Published in final edited form as:
HIV Clin Trials. 2009 ; 10(3): 143–152. doi:10.1310/hct1003-143.

Low Rate of CMV End-Organ Disease in HIV-Infected Patients Despite Low CD4+ Cell Counts and CMV Viremia: Results of ACTG Protocol A5030

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Abstract

Purpose—To describe cytomegalovirus (CMV) end-organ disease (EOD) rate in AIDS patients with low CD4+ cell count despite HAART who were enrolled in a randomized, placebo-controlled trial of preemptive valganciclovir (VGCV) to prevent CMV EOD in those with CMV viremia.

Methods—Subjects (N = 338) were HIV-infected with CD4+ count <100 cells/mm^3, plasma HIV RNA >400 copies/mL, and on stable or no HAART. All underwent plasma CMV DNA PCR testing every 8 weeks (Step 1); those with detectable CMV DNA were randomized to VGCV or placebo (Step 2).

Results—Plasma CMV DNA was detected in 68 (20%), of whom 4 developed CMV EOD. During Step 1, 53 died. Of the 47 who entered Step 2 (24 VGCV, 23 placebo), CMV EOD was diagnosed in 10 (4 VGCV, 6 placebo) and 15 died (7 VGCV, 8 placebo). Of those randomized to placebo, 14% were diagnosed with CMV EOD at 12 months.

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Conclusions—We observed a lower CMV EOD rate among subjects receiving HAART than predicted based on published literature. However, mortality was high in this study. Our findings suggest that preemptive anti-CMV therapy in patients with persistently low CD4+ cell counts in the current treatment era may not be warranted given the low incidence of CMV EOD and high all-cause mortality observed in this study population.

Keywords

AIDS; CMV; opportunistic disease prevention; valganciclovir

Cytomegalovirus (CMV) infection is present in 50% to 95% of HIV-infected individuals in the United States. During advanced AIDS, CMV can produce debilitating end-organ disease (EOD) including retinitis, colitis, and pneumonitis.[1–4] Prior to the advent of highly active antiretroviral therapy (HAART), detection of CMV in the blood was strongly associated with development of CMV EOD and mortality.[5,6] Subsequent to the development of HAART, several studies of patients receiving these potent regimens demonstrated that detection of CMV viremia continued to be predictive of CMV EOD, with CMV viremia producing a 40% to 60% increased risk of CMV EOD.[7–11] Further, CMV viremia has also been associated with heightened risk of mortality – including death not directly related to CMV EOD – in patients prescribed HAART.[10,11]

The enhanced risk of CMV EOD among individuals with HIV infection and CMV viremia led us to conduct a randomized clinical trial of a strategy of preemptive therapy for CMV EOD in patients with suboptimally controlled HIV disease and CMV viremia and therefore at heightened risk for disease due to this opportunistic infection. This strategy entailed regular screening for CMV viremia followed by treatment with oral valganciclovir (VGCV) versus placebo among those with detectable CMV viremia.

Although participants were HIV-infected patients with profound CD4+ cell depletion and uncontrolled HIV viremia despite widespread use of HAART, the rate of CMV EOD during the study was substantially lower than that seen in earlier studies of HAART-receiving patients, which led to the halting of the trial by an independent data and safety monitoring board during a scheduled interim review. We describe the rate of CMV EOD and mortality among this cohort of patients.

METHODS

Study Design and Eligibility

A5030 was a prospective, double-blind, placebo-controlled, randomized trial. Subjects were CMV seropositive (IgG), were without evidence of CMV EOD, and had a CD4+ cell count <100 cells/mm^3 and plasma HIV RNA > 400 copies/mL within 30 days prior to entry. Subjects must either have been receiving HAART continuously for 3 months or not be receiving and not planning to initiate HAART, which was defined as at least a three-drug antiretroviral regimen, including at least one protease inhibitor (PI) and/or non-nucleoside reverse transcriptase inhibitor (NNRTI). Subjects on a three-drug nucleoside reverse transcriptase inhibitor (NRTI) regimen were eligible if treated in the past with a PI or an NNRTI. HAART was prescribed as part of usual clinical care and not determined by the study protocol. The HIV treatment criteria were designed to lead to the enrollment of patients who for various reasons, such as viral resistance and/or medication nonadherence, were not receiving maximal benefit from HAART and thus were most likely to be at risk of CMV EOD.

The study proceeded in three steps. Subjects entered Step 1 and underwent plasma CMV DNA PCR measurements every 8 weeks. Subjects who were CMV DNA PCR positive at entry or

during follow-up were eligible to enter Step 2 and be randomized 1:1 to treatment with VGCV or placebo. Subjects who developed CMV EOD during Steps 1 or 2 were able to enter Step 3 during which subjects with CMV retinitis were offered open-label VGCV.

The institutional review boards at each participating study site approved the protocol, and all participants provided verbal and written informed consent.

Study Treatment

Subjects entering Step 2 were randomized to receive VGCV 900 mg or matching placebo orally administered (po) twice daily after a meal for 3 weeks. Originally, this induction phase was followed by 900 mg daily of study drug for 9 weeks and then 450 mg daily thereafter. However, pharmacokinetic studies that became available during the study indicated that the area under the curve of ganciclovir achieved by VGCV at 450 mg daily is significantly less than that achieved by standard oral ganciclovir dosing of 1 g by mouth three times a day. Therefore, from June 2004 onward, the 900 mg daily dose continued after induction without a subsequent decrease in dose; subjects receiving 450 mg of VGCV daily had the dose increased to 900 mg daily.

Study Evaluations

CMV viremia assay—Quantitative plasma CMV DNA PCR was performed every 8 weeks during Step 1 using COBAS Amplicor CMV Monitor assay (Roche Diagnostics, Indianapolis, Indiana, USA; lower limit of detection of 400 copies/mL). Results were provided to sites in real time and reported as either detectable or undetectable.

HIV viremia assay—Quantitative plasma HIV RNA PCR (standard or ultrasensitive HIV-1 RT PCR; Roche Diagnostics. Indianapolis, Indiana, USA; lower limits of detection of 400 or 50 copies/mL, respectively) was obtained at Step 1 baseline.

CD4+ cell count—Lymphocyte subsets were obtained at Step 1 baseline, at entry into Step 2 and every 16 weeks thereafter, and at entry into Step 3.

Safety laboratories—Blood chemistries and hematology were obtained at Step 1 baseline and the latter every 16 weeks during Step 1. Chemistry and hematology laboratories were collected at Step 2 entry and Weeks 2, 4, 6, 8, 10, and 12 and every 4 weeks thereafter. Adverse events were graded according to the National Institutes of Health (NIH) Division of AIDS Table for Grading Adult Adverse Experiences.[12]

Ocular examinations—Subjects underwent dilated indirect ophthalmoscopy every 8 weeks during Steps 1 and 2. Subjects with suspected CMV retinitis underwent wide-angle fundus photographs using techniques established by the National Eye Institute–supported Studies for the Ocular Complications of AIDS (SOCA) research group.[13] All photographs were reviewed by a central reading center at the University of Wisconsin where the examiners were unaware of the subject's step or treatment assignment.

CMV EOD assessment—Subjects were evaluated for symptoms of ocular and extra-ocular CMV disease at 8-week intervals during Steps 1 and 2. A targeted examination for CMV EOD was performed when symptoms of CMV EOD were detected. Symptoms suspicious for CMV EOD were reported to study site clinician for further evaluation. Criteria for probable and confirmed CMV EOD were established prior to the initiation of the study (Appendix 1).

Statistical Considerations

Sample size for primary endpoints

The primary endpoint was time-to-CMV EOD (combined probable and confirmed) among subjects randomized to VGCV versus placebo on Step 2. Based on previously published data, it was estimated that 40% of subjects randomized to the placebo arm would develop CMV EOD by 1 year. Further, the study team determined that for preemptive therapy to be considered clinically viable, the incidence of CMV EOD with therapy needed to be reduced by at least 75% (i.e., a reduction in incidence from 40% to 12% or hazard ratio [HR] of 4.0). Given these assumptions, to achieve 80% power with a two-sided alpha of 0.05, a sample size of 60 subjects entering Step 2 would be required. Based on estimated rates of CMV DNA PCR positivity, the targeted Step 1 sample size was approximately 350 subjects.

Statistical methods

The primary endpoint was tested with a Cox proportional hazards likelihood ratio test stratified by whether subjects were CMV DNA PCR positive at Step 1 entry. For the primary analysis, subjects were censored at death without CMV EOD. Results were confirmed with cumulative incidence analysis incorporating competing risks.[14]

Study monitoring

This trial was monitored at least annually by an independent Data and Safety Monitoring Board (DSMB) appointed by National Institutes of Allergy and Infectious Diseases (NIAID). In June 2005, it was determined that it was very unlikely that the study would reach the primary objective due to the dramatic fall in the rate of subjects in Step 1 developing detectable CMV DNA to qualify for Step 2 and the unexpectedly low rate of endpoints on the placebo arm. Accrual to both steps would have had to increase prohibitively to detect a clinically meaningful effect size in the face of these observed rates. Thus, the DSMB recommended that follow-up be stopped. No safety issues were identified.

RESULTS

Subject Characteristics and Disposition

A total of 338 subjects were enrolled in Step 1 between August 2000 and April 2004. At study entry, subjects generally had advanced AIDS with a median CD4+ cell count of 30/mm^3. As expected given the entry criteria, subjects had poorly controlled HIV viremia with only 1% having a plasma HIV RNA level <400 copies/mL, even though more than 80% were currently receiving HAART (Table 1). The subject disposition at the time the study was halted by the DSMB is detailed in Figure 1.

CMV Viremia and Rate of CMV EOD

During a median follow-up of 81 weeks, plasma CMV DNA was detected in 68 (20%) subjects, including 20 with detectable virus at Step 1 entry or within 8 weeks after entry. The median time from entry to first detection of CMV viremia among those who were CMV DNA PCR positive after Week 8 was 46 weeks. The median CMV viral load at first detection was 656 copies/mL (range 400–19,500).

Of the 68 subjects who had CMV DNA detected, 4 (5.8%) were diagnosed with CMV EOD after detection of viremia but prior to randomization to VGCV or placebo. The median time from viremia to EOD for these four participants was 6.1 weeks (range 3.0–34.1 weeks). Among the 270 subjects in Step 1 without detected CMV viremia, 6 (2.2%) were diagnosed with CMV EOD. Therefore, during Step 1, 10 of the 338 subjects developed CMV EOD (8 retinitis, 1

colitis, and 1 pancreatitis), just 4 of whom had CMV viremia detected prior to the diagnosis of EOD.

The median study entry CD4+ cell count of those with CMV viremia detected during Step 1 was 13.5/mm^3 compared to 38/mm^3 for those who remained aviremic (i.e., CMV DNA PCR always negative). The median CD4+ cell count just prior to first positive CMV DNA PCR was 10.5/mm^3 (range 0–77), and 65% of subjects with detected CMV DNA were reportedly receiving HAART at entry.

Among the 144 who remained on Step 1 without CMV EOD or becoming CMV DNA PCR positive, median CD4+ cell counts increased from 38/mm^3 at entry to 81.5/mm^3 at last study visit – a median of 137 weeks later. Initiation of HAART during the study was limited: only six subjects who were not receiving HAART at entry were prescribed HAART during Step 1 and there was minimal antiretroviral modification.

CMV EOD After Randomization to VGCV versus Placebo

Of the 68 subjects with CMV DNA detected during Step 1, 47 entered Step 2. Of those not entering Step 2, as described above, four (5.8%) were diagnosed with CMV EOD and three of these subjects directly entered Step 3 while the other subject discontinued study participation. Seventeen (25%) remaining subjects discontinued study participation. Major reasons for premature Step 1 discontinuation among viremic subjects included death (four subjects) and use of prohibited medications such as foscarnet for herpes simplex (five subjects). A variety of other causes (i.e., severe debility, withdrawal of consent, moved from study area) accounted for the remainder.

The Step 2 subjects had similar characteristics to the overall study population at entry to Step 1 except the median CD4+ cell count was lower (12/mm^3 vs. 30/mm^3) (Table 1). Of the subjects entering Step 2, 24 were randomized to VGCV and 23 to placebo. The first 13 of 24 subjects randomized to VGCV initiated maintenance therapy with 450 mg daily following the induction phase. Of these 13, six had the dose of VGCV increased to 900 mg daily following amendment of the protocol. These six subjects received the 450-mg maintenance dose of VGCV for a median of 93.9 weeks (range 13.3–175.1 weeks). The remaining seven subjects who initiated with the lower dose of VGCV completed the study prior to the availability of the pharmacokinetic data that prompted the dose adjustment.

Median on study follow-up during Step 2 was 54.7 weeks (range 5.7–228.7 weeks). Ten Step 2 subjects were diagnosed with CMV EOD (four on VGCV [two and two while receiving VGCV 450-mg or 900-mg maintenance dose, respectively] and six on placebo); the estimated HR was 0.5 and the stratified Cox proportional hazards (PH) likelihood ratio test p value was .29 (p = .29 for CMV EOD in the cumulative incidence analysis). However, the low number of CMV EOD endpoints reduced the statistical power to detect a significant difference between the study arms. Of note, the estimated EOD rate at 1 and 2 years in the placebo arm was 14% and 39%, respectively.

Of the Step 2 subjects developing CMV EOD, the median CD4+ cell count just prior to diagnosis was 8/mm^3 (range 2–84), and 7 of the 10 were receiving HAART at the time of CMV EOD diagnosis.

VGCV was well-tolerated and the rates of adverse events, including hematological abnormalities, experienced by the subjects in the Step 2 study arms (VGCV vs. placebo) were similar.

Survival

During Step 1, 53 subjects died, including 4 with CMV detected by DNA PCR prior to death. Median time from viremia to death was 8.8 weeks (range 2.8–13.6 weeks). The majority of deaths during Step 1 were associated with progression of HIV disease. AIDS wasting or AIDS itself was listed as the cause of death in 24.5%, bacterial infections in 17%, *Pneumocystis jirovecii* pneumonia in 9.4%, AIDS-related malignancies in 7.5%, and Kaposi's sarcoma in 3.8%. Other non-AIDS-associated causes of death included cardiovascular disease in 9.4%, non-AIDS-associated malignancies in 5.7%, and pulmonary diseases, pulmonary embolism, renal failure, and pancytopenia among the remainder. In 17%, the cause of death was not known. No deaths were considered directly related to CMV EOD.

There were 15 deaths during Step 2: 7 in the VGCV arm and 8 in the control group. The causes of death in this step were also largely a consequence of infectious complications (none directly related to CMV) of AIDS wasting or AIDS itself (40%) and bacterial infections (20%), with liver failure, lupus, and AIDS-associated malignancy accounting for the remainder. The median CD4+ cell count just prior to death during Step 1 was 10/mm^3 (range 0–135) and for Step 2 was 5/mm^3 (range 0–33).

DISCUSSION

In a cohort of HIV-infected individuals at risk for CMV EOD, we found a lower incidence of CMV disease than was anticipated based on prior published reports. Previous HAART era studies observed rates of CMV EOD among patients with advanced HIV infection of approximately 40% or greater. Casado and colleagues reported a 12-month incidence rate of 38% among CMV viremic HAART-treated patients compared to 2% among aviremic patients, [7] and remarkably similar results were found in a French study.[8] In the United States, Erice and colleagues found that in a cohort of patients with AIDS, over 85% receiving HAART, the estimated 1-year cumulative incidence of CMV EOD among those with CMV DNA detected in plasma was 50%. In contrast, we observed a 12-month incidence rate of 14% among CMV viremic HAART-treated subjects compared to 1% among aviremic subjects. Even when considering the 68 subjects with detectable plasma CMV DNA during Step 1 who did not receive VGCV during Step 2, the 12-month rate of CMV EOD was 22%.

The reason for the relatively low rate of CMV EOD in this trial is unclear. CD4+ cell counts increased only modestly during the trial, and a large proportion of subjects continued to have very low CD4+ cell counts that should have placed them at risk for CMV disease.[7] Why subjects maintained low CD4+ cell counts during this study is also unclear and is likely a function of viral resistance cultivated during prior antiretroviral regimens, suboptimal immunological response to current HAART, and mediation nonadherence. Inadequate adherence to HAART, especially older and less convenient combination therapies, is common in clinical practice. This study did not supply HAART and did not include an intervention to enhance compliance with HIV treatment. Rather, the study was designed to determine whether a strategy of preemptive anti-CMV therapy would be effective in preventing CMV EOD in modern-era patients considered to be at continued risk of this opportunistic disease.

The lower incidence of CMV EOD in this study compared to studies conducted in the pre-HAART era could be explained in part by HAART-related improvements in immune function not measurable by quantitative CD4+ count that have afforded protection against CMV disease. It is noteworthy that among subjects in Step 1, rates of detection of CMV by PCR fell dramatically over time; no subject in Step 1 had CMV viremia detected in the final 10 months of the study.

The low number of outcomes makes it difficult to arrive at firm conclusions regarding the efficacy of preemptive VGCV. However, these findings do suggest that the strategy of preemptive VGCV for CMV EOD prevention is unlikely to provide benefit, because the risk of such disease is now so small.

Although the incidence of CMV EOD was low, mortality was high among these subjects. There were 53 deaths while subjects were on Step 1 (16%) and 24% of all subjects entering this study eventually died during the trial, most due to AIDS-related causes and disease not related to CMV. Suboptimal adherence to HAART and/or accumulated viral drug resistance likely drove mortality in this cohort. The high mortality rate may also have contributed to the low incidence of CMV EOD, as these are competing events. Patients with advanced AIDS, most at risk for CMV EOD, are also at greatest risk for other opportunistic conditions, many of which can cause severe debility or death. The study intervention was limited to prevention of CMV EOD, however standard prophylaxis for opportunistic infections was permitted. In previous studies, CMV viremia has been associated with increased risk of death.[7–9,11] In this trial, mortality in the VGCV and placebo arms was very similar.

There are a number of limitations to this investigation. Several subjects developed CMV EOD without preceding detectable plasma CMV DNA, and CMV viremia may have occurred transiently between study evaluations and may have been missed by intermittent sampling. Additionally, adherence to antiretroviral therapy was not assessed and under-treatment of HIV disease could have been a driving force for CMV EOD, other opportunistic conditions, and death. It should be noted that patients such as those enrolled in this trial may be increasingly uncommon given the expanded number of antiretroviral options available, their enhanced convenience, and their relative potency. Therefore, as antiretroviral therapy advances in terms of efficacy and tolerability, fewer HIV-infected patients will remain at risk for CMV disease.

In summary, a strategy of CMV viremia screening and preemptive VGCV initiation in patients such as those studied who had low CD4+ cell counts despite receiving HAART appears not to be warranted given the low incidence of CMV EOD and high all-cause mortality observed in this study population.

Acknowledgments

We are grateful to the participants who generously volunteered to enter this trial, Roche Pharmaceuticals and Roche Diagnostics for their support, and the investigators at the participating sites listed below.

This study was supported in part by the AIDS Clinical Trials Group funded by the National Institute of Allergy and Infectious Diseases (AI68636 for ACTG and AI68634 for SDAC), AI69432 to the UC San Diego Medical Center (C. Benson, S. Spector), AI46376 to the UT Southwestern Medical Center (P. Keiser), AI69450 to the University of Colorado Health Sciences Center (G. Ray), AI 69513-01 to the University of Cincinnati, AI69423-01 to the University of North Carolina (D.A. Wohl), AI69439 to Vanderbilt University, AI32783-13 to the University of Pennsylvania, AI069556 to Stanford University, AI27660 to the UCLA Medical Center (S. Chafey), AI069502-01 to San Francisco General Hospital (M.A. Jacobson), AI069434 and AI27664 to the University of Washington, Seattle, AI46370 to Beth Israel Medical Center (C. Crumpacker), AI69532-01 to NYU/NYC HHC at Bellevue, AI69411 the University of Rochester, AI69494-01 to the University of Pittsburgh, AI69474 to Ohio State University, AI069501 to Case Western Reserve University, AI34853 to University of Hawaii at Manoa, AI27659 to Harvard University/Massachusetts General Hospital, AI27661 to University of Minnesota, AI69495 to Washington University, St. Louis (S. Maxwell), AI 69471 to Northwestern University (N. Lurain), AI46381 to Miriam Hospital, AI32782 to University of Texas, Galveston, AI69470-01 to Columbia University/Weil Medical College of Cornell, AI27673 to University of Southern California, A19418 to Emory University, and AI69477-01 to the University of Miami.

This research was supported in part by the General Clinical Research Center Units funded by the National Center for Research Resources, RR00051 to the University of Colorado Health Sciences Center (G. Ray), RR00046 to the University of North Carolina (D.A. Wohl), and M01-RR00096 to NYU/NYC HHC at Bellevue.

Additional support was provided by the University of North Carolina CFAR Grant AI50410 and University of Pennsylvania CFAR Grant 5-P30-AI-045008-07. Participating A5030 sites: J. Hoffman, S. Cahill (UC San Diego

Medical Center); T. Petersen, P. Keiser (UT Southwestern Medical Center); B. Putnam, R. Levinson (University of Colorado Health Sciences Center); J. Feinberg, J. Baer (University of Cincinnati); C. Zelasky, S. Pedersen (University of North Carolina); J. Nicotera, V. Bailey (Vanderbilt University); C. Nichols, J. Quinn (University of Pennsylvania, Philadelphia); J. Norris, S. Valle (Stanford University); A. Moe, A. Johiro (UCLA Medical Center); M. Jacobson, J. Volinski (San Francisco General Hospital); S. Storey, J. Schouten, (University of Washington); D. Mildvan, M. Revuelta (Beth Israel Medical Center); R. Hutt, M. Vasquez (NYU/NYC HHC at Bellevue); C Greisberger, R Reichman, (Rochester University); S. Riddler, B. Rutecki (University of Pittsburgh); S. L. Koletar, D. Gochnour (Ohio State University); R.A. Salata, P. Walton (Case Western Reserve University); University of Hawaii at Manoa, Leahi; Harvard; Massachusetts General Hospital; University of Minnesota; M. Rodriguez, L. Kessels (Washington University); K. Coleman, A. Lyons (Northwestern University); K.T. Tashima, H. Sousa (Miriam Hospital); W.A. O'Brien, C. Mogridge (University of Texas, Galveston); J. Noel Connor, M. Crawford (Columbia Collaborative HIV/AIDS Clinical Trials Unit); University of Southern California; Methodist Hospital of Indiana; M. Palmore, E. R. Patrick (Emory University); and H.H. Bolivar, M.A. Fischl (University of Miami).

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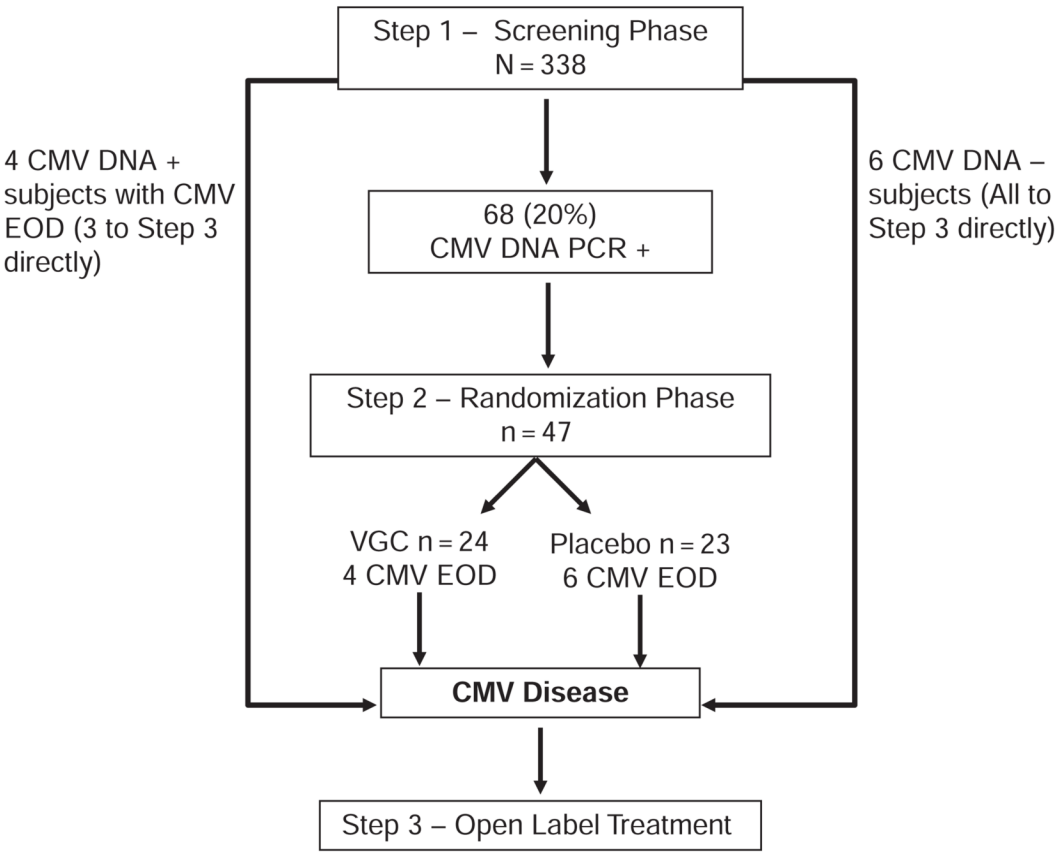

Figure 1.
Study design and subject disposition based on CMV viremia and EOD.

Table 1

Subject characteristics by study step

Characteristic	Step 1 (*N* = 338)	Step 2 (*N* = 47)	Step 3 (*N* = 18)
% Male	88%	94%	100%
% Black, non-Hispanic	30%	15%	11%
% White, Non-Hispanic	56%	60%	67%
% Hispanic	13%	26%	22%
Median age, years	42	46	43
Median CD4+ cell count, /mm^3	30	12	8
Median HIV RNA copies/mL	96,420	–	–
% not receiving HAART	19.5%	21.3%	22.2%

APPENDIX 1

Primary Endpoint Definitions

CMV endpoint	Definition
Confirmed CMV retinitis	Typical lesions including white areas with or without hemorrhages and/or gray-white areas of retinal necrosis with or without hemorrhages. Lesion(s) has/have irregular, dry-appearing, granular border, with little or no overlying vitreous inflammation. Must be diagnosed by an experienced ophthalmologist using indirect ophthalmoscopy and documented by retinal photography that can be independently verified.
Probable CMV retinitis	Typical lesions including white areas with or without hemorrhages and/or gray-white areas of retinal necrosis with or without hemorrhages. Lesion(s) has/have irregular, dry-appearing, granular border, with little or no overlying vitreous inflammation. Must be diagnosed by an experienced ophthalmologist using indirect ophthalmoscopy but is not documented by retinal photographs.
Confirmed CMV esophagitis	• Presence of at least one of the following symptoms: retrosternal pain or odynophagia (pain on swallowing). AND • Appropriate visualization procedure (endoscopy) that reveals mucosal erythema, erosion, or ulceration. AND • Tissue biopsy demonstrating CMV by antigen or characteristic cytopathic changes.
Probable CMV esophagitis	• Presence of at least one of the following symptoms: retrosternal pain or odynophagia (pain on swallowing). AND • Appropriate visualization procedure (endoscopy) that reveals mucosal erythema, erosion, or ulceration. AND • CMV is isolated from the lesion. AND • Anti-CMV therapy initiated or recommended.
Confirmed CMV gastroenteritis	• Presence of abdominal pain. AND • Appropriate visualization procedure (endoscopy) that reveals mucosal erythema, erosion, or ulceration. AND • Tissue biopsy demonstrating CMV by antigen or characteristic cytopathic changes.
Probable CMV gastroenteritis	• Presence of abdominal pain. AND • Appropriate visualization procedure (endoscopy) that reveals mucosal erythema, erosion, or ulceration. AND • CMV is isolated from the lesion. AND • Anti-CMV therapy initiated or recommended.
Confirmed CMV colitis	• Presence of at least one of the following symptoms: abdominal pain or diarrhea (typically in small volume and associated with mucus and blood). AND • Appropriate visualization procedure (colonoscopy, sigmoidoscopy, or endoscopy) that reveals mucosal erythema, erosion, or ulceration. AND

CMV endpoint	Definition
	• Tissue biopsy demonstrating CMV by antigen or characteristic cytopathic changes.
Probable CMV colitis	• Presence of at least one of the following symptoms: abdominal pain or diarrhea (typically in small volume and associated with mucus and blood). AND • Appropriate visualization procedure (colonoscopy, sigmoidoscopy, or endoscopy) that reveals mucosal erythema, erosion, or ulceration. AND • CMV is isolated from the lesion. AND • Anti-CMV therapy initiated or recommended.
Confirmed CMV proctitis	• Presence of rectal pain, often associated with tenesmus, mucus, and blood. AND • Appropriate visualization procedure (colonoscopy, sigmoidoscopy, or proctoscopy) that reveals mucosal erythema, erosion, or ulceration AND • Tissue biopsy demonstrating CMV by antigen or characteristic cytopathic changes.
Probable CMV proctitis	• Presence of rectal pain, often associated with tenesmus, mucus, and blood. AND • Appropriate visualization procedure (colonoscopy, sigmoidoscopy, or proctoscopy) that reveals mucosal erythema, erosion, or ulceration. AND • CMV is isolated from the lesion. AND • Anti-CMV therapy initiated or recommended.
Confirmed CMV pneumonitis	• Hypoxemia and infiltrates on chest X-ray or CT/MRI scan. AND • Tissue biopsy or cells obtained by BAL demonstrating CMV by antigen or characteristic cytopathic changes. AND • No other pathogens identified by routine testing (see instructions) OR signs/symptoms persist or recur after treatment of copathogens.
Probable CMV pneumonitis	• Hypoxemia and infiltrates on chest X-ray or CT/MRI scan. AND • Positive CMV culture or detection of CMV antigen from fluid obtained by BAL. AND • No other pathogens identified by routine testing (see instructions) OR signs/symptoms persist or recur after treatment of copathogens. AND • Anti-CMV therapy initiated or recommended.
Confirmed CMV encephalitis	• Progressive change in mental status, delirium, rapidly progressive cognitive impairment, or signs and symptoms of brain stem injury. AND

CMV endpoint	Definition
	• Detection of viral nucleic acids (e.g., PCR) in CSF or CSF CMV culture positive or brain biopsy demonstrating CMV by antigen, detection of viral nucleic acids (e.g., PCR), or characteristic cytopathic changes.
Probable CMV encephalitis	• Progressive change in mental status, delirium, rapidly progressive cognitive impairment, or signs and symptoms of brain stem injury. AND • MRI or contrast CT scan performed which: a) excludes toxoplasmosis, lymphoma, PML, or other intracranial process, and b) demonstrates periventricular inflammation or meningeal enhancement. AND • Other etiologies ruled out. AND • CMV EOD (e.g., retinitis, colitis) present. AND • Specific therapy initiated, changed, or recommended.
Confirmed other CMV syndromes	Hepatitis or cholangitis: • ALP or ALT significantly elevated above the patient's baseline values AND • Tissue biopsy demonstrating CMV by antigen or characteristic cytopathic changes. Radiculomyelopathy: • Clinical presentation compatible with CMV EOD, including all of the following: **a.** Decreased lower extremity strength and reflexes or syndrome consistent with a cord lesion presently subacutely (over days to weeks); **b.** Myelogram or MRI reveals no mass lesions but lower spinal nerve roots thickened; **c.** CMV-positive culture in CSF OR detection of CMV viral nucleic acids (e.g., PCR) in CSF.
Confirmed cutaneous CMV ulcers	• Direct visualization of oral or vulvovaginal or perianal ulcers. AND • CMV culture of lesion or histologic demonstration of typical CMV cytopathology on biopsy of lesion.
CMV diagnosis not otherwise defined in the ACTG criteria for clinical events, Appendix 50	To report a diagnosis that does not meet the definition on a specific Clinical Event Form, follow the Clinical Event Guidelines in the AACTG Forms Manual for unusual diagnostic cases by completing the specific Clinical Event Form, CESUM10 Form - Clinical Event Summary (Uncommon Events) with a detailed explanation of the diagnosis in the comments section and FAX to the DMC Data Manager for the study. (See Study Management Section for contact information.) In both cases, the form will be reviewed by the Protocol Team and the site will be informed of the Team's decision concerning the diagnosis.