrovirals in nucleoside analogue–intolerant patients are limited. Zidovudine intolerance may occur early (most commonly due to nausea), or late (due to either haematological toxicity or, infrequently, myopathy). The principal studies in zidovudine-intolerant patients[92-96] all suggest that didanosine and zalcitabine have acceptable tolerability in this patient group and provide similar (limited) efficacy. Therapy with stavudine-based combinations with didanosine, lamivudine and/or nelfinavir, have reported activity. Indeed, lamivudine appears to be generally well tolerated in a range of clinical contexts.

Patients with both haematological toxicities and peripheral neuropathy represent poor candidates for nucleoside analogue therapy. In these circumstances, combinations of 2 protease inhibitors or NNRTIs plus protease inhibitors may be necessary. In particular, the combination of ritonavir and saquinavir has been shown to produce durable treatment responses in individuals pretreated with nucleoside analogues and who have CD4 cell counts above 100/mm^3.[97,98] Combinations of NNRTIs have not been investigated to date, although studies are currently under consideration.

7. Other Factors Influencing Choice of Therapy

Most large clinical or small surrogate marker studies use relatively heterogeneous patient populations not stratified for various factors such as SI/non–SI (NSI) phenotype, viral load or presence of resistant virus at baseline. Additionally, most large studies are analysed by intention-to-treat methods, often despite a substantial proportion of patients either changing therapy or being lost to follow-up. This may lead to under- or overestimation of therapeutic effect. Furthermore, many studies are conducted for licensing and approval purposes and therefore do not reflect best clinical practice. Evidence indicating that surrogate endpoints can be used to predict clinical outcome is increasing, potentially allowing for more rapid evaluation of new agents or regimens and suggesting that treatment decisions may be based upon these markers.[99,100] The optimum use of available antiretrovirals, choice of components of a combination regimen and the sequencing of those regimens should depend not only on data from clinical studies with their intrinsic limitations, but on a number of additional factors as outlined in sections 7.1 to 7.6.

7.1 Drug Interactions

Patient history and awareness of concomitant medications is obviously important if overlapping

toxicities and the potential for pharmacokinetic interactions are to be avoided or interactions harnessed to improve the bioavailability of an agent (tables III and IV). Toxicities occurring with nucleoside analogues often occur through similar mechanisms: for example, peripheral neuropathy with didanosine, stavudine and zalcitabine appears to be related to inhibition of human mitochondrial α-DNA polymerase,[101] and exacerbation of zalcitabine-related neuropathy has been described

Table III. Clinically significant drug interactions with antiretroviral agents active against HIV (adapted from Sahai[105])

Drug	Interaction
Nucleoside analogues	
Zidovudine	Ganciclovir (↑ haematological toxicity)
	Stavudine (pharmacokinetic interaction[a])
	Fluconazole (↑ zidovudine concentrations)
Zalcitabine[106]	Drugs associated with peripheral neuropathy (e.g. didanosine, stavudine, vinca alkaloids, isoniazid)
	Aminoglycosides, amphotericin, foscarnet (may ↑ zalcitabine concentrations)
Didanosine[104]	Drugs associated with peripheral neuropathy (e.g. zalcitabine, stavudine, vinca alkaloids, isoniazid)
	Oral ganciclovir (didanosine absorption ↑ by 70%; ganciclovir concentrations ↓), ranitidine (↑ didanosine absorption)
	Ciprofloxacin, itraconazole, ketoconazole, dapsone, tetracycline (coadministration of didanosine ↓ concentrations of these drugs)
	Intravenous pentamidine (↑ risk of pancreatitis)
Stavudine	Drugs associated with peripheral neuropathy (didanosine, zalcitabine, vinca alkaloids, isoniazid)
	Zidovudine (pharmacokinetic interaction[a])
Lamivudine	Cotrimoxazole (trimethoprim + sulfamethoxazole) [lamivudine concentrations ↑ by 30-40%]
Non-nucleoside reverse transcriptase inhibitors	
Nevirapine	May ↓ concentrations of hepatically metabolised drugs such as saquinavir, indinavir and ritonavir
Delavirdine mesylate	Rifampicin (rifampin), rifabutin (↓ DLV levels)
	Didanosine, ketoconazole, itraconazole, clarithromycin, erythromycin (↑ DLV levels)
	Indinavir (approximately 2-fold ↑ in indinavir concentrations),[107] saquinavir (5-fold ↑ in saquinavir concentrations)[108]
	Terfenadine
Protease inhibitors	
Saquinavir	Ketoconazole, itraconazole, clarithromycin, erythromycin, delavirdine mesylate,[108] ritonavir, indinavir, nelfinavir,[109] grapefruit juice (↑ saquinavir concentrations)
	Rifampicin, rifabutin (↓ saquinavir concentrations)
Ritonavir[110]	Drugs metabolised by CYP3A4 [ketoconazole, rifampicin, rifabutin (4-fold ↑ in rifabutin AUC_{0-24})[111], saquinavir, indinavir, nelfinavir, clarithromycin, benzodiazepines, Ca^{++} blockers, cisapride, terfenadine and astemizole)
	Drugs metabolised by CYP2D6 [antiarrhythmics and some antidepressants, e.g. desipramine (AUC ↑ 2.45-fold by ritonavir)[112]]
	Drugs metabolised by CYP2C9 (naproxen, phenytoin and tolbutamide)
	Ethinylestradiol (ethinylestradiol AUC ↓ by 41%)[113]
	Theophylline (AUC of theophylline ↓ by 43%)[114]
Indinavir	Nelfinavir (↑ nelfinavir concentrations, modest ↑ indinavir concentrations),[115] saquinavir (↑ saquinavir concentrations)[116]
	Zidovudine, clarithromycin, stavudine, trimethoprim (indinavir ↑ levels of these agents by 17, 50, 21 and 18%, respectively)
	Ketoconazole (70% ↑ in indinavir AUC)
	Rifabutin (34% ↓ in indinavir AUC, 2- to 3-fold ↑ in rifabutin AUC)
Nelfinavir	Saquinavir (↑ saquinavir concentrations 5-fold),[109] indinavir (↑ nelfinavir concentrations, modest ↑ indinavir concentrations)[115]
	Rifampicin (nelfinavir concentrations ↓ by 80%),[117] rifabutin (nelfinavir concentrations ↓ by 82%)
	Ketoconazole (nelfinavir concentrations ↑ by 30-40%)[117]
	Terfenadine (concentrations ↑ by nelfinavir), ethinylestradiol (ethinylestradiol concentrations ↓ by nelfinavir)

a Intracellular. Please refer to full prescriber information or investigational drug brochure.

Abbreviation and symbols: $AUC_{(0-24)}$ = area under the concentration-time curve (for time zero to 24 hours); CYP = cytochrome P450; DLV = delavirdine mesylate; ↑ = increase; ↓ = decrease.

with both didanosine[102] and lamivudine.[103] Concomitant therapy with these agents should therefore proceed with caution. Additionally, in patients with advanced disease who are beginning therapy, it may be best to discontinue zalcitabine, stavudine or didanosine after a few months, as drug-related toxicities such as peripheral neuropathy and possibly pancreatic dysfunction appear to be related to both total daily and cumulative dosage and are more common in advanced disease.[94,104]

Compatibility of intracellular metabolism is also particularly relevant when combining nucleoside analogues. As these agents require activation by intracellular triphosphorylation, combination therapy with, for example, 2 thymidine-based analogues (such as zidovudine and stavudine) may be less than ideal as they compete for phosphorylation along the same pathway. A similar interaction has been reported between lamivudine and zalcitabine[118] but does not appear to be clinically important.[36,119] Changes in phosphorylation of zidovudine *in vivo* appear to correlate with clinical activity, suggesting that interactions which lead to lower concentrations of the active triphosphate should be avoided.[120] It is not known how long the activity of cellular kinases takes to return to normal after cessation of prolonged nucleoside analogue therapy. It is therefore not known if a drug-free period between nucleoside analogue treatments may enable better response to a subsequent therapy activated by the same kinases.

Some combinations of protease inhibitors, as well as potentially providing antiviral synergy and convergent selective pressure, may lead to higher drug exposures through inhibition of the cytochrome P450 CYP3A4 isoenzyme, the enzyme responsible for metabolism of these compounds.[98] For drugs with limited bioavailability, this metabolic interaction may be exploited to increase blood drug concentrations. This may lead to increased efficacy, albeit with the possibility of increased toxicity. Interactions between protease inhibitors and NNRTIs vary: enzyme inducers such as nevirapine and efavirenz reduce levels of some protease inhibitors [as assessed by area under the concentration-time curve (AUC)], while enzyme inhibitors such as delavirdine mesylate may increase those levels (table III). Similarly, when changing off a regimen containing an enzyme inducer, such as ritonavir or some NNRTIs, it may be prudent to delay initiation of new therapy by 2 weeks or thereabouts to limit the risk of a reduced treatment effect being driven by increased first-pass metabolism.

7.2 *In Vitro* Synergy

In vitro data demonstrate that many antiretroviral combinations have at least additive and often synergistic activity,[121] exceptions being the antagonism observed between zidovudine and stavudine in the setting of zidovudine resistance[122] and possibly saquinavir-indinavir.[123] Such data may be used to guide the selection of optimal combinations, although issues including viral strain, cell line, drug concentrations and timing of drug administration relative to viral exposure should be considered when interpreting *in vitro* data.

7.3 Differential Activity Between Cell Lineages and Phenotypes

Choice of therapy may also be driven by the need to combine agents which are most active in stimulated cells (for example, zidovudine or stavudine) with those most active in resting cells (such as zalcitabine, didanosine and lamivudine),[124]. Alternatively, both cell types (protease inhibitors, possibly abacavir) and those most active in acutely infected cells (nucleoside analogues, NNRTIs) and those active in both acutely and chronically infected cells (protease inhibitors) may be combined, with compounds within the same activity group being substitutable within a regimen.

The presence of virus with an aggressive biological SI phenotype, with high *in vitro* replicative capacity and extensive T-cell tropism, is associated with accelerated disease progression and unresponsiveness to zidovudine therapy.[125-127] The activity of didanosine appears to be maintained *in vivo* in the presence of SI variants.[128] Indeed, didanosine has been reported to facilitate reversal of SI variants to the NSI phenotype.[128] Saquinavir has also been noted to inhibit syncytium formation

in vitro,[129] suggesting that protease inhibitors should be used if SI virus is present. Data on the activity of other antiretrovirals in the presence of SI virus are currently lacking.

7.4 Compartment Penetration

Effective control of HIV replication will require the penetration of sufficient inhibitory concentrations of antiretrovirals into all body compartments. The CNS, in particular, may have a distinct virus population[130-132] with drug resistance developing more slowly,[133] an issue which may necessitate continued use of a CNS-penetrating compound in a regimen despite the presence of resistant virus in the plasma. Zidovudine has the highest CSF **:** plasma ratio of the available drugs (around 0.6) and appears to have a protective effect against AIDS dementia.[134] Zidovudine-resistant virus has, however, been isolated from both CSF and brain tissue.[135]

Of the other nucleoside analogues, zalcitabine, didanosine and stavudine all have CSF **:** plasma ratios of around 0.2 or more, while lamivudine may penetrate less well. Combinations of zidovudine/lamivudine and stavudine/lamivudine have been reported to have a similar effect on HIV RNA levels in the CSF.[136] Nevirapine also appears to penetrate well into the CSF. CNS penetration of protease inhibitors is not established and issues such as high protein binding of several of these compounds, lipid solubility and degree of drug ionisation may mean that CSF **:** plasma ratios do not accurately reflect tissue levels. Both indinavir[137] and saquinavir[138] have been detected in CSF. Of patients with below-detectable plasma viral loads on dual protease inhibitor therapy, 12 of 13 were also below detection levels in the CSF.[97] However, regimens containing nucleoside analogues may be more likely to achieve CSF viral loads below assay detection than those containing protease inhibitors alone.[138]

7.5 Resistance and Cross-Resistance

Evidence linking the presence of drug-resistant viral quasispecies to virological and clinical failure is increasing, and information on patterns of resistance and cross-resistance should therefore be considered when deciding how best to sequence and/or combine agents. Optimum sequences or combinations should comprise agents which select non-overlapping resistance patterns and maintain the widest possible base of future treatment.[139-141] To

Table IV. Potential overlapping toxicities. For additional information, please refer to full prescriber information or investigational drug brochures

Drug	Toxicity
Nucleoside analogues	
Zidovudine	Myelosuppression, myopathy, nausea
Zalcitabine	Peripheral neuropathy, oral ulcers
Didanosine	Pancreatitis, diarrhoea, peripheral neuropathy
Stavudine	Peripheral neuropathy
Lamivudine	Gastrointestinal disturbances, hair loss, myelosuppression, exacerbation of peripheral neuropathy
Abacavir	Rash, raised LFT
Non-nucleoside reverse transcriptase inhibitors	
Delavirdine mesylate	Rash, liver dysfunction
Nevirapine	Rash (17%), ↑ GGT, hepatitis, Stevens-Johnson syndrome (0.5%)
Efavirenz	Dizziness, rash (<5%)
Protease inhibitors	
Saquinavir	Few described at 600 mg tid of HGC or SGC preparations; loose stools and nausea at higher doses
Indinavir	Hyperbilirubinaemia (≈15%), nephrolithiasis (≈5%), ↑ LFTs, initial nausea
Ritonavir	Diarrhoea, nausea and vomiting, ↑ LFTs, ↑ triglycerides, perioral paraesthesia
Nelfinavir	Loose stools, fatigue, nausea, headache

Abbreviations and symbols: GGT = γ-glutamyltransferase; LFT = liver function tests; tid = 3 times daily; ↑ = increase.

date, HIV has proven to be a highly mutable virus whose enzymes exhibit remarkable plasticity, and concerns exist for the potential of selecting for multi-drug–resistant HIV. Again, caution must be used in translating data from interactions observed *in vitro*, even with clinical isolates, to clinical practice.

Prevention of resistance appears to be feasible only when viral replication is fully arrested in all body compartments where antiviral drug concentrations (hence selective pressures) are achieved. The availability of rapid probes to detect resistance-associated mutations has the potential to both contribute to data-driven decision-making and expand our understanding of the clinical importance of resistance. However, more data are required on the interpretation and use of these tools before they are widely used in clinical practice.[141]

Resistance data from ACTG 116B/117 revealed a strong correlation between the presence of phenotypic [concentration which inhibits 50% of the virus (IC_{50}) >1.0 μmol/L] or genotypic (presence of 215 and 41 mutations) zidovudine resistance and disease progression.[77,142] Importantly, the increased risk of progression and death with zidovudine resistance was independent of the benefits associated with switching to didanosine in this trial. Patients with zidovudine-resistant virus were at increased risk of disease progression whether they continued on zidovudine or switched to didanosine, implying that the benefits associated with a change of therapy are not directly related to the suppression of zidovudine-resistant virus. *In vitro* observations of increased cytopathogenicity[143] and increased replicative capacity of zidovudine-resistant virus compared with wild-type virus in drug-free stimulated peripheral blood mononuclear cells (PBMCs)[144] may help to explain these findings.

Quantitative assessment of plasma HIV RNA with or without the 215 mutation has shown that addition of didanosine to ongoing zidovudine therapy results in a decrease in wild-type RNA but not mutant RNA, despite the mutant virus being sensitive to didanosine *in vitro*.[73] Similarly, patients with zidovudine-resistant virus are significantly less likely to achieve a virological response to the addition of zalcitabine than those with wild-type virus at baseline.[80] These data are in keeping with a report suggesting that for every 10-fold reduction in *in vitro* viral susceptibility to zidovudine, there is a corresponding 2.2- and 2-fold decrease in sensitivity to didanosine and zalcitabine, respectively.[145] Additionally, both viral and cellular resistance to zidovudine may limit the future utility of stavudine.[146,147] It would therefore appear that zidovudine resistance has negative consequences for patients, in terms of both disease progression and limitation of subsequent treatment options with nucleoside analogues. However, these properties may not be exclusive to zidovudine as the extent to which these problems are also observed with other antiretrovirals is not fully appreciated.

Monotherapy with didanosine selects for a mutation at codon 74 in 56% of patients at 6 months, which is associated with both virological failure[148] and cross-resistance to zalcitabine.[149] However, resistance to didanosine is generally infrequent when that agent is combined with zidovudine in initial regimens. Similarly, the 184V mutation, which develops almost universally by 12 weeks *in vivo* during both monotherapy and combination therapy in patients treated with lamivudine, and is associated with reduced susceptibility (up to 8-fold) to both zalcitabine and didanosine,[150] raises concerns with lamivudine regarding the limitation of subsequent therapeutic options, an issue which requires clarification.

As lamivudine appears to be active in a range of clinical contexts, including patients with advanced disease and substantial prior zidovudine experience, it may be prudent to save this compound for later in the therapy sequence. Unfavourable changes in sensitivity to both zidovudine and didanosine have been reported during monotherapy with stavudine. However, these observations may be explained by methodological issues in this study.[151] Reduced susceptibility to zalcitabine appears to be slow to develop, with the most well characterised mutation at codon 69[80,152,153] not affecting viral sensitivity to other nucleoside analogues, although mutations at other sites leading to

cross-resistance to didanosine and/or lamivudine have occasionally been reported during zalcitabine therapy.[139]

Potential sequencing of protease inhibitors is equally problematic, with a lack of clear data to guide rational decision making. The protease enzyme is surprisingly flexible, with maintenance of good function despite numerous mutations in its structure. In principal, all protease inhibitors have the potential to select for cross-class–resistant virus; the likelihood is that this is in part a function of the number of accumulated mutations.

A number of mutations have been described that are selected, both *in vitro* and *in vivo*, by both ritonavir and indinavir and that result in cross-resistance to each other.[36,154] Indinavir has also been reported to select for virus *in vivo* which is cross-resistant to saquinavir and VX-478.[151] Ritonavir-resistant virus appears to frequently be cross-resistant to nelfinavir. The key mutations associated with saquinavir resistance are at codon 90 and 48 of the protease gene and for nelfinavir at codon 30.[155,156] These initial mutations do not result in cross-resistance to other agents in the absence of additional accessory mutations. However, studies of subsequent protease inhibitor therapy after initial saquinavir or nelfinavir-containing regimens reveal a range of responses both good and bad.

The predominant resistance pattern for VX-478[157] appears to be different from that for the 4 established protease inhibitors. Responses to subsequent therapy in small studies, mostly with only short term follow-up, are shown in table II.

Cross-class resistance at codons 103 and 181 may limit the value of sequencing or combining NNRTIs. The continued clinical effectiveness of some drug regimens may be achieved with well tolerated agents (e.g. NNRTIs, protease inhibitors) by increasing the dosage to above the inhibitory concentration for resistant virus. However, this approach may result in selection of more highly resistant mutants, within the constraints of replication competence.

7.6 Delaying the Development of Resistance

Viral replication in the presence of the selective pressure of antiretrovirals represents the ideal circumstances for selection of resistant virus. Reduction in viral replication to the lowest achievable levels, therefore, appears to be the best strategy for delaying resistance. Additionally, some combinations of mutations may represent unacceptably dysfunctional changes for HIV and may lead to the delay of resistance appearing to one or more components of a combination, or to selection of an increasingly compromised virus.

Resistance patterns of available drugs have recently been reviewed[139,141] and are likely to represent essential knowledge in the rational use of antiretroviral agents, both in choosing the initial therapy and in designing a salvage regimen.

8. Conclusions

Decisions regarding the use of antiretrovirals should be driven by clinical and surrogate marker data, *in vitro* data and biologically plausible theoretical considerations. Commencement of therapy would appear to be most rational early in the course of the disease and, potentially, during seroconversion.[158] Early intervention has a number of theoretical advantages over initiation of therapy at a later stage of infection, not least of which is treatment of a more homogeneous viral population.[159-161] This approach also maximises the potential for further therapeutic interventions.

Novel approaches which have been proposed include that treatment for HIV could follow a model of induction therapy using 5 or 6 agents to achieve virological remission or ‘knock-down’, followed by a dual or triple combination as a maintenance regimen.[162] However, current limitations on drug availability, tolerability and cost suggest that the sequencing of 3-drug regimens is likely to remain the mainstay of antiretroviral therapy in the foreseeable future. The benefits of early intervention with combination therapy are supported by evidence from ACTG 175,[29] in which a delay in clinical disease progression was ob-

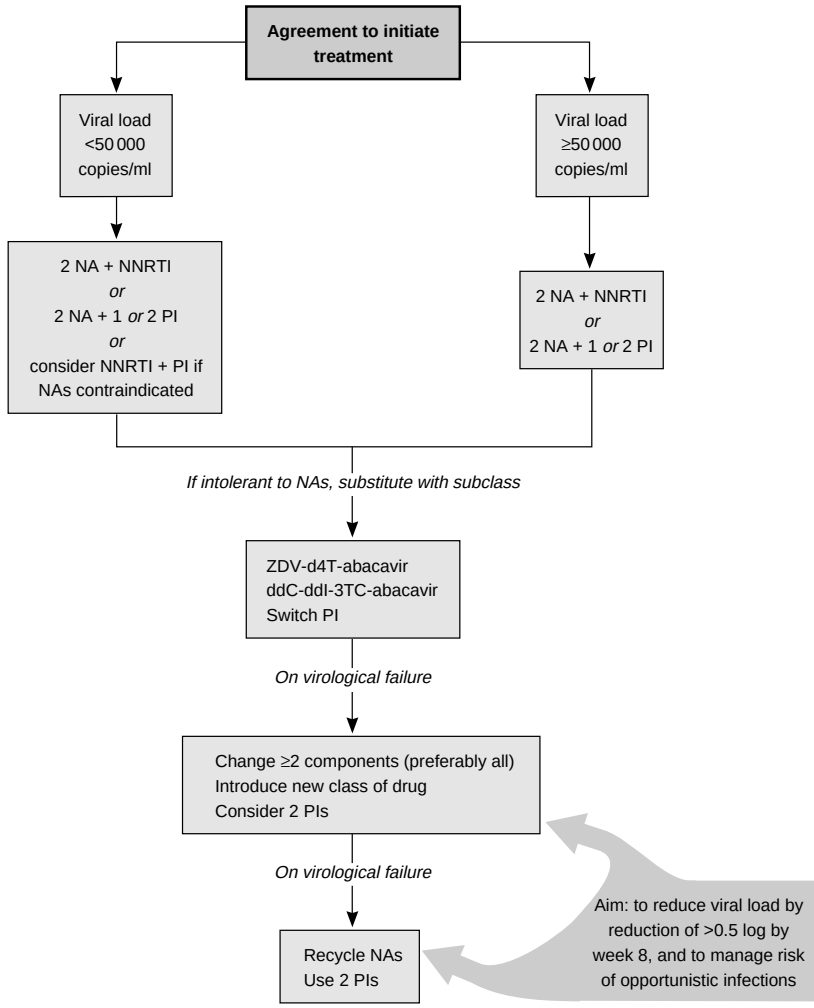

Fig. 1. A proposed simplified algorithm for the treatment of HIV infection. *Abbreviations:* 3TC = lamivudine; d4T = stavudine; ddC = zalcitabine; ddI = didanosine; NA = nucleoside analogue; NNRTI = non-nucleoside reverse transcriptase inhibitor (nevirapine; efavirenz); PI = protease inhibitor (after ritonavir therapy, consider a 2-week drug-free period due to induced cytochrome P450 enzyme CYP3A4); RTV = ritonavir; ZDV = zidovudine.

served in asymptomatic patients with relatively high CD4 cell counts, confirming previous data from EACG 020.[23]

Viral dynamics studies have suggested that HIV replication is extensive and persistent from the first day of infection,[2,163,164] although in some cases measurable viral load is low and associated with slow or prolonged nonprogression of clinical disease.[164-167] It may therefore be reasonable to base decisions regarding the start of therapy on viral load measures, particularly in patients with well maintained CD4 cell counts. A level of 5000 to 10 000 copies/ml appears to be a watershed between risk of progression and nonprogression in

untreated patients.[165-167] Individuals with a low viral load of less than 10 000, and a high CD4 cell count, have a low medium term risk of disease progression.

As well as extending the disease-free period, 'early' intervention appears to be well tolerated and may be more likely to provide substantial immunological and virological responses than initiation of therapy in patients with advanced immunodeficiency.[74,168,169] However, these benefits must be balanced with the risk of toxicity and morbidity caused by antiretroviral agents. As many new drugs and new classes of antiretrovirals are currently in development, intervention with currently recommended therapies should also represent a considered balance between maximising the potential to benefit from future therapies by maintaining CD4 levels and clinical health, versus the risk of limiting the efficacy of subsequent options.

Although no clear definition of therapy failure is currently available other than clinical failure, change of therapy should reasonably be considered once viral load (or a key resistance mutation) has become detectable, or, more conservatively, remains above a level associated with increased risk, perhaps 10 000 copies/ml, on initial therapy. Virological response at as early as 4 weeks may be independently predictive of the potential clinical benefit of a therapy.[170] Return of CD4 to baseline or 50% of baseline has been used as a marker of therapy failure in some studies, while some physicians continue to define therapeutic failure by clinical means. The appearance of genotypic markers of resistance, SI variants or change in cytokine production from a T_H1 to a T_H2 pattern have also been suggested as markers which could be used to modify an individual patient's therapy.[99]

Failure, however defined, should prompt substitution of at least 2 components of the regimen or, preferably, changing the entire combination. Decisions to change therapy may also be driven by intolerance to one or more agents and the need for administration of a medication which may interact at a pharmacokinetic or toxicity level, and may be similarly best managed by rational substitution. In all cases, monotherapy should be avoided.

Activity data in resting and active cell lines suggest that nucleoside analogues may be grouped as zidovudine/stavudine/abacavir and zalcitabine/didanosine/lamivudine/abacavir, with ideal nucleoside combinations containing at least one member of each group. Inclusion of a protease inhibitor in any regimen will widen both cellular and viral strain coverage. More data are required on protease inhibitor combinations; however, the pharmacokinetic interactions and differing resistance patterns described with saquinavir and ritonavir or nelfinavir suggest that combining these agents will be valuable. The role of NNRTIs is less clear: potentially, they may be best used in an initial viral 'knock-down' regimen. A simplified algorithm structure for the management of antiretroviral therapy which can be adapted according to drug availability is shown in figure 1.

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