Foscarnet has in vitro activity against a broad spectrum of viruses, including herpes simplex virus, varicella-zoster virus, cytomegalovirus (CMV), hepatitis B virus, and human immunodeficiency virus (HIV) (8, 12). Several investigations of foscarnet therapy for CMV retinitis in patients with AIDS have described a decrease in the concentration of HIV antigen in serum (6, 9, 11). The present study (designated protocol 028 by the AIDS Clinical Trials Group [ACTG]) was designed to evaluate the safety, pharmacokinetic disposition, and anti-HIV effect of foscarnet in HIV-infected individuals.

The criteria for participation in this trial included confirmed HIV infection with CD4+ lymphocyte count of less than 500/mm³ (on two separate occasions), detectable concentration of HIV antigen in serum equal to or greater than 25 pg/ml, age of ≥12 years, Karnofsky performance status of at least 60%, granulocyte count of >1,000 cells per mm³, platelet count of >75,000/mm³, hemoglobin concentration of ≥9 g/dl, and serum creatinine and bilirubin levels within the normal range. Primary and secondary chemoprophylaxis of Pneumocystis carinii pneumonia was permitted but not required; antiretroviral agents were not allowed. This investigation was approved by the institutional review board of each participating site, and all subjects gave written consent before participation.

Study participants were randomly assigned to groups given 12.5, 25, or 50 mg of foscarnet per kg of body weight every 8 h for the first 28 days. Individuals who were clinically stable after 28 days had the option of receiving maintenance therapy that consisted of a dose of 50 mg/kg given once daily 5 days per week for an indefinite period. During the 28-day induction period, foscarnet was administered in a double-blind manner. The dose was adjusted in any participant whose estimated creatinine clearance was ≤1.3 ml/min/kg. Study participants were required to spend a minimum of 48 h after initiation of therapy as inpatients, after which they were monitored as outpatients.

Patients were monitored frequently for safety and tolerance, as well as to determine their immunologic and virologic responses to therapy. CD4+ lymphocyte cell counts were obtained at screening, entry into study, the second and fourth week of treatment, and then monthly. Serum HIV antigen tests were collected weekly during induction but were otherwise obtained according to the same schedule as that for CD4+ lymphocyte counts. Serum HIV antigen levels were measured with an enzyme-linked immunosorbent assay kit (Abbott Laboratories, North Chicago, Ill.), using purified virion p24 (ACTG Virology Reference Laboratory) as the calibration standard; the limit of detection was 10 pg/ml. All serum samples were stored at −70°C for batch HIV antigen testing. All immunologic and virologic procedures were standardized and quality controlled according to ACTG laboratory guidelines. Subjects who developed grade three or four toxicity (as defined by ACTG criteria) or a serum creatinine concentration of >3 mg/dl were permanently withdrawn from the study.

Blood samples for determination of foscarnet concentration were obtained at the following selected times on day 1 of induction therapy: before the first infusion, at the end of infusion, and at 3 and 6 h after the end of the infusion. Beginning on day 3 of therapy, blood samples were obtained twice weekly. These samples were collected before infusion, at the end of infusion, and at a random time within the dosing interval. All blood samples were centrifuged and the plasma was frozen at −20°C until analyzed. Foscarnet concentrations in plasma were determined by high-performance liquid chromatography in the Antiviral Laboratory at the University of Minnesota by a modified version of the method of Pettersson and Nordgren (10). The practical limit of sensitivity for foscarnet was 15 mg/liter. The interday coefficients of variation (CV) were 11.2 and 6.6% at low and high concentrations, respectively.

A two-sided Wilcoxon signed-rank test was used to evaluate differences in laboratory parameters (including CD4+ lymphocytes) at three time points: baseline, end of induction therapy (study week 4), and study week 10 (during maintenance therapy). These analyses evaluated the hypothesis that changes in laboratory measurements between time points did not differ significantly from zero. All tests were performed with SAS version 6.07. Additionally, serial CD4+ cell counts obtained during induction therapy were analyzed by a normalized (adjusted for baseline) area-under-the-curve (NAUC) method;
NAUC values greater than 1 indicate that the average CD4+ level during therapy increased over baseline.

Serum HIV antigen measurements were analyzed to assess each patient’s antiretroviral response and the overall absolute change in antigen levels between baseline and the end of induction. Response was defined as a 50% or greater drop from baseline (average of two pretherapy antigen values) maintained for two consecutive determinations. A patient must have a measurement in a given week to be included in the response proportion for that week. This method decreases the total number of patients evaluated each week, providing a conservative estimate of the proportion of responders. A two-sided Wilcoxon signed-rank test was used to evaluate the null hypothesis of no change in serum HIV antigen levels.

Induction phase concentration-time data were fit to a two-compartment pharmacokinetic model by a Bayesian estimation strategy (13). The a priori population parameters used were taken from the data for foscarnet in the literature (2, 14, 15). These parameters correspond to a typical half-life at α phase of 0.31 h, a half-life at β phase of 4.4 h, and a clearance of 0.11 liter/kg/h. Error output was modeled by a power variance model, and the parameters of this model were estimated. Data analysis was accomplished with ADAPT II installed on a VAX 6000-520 (VAX Corp., Maynard, Mass.).

Foscarnet concentrations during maintenance therapy were tabulated, and descriptive statistics were determined. These concentrations were evaluated for agreement with those expected. To accomplish this, individual simulations of maintenance-phase concentrations were performed for each patient by using the pharmacokinetic parameters calculated during induction. The ability of these parameters to predict maintenance drug concentrations was determined by calculation of precision and bias.

Pharmacodynamic relationships between a measure of anti-HIV effect and the concentration of foscarnet in the body were sought. The percent suppression from baseline was calculated for each available HIV antigen observation. The cumulative area under the foscarnet concentration-time curve (AUC) corresponding to an HIV antigen determination was calculated for each patient. These data were pooled and evaluated by three different pharmacodynamic models: a linear-effect model, a maximum-effect (Emax) model, and a sigmoid Emax model (5). The ADAPT II package was also used for this analysis. Discrimination between models was accomplished by residual analysis and calculation of the Akaike information criterion (1).

Nine HIV-infected individuals were enrolled in this study at three centers (University of Minnesota, University of Washington, and Ohio State University) between 1 June 1988 and 27 June 1989 (Table 1). Five patients were evaluable at all time points (baseline, week 4, and week 10). Considering the subjects as a group, there were no significant changes in hematologic, renal, or hepatic laboratory parameters. There were, however, individual changes during therapy, which necessitated dose modification. Patient 9 developed grade four hypercalcemia (11.4 mg/dl) on day 11; patient 8 had a temporary dose reduction on day 18 because of an increase in the serum creatinine concentration (to 1.4 mg/dl), the original dose was resumed on day 22 after the serum creatinine concentration fell to 1.2 mg/dl. Two patients had their maintenance dose reduced voluntarily prior to discontinuation of maintenance therapy: (i) patient 1 from 50 to 25 mg/kg once daily and subsequently to 12.5 mg/kg three times weekly because of nausea and vomiting, and (ii) patient 8 from 50 to 29.4 mg/kg because of an increase in the serum creatinine concentration from 1.2 to 1.7 mg/dl.

The pharmacokinetic characteristics for foscarnet are given in Table 2. A total of 96 (average 12/patient) measured foscarnet concentrations were available from the induction phase. The greatest accumulation ratio calculated between the first and last foscarnet concentrations was 1.5, indicating that a deep gamma phase was not evident. Foscarnet dose was related to AUC (r² = 0.928, P = 0.002). Foscarnet clearance (CL) was related to renal function (CL = 0.54CLcr + 40.25; r² = 0.861, P = 0.0076), where creatinine clearance (CLcr) was estimated by the method of Jelliffe and Jelliffe (7).

During once-daily maintenance therapy, 127 blood samples were obtained from five individuals. In 55 paired assessments of peak and trough foscarnet concentrations, peak values were between 130 and 196 mg/liter, with a mean of 163.5 (± 16.5) mg/liter. Trough concentrations ranged from <15 to 25 mg/liter; only 4 of 55 trough determinations were measurable. The ability of the individual pharmacokinetic parameters to predict concentrations in the maintenance phase was as follows:

### Table 1. Characteristics of patients at baseline and outcome of foscarnet therapy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Wt (kg)</th>
<th>HIV disease status</th>
<th>No. of CD4+ cells/mm³</th>
<th>HIV Ag concn (pg/ml)</th>
<th>Induction dose</th>
<th>Duration (days)</th>
<th>Maintenance dose</th>
<th>Duration (days)</th>
<th>Reason for discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33</td>
<td>M</td>
<td>78</td>
<td>ARC</td>
<td>316</td>
<td>396</td>
<td>12.5</td>
<td>28</td>
<td>50</td>
<td>61</td>
<td>Voluntary; nausea and vomiting</td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>M</td>
<td>52</td>
<td>AIDS</td>
<td>50</td>
<td>181</td>
<td>12.5</td>
<td>28</td>
<td>50</td>
<td>35</td>
<td>Neutropenia</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>M</td>
<td>66</td>
<td>AIDS</td>
<td>8</td>
<td>120</td>
<td>12.5</td>
<td>28</td>
<td>50</td>
<td>331</td>
<td>Disseminated MAC</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>M</td>
<td>67</td>
<td>Asympt</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>28</td>
<td>50</td>
<td>154</td>
<td>Hypocalcemia, seizure</td>
</tr>
<tr>
<td>5</td>
<td>51</td>
<td>M</td>
<td>68</td>
<td>AIDS</td>
<td>54</td>
<td>394</td>
<td>50</td>
<td>2</td>
<td>50</td>
<td>2</td>
<td>Seizure or syncopal episode</td>
</tr>
<tr>
<td>6</td>
<td>59</td>
<td>M</td>
<td>74</td>
<td>AIDS</td>
<td>6</td>
<td>116</td>
<td>50</td>
<td>28</td>
<td>50</td>
<td>9</td>
<td>Voluntary; nausea and vomiting</td>
</tr>
<tr>
<td>7</td>
<td>48</td>
<td>M</td>
<td>68</td>
<td>AIDS</td>
<td>30</td>
<td>42</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypercalcemia</td>
</tr>
<tr>
<td>8</td>
<td>28</td>
<td>M</td>
<td>70</td>
<td>AIDS</td>
<td>147</td>
<td>375</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypercalcemia</td>
</tr>
<tr>
<td>9</td>
<td>43</td>
<td>F</td>
<td>59</td>
<td>AIDS</td>
<td>10</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypercalcemia</td>
</tr>
</tbody>
</table>

* M, male; F, female.  
* ARC, AIDS-related complex; Asympt, asymptomatic. These are pre-1993 definitions.  
* Ag, antigen.  
* The indicated dose (in milligrams per kilogram) was given every 8 h.  
* The indicated dose (in milligrams per kilogram) was given once daily for 5 days per week.  
* Dose was reduced (for details, see text).  
* MAC, Mycobacterium avium complex.
precision (root of the mean squared error), 25.3 mg/liter (95% confidence interval, 21.8 to 28.3 mg/liter); and bias, −8.1 mg/liter (95% confidence interval, −13.77 to −2.48 mg/liter).

Seven of nine participants received at least 1 week of foscarnet induction therapy. As a group, these seven experienced a mean increase in CD4+ lymphocyte responses during the 4-week induction therapy by using the criteria of a 50–100 cell/mm³ increase or a 50% increase from baseline. Three individuals, patients 1, 5, and 8, had NAUC values that exceeded 1, and these values were 1.15, 2.13, and 1.2, respectively. For these three patients, there was a strong relationship between the increase in CD4+ cells and their starting CD4+ cell count (y = 7.3 + 0.14x; r² = 0.985).

All seven patients that received at least 1 week of foscarnet induction therapy had decreases in serum HIV antigen levels. Overall, there was a significant decline (P = 0.03) in HIV antigen during the induction period; the mean decrease was 108 pg/ml. Of the six patients who completed the entire induction period, two (patients 4 and 5) had decreases in HIV antigen levels for week 1 that were not sustained for two consecutive measurements. Patient 2 had a sustained decrease of approximately 20%, and three participants (patients 1, 3, and 8) had declines of 50% or greater in serum HIV antigen levels sustained for two consecutive measurements. Patient 9 had a 50% decrease in HIV antigen levels for two measurements but did not complete induction therapy. Pharmacodynamic analysis of the cumulative AUC versus percent suppression in serum HIV antigen data pooled from the five patients with sustained decreases in HIV antigen during the induction period included a total of 16 data points: 4 points each for patients 1, 2, and 3 and 2 points each for patients 8 and 9. The E_max model best described the relationship (Fig. 1). Model parameters were as follows: E_max = 98.2% (CV, 22.4%); cumulative AUC producing 50% of E_max = 1090 mg/liter · h (CV, 52.9%); and r² = 0.53, P < 0.01. Four patients (patients 1, 2, 3, and 4) during the maintenance period had data available on both HIV antigen suppression and foscarnet exposure. HIV antigen suppression was not achieved in patient 4 during maintenance therapy, while patient 2 had a further decline in HIV antigen levels. The other two patients (patients 1 and 3) had increases in HIV antigen levels.

In the first experiment specifically designed to evaluate the anti-HIV effect of foscarnet, we found that the overall mean serum HIV antigen concentration decreased by 108 pg/ml (a 55% drop from baseline) in seven individuals who received at least 1 week of foscarnet induction therapy. Three patients who completed induction therapy had a 50% or greater decline in HIV antigen levels that was maintained for two consecutive measurements in the absence of other antiretroviral therapy. While no overall significant change was observed in CD4+ lymphocyte count during induction therapy, two individual.

![Cumulative Foscarnet AUC (mg/L-h)](http://aac.asm.org/)
patients had responses, as defined by ACTG criteria, and three patients had CD4+ NAUC values greater than 1. These changes suggest an in vivo anti-HIV effect of foscarnet achieved at doses lower than previously reported. While our study was not designed to determine the clinical benefit of foscarnet’s anti-HIV effect, a recent report showed a survival benefit for foscarnet-treated patients with AIDS and CMV retinitis (16).

The anti-HIV effect of foscarnet observed in this study was related to cumulative foscarnet AUC. Other investigators have described a linear relationship between the percent suppression of HIV antigen and foscarnet AUC in the presence of zidovudine (3). In contrast to the linear-effect model, the $E_{\text{max}}$ model was not only a better statistical description of our data but also was more biologically relevant. Two important properties of the $E_{\text{max}}$ model are as follows: there is no effect without drug present, and higher concentrations of drug produce a greater effect only up to the maximum effect that can be achieved (5). These properties are not shared by the linear-effect model. The pharmacodynamic relationship we report is not completely satisfactory for several reasons. Because of limited data, the pharmacodynamic analysis pooled data from all patients, whereas characterization of each individual patient’s pharmacodynamics would have been preferable. Second, while the model provided some understanding of the foscarnet exposure necessary to achieve suppression of HIV antigen, it did not indicate the best method of administration (i.e., rapid or gradual induction therapy) to obtain the desired effect. Third, susceptibility patterns of HIV isolates to foscarnet are an important pharmacodynamic variable not included in our analysis. Finally, we do not know the best method to maintain an antiretroviral effect once the desired suppression has been achieved. Loss of HIV antigen suppression has been observed in some patients receiving once-daily maintenance therapy following induction for the treatment of CMV retinitis (9). This finding suggests that achieving certain peak and trough concentrations in addition to a cumulative exposure may be needed to maintain antigen suppression.

The aggregate data from this and other investigations present compelling evidence for an anti-HIV effect of foscarnet. The pharmacodynamic description of the foscarnet concentration and HIV antigen effect relationship requires further clarification and application in the context of foscarnet monotherapy or in combination with other antiretroviral agents. We suggest these studies employ a concentration-controlled paradigm in order to explore the relationship between concentration and effect.

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