Antiretroviral therapy for patients with HIV disease

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Introduction

Our approach to the treatment of patients infected with the human immunodeficiency virus (HIV) has changed significantly over the past 2 years. This follows a number of recent advances which include a better understanding of HIV pathogenesis, the development of new techniques for sensitive and accurate quantification of HIV-1 RNA in plasma, availability of newer antiretroviral agents and the demonstration that combination therapy is more effective than monotherapy [1–6]. Consequently, there are now fewer HIV related deaths and opportunistic infections in addition to a reduction in hospital admissions and lengths of stay [7–8]. We review these recent advances and how they influence the management of HIV disease in the clinical setting.

HIV pathogenesis and replication

Infection with HIV-1 initiates progressive destruction of the CD4 T lymphocyte. The rate of CD4 T-cell decline determines the rate of immunodeficiency and the subsequent development of HIV related opportunistic infections and malignancies [9, 10]. This destruction of the T-cell is due mainly to active viral replication which demonstrates considerable interindividual variability. The average time to development of the acquired immunodeficiency syndrome (AIDS) following HIV-1 infection is approximately 10 years. However some individuals (20%) will develop AIDS within 5 years of infection whereas a smaller proportion (5%) will remain asymptomatic for over 10 years without a significant decline in CD4 T cell count. For these patients with slowly progressive HIV disease viral replication is contained and proceeds at extremely low levels [11]. The development of new techniques for sensitive and accurate quantification of HIV-1 RNA in plasma has enhanced our knowledge and understanding of HIV replication and the pathogenesis of AIDS. Using methodology such as target amplification (e.g. quantitative reverse transcriptase polymerase chain amplification, Amplicor Roche Molecular Systems) enables the determination of HIV-1 RNA levels as low as 20 copies ml⁻¹. Whilst the results from the commonly used assays are strongly correlated the absolute values of HIV RNA measured in the same sample can differ by threefold. Therefore measurement of two samples at baseline in clinically stable patients is recommended as a means of reducing the variability of plasma HIV RNA assays.

The quantity of HIV-1 RNA in the plasma accurately reflects the extent of virus replication as even moderate levels of HIV RNA are associated with active replication in lymphoreticular tissue [12, 13]. Viral replication in some compartments e.g. central nervous system may not be

accurately reflected by plasma HIV RNA. Plasma HIV RNA may show significant variation depending on the stage of infection. In primary HIV-1 infection concentrations of plasma HIV RNA may exceed 10⁷ copies ml⁻¹ [14]. The emergence of an immune response results in a steady state level after approximately 6 months. This level is referred to as the viral load 'set point' which will vary between patients but will frequently lie between 10³ and 10⁵ copies HIV RNA per ml (Figure 1). This set point may remain stable for many years but eventually the HIV RNA value increases with a deterioration in immune function and the development of opportunistic infections and neoplasms. HIV infection is a dynamic process of CD4 T cell production and destruction mediated by viral replication. It has been estimated that 10⁸ virus particles are produced each day to maintain steady state. Recent work demonstrates the prognostic value of HIV RNA measurement at steady state (set point) [15, 16]. A clear gradient of disease progression and death with increasing concentrations of plasma HIV RNA has been shown (Table 1). In contrast baseline CD4 T cell counts had no discriminatory value in predicting disease progression except when counts fall below 320 × 10⁶ l⁻¹. The independence of viral load information from CD4 counts is demonstrated by the findings from patients with CD4 counts greater than 500 × 10⁶ l⁻¹ where 50% of patients with HIV RNA levels greater than 10 900 copies ml⁻¹ died within 6 years compared with 5% with HIV RNA levels below 10 900 copies ml⁻¹ [15]. Such information is reflected in recent guidelines for initiation of antiretroviral therapy in HIV disease.

Initiating antiretroviral therapy

Most clinicians would agree that antiretroviral therapy should be introduced before substantial immunodeficiency

Figure 1 Plasma HIV RNA and CD4 count during the course of HIV-1 infection.

HIV RNA set point (copies ml ⁻¹)	Percentage surviving after 10 years
<5260	65–70%
5261–12 890	45–50%
12 891–37 020	25–30%
>37 020	10–20%

ensues. As the onset of HIV related symptoms (e.g. recurrent oral candidiasis, oral hairy leukoplakia, chronic fever, weight loss) is a strong predictor of further progression to HIV related opportunistic infections all patients with symptomatic HIV disease should be treated [17]. The difficulty arises for patients who are asymptomatic, hence the need for a marker that can predict the rate of disease progression. Since the availability of HIV RNA levels there have been a number of guidelines on initiation of anti HIV therapy, the most recent published in June 1997 [18–20]. For asymptomatic patients therapy is recommended if the CD4 cell count falls below $500 \times 10^6 \text{ l}^{-1}$, this is particularly useful if HIV RNA assays are not available. Treatment with anti HIV drugs is now advised for all patients with plasma HIV RNA concentrations greater than 5000 to 10 000 copies ml⁻¹ regardless of the CD4 cell count (Table 2). The recent trend has certainly been towards the early introduction of antiretroviral therapy. Having decided to treat a patient with anti-HIV drugs the clinician must then decide which drugs to use.

Treatment

The first group of drugs available for the treatment of HIV disease inhibited the HIV reverse transcriptase enzyme. These included the nucleoside analogues zidovudine (ZDV), didanosine (ddI), zalcitabine (ddC), lamivudine (3TC) and stavudine (d4T). The nucleosides are taken up by target cells, phosphorylated to the 5'-triphosphate by cellular enzymes to produce the active drug [21]. Also inhibiting reverse transcriptase are the non nucleosides nevirapine (NVP) and delavirdine (DEL) [22]. The third group of drugs now available for the treatment of HIV disease are the protease inhibitors [23]. The HIV protease enzyme is responsible for the post translational processing of *gag* and *gag-pol* polyprotein precursors into their functional products. Inhibition of this enzyme results in the production of non infectious virus [24]. Protease inhibitors currently available are saquinavir (SQV), zidovudine (ZDV), indinavir (IND) and

nelfinavir (NEL). The site of action of these drugs is shown in Figure 2.

The efficacy of zidovudine in the treatment of patients with AIDS and advanced HIV disease was first reported in 1987, however clinical experience with ZDV demonstrated that its beneficial effects were not sustained due in part to the emergence of resistant viral strains [25, 26]. In an attempt to improve clinical outcome combinations of ZDV with other nucleoside analogues were considered, as synergistic anti HIV effects had been demonstrated *in vitro* [27]. This raised the possibility of a delay in the emergence of resistant viruses with a more sustained antiviral effect. This was supported by surrogate marker changes from a number of short term studies [28, 29]. Therefore a number of large scale randomized trials were undertaken to investigate the potential benefits of combination therapy with nucleoside analogues. These trials began in 1991 (ACTG 175), 1992 (Delta, CPCRA) and 1995 (CAESAR). The preliminary results of these trials were published in 1995 demonstrating the beneficial effects of combination therapy and thus brought an end to the era of monotherapy [30]. The important findings from these trials are discussed below.

AIDS Clinical Trials Group study 175 (ACTG 175)

ACTG 175 was a randomized, double-blind, placebo-controlled trial to compare monotherapy with zidovudine (ZDV) or didanosine (ddI) with combination therapy including ZDV plus ddI or ZDV plus zalcitabine (ddC) in adults infected with HIV-1 [4]. All 2467 patients had CD4 cell counts between 200 and $500 \times 10^6 \text{ l}^{-1}$ and were randomized to the following regimens ZDV 600 mg daily, ZDV 600 mg + ddI 400 mg daily, ZDV 600 mg + ddC 2.25 mg daily or ddI 400 mg daily. The primary end point for the study was a greater than 50% decline in the CD4 count, development of AIDS, or death. The median follow up was 143 weeks. Progression to the primary end point was more frequent with ZDV monotherapy (32%) when compared with ZDV + ddI (18%), ZDV + ddC (20%) or

Table 2 Recommendations for initiation of antiretroviral therapy.

Recommendations for initiation of antiretroviral therapy	
HIV RNA	Therapy is recommended for all patients with HIV RNA above 5000 to 10 000 copies per ml of plasma
CD4 count	Consider treatment at all CD4 counts particularly if less than $500 \times 10^6 \text{ l}^{-1}$. Treatment may be deferred if CD4 counts are stable between 350 and $500 \times 10^6 \text{ l}^{-1}$ and plasma HIV RNA levels are below 5000 to 10 000 copies ml ⁻¹ . Treatment also indicated for rapidly declining counts i.e. $>300 \times 10^6 \text{ l}^{-1}$ over 12 months
Clinical symptoms	All HIV patients who present with symptoms should receive antiretroviral therapy

Figure 2 Life cycle of HIV-1 demonstrating the sites of action of currently available antiretroviral drugs.

ddI monotherapy (22%). The incidence of an AIDS defining event or death was 16% for ZDV monotherapy, 11% for ZDV+ddI, 12% with ZDV+ddC and 11% for ddI monotherapy. The difference between ZDV alone and each of the two ddI groups was statistically significant. Similarly the mortality rate was significantly reduced in patients treated with ZDV+ddI (5%), ddI (5%) but not for ZDV+ddC (7%) when compared with ZDV monotherapy (9%). Therefore despite the fact that changes in CD4 cell count constituted 71% of primary end points, regimens containing ddI were superior to ZDV monotherapy in preventing clinical end points. Sub group analysis among patients with no prior antiretroviral therapy demonstrated all treatments were superior to ZDV alone in preventing a primary end point. In preventing AIDS or death, only ZDV+ddC proved superior to ZDV alone whereas no difference in mortality was demonstrated between the four treatment groups reflecting the lower incidence of end points in the antiretroviral naïve group. Subgroup analysis of the 57% of patients with previous antiretroviral therapy demonstrated the superiority of ddI containing regimens in reducing the incidence of clinical end points. The mortality in patients treated with ZDV+ddI was 6%, ddI alone 5%, ZDV+ddC 9% and ZDV monotherapy 10%. The ACTG 175 study suggests that for patients with no prior antiretroviral therapy treatment with ZDV+ddI, ZDV+ddC or ddI monotherapy will be superior to ZDV monotherapy and for patients who have been treated with antiretroviral therapy a change to ZDV+ddI or ddI monotherapy would be beneficial. The study also suggests that treatment of

patients with relatively early HIV disease using ZDV+ddI or ddI may produce substantial clinical benefits. With respect to adverse effects there was no significant increase in symptoms reported by patients treated with combination therapy. However laboratory abnormalities were higher as subjects treated with ZDV+ddI had the highest elevation in liver enzymes (9.9%) and ZDV+ddC produced greater haematological abnormalities (anaemia and neutropenia) in 10% of patients. It must be noted that 53% of patients in ACTG 175 discontinued the study treatment prematurely and 19% were lost to follow up, however the investigators argued that this did not negate the differences between treatments.

Delta study

The European Australian Delta study was a randomized, double-blind study comparing ZDV 600 mg daily with ZDV 600 mg+ddI 400 mg daily or ZDV 600 mg+ddC 2.25 mg daily in patients with HIV disease [5]. All 3207 patients had a CD4 count less than $350 \times 10^6 l^{-1}$ or had symptoms of HIV disease. Patients with AIDS had CD4 counts greater than $50 \times 10^6 l^{-1}$. The primary end points were death and AIDS or death in patients without AIDS at entry. The median follow up was 30 months. The Delta study was subdivided into two groups consisting of patients who had not had ZDV prior to study (Delta 1) and for those who had at least 3 months ZDV therapy (Delta 2). For patients without prior ZDV therapy the mortality among patients treated with ZDV alone was 21% compared

with 13% for ZDV+ddI and 15% for ZDV+ddC. The reduction in mortality produced by combination therapy was statistically significant. For ZDV experienced patients mortality was 35% for ZDV, 28% for ZDV+ddI and 33% for ZDV+ddC. Only the ZDV+ddI combination resulted in a significant reduction in mortality. For patients ZDV naïve and without an AIDS defining illness at study entry there was a delay in disease progression in the ZDV+ddI treatment group. Patients with an AIDS diagnosis at study entry did benefit from combination therapy with ZDV+ddI and ZDV+ddC reducing progression to advanced AIDS or death by 54% and 44% respectively in Delta 1. In Delta 2 only the ZDV+ddI combination reduced disease progression (by 40%) in patients with AIDS. When compared with the ACTG 175 study, participants in Delta had more advanced disease (45% symptomatic) and less exposure to antiretroviral therapy (66% ZDV naïve).

The important finding from the Delta trial was the significant reduction in mortality associated with combination therapy with ZDV+ddI or ZDV+ddC when compared with ZDV monotherapy. The benefit was more pronounced among patients without prior antiretroviral therapy. In patients with previous ZDV exposure the addition of ddI, but not ddC, improved survival. As in the ACTG 175 study many patients in Delta discontinued trial therapy for non protocol reasons (74% at the close of the study). Participants remained on their allocated treatment for a median of 18 months and the discontinuation rate probably resulted in an underestimate of therapeutic effect. There was no significant difference in the number of adverse events leading to discontinuation of therapy between the combination therapy groups and for ZDV monotherapy.

CAESAR study

The CAESAR trial (CAESAR is an acronym for the areas that participated i.e. Canada, Australia, Europe and South Africa) was a randomized, controlled double-blind trial to compare the efficacy and safety of the nucleoside analogue 3TC, *vs* 3TC+loviride *vs* placebo when added to ZDV containing regimens in patients with HIV disease [6]. All 1840 patients had a CD4 count between 25 and $250 \times 10^6 \text{ l}^{-1}$, 60% had been treated with ZDV monotherapy and 40% received either ZDV+ddI or ZDV+ddC prior to the study. The primary efficacy outcome was the development of new AIDS defining events or death. The median duration of follow up was 52 weeks. There was a 55% reduction in disease progression or death in the 3TC containing arms (placebo 20%, 3TC 9%, 3TC+loviride 9% $P < 0.0001$). Mortality was also significantly reduced by 50% in the 3TC arms compared with placebo. Subgroup analysis confirmed a significant 54% reduction in disease progression in the 3TC containing arms in patients entering the trial on ZDV monotherapy. Fewer patients in the 3TC group required hospital admission, unscheduled visits or prescribed medications for HIV related events. The CAESAR study demonstrated the addition of 3TC to ZDV treatment regimens significantly slowed the progression of HIV disease and improved survival thus providing further evidence of the benefit of combination therapy in the treatment of HIV disease.

CPCRA study

In the CPCRA study (Community Programs for Clinical Research on AIDS) 1102 patients with AIDS or fewer than $200 \times 10^6 \text{ l}^{-1}$ CD4 cells were randomised to receive ZDV 600 mg daily, ZDV 600 mg+ddI 400 mg daily or ZDV 600 mg+ddC 2.25 mg daily [31]. The primary end point was disease progression or death over a median follow up of 35 months. Disease progression or death occurred in 65% of patients treated with ZDV alone, 62% of patients treated with ZDV+ddI and 63% for the ZDV+ddC group. Similarly there was no significant difference in mortality between the three groups (ZDV alone 51%, ZDV+ddI 48%, ZDV+ddC 49%). A subgroup analysis did show a benefit for combination therapy in patients who had previously received ZDV for less than 12 months. Participants in the CPCRA study had advanced HIV disease (median CD4 counts between 87 and $102 \times 10^6 \text{ l}^{-1}$, over 30% had an AIDS defining illness) and approximately 77% had received prior treatment with ZDV. Adverse effects were more frequent among patients receiving combination therapy.

The results of these large randomized trials brought an end to the use of ZDV monotherapy (Table 3). Combination therapy with ZDV+ddI or ZDV+ddC is superior to ZDV alone for patients without prior antiretroviral therapy. For patients who are ZDV experienced the addition of ddI or 3TC will reduce mortality and disease progression to AIDS. The addition of ddC to ZDV experienced patients does not provide a clinical benefit. The trials also suggest that combination therapy is beneficial for asymptomatic patients with CD4 counts less than $500 \times 10^6 \text{ l}^{-1}$ and perhaps more importantly, demonstrate the absence of any clear benefit of combination therapy in ZDV experienced patients with advanced disease. This finding may be related to the higher viral load among patients with advanced disease and a more rapid emergence of viral resistance [32, 33]. The studies also confirm the reduced tolerability of the nucleosides with increasing severity of HIV disease. As a result of the major clinical trials documented above, guidelines for antiretroviral therapy were issued by the International AIDS Society-USA in July 1996 [18]. The recommended initial therapy at that time included ZDV+ddI, ZDV+ddC, ZDV+3TC.

Further progress in the treatment of HIV infection followed the introduction of the protease inhibitors in 1996. Initial studies demonstrated the protease inhibitors to be potent anti-HIV drugs e.g. RIT produced a 1.7 log reduction in plasma HIV RNA which was similar to that produced by the combination of ZDV+3TC [34]. A recent study of 1090 patients with advanced HIV disease (mean CD4 count of $30 \times 10^6 \text{ l}^{-1}$) demonstrated the ability of RIT to reduce disease progression and mortality when added to existing therapy (the majority receiving ZDV) [35]. Treatment with a 'triple therapy' regimen of two nucleosides ZDV+ddC+SQV (protease inhibitor) reduced HIV replication and increased CD4 cell counts to a greater extent when compared with the two nucleosides ZDV+ddC (or ZDV+SQV) [36]. Similarly the triple combination ZDV+3TC+IND had greater antiviral efficacy as compared with ZDV+3TC. When administered to HIV patients with a CD4 count ranging from 50 to

Table 3 The efficacy of combination therapy and ddI monotherapy in comparison with zidovudine monotherapy in reducing mortality and disease progression to AIDS and death in the major trials ACTG 175, Delta, CAESAR and CPCRA. (ZDV = zidovudine, ddI = didanosine, ddC = zalcitabine, 3TC = lamivudine, LOV = loviride, N.S. = non significant change).

	ACTG 175	Delta	CAESAR	CPCRA
Patients	2467	3207	1840	1102
CD4 cells $\times 10^6 l^{-1}$	200–500	<350	25–250	<200
Treatment	ZDV + ddI; ZDV + ddC; ddI <i>vs</i> ZDV	ZDV + ddI; ZDV + ddC <i>vs</i> ZDV	Placebo/3TC/3TC + LOV + Current R _x	ZDV + ddI; ZDV + ddC <i>vs</i> ZDV
Reduced mortality	ZDV + ddI (43%) ddI (46%)	ZDV + ddI (33%) ZDV + ddC (21%)	Current R _x + 3TC (50%)	NS
Decreased progression to AIDS or death	ZDV + ddI (32%) ddI (26%)	ZDV + ddI (22%)	Current R _x + 3TC (55%)	NS

Table 4 Initial anti retroviral therapy.

(i)	Two nucleoside analogues + one protease inhibitor ZDV + ddI/ddC/3TC + IND/NEL/RIT d4T + ddI/ddC/3TC + IND/NEL/RIT
(ii)	Two nucleoside analogues + Non nucleoside reverse transcriptase inhibitor ZDV + ddI/ddC/3TC + NVP/DEL d4T + ddI/ddC/3TC + NVP/DEL

$400 \times 10^6 l^{-1}$, at least 20 000 copies of HIV RNA ml^{-1} and previous ZDV monotherapy the triple therapy regimen decreased HIV RNA below 500 copies ml^{-1} over the first 24 weeks in 90% of patients *vs* 0% for the ZDV + 3TC combination [37]. The mean increase in CD4 cell count was also significantly greater in the triple therapy group ($86 \text{ vs } 46 \times 10^6 l^{-1}$). These changes in HIV viral load and CD4 cell count persisted for up to 52 weeks. Recent work has confirmed, on the basis of clinical endpoints, the superiority of the three drug combination. Treatment with ZDV + 3TC + IND as compared with ZDV + 3TC significantly slows the progression of HIV disease in patients with 200 CD4 cells or less and prior ZDV monotherapy. The proportion of patients with disease progression to AIDS or death was lower (6% *vs* 11%) and mortality reduced (1.4% *vs* 3.1%) in patients receiving triple therapy [38].

Initial antiretroviral regimens

The risk of HIV disease progression and the efficacy of antiretroviral therapy are strongly associated with the plasma level of HIV RNA. Furthermore changes in plasma HIV RNA predict both changes in CD4 cell counts and survival after treatment with nucleoside analogues [33]. Therefore the British HIV Association (BHIVA) guidelines for anti-retroviral treatment, issued in April 1997, stated that the aim of initial therapy was to reduce plasma viral load as low as possible for as long as possible, preferably below the assay detection limit, hence improving clinical outcome [19]. However some physicians had difficulty with the BHIVA recommendation to use dual therapy combinations of ZDV plus ddI, 3TC or ddC as triple therapy including a protease

inhibitor is more likely to achieve the stated therapeutic aim.

The latest recommendations of the International AIDS Society-USA Panel (June 1997) confirms that the preferred initial regimen is one that is most likely to reduce and maintain plasma HIV RNA levels below the level of detection i.e. less than 400 copies ml^{-1} [20]. These guidelines are very clear in stating that at this point in time the preferred regimen will consist of two nucleoside analogues plus a protease inhibitor with high *in vivo* potency. Examples of potential combinations to be used are shown in Table 4. When combining nucleoside analogues an attempt is made to avoid overlapping toxicities and to avoid combining two nucleosides that are activated by similar phosphorylation pathways as these drugs may compete for the same enzymes. Therefore combinations including ZDV + d4T and 3TC + ddC should be avoided [39]. For all the regimens an attempt is made to include either ZDV or d4T as these drugs cross the blood brain barrier to a greater extent as compared with other anti-HIV drugs [40, 41]. Clinicians will also be mindful of cross resistance between nucleosides. The presence of ZDV resistance does appear to be an independent predictor of subsequent disease progression and as 3TC is the only nucleoside reported to delay ZDV resistance it would appear that ZDV + 3TC is an attractive option [42, 43]. However, 3TC resistance may limit future ddC and ddI efficacy thus ZDV + ddI can be used as initial therapy. Recently d4T + ddI has been demonstrated to be a very potent nucleoside combination and for many clinicians will be the nucleosides of choice in any initial regimen [44]. When considering which protease inhibitor to include in a triple therapy regimen similar

considerations apply. Pharmacokinetic issues include bioavailability, tolerability and drug interactions [45]. The bioavailability of RIT (75%), IND (13–70%) and NEL (17–47%) is satisfactory however SQV hard gelatin bioavailability is only 4% which results in very low plasma levels in some patients. We have documented trough concentrations of SQV below the limit of detection ($<20 \text{ ng ml}^{-1}$) in 17% of patients and below the IC_{90} in 27% [46]. This explains, in part, the absence of SQV from the current guidelines [47]. A new formulation of SQV (soft gelatin capsule) will soon be available and this should provide higher plasma concentrations. Tolerability is an important issue when prescribing protease inhibitor drugs. We have documented a 28% discontinuation rate for RIT compared with 10% for SQV and 5% for IND [48]. Furthermore the huge potential for drug interactions with RIT (due to inhibition of cytochrome P450 and induction of glucuronyl transferase) make this drug a less likely choice in triple therapy regimens [49, 50]. The development of cross resistance among the protease inhibitors is also a relevant factor and the efficacy of future combinations may be compromised by poor compliance. Use of IND may select for cross resistance to RIT and *vice versa* [51]. Cross resistance among protease inhibitors may pose a major challenge in the future and rapid assays of resistance are not currently available for routine clinical use.

The recommendations acknowledge that although triple therapy including a protease inhibitor may be the regimen of choice it may not be suitable for all patients due to some of the problems mentioned above. In this setting the primary recommended alternative is a combination of two nucleosides plus a non nucleoside reverse transcriptase inhibitor (NNRTI). In the INCAS trial (conducted in Italy, Netherlands, Canada and Australia), NVP + ZDV + ddI reduced plasma HIV RNA below $20 \text{ copies ml}^{-1}$ in 55% of patients for at least 52 weeks when administered to patients with CD4 counts between $200\text{--}600 \times 10^6 \text{ l}^{-1}$ [52]. The INCAS study suggests that the use of currently available NNRTIs is maximized when combined with other drugs when the patient is antiretroviral naïve. The NNRTIs have good bioavailability e.g. NVP (90%) and DEL (85%) and are extensively metabolised by cytochrome P450. Drug interactions are likely to occur if prescribed with protease inhibitors as NVP is an enzyme inducer and DEL is an enzyme inhibitor [52, 53]. The NNRTIs would not be expected to interfere with nucleoside phosphorylation. There are few direct comparisons of protease inhibitor and NNRTI containing triple therapy regimens but the extent and duration of HIV RNA suppression appears to be greater with a protease inhibitor drug. Data on double protease inhibitor combinations (e.g. RIT + SQV) and triple therapy that combines a nucleoside + NNRTI + protease inhibitor are not sufficient to determine a role for these approaches to initial therapy.

For patients who are not candidates for triple drug regimens but are at high risk of disease progression initiation of dual nucleoside therapy e.g. ZDV + 3TC is desirable. However it must be appreciated that dual nucleoside therapy is more appropriately used in combination with a protease inhibitor. If dual nucleoside therapy is used then more frequent viral load monitoring is required to facilitate a

more aggressive treatment regimen if there is significant sustained increase in HIV RNA.

Changing antiretroviral therapy

A change in the antiretroviral regimen may be necessary due to treatment failure, adverse effects, poor compliance, potential drug interactions or current use of a suboptimal regimen. For patients who have achieved viral loads below the limit of detection a documented increase in plasma HIV RNA to greater than 2000 to 5000 copies ml^{-1} is an indication to change therapy. For patients who had a significant decrease in HIV RNA initially but not below the limit of detection an increase to greater than 5000 to 10 000 copies ml^{-1} should indicate a treatment change [20]. However if patients achieved a substantial initial reduction in HIV RNA (1.5 to 2.0 log drop) and their viral load did not fall below the limit of detection an alternative approach to changing therapy would involve close observation until there is a confirmed substantial rise above the maximum reduction achieved. Factors other than viral resistance may lead to loss of viral suppression including recent vaccinations, intercurrent illness and of course non compliance. A triple therapy regimen will reduce HIV RNA within 2 to 4 weeks however for patients with a high pretreatment viral load maximal suppression may not be seen until 12 to 24 weeks of potent therapy because of the slower 'second phase' decline in HIV RNA. Therefore it is essential not to prematurely abandon a given regimen.

In the presence of adverse effects that require discontinuation of a given regimen a number of principles apply. Dose reductions of the protease inhibitor should be avoided. If the adverse effect is considered due to a nucleoside analogue then this should be stopped and replaced with another nucleoside. If the drug responsible for the adverse effects is not readily identified then a brief and complete interruption of the full therapeutic regimen is generally performed. Following resolution of the toxicity a decision to replace one drug or to change to an entirely new triple therapy must be made.

Patients who are currently taking two nucleosides should be evaluated for signs of treatment failure. Should the viral load be undetectable then the two nucleosides may be safely continued with frequent follow up including repeat viral load measurements. Those with a viral load greater than 5000 to 10 000 copies ml^{-1} should be considered as having failed therapy and an alternative triple therapy regimen added. It is generally agreed that changing therapy while the HIV RNA level is reasonably low will limit the degree of antiretroviral resistance enabling a new drug regimen to reduce the viral load below the limit of detection.

Alternative antiretroviral regimens for treatment failure

The guiding principle is to change all drugs or at least to include a minimum of two new drugs in the revised regimen [20]. The addition of a single drug to a regimen which has failed is strongly discouraged and is considered to be equivalent to sequential monotherapy which will result in a more rapid emergence of drug resistance. The best

Table 5 Alternative antiretroviral regimens for treatment failure.

Initial regimen	Alternative regimen
ZDV + ddI + IND	d4T + 3TC + NEL d4T + 3TC + NVP RIT + SQV + 3TC
ZDV + 3TC + IND	d4T + ddI + NEL d4T + ddI + NVP RIT + SQV + d4T
d4T + 3TC + IND	ZDV + ddI + NEL ZDV + ddI + NVP RIT + SQV + ZDV
ZDV + ddI + NVP	d4T + 3TC + IND ZDV + 3TC + IND

alternative protease inhibitor after failing on initial protease inhibitor regimen is unknown. It is known that cross resistance between IND and RIT is almost complete thus use of one will limit the use of the other [54]. Using IND and RIT may not select for cross resistance to nelfinavir. The use of an NNRTI is unlikely to produce undetectable HIV RNA when used in antiretroviral experienced patients. One alternative is the combination of RIT + SQV. Due to the potent inhibition of cytochrome P450 3A4 by RIT the levels of SQV are greatly enhanced [55]. If both drugs are administered at the recommended doses then SQV AUC may be increased by up to 20-fold [56]. Therefore the dose of SQV required may be greatly reduced and in our experience SQV 200 mg twice daily may suffice in the presence of RIT. This represents a 4.5 fold reduction in SQV dose. There is little change in RIT levels in the presence of SQV. The efficacy and safety of the RIT + SQV combination needs further study, which is ongoing. Examples of alternative antiretroviral regimens for treatment failure are shown in Table 5.

Conclusion

When treating patients with HIV disease the aim is maximal suppression of HIV replication for as long as possible. The availability of sensitive assays for determination of plasma HIV RNA and new potent anti HIV drugs facilitates this aim. The era of ZDV monotherapy is over. The current standard of care for HIV patients is a three drug combination consisting of two nucleoside analogues plus a protease inhibitor. This is a therapeutic area in a constant state of flux. Future developments may well include the use of four antiretroviral drugs in combination. Studies are already underway to assess this strategy.

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