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The use of surrogate markers in the antiretroviral treatment of HIV-1 infection

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CHAPTER 4

Prediction of HIV-1 RNA suppression and its durability during treatment with zidovudine/lamivudine.

Milos Opravil, Andrew M Hill, Ralph DeMasi and Debra Dawson. [the first two authors contributed equally to this manuscript]

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CHAPTER 4

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Prediction of HIV-1 RNA suppression and its durability during treatment with zidovudine/lamivudine.

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Abstract

To predict the probability of long-term viral suppression during treatment with zidovudine and lamivudine, human immunodeficiency virus type 1 (HIV-1) RNA values were retrospectively pooled for 1083 patients from six randomised, double-blind clinical trials. All analyses of HIV-1 RNA were obtained using the Roche Amplicor assay or its earlier prototype. Time to loss of response was evaluated by Kaplan-Meier analysis; Cox proportional hazards models were used to assess the influence of baseline variables. Among 523 patients with ≤6 months of prior zidovudine treatment, the probability of HIV-1 RNA suppression below 400 copies/ml at 48 weeks was 71% in those with HIV-1 RNA <5000 copies, but only 14% in those with HIV-1 RNA between 50,000 and 200,000 copies/ml. Among 560 patients with >6 months of prior zidovudine treatment, the rates of sustained viral suppression were lower, but also significantly associated with the baseline HIV-1 RNA. Multivariate analyses showed no independent effect of CD4 cell count, age, sex, race or CDC disease stage on the probability of sustained HIV-1 RNA suppression. When patients were ≤6 months of prior therapy were stratified based on the magnitude of HIV-1 RNA nadir achieved during treatment, those who reached a nadir of <400 copies/ml retained this response for significantly longer time periods than the ones who only achieved partial viral suppression. In conclusion, baseline HIV-1 RNA levels and the duration of prior zidovudine therapy strongly predict the antiretroviral efficacy of zidovudine/lamivudine. The baseline parameters should influence the choice of the antiretroviral regimen.

Introduction

The current aim of antiretroviral treatment for human immunodeficiency virus type 1 (HIV-1) infection is to suppress viral replication as completely as possible, ideally to below the detection limits of available HIV-1 RNA assays1. Not only are initial HIV-1 RNA levels strongly predictive of subsequent clinical progression2,3, but treatment-induced reductions of HIV-1 RNA levels are associated with a lower risk of progression to AIDS and death2,3. Rebound of HIV-1 RNA levels after an initial treatment-induced response is associated with the development of drug resistance mutations4,5, and both high HIV-1 RNA levels and drug resistance are predictive of subsequent therapeutic failure3,6. Highly active antiretroviral regimens have been shown to achieve sustained suppression of viral replication and to prevent development of resistance7-10. Patients with only a partial reduction in HIV-1 RNA, to a level about the lower limit of detection, remain at risk of acquiring resistance mutations11. Given the potential for cross-resistance between nucleoside analogue reverse transcriptase inhibitors (NRTIs)12, as well as between protease inhibitors13, patients developing resistance to one treatment through inadequate suppression of HIV-1 RNA are liable to compromise their future treatment options1,14.
Combination therapies including NRTIs plus a non-nucleoside reverse transcriptase inhibitor (NNRTI) or one or two protease inhibitors\(^1\), \(^3\), \(^9\), \(^12\) lead to a higher proportion of patients with undetectable HIV-1 RNA than treatment with two NRTIs\(^6\). However, even triple combination treatments fail to maintain HIV-1 RNA at undetectable levels in a meaningful proportion of the population\(^1\),\(^9\). Despite recommendations to treat almost every HIV-infected patient with triple combination therapy, groups of patients exist for whom such a regimen is not appropriate and not possible, owing to poor compliance or risk of drug interactions of toxicity\(^1\). In addition, the benefit of triple combination therapy over double NRTI combinations has not been clearly defined for patients with low plasma HIV-1 RNA levels (e.g. <5000 copies/ml). In order to investigate the treatment effect at different levels of HIV-1 RNA and to identify correlates with sustained HIV-1 RNA suppression during NRTI combination treatment, the virological response in patients treated with zidovudine/lamivudine within six prospective, randomised trials was pooled and retrospectively analysed.

**Patients and Methods**

**Patients**

Data for patients treated with zidovudine/lamivudine and with available HIV-1 RNA measurements were pooled from six double-blind, randomised studies. The NUCA 3001\(^21\) and NUCA 3002\(^22\) trials were comparisons of 52 weeks of zidovudine/lamivudine treatment versus control monotherapy regimens of zidovudine or lamivudine (NUCA 3001) or zidovudine/zalcitabine (NUCA 3002). NUCA 3001 recruited patients with less than 4 weeks of prior NRTI treatment, while NUCA 3002 recruited those with over 6 months of prior treatment. The NUCB 3001\(^23\) and NUCB 3002\(^24\) trials were comparisons of 24 weeks of treatment with zidovudine/lamivudine versus zidovudine, followed by an open-label phase when all patients could receive zidovudine/lamivudine. NUCA 3001 recruited patients with less than 4 weeks of prior NRTI treatment, while NUCB 3002 recruited those with over 6 months of prior treatment. The CAESAR trial\(^25\) compared 52 weeks of treatment with either placebo, lamivudine, or lamivudine plus loviride in addition to current treatment, which could be either zidovudine monotherapy, zidovudine/didanosine or zidovudine/zalcitabine. The AVANTI trial\(^26\) was a comparison of 52 weeks of treatment with either zidovudine/lamivudine or zidovudine/lamivudine/loviride. Based on the different study designs, all participants in the present analysis were stratified by those who had received ≤6 months or more than 6 months of prior antiretroviral treatment. Pre-treatment always included zidovudine but excluded non-nucleoside reverse transcriptase inhibitors or protease inhibitors. Two hundred and thirty-nine patients from the CAESAR and AVANTI-I trials were randomised to receive loviride in addition to zidovudine/lamivudine. Because the combination of zidovudine/lamivudine/loviride lacked a significant clinical benefit in comparison to zidovudine/lamivudine alone\(^25\), these patients were also included in this analysis. All studies were approved by the Ethics Committees of the participating centres and informed consent was obtained from all patients prior to the start of the studies.

The analyses of HIV-1 RNA were obtained using the Roche Amplicor assay except in the NUCA 3001 and NUCA 3002 trials in which the prototype Roche Molecular Systems’ reverse transcriptase-PCR assay was used with a lower detection limit of 200 copies/ml. All patients in the NUCA 3001, NUCA 3002 and AVANTI-1 trials were analysed. Thirty-one patients from non-French centres in NUCB 3001, and 31 patients from various centres in NUCB 3002, were assessed for HIV-1 RNA. For the CAESAR trial, HIV-1 RNA was obtained for (i) all patients in the French and Belgian trial centres, (ii) all patients treatment naïve at baseline, and (iii) all patients who progressed to the primary endpoint of AIDS or death, plus a random sample of patients who did not progress. Five hundred and eighty-six patients were tested at least once for HIV-1 RNA at baseline and during treatment in CAESAR.

In all trials, HIV-1 RNA was assessed at baseline and then approximately every 4-8 weeks thereafter up to week 24 for trials NUCB 3001 and NUCB 3002, and up to week 52 for trials NUCA 3001, NUCA 3002, AVANTI-1 and CAESAR.
Statistical methods

The justification for pooling data from the six trials in the analyses was (i) the trials were all conducted between 1993 and 1996, using the same doses of zidovudine and lamivudine; (ii) the Roche Amplicor assay was used to assess HIV-1 RNA (or its prototype in the NUCA3001 and NUCA3002 trials); (iii) all trials were of 12 months duration; (iv) all randomised trials of zidovudine/lamivudine conducted and completed by Glaxo-Wellcome during this period were included in these analyses, with no data exclusions which could confound or bias the analyses.

Participants in the analysis were stratified into those with ≤6 months, and those with >6 months prior antiretroviral therapy. Kaplan-Meier plots of time to loss of response (‘virological failure’, defined as HIV-1 RNA levels above 400 copies/ml in two consecutive measurements) were constructed. The ‘time zero’ was the time point when HIV-1 RNA levels first fell below 400 copies/ml. Patients who did not achieve HIV-1 RNA suppression below this threshold were defined as having failed treatment on day 0. The time of virological failure was the date that HIV-1 RNA levels first rose above 400 copies/ml, provided that this was confirmed at the next visit. Data was excluded after permanent study drug discontinuation.

These analyses were then repeated stratifying for baseline HIV-1 RNA of <5000 copies/ml, 5000-20000 copies/ml; 20000-50000 copies/ml; 50000-200000 copies/ml; >200000 copies/ml. Cox proportional hazards models were used to assess the influence of baseline variables on the time to virological failure.

To compare the durability of a partial with a full HIV-1 RNA response, we analysed how long patients remained within 0.5 log_{10} copies/ml of a defined HIV-1 RNA nadir. For these analyses, three different nadir levels of <400; 400-1000, and 1000-5000 copies/ml were constructed, based on the single lowest value ever achieved during treatment. The analyses were restricted to patients who showed at least a 0.5 log reduction in HIV-1 RNA on treatment. If two subsequent, consecutive HIV-1 RNA measurements were at least 0.5 log_{10} copies above the respective nadir, the response was defined as lost. Kaplan-Meier estimates of the percentage of patients with HIV-1 RNA levels that remained within 0.5 log_{10} copies/ml of each of the three nadir levels were then obtained and compared with each other.

Results

A total of 1083 patients, evaluated for HIV-1 RNA in the six studies, were included in these analyses. The baseline characteristics were comparable for the two stratified groups except for the CD4 lymphocytes that were significantly lower in the pre-treated patients (Table 1).
Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Prior NRTI treatment</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤6 months</td>
<td>&gt;6 months</td>
<td>All patients</td>
</tr>
<tr>
<td>Number of patients</td>
<td>523</td>
<td>560</td>
<td>1083</td>
</tr>
<tr>
<td>Male</td>
<td>439 (84%)</td>
<td>487 (87%)</td>
<td>926 (86%)</td>
</tr>
<tr>
<td>Mean age (range), years</td>
<td>36.4 (18-68)</td>
<td>38.0 (19-67)</td>
<td>37.2 (18-68)</td>
</tr>
<tr>
<td>CDC stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A (asymptomatic)</td>
<td>323 (44%)</td>
<td>189 (34%)</td>
<td>421 (39%)</td>
</tr>
<tr>
<td>B</td>
<td>216 (41%)</td>
<td>253 (45%)</td>
<td>469 (43%)</td>
</tr>
<tr>
<td>C (AIDS)</td>
<td>75 (14%)</td>
<td>118 (21%)</td>
<td>193 (18%)</td>
</tr>
<tr>
<td>Prior antiretroviral treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>354 (68%)</td>
<td>560 (100%)</td>
<td>914 (84%)</td>
</tr>
<tr>
<td>Prior ZDV/ddC or ZDV/ddl</td>
<td>10 (2%)</td>
<td>197 (35%)</td>
<td>207 (19%)</td>
</tr>
<tr>
<td>Mean CD4 cell count/μl (range)</td>
<td>248 (31-690)*</td>
<td>159 (26-754)*</td>
<td>202 (26-754)</td>
</tr>
<tr>
<td>Mean log_{10} HIV-1 RNA/ml</td>
<td>4.8 (2.6-6.5)</td>
<td>4.8 (2.6-6.5)</td>
<td>4.8 (2.6-6.5)</td>
</tr>
<tr>
<td>Number of patients with HIV-1 RNA in the range (copies/ml):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5000</td>
<td>43 (8%)</td>
<td>58 (10%)</td>
<td>101 (9%)</td>
</tr>
<tr>
<td>5000-20000</td>
<td>79 (15%)</td>
<td>84 (15%)</td>
<td>163 (15%)</td>
</tr>
<tr>
<td>20000-50000</td>
<td>83 (16%)</td>
<td>80 (14%)</td>
<td>163 (15%)</td>
</tr>
<tr>
<td>50000-200000</td>
<td>179 (34%)</td>
<td>185 (33%)</td>
<td>364 (34%)</td>
</tr>
<tr>
<td>&gt;2000000</td>
<td>139 (27%)</td>
<td>153 (27%)</td>
<td>292 (27%)</td>
</tr>
</tbody>
</table>

*p = 0.0001

Treatment with zidovudine/lamivudine resulted in a maximum HIV-1 RNA reduction by median 1.9 log_{10} and 1.3 log_{10} in patients with ≤6 months and >6 months of prior NRTI therapy, accompanied by increases in CD4 cell count of 70 and 49 cells/mm³, respectively. After 48 weeks, HIV-1 RNA was still reduced by median 0.8 log_{10} and 0.5 log_{10}, respectively. Based on Kaplan-Meier estimates, 49% and 20% of patients with ≤6 months and >6 months of prior treatment achieved suppression of HIV-1 RNA below 400 copies/ml on at least one occasion during treatment with zidovudine/lamivudine. In both groups, 80-90% of treatment responses occurred within the first 8-12 weeks of treatment (Figure 1).

Figure 1. Cumulative time to first HIV-1 RNA suppression below 400 copies/ml (Kaplan-Meier estimates) in patients with ≤6 months (dashed line) and >6 months (solid line) of prior treatment.

However, most patients whose HIV-1 RNA levels fell below the lower limit of detection (400 copies/ml) showed a subsequent rise. In both groups, the rate of treatment failure was significantly faster for those patients with higher baseline HIV-1 RNA levels.

The times from the initial treatment response to a possible subsequent treatment failure were then combined in a single measurement of sustained HIV-1 RNA suppression. Patients were defined as
treatment failures at day 0 of treatment if their HIV-1 RNA never fell below 400 copies/ml. For those patients whose HIV-1 RNA had become undetectable, the time to treatment failure was estimated by the subsequent duration on treatment. Kaplan-Meier plots of the proportion of patients showing sustained HIV-1 RNA suppression over time are shown in Figure 2.

Figure 2. Time to virological failure after HIV-1 RNA suppression below 400 copies/ml, stratified by baseline HIV-1 RNA level (Kaplan-Meier estimates, non-responders included as failure at day 0)

There were striking differences in the probability of both achieving a reduction below 400 copies/ml and sustaining this reduction according to the baseline HIV-1 RNA level. In patients with ≤6 months of prior treatment HIV-1 RNA fell below 400 copies/ml in 89% of those with baseline HIV-1 RNA <5000 copies/ml, and 71% of patients sustained this reduction for 48 weeks. In contrast, only 39% of patients with baseline HIV-1 RNA of 50000-200000 copies/ml achieved undetectable HIV-1 RNA, and only 14% maintained this response for 48 weeks (Figure 2a). In patients with >6 months of prior treatment, fewer achieved and maintained treatment effect. Among those with baseline HIV-1 RNA <5000 copies/ml, 66% achieved levels below 400 copies/ml and 41% sustained this reduction over 48 weeks. In patients with baseline HIV-1 RNA of 50000-200000 copies/ml, only 6% reached levels below 400 copies/ml, and 1% sustained this reduction over 48 weeks (Figure 2b).

Multivariate Cox proportional hazard rates models were used to determine the relative effects of prior NRTI treatment, baseline HIV-1 RNA level, CD4 cell count, and demographic parameters on the durability of viral suppression below 400 copies/ml. Higher baseline HIV-1 RNA levels and >6 months of prior NRTI treatment were significant and independent predictors of failure to maintain HIV-1 RNA suppression below 400 copies/ml. When these two variables were included in the
multivariate model, there was no additional independent effect of age, sex, race, CDC disease stage or baseline CD4 cell count on the risk of virological failure. (Table 2)

Table 2. Risk of failure to achieve sustained HIV-1 RNA suppression below 400 copies/ml (all patients, Cox proportional regression analyses)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Univariate</th>
<th>Multivariate</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>HR</td>
</tr>
<tr>
<td>Baseline HIV-1 RNA</td>
<td>1.74</td>
<td>1.57-1.92</td>
<td>1.76</td>
</tr>
<tr>
<td>Baseline CD4 cell count</td>
<td>0.90</td>
<td>0.88-0.93</td>
<td>0.98</td>
</tr>
<tr>
<td>&lt;6 months NRTI</td>
<td>0.70</td>
<td>0.62-0.81</td>
<td>0.68</td>
</tr>
<tr>
<td>Age</td>
<td>1.00</td>
<td>0.99-1.01</td>
<td>0.99</td>
</tr>
<tr>
<td>Gender</td>
<td>1.16</td>
<td>0.96-1.40</td>
<td>1.13</td>
</tr>
<tr>
<td>Race</td>
<td>1.06</td>
<td>0.91-1.25</td>
<td>0.88</td>
</tr>
<tr>
<td>CDC Stage</td>
<td>0.84</td>
<td>0.77-0.92</td>
<td>1.03</td>
</tr>
</tbody>
</table>

HR, Hazard ratio; 95% CI, 95% confidence intervals

Patients with at least a 0.5 log_{10} reduction in HIV-1 RNA were divided in three groups based on the magnitude of HIV-1 RNA nadir achieved during treatment: <400 copies/ml (full virological response), and 400-1000 and 1000-5000 copies/ml (partial virological responses). The three groups were then compared regarding the time to the loss of this response, defined as subsequent HIV-1 RNA rise of at least 0.5 log_{10} copies/ml above the respective nadir level. Patients with ≤6 months of prior treatment who achieved an HIV-1 RNA nadir of 400 copies/ml retained this response for significantly longer time periods (median 13.1 weeks) than those who only reached between 400 and 1000 or between 1000 and 5000 copies/ml (median 5.9 and 5.4 weeks, respectively, P<0.0001). For patients with >6 months of prior treatment, however, there was no significant difference in the time to a rebound in HIV-1 RNA above the nadir level between those with full versus those with partial virological responses. (Figure 3)
Loss of virological response was defined as the $>0.5 \log_{10}$ copies/ml of the lowest (nadir) HIV-1 RNA achieved on treatment. (a) Patients with <6 months of prior NRTI who achieved an HIV-1 RNA nadir of <400 (n=132), 400–1000 (n=66), or 1000–5000 copies/ml (n=100); P<0.0001 for comparison between the groups. (b) Patients with >6 months of prior NRTI who achieved an HIV-1 RNA nadir of <400 (n=45), 400–1000 (n=27), or 1000–5000 copies/ml (n=78); comparison between the groups not statistically significant.

Discussion

Treatment with zidovudine/lamivudine induced a virological response in 49% of patients with ≤6 months prior treatment and in 20% of patients with >6 months prior treatment. This response, defined as suppression of HIV-1 RNA below 400 copies/ml, was achieved by 80-90% of all responding patients within 8-12 weeks of starting treatment. The rapid onset and magnitude of virological efficacy of zidovudine/lamivudine was comparable with the effects of zidovudine/didanosine as assessed in the Delta trial. In a similar population, using the slightly higher HIV-1 RNA detection limit of 800 copies/ml, 61% of treatment-naive patients and 24% of zidovudine-experienced patients achieved undetectable HIV-1 RNA levels following treatment with zidovudine/didanosine. The efficacy of zidovudine/zalcitabine, also assessed in the Delta trial, suppressed HIV-1 RNA below 800 copies/ml in 40% and 28% of patients respectively. The reductions of HIV-1 RNA following treatment with both zidovudine/didanosine and zidovudine/zalcitabine have been associated with documented clinical benefit over zidovudine monotherapy. Similarly, a significant reduction in morbidity and mortality was also achieved using zidovudine/lamivudine, despite sustained suppression of HIV-1 RNA below 400 copies/ml in only a minority of patients. After these studies were conducted, the comparison of a double NRTI combination with a triple combination treatment including the protease inhibitor indinavir demonstrated that the latter induced a more efficient
suppression of HIV-1 RNA and an additional reduction in progression to AIDS and death. Treatment with highly active antiretroviral combination treatments which increase the chance of HIV-1 RNA suppression to under 400 copies/ml has therefore become the standard of care and the combination zidovudine/lamivudine should ideally be used only as part of fully suppressive regimens based on current guidelines.

In this analysis, the probability of achieving a sustained reduction in HIV-1 RNA was highly dependent on baseline HIV-1 RNA level and on the duration of previous NRTI therapy. A concordant result was also reported from the Delta trial in which time to virological failure was significantly longer in patients with baseline HIV-1 RNA below 800 copies/ml. In our analysis, only patients with baseline HIV-1 RNA <5000 copies/ml and little previous NRTI exposure had a reasonable probability (71%) of sustaining undetectable HIV-1 RNA at 48 weeks on zidovudine/lamivudine, whereas those with higher baseline HIV-1 RNA levels, and all those with longer prior treatment, were unlikely to achieve sustained HIV-1 RNA suppression. Given the strong impact of the baseline HIV-1 RNA level on the magnitude and durability of the virological response, it is conceivable that even triple combination treatment will be insufficient to induce sustained viral suppression in patients with very high baseline HIV-1 RNA levels, i.e., those with >200000 copies/ml. The predictive value of baseline HIV-1 RNA also supports the concept of the individually variable virologic setpoint in which the level of viral load in plasma parallels the rate of viral replication. Higher numbers of resistance mutations produced by high levels of viral replication before the start of treatment would lead to an increased risk for loss of treatment efficacy owing to pre-existing resistant virus that has either retained the ability to replicate or becomes activated from its latent stage despite treatment.

The majority of patients who showed initial suppression in HIV-1 RNA lost this treatment effect within the 52 weeks follow-up in the trials. The virological response lasted the longest in patients who achieved an HIV-1 RNA nadir below 400 copies/ml and who were not heavily pre-treated. In the other patients, particularly those who only reached an HIV-1 RNA nadir that was higher than 400 copies/ml, the virological failure occurred between 5.4 and 8 weeks after the initial response. These results indicate that the duration of HIV-1 RNA suppression is dependent on the ability of an antiretroviral regimen to suppress HIV replication as strongly as possible – a principle that has been recently confirmed by viral load measurements under combination regimens including an NNRTI or a protease inhibitor.

The loss of maximal treatment response in our analysis is obviously related to the emergence of virus resistant to zidovudine and lamivudine. Treatment with zidovudine/lamivudine typically causes substantial early reductions in HIV-1 RNA when virus sensitive to lamivudine can no longer replicate. A subsequent rise in HIV-1 RNA levels coincides with the emergence of lamivudine-resistant HIV-1, but mean HIV-1 RNA levels remain below baseline for most patients. This may be due to the continued action of zidovudine, reduced replication competence of lamivudine-resistant HIV-1, or a combination of these factors.

There are four aspects specific to the datasets used. Firstly, the data allow prediction of HIV-1 RNA suppression in the short-term (up to 1 year), but these results cannot necessarily be extrapolated to longer-term follow up. Secondly, zidovudine/lamivudine combination treatment does not suppress HIV-1 RNA to undetectable levels in the vast majority of patients as reported for highly active combinations such as zidovudine/lamivudine/indinavir, zidovudine/didanosine/nevirapine, or ritonavir/saquinavir. The correlation between early suppression of HIV-1 RNA, long-term viral suppression and clinical progression may be different for such combinations. Thirdly, treatment with zidovudine/lamivudine reduces HIV-1 RNA levels sharply, followed by a rebound towards baseline coincident with the emergence of lamivudine-resistant virus. However, HIV-1 RNA levels remain partially suppressed at detectable levels. Different combination treatments with alternative resistance profiles of influence on viral fitness could show other correlations between baseline HIV-1 RNA and the likelihood of sustained suppression below 400 copies/ml. Finally, analysis of HIV-1 RNA levels using more sensitive ‘ultra-direct’ PCR methods has shown that a subset of patients with reductions below 400 copies retain plasma HIV-1 RNA levels between 20-400 copies/ml.
Replication may be ongoing, and mutations may emerge in these patients, albeit at a slow rate, and the earlier detection of virological failure could influence the interpretation of the results. Reduction of HIV-1 RNA to below 20 copies/ml seems to be necessary to accomplish a long-lasting suppression of viral replication.\textsuperscript{11,13} Given the high virological failure rate on zidovudine/lamivudine in this analysis and assuming that not all patients with HIV-1 RNA below 400 copies/ml would also be below the lower detection limit of an ultrasensitive test, double combination treatments with NRTIs should only be recommended in exceptional circumstances.

Our results have also implications for the timing of HIV-1 RNA monitoring. Maximum virological response was demonstrated for 80-90% of patients before week 12, with the greatest risk of failure usually seen by week 20. Thus, monitoring of HIV-1 RNA every 2-3 months after starting zidovudine/lamivudine seems sufficient to allow early detection of treatment failure, whereas less frequent monitoring (e.g., every 3-4 months) may be justified at a later stage to confirm the maintenance of virological response. The time required for the majority of patients to show full virological response, however, is longer (4 to 6 months) if more sensitive ultra-direct PCR methods are used for HIV-1 RNA detection.\textsuperscript{11,13,19}

In summary, our data demonstrate that baseline HIV-1 RNA should influence the choice of antiretroviral treatment regimen. While double NRTI treatment may offer a chance of sustained virological suppression to selected patients with low baseline HIV-1 RNA and little prior treatment, highly active antiretroviral therapy, preferentially including a protease inhibitor, is generally necessary to achieve sustained suppression of HIV.

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References


38


