Randomised trial of addition of lamivudine or lamivudine plus loviride to zidovudine-containing regimens for patients with HIV-1 infection: the CAESAR trial

CAESAR Coordinating Committee, [Unknown]; Study group members AMC, ;; Kroon, E.D.M.B.; Wit, F.W.N.M.

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CAESAR Coordinating Committee*

Summary

Background Previous studies have shown that combination therapy with lamivudine plus zidovudine causes pronounced and sustained increases in CD4 counts and reductions in viral load in individuals infected with HIV-1. We assessed the clinical benefit of the addition of lamivudine to zidovudine-based regimens in patients infected with HIV-1 who had CD4 counts of 25–250/µL.

Methods Eligible patients receiving zidovudine monotherapy or zidovudine plus zalcitabine or didanosine combination therapy were assigned 52 weeks of treatment with the addition of placebo, lamivudine (150 mg twice a day), or lamivudine (150 mg twice a day) plus loviride (100 mg three times a day). Patients were unaware of type of treatment allocated. The primary endpoint was progression to a new protocol-defined AIDS event or death.

Findings The study was terminated following the second interim analysis because of a highly significant reduction in progression to AIDS or death in the patients treated with lamivudine rather than placebo. In the final analysis of 1840 patients, progression had occurred in 95 (20%) of 471 placebo-treated patients, 86 (9%) of 907 lamivudine-treated patients, and 42 (9%) of 462 patients who received lamivudine plus loviride (p=0·0001, relative hazard 0·42 [95% CI 0·32–0·57]). A significant survival benefit was also seen (p=0·0007, relative hazard 0·40 [0·23–0·69]). Significantly fewer patients in the lamivudine group than in the placebo group required hospital admission, unscheduled visits, or prescribed medications for HIV-related events. There were no differences in the frequency or severity of clinical or laboratory toxicities between the treatment groups.

Interpretation The addition of lamivudine to zidovudine-containing treatment regimens significantly slowed the progression of HIV disease and improved survival. However, it is unlikely that this combination alone would be sufficient to achieve long-term complete suppression of viral replication in all patients.

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See Commentary page 1408

*Investigators, CAESAR Coordinating Committee, and participating institutions are listed at end of paper.

Correspondence to: Prof David Cooper, National Centre in HIV Epidemiology and Clinical Research, Faculty of Medicine, University of New South Wales, 376 Victoria Street, Sydney, NSW 2010, Australia
required and by each institution's ethics committee or institutional review board. Each participant gave written informed consent.

After the results of the Delta and AIDS Clinical Trials Group (ACTG) 175 trials were announced in September, 1995, the protocol was amended to give patients who had entered CAESAR on zidovudine monotherapy the option of adding didanosine or zalcitabine to their treatment regimen.

Trial endpoints
The primary endpoint of the trial was progression to a new protocol-defined AIDS event or death. AIDS-defining events, classified according to the 1993 CDC case definition were divided by severity into group 1 events (mucocutaneous Kaposi’s sarcoma, pulmonary and extrapulmonary tuberculosis, oesophageal candidosis, chronic herpes-simplex ulceration, recurrent bacterial pneumonia) and group 2 events (all other AIDS-defining events). This grading system was based on analyses of survival after diagnosis of AIDS events in two large cohort studies. Disease progression was defined according to an individual's baseline disease stage: for patients without AIDS at enrolment in the trial, progression was classified as any new AIDS event or death; for patients with a group 1 AIDS event at baseline, progression was classified as development of any group 2 AIDS event or death; and for patients with a group 2 event at baseline, progression was classified as development of any new group 2 event or death (ie, for patients with a previous diagnosis of AIDS at baseline, the development of a group 1 AIDS event was not classified as a study endpoint). All AIDS events and deaths were independently assessed in real time by members of a review committee who had no knowledge of treatment allocation. Three interim analyses of efficacy and safety, for review by an independent data and safety monitoring board under blinded conditions, were planned. The Peto rule (p=0.001 for the primary efficacy comparison of the lamivudine and placebo arms) was used as a guideline for stopping the trial.

Statistical analyses
All analyses were done on an intent-to-treat basis, including all data available on patients who received at least one dose of study drugs, irrespective of discontinuation of study drug or withdrawal from the trial. The primary outcome, time to progression to a new protocol-defined AIDS event or death, was compared for those taking lamivudine relative to those taking placebo by the log-rank test stratified by baseline CD4 count, AIDS diagnosis, and current treatment at screening. Patients were assessed at enrolment, week 2, week 4, week 8, and week 12 and then every 8 weeks up to week 52. All laboratory tests were done in central laboratories. Patients who discontinued trial medication or withdrew from the trial for any reason were followed up for information on adverse events and HIV-1 disease events. Clinical and laboratory adverse events were collected and classified according to the ACTG grading system. Three interim analyses of efficacy and safety, for review by an independent data and safety monitoring board under blinded conditions, were planned. The Peto rule (p=0.001 for the primary efficacy comparison of the lamivudine and placebo arms) was used as a guideline for stopping the trial.
placebo, with associated 95% CIs. The analyses were then repeated for preplanned subgroups defined by screening CD4 count (25–100/µL, >100–175/µL, and >175–250/µL), presence of AIDS at baseline, and current treatment at screening (monotherapy or combination therapy). An additional post-hoc subgroup analysis was done for groups who had less than 6 months, 6–24 months, and more than 24 months of previous antiretroviral therapy at enrolment. The primary analysis was also repeated with an endpoint of death or any new AIDS-defining events (irrespective of the group 1 or 2 staging system).

The study was designed to have more than 80% power to detect a difference in the rates of progression over 52 weeks between 16% in the group taking placebo and 10% in the group taking lamivudine.

Summary statistics of change in CD4 count and HIV-1 RNA were compared between treatment arms by the Van Elteren test 14 stratified by baseline CD4 count, AIDS, and current treatment at screening. The time to first grade 3 or 4 clinical and/or laboratory toxicity was compared between treatment arms by the log-rank test. The frequency of specific adverse events was compared between treatment arms by Fisher’s-exact test. Two-sided tests of significance were used throughout.

Results

Enrolment and baseline demography

A total of 1895 patients were randomly assigned drug treatment (figure 1). Data from all patients were included in the second interim analysis, upon which the decision was made to stop the study. 55 patients were excluded because of concerns over the quality of the data collected in this centre. 1840 patients were included in the final analysis.

The baseline characteristics of the study population are listed in table 1. Treatment groups were well matched with no significant differences between the three arms of the trial. The median CD4 count at entry was 126/µL, 1598 (87%) of the patients in the study were male, and 1594 (87%) of the population acquired HIV-1 via sexual contact. 1353 (74%) patients had no previous AIDS-defining event at enrolment. 310 (17%) patients were naive to antiretroviral therapy at baseline (i.e. placebo arm) who entered the trial, 698 (38%) patients received concurrent combination therapy.

Study termination: interim analysis

The CAESAR study was terminated following independent review of the second interim analysis by the Data and Safety Monitoring Board. At this time 70% of the total projected follow-up time (1315 of 1895 patient years) had been completed. All patients remaining on study medication at the time of trial termination had the medication withdrawn at their next clinic visit. Based on the recommendation of the Data and Safety Monitoring Board, the study was stopped. Given the high proportion of total follow-up completed, we concluded that there was no benefit in continuing the two lamivudine-containing arms of the trial as there would be no possibility of detecting any further difference between these two arms.

The disposition of the study population at the time of the final analysis is given in figure 1. The median duration of follow-up for the whole study population was 52 weeks. The median time on study drug was 52 weeks, with no significant difference between the three treatment arms as there would be no possibility of detecting any further difference between these three arms.

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80 (9%) of 935 patients in the current treatment plus lamivudine group, and 38 (8%) of 475 patients in the current treatment plus lamivudine plus loviride group (p<0·0001, relative hazard 0·46 [95% CI 0·34–0·63], relative reduction in risk of progression 54% for the comparison of lamivudine with placebo arms).

Clinical outcome: final analysis

Between the second interim analysis and the final data cutoff following termination of the trial, an additional 24 primary endpoints occurred. The most common primary endpoint in the final analysis was progression to a new protocol-defined AIDS event (186 [83%] of 223 events). Death was the primary endpoint for 37 patients (17% of primary endpoints). 140 (63%) endpoints occurred in patients who were symptom free or CDC stage B at baseline, and 83 (37%) primary endpoints occurred in patients who entered the trial with a previous AIDS diagnosis.

Progression to AIDS or death

In the final intention-to-treat analysis the progression rates were: placebo 95 (20%) of 471; lamivudine 86 (9%) of 907; lamivudine plus loviride 42 (9%) of 462 (p<0·0001, relative hazard 0·42 [0·32–0·57], relative reduction in risk of progression 57% for the comparison of lamivudine to placebo arms).

Although there was no difference in the progression rates between the lamivudine and lamivudine plus loviride arms overall, an analysis of progression rates stratified by duration of previous antiretroviral treatment on outcome (<6 months; 6-24 months; >24 months). The progression rates, hazard ratios, and 95% CIs for these subgroups are indicated in table 3 and figure 3. A consistent reduction in risk for the lamivudine group compared with placebo was apparent in each of the subgroups analysed.

Table 2: Rates of progression to AIDS and death

<table>
<thead>
<tr>
<th></th>
<th>Current treatment plus placebo</th>
<th>Current treatment plus lamivudine</th>
<th>Current treatment plus lamivudine and loviride</th>
<th>p*</th>
<th>Relative hazard (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>471</td>
<td>907</td>
<td>462</td>
<td>&lt;0·0001</td>
<td>0·43 [0·32–0·57]</td>
</tr>
<tr>
<td>Protocol-defined new AIDS or death</td>
<td>95 (20%)</td>
<td>86 (9%)</td>
<td>42 (9%)</td>
<td>&lt;0·0001</td>
<td>0·40 [0·31–0·55]</td>
</tr>
<tr>
<td>New AIDS or death</td>
<td>103 (22%)</td>
<td>91 (10%)</td>
<td>46 (10%)</td>
<td>&lt;0·0001</td>
<td>0·40 [0·31–0·55]</td>
</tr>
<tr>
<td>Death</td>
<td>28 (6%)</td>
<td>23 (3%)</td>
<td>14 (3%)</td>
<td>0·0007</td>
<td>0·40 [0·23–0·69]</td>
</tr>
</tbody>
</table>

* Log-rank test stratified by CD4 count, AIDS diagnosis, and current treatment at baseline for comparison of placebo and lamivudine arms.
**Changes in CD4 count and viral load**

CD4 counts and plasma HIV-1 viral load were measured prospectively over the first 28 weeks of treatment in the 326 patients recruited in France and Belgium. There was a minimal response in the CD4 count and viral load of patients continuing current treatment alone (figure 4). Patients in the lamivudine and lamivudine plus loviride arms experienced median peak CD4 cell increases of 43/µL and 74/µL from baseline at week 4, which remained at 23/µL and 22/µL, respectively, above baseline at week 28. The difference in CD4-cell counts between the lamivudine-containing arms and the placebo arm was about 34/µL at week 28. The maximum change in viral load for patients in the lamivudine arm was a median reduction of 0·67 log₁₀ HIV-1 RNA copies at week 2, returning to 0·1 log₁₀ below baseline by week 28. The corresponding reductions at weeks 2 and 28 for patients in the lamivudine plus loviride arm were 0·79 log₁₀ and 0·25 log₁₀ HIV-1 RNA copies below baseline, respectively.

**Use of healthcare resources**

The numbers of patients requiring at least one hospital admission, unscheduled visit, or prescribed medication for any HIV-1-related event during the course of the study are shown in table 4. Significantly fewer patients in the lamivudine arm than in the placebo arm required hospital admission (p=0·002), unscheduled outpatient visits (p=0·013), or prescribed medications (p=0·001) for HIV-1-related events. No significant additional reduction in healthcare use was observed in patients receiving loviride plus lamivudine compared with lamivudine.
the meta-analysis of the four surrogate marker studies of lamivudine plus zidovudine combination therapy, which showed a 49% reduction in the risk of progression to new CDC B or C events for patients treated with lamivudine plus zidovudine compared with control patients.9

The clinical benefit of lamivudine plus zidovudine treatment was apparent early in the trial, with a divergence between the lamivudine and placebo arms of the study occurring in the time-to-event analysis after the first 3 to 4 months of treatment. The magnitude of the clinical benefit seen for the addition of lamivudine was consistent irrespective of CD4 count, disease stage, or current treatment at entry. A subgroup analysis stratified by duration of previous treatment suggested that the magnitude of clinical benefit increased as the duration of previous antiretroviral exposure decreased. This conclusion is supported by earlier studies of lamivudine, which demonstrated greater and more durable responses to lamivudine plus zidovudine in terms of CD4-count increases and viral-load decreases in patients who had received no previous antiretroviral treatment, than in patients who had received previous zidovudine therapy.5–8

These data together support the conclusion that a combination of lamivudine plus zidovudine will provide the greatest clinical benefit to patients who have not previously received other antiretroviral therapies.

The continued use of didanosine or zalcitabine did not appear to provide any additional clinical benefit for patients receiving lamivudine plus zidovudine therapy. A multivariate analysis, controlling for CD4 counts and disease stage at baseline, and including only patients who had received antiretroviral treatment before study entry, showed no independent benefit from the presence of didanosine or zalcitabine in combination with lamivudine and zidovudine, compared with lamivudine in combination with zidovudine alone (data not shown).

<table>
<thead>
<tr>
<th>Current treatment plus placebo (n=471)</th>
<th>Current treatment plus lamivudine (n=907)</th>
<th>Current treatment plus lamivudine and loviride (n=461)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients with at least one hospital admission for an HIV-related illness</td>
<td>53 (11%)</td>
<td>57 (6%)</td>
<td>24 (5%)</td>
</tr>
<tr>
<td>Total number of patients with at least one unscheduled outpatient visit for an HIV-related illness</td>
<td>69 (15%)</td>
<td>91 (10%)</td>
<td>39 (8%)</td>
</tr>
<tr>
<td>Total number of patients with at least one prescription for an HIV-related illness</td>
<td>204 (43%)</td>
<td>271 (30%)</td>
<td>123 (27%)</td>
</tr>
</tbody>
</table>

*Fisher’s exact test for comparison of placebo and lamivudine arms. †Includes all ambulatory visits: unscheduled outpatient and emergency-care visits.

Table 4: Healthcare resource use for new or recurrent HIV-related events

Figure 4: Median (SE) change from baseline in CD4 count and log_{10} copies per mL HIV RNA by treatment group
This was not a preplanned comparison and patients receiving lamivudine in combination with didanosine or zalcitabine may have differed from those receiving zidovudine alone in ways not controlled for in this multivariate analysis.

Three trials have been reported which were designed to assess the clinical benefit of combinations of zidovudine with zalcitabine or didanosine compared with zidovudine alone.1,15 In the Delta and ACTG 175 trials, based on CD4 counts at entry and the percentages of patients with a previous AIDS diagnosis at entry into the study, patients were enrolled at an earlier stage in their HIV-1 infection than in the CAESAR study. Based on the same criteria the Community Programs for Clinical Research on AIDS (CPCRA) 007 study enrolled patients with slightly more advanced disease than the patients in CAESAR.

Subgroup analyses were reported in Delta and ACTG 175 for populations defined by the amount of previous antiretroviral treatment.1 The relative reductions in the risk of progression to AIDS or death in favour of zidovudine plus didanosine or zalcitabine therapy compared with zidovudine alone were within the range of 20-51% for previously untreated patients, and 5-35% for patients who had received previous antiretroviral treatment. In the CPCRA 007 study a subgroup analysis showed that a treatment benefit in favour of combination therapy was only present for patients who had received less than 12 months of previous zidovudine treatment (relative risk reduction 24-28%).

The relative reduction in risk for the lamivudine plus zidovudine arm in CAESAR, which contained predominantly antiretroviral-experienced patients (median duration of therapy at baseline 28 months), was 51%. Although comparisons between trials should be treated with caution, because of differences in the populations studied, variable follow-up periods, and possible differences in adjunctive prophylactic therapies, we suggest that the addition of lamivudine to zidovudine treatment provides greater clinical benefit in pretreated patients at least compared with other combinations of two nucleoside analogues.

Data from the EUROSIDA study group also suggested that treatment with lamivudine plus zidovudine may be more effective than combinations of zidovudine with other nucleoside analogues.16 Mortality data were reported on a total of 2410 patients from the observational-EUROSIDA cohort study in patients who had begun antiretroviral therapy with a regimen that included zidovudine either before study entry or during the study follow-up period. In a multivariate analysis that adjusted for CD4 count, development of AIDS, age, and year of starting therapy, a reduced risk of death was associated with the use of lamivudine, didanosine, stavudine, or zalcitabine used in combination with zidovudine. The risk of death was lowest for the combination of lamivudine with zidovudine (relative hazard 0.41 [95% CI 0.28-0.62]), followed by smaller reductions in risk for the other combinations of nucleoside analogues. The reduction in risk of death associated with lamivudine plus zidovudine therapy of 59% in the cohort was very consistent with the 60% reduction in risk of death seen in CAESAR.

Several explanations have been proposed to account for the relative potency of lamivudine therapy in combination with zidovudine in this setting. Treatment with lamivudine induces a drug-resistant variant of HIV-1 as a result of a single base-pair change at codon 184.17 In-vitro studies have suggested that lamivudine-resistant HIV-1 variants have a reduced replication capacity or viral fitness compared with wild-type virus.18 In addition, such variants may enhance the fidelity of reverse transcription leading to less genetic variability in the virus;19 this could render the virus more susceptible to zidovudine by delaying the time to onset of mutations conferring resistance to zidovudine. Indeed, in naive patients lamivudine delays the onset of zidovudine-associated mutations.20 In contrast, didanosine or zalcitabine do not appear to delay the onset of zidovudine-associated mutations.21 Other studies have shown that HIV-1 variants that are resistant to zidovudine regain phenotypic sensitivity to zidovudine in the presence of lamivudine.22 The increase in the number of mutations required to confer phenotypic resistance to zidovudine in the presence of lamivudine has been proposed as a mechanism for this observation.23

Although the trial did not have power to detect additional clinical benefit between the lamivudine and the lamivudine plus loviride arms, the effect of loviride in our study population was marginal. The CD4 and viral-load data indicated an incremental benefit in the initial response to treatment for the lamivudine plus loviride arm over the lamivudine arm in the overall population. In patients with higher CD4 counts there was some preliminary evidence of a treatment benefit for the addition of loviride, with fewer clinical endpoints in the lamivudine plus loviride arm compared with the lamivudine arm (three [2%] of 135 vs five [6%] of 251), although this difference was not significant. Data from the AVANT I trial, in which zidovudine plus lamivudine plus loviride and zidovudine plus lamivudine were compared in patients with CD4 counts of 150-500/µL also suggested some additional benefit from the use of loviride in patients with higher CD4 counts.24 A further study is in progress to confirm these preliminary observations.

Data from other studies of NNRTIs suggest that the role of these compounds will be as part of potent combination therapy regimens for first-line treatment of HIV-1 infection where complete viral suppression will be the goal.25,26 In partially suppressive regimens, the rapid development of resistance to NNRTIs appears to limit their efficacy. In addition to the prospective CD4 and viral-load variables measured in the substudy of CAESAR, a retrospective case-cohort analysis of patients who reached a clinical endpoint versus patients who did not progress is currently being done and will be reported elsewhere.

Lamivudine and loviride were well tolerated in this study, which involved combination regimens of up to four different antiretroviral agents. There were no differences in the frequency of toxic effects between the three treatment arms and the most common laboratory and clinical toxic effects observed were those which have been previously associated with the use of zidovudine. With the advent of more aggressive treatment regimens employing three or four potent antiretroviral drugs, it is encouraging that combination regimens which are well tolerated can be identified.

Management of HIV-1-related events can place a great burden on healthcare services. In this study we observed that the delayed disease progression associated with lamivudine use resulted in significantly fewer patients...
needing hospital admission, unscheduled outpatient and emergency-care visits, and HIV-1-related medications.

The standard of care in the treatment of HIV-1 infection has changed rapidly in recent years, as indicated by recent consensus guidelines, and a difficulty with recent guidelines, as indicated by recent trends in viral load reduction.

Two nucleoside analogues plus a protease inhibitor are the combination antiretroviral therapy seen to date and the most compelling evidence of the clinical benefit of zidovudine and lamivudine in the CAESAR study increasing survival over that seen for the combination of plus lamivudine therapy adds another powerful level of detectability over periods up to 76 weeks.

Results of the ACTG 320 study, which compared a triple combination of lamivudine plus lamivudine plus indinavir with lamivudine plus lamivudine, confirm that the addition of a potent protease inhibitor to zidovudine plus lamivudine therapy adds another powerful incremental benefit in delaying disease progression and increasing survival over that seen for the combination of lamivudine and lamivudine in the CAESAR study (ACTG 320 executive summary). These results provide the most compelling evidence of the clinical benefit of combination antiretroviral therapy seen to date and indicate that treatments based on triple combinations of two nucleoside analogues plus a protease inhibitor are likely to become the benchmark against which further therapeutic advances will be measured.

CAESAR: study organisation

Writing committee—D A Cooper, C K Atzama, J M ontaner P J Collis.


Clinical endpoint review committee—D A Cooper, C K Atzama, J M ontaner

Centres and investigators—Australia: S M allal, M French, A Cain (Royal Perth Hospital; A Beveridge, W Genn, S Hales (Groote Schuur Hospital, Cape Town); D Cooper, A Carr, H Wood (St Vincent’s Hospital, Sydney); P A Plewan (Alfred Hospital, Melbourne); R M M Carty, R P Elyea, N Cai (Monash University, Melbourne); L Thomson, N M Goodall, J M ontaner, M Moroni, G Norkrans, M Opravil, A Hill, C Katlama, S Korsa, L Lange, M McCullum, M Mollison, M Moroni, G Norkrans, M Opravil, P Reiss, W Rozenbaum, J Scott, D Smith, S Staszewski, P Stoffels.

Clinical endpoint review committee—D A Cooper, C K Atzama, J M ontaner

Centres and investigators—Australia: S M allal, M French, A Cain (Royal Perth Hospital; A Beveridge, W Genn, S Hales (Groote Schuur Hospital, Cape Town); D Cooper, A Carr, H Wood (St Vincent’s Hospital, Sydney); P A Plewan (Alfred Hospital, Melbourne); R M M Carty, R P Elyea, N Cai (Monash University, Melbourne); L Thomson, N M Goodall, J M ontaner, M Moroni, G Norkrans, M Opravil, A Hill, C Katlama, S Korsa, L Lange, M McCullum, M Mollison, M Moroni, G Norkrans, M Opravil, P Reiss, W Rozenbaum, J Scott, D Smith, S Staszewski, P Stoffels.

Data and safety monitoring board—J Bartlett, D Jones, J Naylor, R Orby (chair), L Walters, P Yeni.

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