Clinical Efficacy of High-Dose Acyclovir in Patients with Human Immunodeficiency Virus Infection: A Meta-Analysis of Randomized Individual Patient Data


A meta-analysis of 8 randomized trials (1792 patients, 2947 patient-years of follow-up) showed that acyclovir (≥3200 mg/day) offered a significant survival benefit (P = .006 by log-rank test) in human immunodeficiency virus (HIV) infection. The treatment effect did not vary significantly in patient subgroups of different CD4 cell counts, hemoglobin levels, age, race, and sex, and with or without AIDS diagnosis. Acyclovir treatment (hazard ratio, 0.78; 95% confidence interval [CI], 0.65–0.93), higher CD4 cell count (P < .001), higher hemoglobin level (P < .001), and younger age (P < .001) reduced the hazard of mortality. Acyclovir decreased herpes simplex virus infections (odds ratio [OR], 0.28; 95% CI, 0.21–0.37) and varicella-zoster virus infections (OR, 0.29; 95% CI, 0.13–0.63) but not cytomegalovirus disease or mortality from lymphoma or Kaposi’s sarcoma. A survival advantage was seen specifically in studies with high incidence of clinical herpesvirus infections (≥25% per year). Given the wide confidence intervals, the small effect in low-risk patients, and recent changes in HIV therapeutics, the results should be interpreted cautiously, but the meta-analysis supports the importance of pathogenetic interactions between herpesviruses and HIV.

The high incidence of morbidity related to herpesviruses in human immunodeficiency virus (HIV)—infected patients, and the recognition that these agents may be important copathogens [1–3], may induce HIV replication [1, 2], and may potentially accelerate the destruction of the immune system, has long prompted interest in the assessment of antiviral interventions in HIV infection. Acyclovir was one of the first agents with antiviral activity tested for its clinical efficacy in HIV-infected patients. Despite 10 years of clinical research, a final consensus on its efficacy or lack thereof has not been reached. Nonrandomized cohort studies reached conflicting conclusions, ranging from large and clinically meaningful efficacy [4] to potential harm [5]. Nonrandomized studies may be prone to bias that is impossible to adjust for and interpret. However, a large body of randomized evidence has also been accumulated on acyclovir. Early clinical trials suggested large survival benefits in patients with advanced HIV disease after 1 year of follow-up [6, 7]. However, 2 subsequent sizable acyclovir trials [8, 9] failed to demonstrate any substantial impact on patient mortality and disease progression. It is unknown whether individual clinical trials may have arrived at different conclusions, either because of chance or because of genuine diversity among them. Both the clinical role of acyclovir and the pathogenetic implications of the results of these clinical trials remain uncertain.

To address these issues, we performed a meta-analysis of all of the controlled randomized evidence on acyclovir in HIV-infected patients. The meta-analysis used individual patient data [10] from all of the major studies, with updated survival
follow-up whenever possible, beyond the original analysis of the data and with detailed individual patient information on important covariates that may predict mortality in HIV-infected patients. This offered an opportunity to synthesize all of the available evidence and to assess the extent and reasons of potential heterogeneity in the study results.

**Methods**

**Identification and Selection of Studies**

The protocol considered all randomized efficacy trials that compared high-dose oral acyclovir (at least 3200 mg per day) against no therapy or placebo in patients with HIV infection addressing clinical outcomes including survival. Trials were identified through a Medline search, complemented by searching of abstracts from major meetings, trial directories, and communications with experts, investigators of the identified trials, and industry researchers. More than 100 people were contacted, and retrieval of the databases required coordinated efforts at several data archives in the United States and Europe over a period of almost 2 years.

**Data Collected**

Investigators and sponsoring agencies were asked to provide the following data on all randomized subjects: patient identification number, treatment assignment, date of randomization (start), latest date known to be alive and survival status, and baseline characteristics including—at the minimum—age, sex, race, baseline CD4 cell count, hemoglobin level, and previously recorded diagnosis of AIDS. These data were consistently collected and recorded for all trials. Investigators were asked to provide all follow-up data, including follow-up beyond what had been reported in original publications or in original executive summaries of unpublished studies. Additional data collected across trials included causes of death and occurrence of disease attributable to cytomegalovirus (CMV), herpes simplex virus (HSV), or varicella-zoster virus (VZV) infections, but for these data information was typically limited to the original trial follow-up, with no information on the extension periods. The few identified data inconsistencies were clarified with communications between the meta-analysis team and the local data managers and investigators.

**End Points**

The major end point addressed in the meta-analysis was survival, based on individual patient data. Secondary end points addressed included recorded morbidity that is related to acyclovir-susceptible herpesviridae, including HSV and VZV infections; occurrence of new CMV end-organ disease; and death from lymphoma and from Kaposi’s sarcoma because of their potential associations with herpesviruses (Epstein-Barr virus and human herpesvirus 8, respectively). Incidence data on new diagnoses of lymphoma and Kaposi’s sarcoma were not consistently available. Secondary end points were analyzed based on group data from each trial. All analyses followed the intention-to-treat principle and no patients were excluded.

**Statistical Methods**

**Pooled analysis.** The mortality data of each trial separately and of all trials together stratified according to study were analyzed with Kaplan-Meier plots, with comparisons made with the log-rank test [11].

**Fixed- and random-effects meta-analysis.** Odds ratios (ORs) and confidence intervals (CIs) were estimated for different time intervals on the basis of deaths occurring within each time interval among the randomized patients still at risk at the beginning of the interval. Heterogeneity between trials was assessed with a $\chi^2$ statistic. Since the statistic can be fairly insensitive, heterogeneity was considered significant for $P < .10$. The ORs were then combined by two different methods: the Mantel-Haenszel [12] fixed-effects model, which considers only heterogeneity within studies and assumes that differences between the various studies are only due to chance, and the DerSimonian and Laird model [13], which considers heterogeneity both within and among studies to calculate the range of possible true treatment effects across studies. Unless stated otherwise, we report only random-effects estimates. The random-effects model is more conservative and tends to provide wider CIs. In the presence of significant heterogeneity, the fixed-effects model would not be as appropriate as the random-effects model, while in the absence of among-study heterogeneity, the results of the two models are identical [14]. Separate analyses were done for survival at 6, 12, 24, 36, and 48 months and for the complete follow-up. The OR has been traditionally used in the analysis of clinical trials. However, it may overestimate the magnitude of the treatment effect when it is interpreted as a risk ratio. Therefore, for the analysis of the complete follow-up, we also obtained the more conservative pooled incidence risk ratios (representing the ratio of events per patient-years of follow-up in the acyclovir arm divided by events per patient-years of follow-up in the control arm) [15].

**Subgroup analyses.** Subgroup analyses were done along the same principles as the main analyses, focusing on data from the whole duration of follow-up and using only the patients belonging to each specific subgroup from each trial. Subgroups were considered for age at entry (<30, $\geq 30$), sex, race (white vs. other), baseline CD4 cell count (>$100$ and $\leq 100$/mm$^3$), baseline hemoglobin level ($<11$ and $\geq 11$ g/dL), and reported diagnosis of AIDS at entry. The cutoff values for the main subgroup analyses were pre-specified before analyses were undertaken. Heterogeneity within and among subgroups was assessed by the $\chi^2$ test.

**Proportional hazards modeling.** A separate approach used a proportional hazards model for the time to death [16]. Hazard ratios were estimated for acyclovir treatment versus placebo or no treatment, both unadjusted and adjusted for study and for age, sex, race, baseline CD4 cell count (used as the square root of the value), baseline hemoglobin level, and diagnosis of AIDS at entry in multivariate models. A multivariate model including only variables selected from forward selection according to a log likelihood ratio with $P < .05$ for entry and $P > .10$ for removal of variables gave similar results for the significant predictors (not reported). For missing predictor values, we performed one analysis excluding these patients and a separate analysis imputing median study values. The results were practically identical, and only the latter are reported.
Predictive score. A predictive score was built for the hazard of death on the basis of baseline CD4 cell count, baseline hemoglobin level, age, and prior recorded AIDS diagnosis. The efficacy of acyclovir was evaluated separately in the four quartiles of patients with low, moderate, high, and very high risk.

Secondary end points. For secondary end points, data were more limited to allow analyses at different time points. ORs for events recorded during the whole conduct of each trial were pooled according to the same principles of fixed- and random-effects models as for the primary end point, and heterogeneity was similarly assessed. Since there were several secondary end points, we agreed a priori to use a more strict level of statistical significance (α = .01) to account for multiple comparisons.

Finally, we evaluated whether the effect of acyclovir on survival was different in trials with different incidence of recorded acyclovir-susceptible herpesvirus (HSV and VZV) infection episodes in both arms combined. This analysis was also based on group data and should thus be extrapolated cautiously to the individual patient level. Nevertheless, even if detailed individual patient data were available regarding which patients had clinical HSV or VZV infections, most patients infected with herpesviruses have subclinical infections on HSV reactivation and thus there would have been classification errors for many persons. On the contrary, the group-level data may provide a more accurate estimate of the relative frequency of clinically manifest HSV and VZV reactivation in each of these populations.

Statistical analyses were done in SPSS [17] and in Meta-Analyst [18]. All P values are two-tailed.

### Results

**Characteristics of individual trials.** We obtained information on the existence of 11 randomized controlled trials [6–9, 19–24] of acyclovir in HIV-infected patients. We found no trials comparing low-dose oral acyclovir against placebo or no treatment. One small study of 30 patients [19] was excluded from the meta-analysis because it used intravenous acyclovir (50 mg/kg) only once weekly and in this trial, over its short-term follow-up (4 months), no deaths were recorded. Two more small trials of 12 and 21 patients, respectively [23, 24], were not included, as their focus was on pathogenesis, no deaths occurred among their participants, and secondary end points were not recorded. Characteristics of the remaining qualifying 8 trials with 1792 patients are shown in table 1. A large part of the available randomized evidence (4 studies with 1184 patients) remained unpublished as of late 1997, publication probably being delayed or deferred because results were not statistically significant [25]. Of the 4 unpublished studies, 1 was published shortly after the meta-analysis was completed [9].

As shown in table 1, the studies targeted patient populations in very different stages of the disease. Three studies included only patients with a diagnosis of AIDS (or stage IV disease), 4 studies excluded such patients, and 1 targeted a mixed population of patients with and without AIDS. All of these studies were first launched between 1986 and 1989, with the exception

### Table 1. Randomized trials of high-dose oral acyclovir in HIV-infected patients.

<table>
<thead>
<tr>
<th>Trial [ref]</th>
<th>n</th>
<th>Acyclovir dose (mg/day)</th>
<th>CD4 cells/mm², median (IQR)</th>
<th>AIDS,*</th>
<th>Hemoglobin, median g/dL</th>
<th>Median follow-up, years</th>
<th>Maximum follow-up, years</th>
<th>Total patient-years</th>
<th>Deaths/patients</th>
<th>Acyclovir episodes during main study (per 100 patient-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H14-325 [6]</td>
<td>302</td>
<td>3200</td>
<td>40 (18–80)</td>
<td>100</td>
<td>12.2</td>
<td>1.43</td>
<td>4.6</td>
<td>503</td>
<td>0.6</td>
<td>123/153, 125/149</td>
</tr>
<tr>
<td>H56-AIDS [7]</td>
<td>131</td>
<td>3200</td>
<td>34 (14–110)</td>
<td>100</td>
<td>12.0</td>
<td>1.01</td>
<td>3.5</td>
<td>168</td>
<td>1.0</td>
<td>40/62, 54/69</td>
</tr>
<tr>
<td>H56-KS [21]</td>
<td>46</td>
<td>3200</td>
<td>185 (113–323)</td>
<td>100</td>
<td>13.7</td>
<td>0.46</td>
<td>1.6</td>
<td>22</td>
<td>0.4</td>
<td>6/23, 5/23</td>
</tr>
<tr>
<td>ACTG 010 [20]</td>
<td>411</td>
<td>4800</td>
<td>306 (206–404)</td>
<td>—</td>
<td>14.0</td>
<td>0.82</td>
<td>2.1</td>
<td>38</td>
<td>0.8</td>
<td>1/19, 3/22</td>
</tr>
<tr>
<td>ACTG 063 [9]</td>
<td>334</td>
<td>4000</td>
<td>64 (30–139)</td>
<td>57</td>
<td>12.2</td>
<td>1.29</td>
<td>5.1</td>
<td>505</td>
<td>0.8</td>
<td>52/169, 54/165</td>
</tr>
<tr>
<td>P53 [8]</td>
<td>693</td>
<td>4800</td>
<td>434 (330–550)</td>
<td>—</td>
<td>14.8</td>
<td>2.18</td>
<td>3.4</td>
<td>1338</td>
<td>1.8</td>
<td>7/345, 7/348</td>
</tr>
<tr>
<td>H14-326 [22]</td>
<td>111</td>
<td>3200</td>
<td>607 (535–721)</td>
<td>—</td>
<td>14.6</td>
<td>1.84</td>
<td>1.9</td>
<td>135</td>
<td>1.8</td>
<td>1/57, 1/54</td>
</tr>
</tbody>
</table>

NOTE. IQR: interquartile range; HSV: herpes simplex virus; VZV: varicella-zoster virus; ACTG: AIDS Clinical Trials Group; ARC: AIDS-related complex; KS: Kaposi’s sarcoma.

* Criteria for AIDS were reflective of CDC definitions available at time studies were first launched (1982 definition for H56-002 AIDS and 1987 definition for ACTG 063). Patients in H14-325 were eligible for enrollment if they had <150 CD4 cells/mm² and stage IV disease (which could include IVC2) by 1987 criteria. Patients with ARC in H56-002 ARC were eligible if they had weight loss of >10% or >7 kg and/or oral candidiasis and at least 1 of following: diarrhea of unknown cause, fever of unknown cause >38°C for >3 weeks, oral hairy leukoplakia, herpes zoster, or persistent lymphadenopathy involving >2 extrainguinal sites.

† No. of HSV/VZV episodes during main study pertains to acyclovir and control arms combined. Given large efficacy of acyclovir to suppress clinical HSV and VZV infections, large majority of events occurred in control arm; therefore, rates of HSV/VZV are largely reflective of risk of clinical herpesvirus infections in each study population and not so much of length of ACV exposure.

§ Does not include HSV or VZV recurrences that were not systematically recorded in ACTG 063; in other trials, recurrences accounted for ~25% of count of episodes.

\[\text{\textcopyright JID 1998; 178 (August) Acyclovir in HIV Infection: A Meta-Analysis 351} \]
of H14-326, which was launched in 1992. The use of *Pneumocystis carinii* pneumonia prophylaxis was not systematically recorded but was uncommon in the main follow-up of studies launched before 1988 (H56 studies and ACTG 010), while it became standard in studies launched in 1989 or later, in particular ACTG 063 and H14-325, whose patients would qualify for *P. carinii* prophylaxis (P53 and H14-326 targeted patients with early disease).

The median CD4 cell count in the included studies varied from 34 to 607/mm³. With the exception of 2 studies that left antiretroviral therapy at the discretion of the investigator from the onset [6, 22], most studies used zidovudine as original background therapy. With the exception of 2 small studies [20, 21] that did not systematically collect long-term follow-up information, the median follow-up was >1 year in all studies, and the maximal follow-up was 3.4–5.1 years. The 2 small studies with suboptimal follow-up information had inconclusive results, with soft trends in opposite directions. The total follow-up of all studies amounted to 2947 person-years. The median duration of acyclovir treatment on study varied from 0.4 to 1.8 years. Overall, 523 deaths (29% of randomized patients) were recorded, including 247 of 895 patients allocated

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**Figure 1.** Kaplan-Meier plots for survival in different studies included in meta-analysis and for pooled data. Acyclovir arm is shown by continuous line (bold in plot of all data pooled) and control patients by discontinuous line. For each trial, box in lower left corner shows median duration of study treatment in acyclovir arm. Not shown is trial H14-326, which recorded only 1 death in each arm (a Kaplan-Meier plot is practically meaningless). Survival scale for study P53, in which death rate was very low, is different (0.8–1.0 instead of 0–1.0) so as to better show Kaplan-Meier curves. ARC, AIDS-related complex; KS, Kaposi’s sarcoma; ACTG, AIDS Clinical Trials Group.
to acyclovir and 276 of 897 patients allocated to the control arm. The incidence of HSV and VZV infections during the main study follow-up ranged from 11 to 62 episodes/100 patient-years.

**Primary end point.** Figure 1 shows the analysis for survival for each of the trials separately and a survival analysis including the data from all trials. There was evidence for superiority of acyclovir over no treatment ($P = .046$, unstratified log-rank test; $P = .006$, log-rank test stratified for study). A cyclovir gained superiority over no treatment within the first 6 months. There was a suggestion that the two survival curves approached each other during the second year. This may reflect crossover to acyclovir from the control arm, which occurred usually at the end of 1 year in most trials, or it could be only chance fluctuation. The extent of acyclovir use beyond the original main follow-up has not been recorded in these trials. Table 2 shows the pooled OR for different time intervals. There was no significant heterogeneity between the results of different studies, both for the whole follow-up and within specific time intervals. The pooled results suggested a marginally significant reduction in the odds of mortality in the acyclovir-allocated patients (OR, $0.75; 95\% CI, 0.57–1.00$ [figure 2A]; incidence risk ratio, 0.81; 95\% CI, 0.68–0.96 [figure 2B]; no heterogeneity between studies).

The results of pre-specified subgroup analyses are shown in table 3. For all of the considered covariates of interest, there was no evidence of significant heterogeneity in the treatment benefit from acyclovir in different patient categories. The benefit of acyclovir was fairly similar in patients with $\leq 100$ or $>100$ CD4 cells/mm$^3$, in patients with or without anemia, and in patients with or without AIDS at entry. The treatment effect was similarly not significantly affected by age, sex, and race. An exploratory a posteriori analysis looking at smaller CD4 cell count subgroups also did not reveal statistically significant differences among CD4 cell count subgroups ($P > .3$ for heterogeneity between CD4 cell count subgroups). The random effects ORs were $0.54 (95\% CI, 0.22–1.32)$ for patients with $0–25$ CD4 cells/mm$^3$, $0.82 (95\% CI, 0.49–1.38)$ for patients with $26–75$ cells/mm$^3$, $0.93 (95\% CI, 0.49–1.77)$ for patients with $76–150$ CD4 cells/mm$^3$, and $0.76 (95\% CI, 0.44–1.32)$ for patients with $>150$ CD4 cells/mm$^3$. Any observed soft trends should be interpreted with great caution for this analysis.

In a proportional hazards model (table 4), the hazard of death was significantly decreased with acyclovir ($P = .006$). Higher baseline CD4 cell count, higher baseline hemoglobin level, and younger age were also significantly associated with reduced hazard of mortality ($P < .001$ for all adjusting covariates). The results were similar when multivariate models were used and were not affected by the model-building approach, and the effect of acyclovir was still significant ($P = .005$).

The results were similar when patients were stratified in quartiles according to their estimated risk of death on the basis of their baseline CD4 cell count and hemoglobin level, age, and history or not of AIDS at entry (table 5). There was no heterogeneity of the OR in different quartiles. However, in the low-risk quartile, the risk of mortality was very small (0.9\% over a median follow-up of almost 2 years), so the absolute magnitude of any survival benefit would be negligible.

**Secondary end points.** A cyclovir significantly decreased the number of patients who had clinically evident HSV infections (70 vs. 205; OR, $0.28; 95\% CI, 0.21–0.37; P < .001$) and VZV infections (14 vs. 54; OR, $0.29; 95\% CI, 0.13–0.63; P = .002$) (figure 3). There was no significant difference between the acyclovir and control arms in the occurrence of CMV disease (40 vs. 39; OR, $1.02; 95\% CI, 0.64–1.63$) and in deaths primarily due to Kaposi’s sarcoma (11 vs. 18; OR, $0.62; 95\% CI, 0.29–1.36$) or due to lymphoma (10 vs. 12; OR, $0.83; 95\% CI, 0.35–1.92$). There was no significant heterogeneity between studies for any of the secondary end points ($P > .2$ for all).

The incidence of clinical HSV and VZV infections varied substantially among the different trials. Three studies recorded $\leq 18$ episodes/100 patient-years of follow-up, while the other 4 studies in which data were available recorded anywhere from 25 to 62 episodes/100 patient-years of follow-up (table 1). There was a significant survival benefit in the latter studies (OR, $0.64; 95\% CI, 0.44–0.93; P = .02$), while there was no evidence of a survival advantage in the 3 studies with a low incidence of HSV and VZV infections (OR, $0.93; 95\% CI, 0.61–1.41$), but it is possible that the difference could have been due to chance ($P = .25$ for heterogeneity between the 2 groups).

### Table 2. Pooled odds ratios at different time points for acyclovir versus control.

<table>
<thead>
<tr>
<th>Follow-up time</th>
<th>Deaths/patients at risk*</th>
<th>Pooled odds ratio† (95% CI)</th>
<th>Acyclovir</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>All follow-up†</td>
<td>247/895 276/897</td>
<td>0.75 (0.57–1.00)</td>
<td>0.74 (0.44–1.26)</td>
<td></td>
</tr>
<tr>
<td>0–6 months</td>
<td>27/895 37/897</td>
<td>0.74 (0.44–1.26)</td>
<td>0.61 (0.36–1.01)</td>
<td></td>
</tr>
<tr>
<td>6–12 months</td>
<td>48/779 72/758</td>
<td>1.10 (0.77–1.58)</td>
<td>0.53 (0.32–0.86)</td>
<td></td>
</tr>
<tr>
<td>12–24 months</td>
<td>106/626 86/591</td>
<td>0.61 (0.36–1.01)</td>
<td>0.62 (0.29–1.36)</td>
<td></td>
</tr>
<tr>
<td>24–36 months</td>
<td>49/343 67/335</td>
<td>0.61 (0.36–1.01)</td>
<td>0.72 (0.29–1.83)</td>
<td></td>
</tr>
<tr>
<td>36–48 months</td>
<td>19/75 12/59</td>
<td>0.61 (0.36–1.01)</td>
<td>0.75 (0.57–1.00)</td>
<td></td>
</tr>
</tbody>
</table>

* No. of patients at risk at beginning of time interval.
† According to DerSimonian and Laird model [13]; there was no heterogeneity among trials within any analyzed subgroup; thus, fixed-effects estimates were very similar (not reported). CI, confidence interval.
‡ 2 patients in each arm died after >4 years of follow-up.

### Discussion

This meta-analysis of updated individual patient data shows that acyclovir offered a modest survival benefit to HIV-infected patients in randomized trials. The variable conclusions of individual trials could well have been due to chance or may reflect a difference in the frequency of acyclovir-susceptible herpesvirus
infections in the different trial populations. Acyclovir had no effect on mortality from Kaposi's sarcoma or lymphoma and did not affect the incidence of CMV disease. There was no significant evidence that the benefit from acyclovir varied among different age groups, in patients with different CD4 cell counts and hemoglobin levels, or in those with or without a prior diagnosis of AIDS, although all of these covariates were associated with the risk of death. Any survival benefits would be clinically negligible for patients at low risk of death.

The mechanism by which acyclovir might have prolonged survival is unknown, but the reduction in the incidence of HSV and VZV infections in all studies suggests that suppression of the bursts of HIV replication occurring during active herpesvirus infections is one potential explanation [1, 2, 26, 27]. Differences across different trials could have been due to chance alone, but it is intriguing that it was only trials with a very high incidence of clinically identifiable HSV and VZV infections that showed a survival benefit from acyclovir. All of the trials we analyzed used high doses of acyclovir and were designed with the hypothesis that prevention of herpesviruses affected by high doses of acyclovir would enhance outcome. The observation that patients with higher CD4 cell counts seemed to experience the same benefit suggests that herpesviruses that reactivate frequently, even at CD4 cell counts >100, may be a factor in acyclovir effects. Given the known susceptibility profiles of herpesviruses, the effect could have been mediated through an effect on HSV and VZV, although a mechanism involving human herpesvirus 6 [3] or Epstein-Barr virus or a still-unknown susceptible herpesvirus as well cannot be completely excluded. Recent investigations have shown that the frequency of HSV reactivation in HIV-infected patients is substantially larger than what is suggested by the number of clinically identifiable recurrences [28]. If the beneficial effect is mediated through HSV and VZV, then lower doses of

![Figure 2. Random effects meta-analysis for mortality showing odds ratio (A) and incidence risk ratio (B) in randomized controlled acyclovir trials. Values \(<1\) favor acyclovir. Point estimates and 95% confidence intervals (CIs) are shown for each study and for pooled results. Year of study completion/analysis and no. of patients (or person-years, for incidence risk ratio calculations) in each study are also shown next to year. ARC, AIDS-related complex; KS, Kaposi’s sarcoma; ACTG, AIDS Clinical Trials Group.](image-url)
Table 3. Subgroup analyses for mortality.

<table>
<thead>
<tr>
<th>Variable, subgroup</th>
<th>Events/patients</th>
<th>Pooled odds ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acyclovir</td>
<td>Control</td>
</tr>
<tr>
<td>Baseline CD4 cell count/mm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤100</td>
<td>181/305</td>
<td>201/308</td>
</tr>
<tr>
<td>&gt;100</td>
<td>65/574</td>
<td>74/574</td>
</tr>
<tr>
<td>Baseline hemoglobin level (g/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥11</td>
<td>193/764</td>
<td>203/762</td>
</tr>
<tr>
<td>&lt;11</td>
<td>47/95</td>
<td>62/97</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30</td>
<td>201/691</td>
<td>214/674</td>
</tr>
<tr>
<td>&lt;30</td>
<td>46/203</td>
<td>61/221</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>234/846</td>
<td>259/846</td>
</tr>
<tr>
<td>Female</td>
<td>13/48</td>
<td>17/50</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>225/777</td>
<td>255/781</td>
</tr>
<tr>
<td>Other</td>
<td>22/117</td>
<td>21/115</td>
</tr>
<tr>
<td>AIDS diagnosis at entry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>204/337</td>
<td>217/330</td>
</tr>
<tr>
<td>No</td>
<td>43/558</td>
<td>59/567</td>
</tr>
</tbody>
</table>

* According to DerSimonian and Laird model [13]: there was no heterogeneity among trials within any analyzed subgroup; thus, fixed-effects estimates were very similar (not reported). Also, there was no significant heterogeneity between subgroups for any of considered predictors. There were missing baseline CD4 cell counts, baseline hemoglobin measurements, age, sex, and race data for 31 (1.7%), 74 (4.1%), 3 (0.2%), 2 (0.1%), and 2 (0.1%) patients, respectively; 46 of 74 baseline missing hemoglobin data were from ACTG 010, in which hemoglobin files could not be retrieved, but it is known that no patients had anemia (thus, imputed median value is likely to be largely accurate). CI, confidence interval.

Acyclovir may be as good. Acyclovir has little inhibitory effect on CMV in vitro. Most in vitro [29] and observational [30, 31] clinical studies suggest that acyclovir would also have little effect on the recently discovered Kaposi’s sarcoma herpesvirus (human herpesvirus 8). In the meta-analysis, there was no evidence of decreased CMV disease or decreased mortality due to Kaposi’s sarcoma. Some data have been presented from these studies suggesting that acyclovir also had no effect on the incidence of new Kaposi’s sarcoma [32]. Finally, our data showed that acyclovir did not affect mortality related to lymphoma, although the power to show an effect was very small and the histologic types and sites of lymphoma (Hodgkin’s vs. non-Hodgkin’s, central nervous system lymphoma vs. others) could not be differentiated in the available trial databases. An observational study [33] has suggested a reduced incidence of non-Hodgkin’s lymphoma (where Epstein-Barr virus has been implicated) in association with high-dose acyclovir use.

The acyclovir studies included in the meta-analysis were launched before virus load measurements become available, and no data on HIV RNA (arguably the most relevant prognostic indicator in HIV disease [34, 35]) were collected by any study. Two studies evaluated p24 antigen, and there was suggestion of a larger decrease in p24 antigen in the acyclovir arm in one study [8], while no difference was discerned in another [36]. p24 data should be interpreted cautiously. More accurate HIV RNA measurements would be required to determine if acyclovir has any direct or indirect effect on the levels of HIV replication. Interestingly, a recent study [37] showed that HIV-infected patients had lower levels of HIV RNA as determined by reverse transcription–polymerase chain reaction when they were taking suppressive acyclovir therapy than they did when they were not taking this medication. The difference was small (~0.5 log), but if real, it may translate to the observed modest survival benefit. It would be very interesting to obtain more data regarding effects of acyclovir on HIV RNA, in particular for patients with suppressed HIV viremia, to examine whether acyclovir may prohibit or delay HIV rebound directly or indirectly. Besides indirect effects through suppression of herpesvirus-induced reactivation of HIV, it is still possible that acyclovir may have a small, more direct effect on HIV; for example, it may synergize with zidovudine, as suggested by an early study [38]. However, opposite data have also been presented [39], and a direct synergistic anti-HIV effect is controversial.

The long controversy of herpes prophylaxis in HIV infection highlights the difficulty of drawing conclusions from observational studies or even a single large randomized trial. Great Table 4. Proportional hazards models for mortality (stratified for study).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate hazard ratio (95% CI)</th>
<th>Multivariate hazard ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir assignment</td>
<td>0.79 (0.66–0.93)</td>
<td>0.78 (0.65–0.93)</td>
</tr>
<tr>
<td>Baseline CD4 cell count (square root)</td>
<td>0.89 (0.87–0.91)</td>
<td>0.89 (0.87–0.91)</td>
</tr>
<tr>
<td>Baseline hemoglobin level (per g/dL)</td>
<td>0.81 (0.77–0.86)</td>
<td>0.84 (0.80–0.89)</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>1.013 (1.003–1.022)</td>
<td>1.021 (1.011–1.031)</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.86 (0.59–1.25)</td>
<td>0.71 (0.48–1.05)</td>
</tr>
<tr>
<td>Nonwhite race</td>
<td>0.84 (0.61–1.18)</td>
<td>0.93 (0.66–1.30)</td>
</tr>
<tr>
<td>AIDS diagnosis at entry</td>
<td>1.30 (0.87–1.95)</td>
<td>1.18 (0.79–1.77)</td>
</tr>
</tbody>
</table>

NOTE. Values <1 mean reduced mortality. Proportional hazards assumptions were tested by considering additional variable of time-treatment interaction and time interval (second year) treatment interaction, and hypothesis of time-independent proportionality was not rejected (P = .25 and P = .11, respectively, for 2 approaches). CI, confidence interval.
Table 5. Survival end point: analysis according to quartiles of predicted risk.

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Death rate (per 100 patient-years)</th>
<th>Deaths/patients</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk</td>
<td>0.5</td>
<td>2/217</td>
<td>2/230</td>
</tr>
<tr>
<td>Moderate-risk</td>
<td>2.8</td>
<td>10/230</td>
<td>14/219</td>
</tr>
<tr>
<td>High-risk</td>
<td>25</td>
<td>80/224</td>
<td>96/224</td>
</tr>
<tr>
<td>Very-high-risk</td>
<td>53</td>
<td>155/224</td>
<td>164/224</td>
</tr>
</tbody>
</table>

NOTE. Pooled odds ratio is obtained by DerSimonian and Laird model [13]. For each quartile, each study is represented in pooling by patients belonging to this quartile of risk. There was no significant heterogeneity for any quartile between different studies, and fixed-effects estimates would be very similar. Predictive score for categorizing patients was obtained from multivariate Cox model and is given by sum of 0.6421 (prior AIDS diagnosis: yes = 1; no = 0) + 0.0226 (age in years) − 0.1665 (hemoglobin, g/dL) − 0.1371 (square root of CD4 cell count/mm³). Predictive score cutoff values separating quartiles are −1.74, −3.41, and −4.57; e.g., 35-year-old patient with hemoglobin of 14 g/dL and no AIDS diagnosis would belong to low-risk quartile for CD4 cell count >490/mm³, to moderate-risk quartile for CD4 cell count between 186 and 490/mm³, and to high-risk quartile for CD4 cell count between 3 and 186/mm³; 35-year-old AIDS patient with hemoglobin of 14 g/dL would belong to very-high-risk quartile for CD4 cell count <37/mm³ and to high-risk quartile for CD4 cell count between 37 and 335/mm³.

Figure 3. Odds ratio for herpes simplex virus infections (A) and for varicella-zoster virus infections (B) in randomized controlled acyclovir trials. Values <1 favor acyclovir. Point estimates and 95% confidence intervals (CIs) are shown for each study and for pooled results obtained by random effects. Fixed-effects estimates were similar. Year of study completion/analysis and no. of patients in each study are also shown next to trial name. No data were available for ACTG (AIDS Clinical Trials Group) 010. ARC, AIDS-related complex; KS, Kaposi’s sarcoma.
caution is needed in the interpretation of survival differences in single trials of heterogeneous populations of late-stage HIV disease, in which individual patients may have very different mortality risks [40]. Observational studies are even less likely to avoid bias, even if meticulous state-of-the-art attempts are made to account for various sources of confounding [41]. This is easily exemplified in the case of observational studies of acyclovir done by experienced epidemiologists: 1 study [4] suggested a remarkable, but probably exaggerated, 44% reduction in mortality for patients starting acyclovir after the diagnosis of AIDS, while 2 others estimated equally improbable 28% [5] and 48% [42] increases in the odds of death. The observed harm may reflect confounding of the decision to use acyclovir with perceived disease deterioration, intermittent use of acyclovir, use in conjunction with a herpes management indication, or other unknown confounders. Meta-analyses, and particularly meta-analyses of randomized individual patient data, are difficult and time-consuming to conduct [10], but, if appropriately done, they have advantages [43, 44] when maximal precision, adjustment for important risk factors, and the ability to perform accurate sensitivity analyses are needed to detect moderate or small treatment effects and to explain differing results across trials. The approach should be encouraged in other questions of HIV and infectious disease therapeutics. Even with the advent of more effective therapies for HIV, it is still important to understand the long-term effects of therapeutic regimens and strategies, and small differences between treatments, as is probably the case with acyclovir, are likely to become the rule rather than the exception.

Some caveats exist about the interpretation of this meta-analysis. First, the analyzed trials were mostly conducted in the era of zidovudine monotherapy, and follow-up largely preceded the widespread use of combinations of antiretrovirals. It is unclear whether any survival benefit would be seen in current practice with acyclovir, in which the routinely recommended highly active antiretroviral regimens [45] may mitigate increases in HIV load due to acute herpesvirus infections. Given the change in the rates of disease progression and the large decrease in death rates among HIV-infected patients with more potent antiretrovirals, the results of the meta-analysis should definitely not be viewed as evidence that acyclovir use should be routinely implemented in current practice [46]. On the contrary, the meta-analysis demonstrates that probably acyclovir would offer a very small survival benefit in patients at low risk of death, and the clinical significance of such a benefit is uncertain, especially in the current era. Second, the confidence intervals are wide enough to warrant caution in interpreting the results. On the other hand, the observed treatment effect is more likely to be an underestimate, rather than overestimate, of the truth because of the influence of crossovers, the potential open-label use in some control patients after the end of the trial, and the relatively short median duration of study treatment (typically <1 year) in these patients. Finally, our efforts to retrieve all published and unpublished evidence should have minimized the chances of having missed unpublished studies with equivocal or negative results [25].

Overall, our results suggest that antiretroviral therapies may possibly have a role in HIV therapeutics, especially in high-risk HIV-infected patients with frequent herpesvirus infections. Prospective studies have indicated that the frequency of HSV reactivation among HIV-infected patients has been underestimated and that most of these reactivations are subclinical [28]. This raises the issue that the effect of antivirals on reducing herpesvirus reactivation in currently treated cohorts is of importance and should also be studied. More important than any clinical practice implications, the meta-analysis provides additional data to support the importance of the postulated interactions between herpesviruses and HIV-1 [1, 2, 47, 48]. Other agents with broad antiretroviral activity, and preferably anticytomegalovirus activity, acceptable tolerability, and convenient dosing, may warrant development and clinical testing in HIV infection. The role of currently available antiretroviral agents, such as valaciclovir (the acyclovir ester) [49–51], cidofovir [52], and adefovir [53, 54], in HIV infection needs to be better defined. Finally, further pathogenesis research on still-unknown viral interactions in coinfected persons should be encouraged.

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Additional Investigators

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