Studies of the Ocular Complications of Aids (SOCA)

CMV Retinitis Retreatment Trial
CRRT, ACTG 228

Protocol

Version 2.2

1 December 1992

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Abstract

The CMV Retinitis Retreatment Trial (CRRT, ACTG 228) is a multicenter clinical trial with the primary objective of comparing the safety and efficacy of three therapeutic regimens for AIDS-related CMV retinitis in patients who were treated with foscarnet or ganciclovir and whose retinitis progressed or recurred. Additionally, the safety and efficacy of continuing to treat patients with the same anti-CMV drug versus being switched to the alternative drug as a result of randomization will be compared. Outcome measures include mortality, retinitis progression, and loss of visual function.

Patients will be randomized into one of three treatment groups: Fos-120, Gcv-10, or Cmb-90/5, labeled for the initial assigned trial drug(s) and corresponding maintenance dose(s). The treatment regimen for each group may consist of 2 steps, the first step is assigned at randomization. If a patient's retinitis continues to progress or a patient is intolerant of the first step drug treatment, the second step treatment will be administered. Treatment at the first step will be foscarnet for patients assigned to Fos-120, ganciclovir for patients assigned to Gcv-10, and the combination of foscarnet and ganciclovir for patients assigned to Cmb-90/5. For patients assigned to Fos-120 or Gcv-10, the second step will be changing to treatment with ganciclovir or foscarnet, respectively. For patients assigned to Cmb-90/5, treatment at the second step will be foscarnet for patients intolerant of ganciclovir, ganciclovir for patients intolerant of foscarnet, or increased doses of combination treatment for patients whose retinitis continues to progress.

Three-hundred (300) patients are to be recruited and randomized. Randomization will be stratified by clinic and the patient's previous retinitis treatment (oral or intravenous ganciclovir or foscarnet); the assignment ratio will be 1:1:1. Patients will be seen at baseline, monthly for six months, and then every three months until death or termination of the trial. Treatment administration will not be masked, however, reading of the fundus photographs will be masked.

History

Ad hoc protocol committee:

Janet Davis, Matthew Davis, Douglas Dieterich, David Hardy, Janet Holbrook, Douglas Jabs, Richard Lewis, Curtis Meinert, Bruce Polsky, James Tonascia, Mark Van Natta

Reviews

27 May 1992 Ad hoc committee meeting (Conference call)
29 May 1992 Policy and Data Monitoring Board (Baltimore)

Approvals

08 Jun 1992 JHU Committee on Human Research 1992

Previous release

- 08 May 1992
- 17 Jun 1992
- 10 Aug 1992

Changes in this version

- Collection of specimens for assessments of CD4 counts and CMV viremia and viuria at 3, 6, and 12 month followup visits were eliminated.

Contents

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Protocol

1. Background

Cytomegalovirus (CMV) retinitis is the most common intraocular opportunistic infection in people with the acquired immune deficiency syndrome (AIDS). It is estimated that about 20% of people with AIDS will develop CMV retinitis [1-9]. To date, only two drugs have been approved for use against CMV retinitis, ganciclovir, approved in 1989 [7-17], and foscarnet, approved in 1991 [18-20]. The Foscarnet-Ganciclovir CMV Retinitis Trial was designed to compare the efficacy of these two drugs used as an initial treatment for CMV retinitis. Results from that trial suggest that the two drugs have similar efficacy in controlling the retinitis. However, the rate of mortality in the group of patients assigned to ganciclovir was higher than in the group assigned to foscarnet; patients in the foscarnet-assigned group lived, on average, 4 months longer and the relative risk (Gcv:Fos) of death was 1.77 [21]. The observed mortality difference may have been due to greater use of zidovudine by the foscarnet assigned group or an independent anti-HIV effect of foscarnet. It is not possible to explain the mortality difference given the results of that clinical trial.

Ganciclovir is normally administered in two dosing phases; 10 to 14 days at an induction dose of 5 mg/kg twice daily followed by maintenance at 5 mg/kg/day. Maintenance therapy is administered via a long-term central venous line (CVL) such as a Hickman catheter. The major toxicity of ganciclovir is hematologic; severe neutropenia, defined as an absolute neutrophil count (ANC) $\leq$ 500 cells/μl, occurred in 36% of patients in our previous trial [21]. Neutropenia is generally reversible and is treated or prevented with hemopoietic growth factors such as granulocyte colony stimulating factor (filgrastim, G-CSF) or granulocyte macrophage colony stimulating factor (sagramostin, GM-CSF) [22]. However, interruptions of treatment with ganciclovir may still be required.

Because of their similar hematologic toxicities, the concomitant use of ganciclovir and zidovudine (AZT) is not recommended. However, the introduction of hemopoietic growth factors has made concomitant use of ganciclovir and zidovudine possible for more patients. Alternatively, patients may be treated with other anti-retroviral drugs such as didanosine (ddI) or zalcitabine (ddC).

Foscarnet also is given in two dosing phases; a 10-14 day induction period followed by long-term maintenance therapy. Maintenance therapy is also given through a CVL such as a Hickman catheter. The induction dose is 60 mg/kg three times daily. The maintenance dose is 90 to 120 mg/kg daily. Foscarnet is excreted by the kidneys and the dose must be adjusted for renal function.

Nephrotoxicity is the major toxicity of foscarnet, occurring in 9 to 40% of patients [18-21]. The drug is given over a two hour period with hydration to minimize nephrotoxicity. When nephrotoxicity occurs, the use of the drug must be stopped. In the Foscarnet-Ganciclovir CMV Retinitis Trial, 9% of patients experienced nephrotoxicity severe enough (defined as serum creatinine $\geq$ 2.9 mg/dl) to interrupt drug treatment [21]. Other toxicities include electrolyte abnormalities, particularly of calcium and magnesium, penile ulcers, and seizures [21].

CRRT Protocol

1. Background

Treatment with ganciclovir or foscarnet halts retinitis progression in 90% of treated patients. However, despite continued maintenance therapy, relapse occurs in 75% of patients within 4 months (unpublished data from the Foscarnet-Ganciclovir CMV Retinitis Trial). Furthermore, periods of remission shorten as the number of relapses increases. Median times to first, second, and third relapse as measured by time to re-initiation of induction therapy were 112, 56, and 31 days, respectively, for patients treated with either ganciclovir or foscarnet (unpublished data from the Foscarnet-Ganciclovir CMV Retinitis Trial). The accelerating rate of relapse may be due to the development of drug resistant viral strains, deteriorating immune function, or a combination of these and other factors. Strains of virus resistant to ganciclovir [23,24] or foscarnet [25] have been isolated from patients treated with each of these drugs.

Standard therapy for recurrent disease has been to start another course of induction. However, since there are now two licensed drugs and new adjuvant therapies available, treatment options have increased. Patients whose retinitis progresses or recurs may be changed from ganciclovir to foscarnet or vice-versa; higher doses of the original drug may be used; or both drugs may be used concomitantly, ie, combination therapy.

There are anecdotal reports of success with higher maintenance doses of ganciclovir for patients whose retinitis has relapsed. The maintenance dose of ganciclovir, 5 mg/kg/day, was chosen in order to minimize toxicity from extended use of ganciclovir. The beneficial effect of induction therapy at 5 mg/kg/12 hours on retinitis suggests that higher doses of ganciclovir may suppress CMV retinitis that would otherwise relapse on the current standard maintenance therapy. In early non-randomized studies, doses as high as 15 mg/kg/day were tested without increased rates of neutropenia or other untoward side effects [38,39]. Since hemopoietic growth factors are now available, patients can be treated for ganciclovir-induced neutropenia without interruption of treatment or reduction in dose. However, there have not been any controlled trials of the efficacy of higher doses on retinitis remission in patients whose retinitis has relapsed.

An alternative approach to therapy for patients with persistently active disease or with relapse is to use a combination of ganciclovir and foscarnet. Given the emergence of drug resistant viral strains after prolonged treatment for CMV with single drugs, combination therapy offers possible advantages. A case report of foscarnet-ganciclovir combination therapy for CMV retinitis suggests efficacy [35]. Further, data from 11 patients treated with combination therapy also suggests efficacy and a tolerable safety profile [36]. In that series, 9 of 10 patients with CMV previously unresponsive to therapy with a single drug, responded to combination therapy similar to the combination therapy specified for this trial. Only 1 of the 10 patients developed severe neutropenia. There were not any episodes of severe nephrotoxicity noted. Three patients from the Foscarnet-Ganciclovir CMV Retinitis Trial were treated with combination therapy after they failed to respond to foscarnet or ganciclovir alone. To date, severe neutropenia or nephrotoxicity has not been noted in these patients [unpublished data].

Which, if any, of these therapeutic strategies is optimal for patients who relapse is unknown.

2. Objectives

The objective of the CMV Retinitis Retreatment Trial is to assess the safety and efficacy of three therapeutic regimens for recurrent or persistent AIDS-related CMV retinitis. A secondary objective is to assess the safety and efficacy of continuing to treat patients with the same anti-CMV drug they received prior to enrollment into the trial versus switching to treatment with the alternative drug, ie, foscarnet or ganciclovir. Outcomes of major interest are mortality, retinitis progression and loss of visual function.

3. Study treatments

Patients will be randomized to be treated according to one of three treatment regimens. Treatment regimens consist of 2 treatment steps. The first step treatment is a course of induction followed by continuous maintenance therapy with the assigned treatment, ie, foscarnet, ganciclovir, or a combination of the two drugs. A course of induction followed by maintenance therapy constitutes what is referred to herein as a treatment cycle. Patients may undergo a single cycle or multiple cycles with the first step treatment depending on the response of their retinitis and their ability to tolerate that treatment. Treatment for patients whose retinitis continues to progress (section 6.1.2) or are unable to tolerate the first step treatment will be changed to the second step treatment of the assigned regimen. Treatment will be according to the best medical judgment of treating physicians for patients whose retinitis continues to progress while on second step treatment or are intolerant of those treatments. The treatment regiments are as follows (also see section 6):

Fos-120

Step 1:	Induction with foscarnet at 90 mg/kg/12 hours for 14 days followed by continuous maintenance at 120 mg/kg/day
Step 2:	Induction with ganciclovir at 5 mg/kg/12 hours for 14 days followed by continuous maintenance at 10 mg/kg/day. After the initial treatment cycle, the induction dose will be increased to 7.5 mg/kg/12 hours

Gcv-10

Step 1:	Induction with ganciclovir at 5 mg/kg/12 hours for 14 days followed by continuous maintenance at 10 mg/kg/day. After the initial treatment cycle, the induction dose will be increased to 7.5 mg/kg/12 hours.
Step 2:	Induction with foscarnet at 90 mg/kg/12 hours for 14 days followed by continuous maintenance at 120 mg/kg/day

Cmb-90/5

Step 1: Induction for patients in the foscarnet stratum will be ganciclovir at 5 mg/kg/12 hours and foscarnet at 90 mg/kg/day for 14 days. Induction for patients in the ganciclovir stratum will be foscarnet at 90 mg/kg/12 hours and ganciclovir at 5 mg/kg/day for 14 days. Maintenance therapy for both strata will be foscarnet at 90 mg/kg/day and ganciclovir at 5 mg/kg/day

Step 2: For patients with continued progression, induction will be foscarnet at 90 mg/kg/12 hours and ganciclovir at 5 mg/kg/12 hours for 14 days followed by maintenance therapy with foscarnet at 120 mg/kg/day and ganciclovir at 5 mg/kg/day. Patients intolerant of ganciclovir will be treated according to first step of the Fos-120 regimen. Patients intolerant of foscarnet will be treated according to the first step of the Gcv-10 regimen.

For the purpose of this protocol the term "treatment switch" or variations thereof, refers to a change in drug treatment occurring as a result of randomization. For example, a patient enrolling in the trial having been treated with ganciclovir and assigned to Fos-120 will be considered to have undergone a treatment switch. The term "treatment change", or variations thereof, refers to changes in the drug used for treatment that occur after randomization. For example, a patient assigned to the Gcv-10 regimen who, because of continued progression or intolerance of ganciclovir, is treated with foscarnet (second step treatment) will be considered to have undergone a treatment change

4. Patient enrollment

Recruitment, assessment of eligibility, and enrollment will be performed at participating SOCA clinics. The sample size for the trial is 300 patients, 100 per treatment group. In order to recruit 300 patients within two years, the recruitment rate for the 11 clinics will need to be 14 patients per year per clinic. This is the same as the recruitment rate achieved in the Foscarnet-Ganciclovir CMV Retinitis Trial.

Once it has been determined that a patient is eligible for the trial, the specifics of the trial will be explained and discussed with that person. Patients considering participating in the trial will be given the consent statement and other informational materials and should be allowed 24 hours to think about enrolling in the trial. All baseline evaluations should be conducted prior to randomization and within the 5 days up to and including randomization. Patients unable to complete the baseline evaluations will not be eligible for participation in the trial.

4.1. Inclusion criteria

- Active CMV retinitis in one or both eyes; SOCA-certified ophthalmologist confirms diagnosis at time of enrollment
- Treatment for CMV retinitis with ganciclovir or foscarnet within the past 28 days and having received at least 28 days of treatment with one of those drugs
- At least one lesion with one-quarter disc area or more that can be photographed
- Diagnosis of AIDS as defined by the CDC criteria [26] or a documented HIV infection
- 18 years of age or older on entry
- Visual acuity in an affected eye of 3 or more letters on ETDRS chart at 1 meter distance (Snellen equivalent 5/200). Patients with poorer visual acuity may be enrolled if the visual acuity impairment is possibly reversible (eg, due to optic disc edema) and vision is at least light perception in that eye
- Baseline absolute neutrophil count (ANC) $\geq$ 500 cells/μl
- Baseline platelet count of 20,000 cells/μl
- Baseline serum creatinine $\leq$ 2.5 mg/dl
- Baseline Karnofsky score $\geq$ 60
- Willingness and the ability, with assistance of a care-giver if necessary, to comply with followup schedule
- Signed consent statement

4.2. Exclusion criteria

- History of intolerance to ganciclovir or foscarnet sufficient to contraindicate use
- History of therapy involving the combination of foscarnet and ganciclovir
- Unwillingness to practice appropriate birth control

- Active drug or alcohol abuse, considered sufficient to make compliance with treatment of followup procedures problematic
- Media opacity that precludes visualization of the fundus of both eyes
- Retinal detachment not scheduled for surgical repair

4.3. Randomization

Randomization will be performed within strata defined by clinic and prior retinitis treatment (oral or intravenous ganciclovir or foscarnet). The randomization schedules will be written and controlled by the SOCA Coordinating Center and will be designed to yield an expected assignment ratio of 1:1:1. Assignments will be generated in permuted blocks of varying lengths.

Clinic personnel will request assignments as needed from the Coordinating Center and assignments will be sent in a sealed envelope for overnight delivery except in emergencies. Assignments will be revealed after eligibility has been established, all baseline data have been collected and recorded, and signed consent has been obtained. Once an envelope is opened, the patient is enrolled in the trial and counted in the assigned treatment group for primary analysis regardless of subsequent treatment or compliance. If a patient refuses to participate or is otherwise determined ineligible before the envelope containing the treatment assignment is opened, it should be return unopened to the Coordinating Center.

5. Outcome measures

The outcomes of primary interest are mortality, retinitis progression, and loss of visual function. Mortality will be measured from time of randomization to death or censored at the end of followup. Time to retinitis progression is the time from randomization to the next retinitis progression. Loss of visual function is defined as dropping $\geq$ 2 lines on an ETDRS chart from the baseline visual acuity in an affected eye. Other outcomes of interest include measures of drug toxicity, retinal detachment, morbidity, and quality of life.

Retinitis progression will be measured by masked readings of fundus photographs by the central Fundus Photography Reading Center (FPRC). For the purposes of this protocol, the criteria the FPRC will use to define retinitis progression are: (1) advancement of the border of an existing lesion by one-half the diameter of the optic disc (0.5 disc diameters = 750μ[1]) perpendicularly from the edge and along $\geq$ 750μ of it; or (2) occurrence of new lesion $\geq$ one-

[1]For convenience, the long-standing clinical convention of considering the diameter of the average optic disc to be 1,500μ will be followed, even though 1,800 to 1,900μ is probably a more accurate estimate.

quarter disc area in size (a circle, $\geq$ 750μ in diameter), separate from the previous lesion in the same eye or in a previously uninvolved eye.

The border of a CMV lesion is defined as a zone that is 1,000μ in width extending into the lesion from its junction with normal retina. Lesion borders will be classified as active or inactive. Active lesions are composed of diffuse, white, opaque retinitis, which may have a solid or granular appearance. Lesion borders containing multiple satellites with intervening normal retina will also be classified as active. Inactive borders are composed of retinal and RPE atrophy, with or without white deposits and/or areas of gliosis.

Assessment of visual function and other outcomes will be performed by clinic personnel not masked to treatment.

6. Treatment administration

6.1. Treatment plan

A treatment regimen is the set of treatment steps specified by the treatment assignment. All regimens consists of 2 treatment steps; therapy is started with the first step treatment and changed to a second step treatment, when and if, criteria are met for continued progression or drug intolerance. The second step treatment may vary depending on the reason the first step treatment was stopped. Treatment decisions will be dictated by retinitis status in the more severely involved eye or drug intolerance.

Treatment with the assigned therapy should be started as soon as possible after randomization and be administered unmasked. The procedures for drug administration are similar for foscarnet and ganciclovir. Drugs are administered intravenously; an indwelling catheter will be used for long-term administration. Patients may require surgery for the placement of an indwelling catheter. Maintenance therapy should begin immediately after induction therapy has been completed and ordinarily will be administered on an outpatient basis. It will be left to the discretion of the trial ophthalmologist and internist as to whether admission to a hospital will be necessary for induction therapy.

All patients will be instructed to contact the clinic if they experience any problems with their treatment or eyes, noticeable changes in their vision, or other symptoms. If a trial physician considers continuing or restarting therapy with the assigned treatment to be inappropriate medical care for a patient, treatment will be according to the best medical judgement of treating physicians. If a woman becomes pregnant while enrolled in the trial, she and her physician will decide what drug treatment she will receive. Regardless of the treatment administered, all

patients should continue to be evaluated at scheduled followup visits until death or trial followup is terminated.

6.1.1. Treatment cycles

Retinitis progression will be assessed at least 28 days after the start of the first treatment cycle. Under most circumstances, a treatment cycle should be repeated at least once before changing to the second step treatment. Another cycle of treatment with the same drug(s) will be started if any of the following occur:

- Border progression: (1) advancement of the edge of an existing lesion by one-half the diameter of the optic disc (designated here as 750μ) perpendicularly from the edge and along $\geq$ 750μ of it; or (2) occurrence of new lesion $\geq$ one-quarter disc area in size (a circle, $\geq$ 750μ in diameter), separate from the previous lesion in the same eye or in a previously uninvolved eye. In some cases, the edge of a CMV lesion is difficult to define, because of the presence of small (100 to 400μ diameter) white foci of active retinitis ("satellites") surrounded by normal appearing retina in a zone of variable width adjacent to the solid white (or atrophic) marginal zone of the lesion. In the clinical assessment of progression, the responsible investigator will use his or her best judgement in defining the lesion edge. When satellites are extensive and occupy a narrow zone adjacent to the solid marginal edge, it is recommended that the junction of the satellite zone and the normal retina be used.

- Persistent activity in the safety zone: In situations where progression of less than 750μ may lead to irreversible damage to the center of the macula or the optic nerve, the criterion for initiation of another treatment cycle after 28 days is persistent activity since the beginning of the most recent induction phase. Persistent activity refers to retinitis that is as active or more active than at the start of induction therapy, presenting clear evidence of a failure of the drug to control disease. Therefore, if the center of the macula or the optic nerve is threatened by active retinitis, another treatment cycle may be started even though the border progression criterion is not met.

- Development of extra-ocular CMV disease confirmed by tissue biopsy; positive culture alone is not sufficient documentation.

Drug therapy may be interrupted because of safety considerations. In most situations, a patient should be treated again with the same drug therapy after an interruption of therapy for toxicity. If a serious drug-related abnormality develops in a laboratory measure and is asymptomatic, drug therapy should be interrupted if the abnormality also represents an increase in severity of $\geq$ 2 grades from the baseline measurement (see SOCA Handbook for toxicity grading). When drug therapy is resumed, the dose administered should be the same as the dose

being administered at the time of interruption. For example, a patient on maintenance therapy when treatment was interrupted and whose retinitis has not progressed should resume treatment at the maintenance dose.

6.1.2. Treatment steps

The first step treatment is started as soon as possible after randomization. The second treatment step is started if retinitis continues to progress or a patient is intolerant of the first step treatment (Figure 2).

The treatment trigger for lack of efficacy is progression after two treatment cycles with the same anti-CMV therapy within 10 weeks, ie, continued progression. The criteria for continued progression are two occurrences of retinitis border progression, persistent or increased border activity in the safety zone, or development of an extra-ocular CMV infection (as defined in section 6.1.1) after two treatment cycles within 10 weeks.

The treatment trigger for drug intolerance is recurrent or persistent, serious (grade 4) drug-related toxicity. Furthermore, drug therapy may be interrupted for any toxicity if, in the judgement of a trial physician, continuing therapy represents a significant hazard to the patient. Recurrent and persistent toxicity are defined as follows:

- Recurrent drug toxicity: The occurrence of two episodes of any one toxicity (grade 4) requiring interruption of therapy within 28 days

- Persistent drug toxicity: Persistent, uncontrolled, and study drug-related toxicity (grade 4) after stopping treatment with the study drug for 14 days. If CMV lesions threaten the optic nerve or the center of the macula, patients with toxicity may be changed to the second step treatment before 14 days has elapsed

6.2. Drug treatments

6.2.1. Foscarnet treatment

Treatment with foscarnet (Table 2) is the first treatment step for patients assigned to Fos-120. It is the second treatment step for patients assigned to Gcv-10 and for patients assigned to Cmb-90/5 who can not tolerate ganciclovir.

The foscarnet induction dose is 90 mg/kg/12 hours accompanied by 0.50 to 0.75 liters of 0.9N saline. Hydration should be given simultaneously with foscarnet and hydration volume should be adjusted to prevent fluid overload. Oral hydration may be used if serum creatinine levels are within the normal range. However, at the first evidence of elevated serum creatinine

(grade 1), intravenous hydration should be started. Serum creatinine levels must be ≤ 2.5 mg/dl to start therapy; induction dosage should be reduced if predicted creatinine clearance is below 1.6 ml/min/kg. The induction phase should last for 14 days; serum chemistries are to be monitored twice per week.

Maintenance therapy is to start immediately following completion of induction therapy. The maintenance therapy for foscarnet is 120 mg/kg/day accompanied by infusions of 1 liter of a 0.9N saline solution, 7 days a week. Hydration should be given simultaneously with foscarnet and hydration volume should be adjusted to prevent fluid overload. Oral hydration may be used if serum creatinine levels are within the normal range. However, at the first evidence of elevated serum creatinine (grade 1), intravenous hydration should be started. Dose levels should be reduced if predicted creatinine clearance is below 1.6 ml/min/kg. Hematology and serum chemistries are to be monitored weekly during maintenance therapy.

The most significant documented side-effects of foscarnet are impairment of renal function, serum electrolyte abnormalities, seizures, and nausea. If serum creatinine is ≥ 3.0 mg/dl, foscarnet therapy should be interrupted. Foscarnet treatment can be re-started when serum creatinine falls to ≤ 2.0 mg/dl. If serum calcium, phosphate or magnesium are significantly lowered (grade 2 or 3), oral or intravenous supplementation should be given. If a patient develops symptoms consistent with hypocalcemia (eg, muscle irritability, paresthesia, tetany), or other unexplained neurologic events including seizures, blood should be drawn for assessment of serum ionized calcium immediately after the completion of the next dose of foscarnet. Patients who experience nausea associated with infusions of foscarnet should be given antiemetic therapy. Foscarnet therapy is to be interrupted if severe (grade 4) abnormalities of serum calcium or magnesium, or other severe (grade 4) drug-related toxicity develops.

6.2.2. Ganciclovir treatment

The ganciclovir treatment (Table 3) is the first treatment step for patients assigned to Gcv-10. It is the second treatment step for patients assigned to Fos-120 and for patients assigned to Cmb-90/5 who can not tolerate foscarnet.

The induction dose for ganciclovir is 5 mg/kg/12 hours. ANC and platelet counts should exceed 500 cells/μl and 20,000 cells/μl, respectively, to start induction therapy. Doses should be reduced if predicted creatinine clearance is below 1.1 ml/min/kg. Induction should be continued for 14 days; hematology are to be monitored two times per week. The induction dose for ganciclovir will be increased to 7.5 mg/kg/12 hours for patients who require additional cycles of ganciclovir therapy.

Maintenance therapy should start immediately following completion of induction therapy. Maintenance therapy for ganciclovir is 10 mg/kg every day, 7 days a week. Dose levels should

be reduced if predicted creatinine clearance falls below 1.1 ml/min/kg. Hematology and serum chemistries are to be monitored weekly during maintenance therapy.

The most significant documented side-effects of ganciclovir are neutropenia and thrombocytopenia. The hematopoietic growth factor filgrastim (Neupogen®, G-CSF) should be administered to patients whose ANC falls below 1,000 cells/μl (section 7.1). If ANC falls below 500 cells/μl, ganciclovir therapy should be interrupted. Ganciclovir can be re-started after ANC rises to $\geq$ 750 cells/μl. Therapy should be interrupted if platelet counts are $\leq$ 10,000 cells/μl; therapy can be re-started when platelet count rises to $\geq$ 20,000 cells/μl. Ganciclovir therapy should be interrupted if other severe (grade 4) drug-related toxicities develop.

6.2.3. Combination treatment

The doses of foscarnet and ganciclovir administered for induction therapy will depend on the stratum defined by retinitis treatment prior to randomization. Patients who received foscarnet prior to randomization, will receive induction therapy with ganciclovir at 5 mg/kg/12 hours and foscarnet at 90 mg/kg/day. Patients who received ganciclovir prior to randomization will receive induction therapy with foscarnet at 90 mg/kg/12 hours and ganciclovir at 5 mg/kg/day. The two drugs can be given sequentially; they should not be administered simultaneously. Full doses of both drugs are to be administered each day and hydration should be given simultaneously with foscarnet. Hematology and serum chemistries are to be monitored twice per week during induction therapy.

The maintenance phase of the treatment cycle will be the same for patients in both strata. Maintenance doses for combination therapy are 90 mg/kg/day for foscarnet with hydration and 5 mg/kg/day for ganciclovir, 7 days a week. Hematology and serum chemistries are to be monitored weekly during maintenance therapy. Oral hydration may be used if serum creatinine levels are within the normal range. However, at the first indication of elevated serum creatinine (grade 1), intravenous hydration should be started. The two drugs are to be given sequentially; they should not be administered simultaneously. Full doses of both drugs are to be administered each day.

The guidelines for modification, interruption and re-start of foscarnet or ganciclovir therapy for the combination treatment cycle are the same as for those on the foscarnet or ganciclovir treatment cycles, respectively (Table 4). Filgrastim therapy should be initiated if ANC levels fall below 1,000 cells/μl (Section 7.1).

7. Other study medications

7.1. Filgrastim

Filgrastim (Neupogen®, G-CSF) therapy should be initiated for all patients receiving ganciclovir whose ANC falls below 1,000 cells/μl. The goal of therapy is to maintain ANC levels between 1,000 and 10,000 cells/μl (target range). The most common side effect associated with filgrastim therapy is bone pain. The initial dose of filgrastim is 1 μg/kg/day for three days. After three days, ANC levels should be checked and the dose modified as follows:

- If ANC levels remain below 1,000 cells/μl, the daily dose of filgrastim should be increased. Filgrastim doses should be increased from 1 to 3 μg/kg/day, from 3 to 5 μg/kg/day, and from 5 to 10 μg/kg/day until ANC levels exceed 1,000 cells/μl or until the maximum dose of filgrastim, 10 μg/kg/day, is reached. Dose escalations should be implemented every three days, ANC levels should be checked prior to a dose escalation.

- If ANC levels equal or exceed 1,000 cells/μl, patients should continue on that daily dose of filgrastim for 7 days. If ANC levels remain in the target range for that period, the frequency of filgrastim administration should be reduced from daily to three times per week, followed by a reduction to two doses per week, followed by a reduction to one dose per week, and then discontinuation of filgrastim. These reductions should be done at weekly intervals in patients whose ANC levels remain in the target range for the preceding week. ANC levels should be checked once a week.

- If reduced frequency of administration or discontinuation of filgrastim doses is followed by a drop in ANC levels to less than 1,000 cells/μl, daily filgrastim doses should be restarted. The dose of filgrastim should be the daily dose previously required to achieve ANC levels within the target range; if necessary that dose should be increased as described above. After ANC levels within the target range are achieved, frequency of filgrastim administration should be reduced as described above to the minimum number of doses per week required to maintain ANC levels in that range.

- If the administration of filgrastim results in ANC levels that exceed 10,000 cells/μl, the dose should be decreased by 25%. Dosages should be reduced at one week intervals until ANC levels are within the target range. Once ANC levels within the target range are achieved, the frequency of administration can be reduced as described above.

- If ANC levels fall below 500 cells/μl, ganciclovir therapy should be interrupted until ANC levels equal or exceed 750 cells/μl.

- Filgrastim may also be used to treat patients with neutropenia who are not receiving ganciclovir, the same schema for administration should be used.

7.2. Anti-retrovirals

Maintaining or initiating anti-retroviral therapy (licensed or available through expanded access programs or research studies) should be considered an integral part of optimal medical care for people enrolled in this trial. Anti-retroviral therapy with zidovudine has been shown to extend life and delay progression of complications associated with HIV-induced immunosuppression. Other anti-retroviral medications such as didanosine (ddI) and dideoxycytidine (ddC), may have similar effects in addition to their in vivo anti-retroviral effect. Patients in this trial should be treated with an anti-retroviral regimen as suggested by the following guidelines.

- Zidovudine, (AZT, Retrovir®) as a single agent or in combination with other anti-retroviral therapy, at a minimum of 300 mg/day; the recommended dose is 500 to 600 mg/day.

- Didanosine (ddI, Videx®) as a single agent or in combination with zidovudine at a minimum of 200 mg twice per day (BID).

- Zalcitabine (ddC, HIVID®) in combination with zidovudine, at a minimum of 0.75 mg three times per day (TID).

- Investigational anti-retroviral therapy administered as per an Investigational New Drug (IND) approved protocol.

- Other experimental anti-retroviral therapies received by the trial patient on a continuous basis (eg, passive HIV-hyper immune globulin).

Exceptions to the guidelines for anti-retroviral therapy will include:

- Evidence of intolerance necessitating discontinuation of all available anti-retroviral therapies.

- Refusal by the patient to take anti-retroviral therapy for any personal reason based upon the patient's clear understanding of the life-extending potential of such therapy.

- Primary care provider's or trial physician's best medical judgement that such therapy may be deleterious to the patient's general health.

7.3. Other medications

Use of either marrow toxic agents with ganciclovir or nephrotoxic agents with foscarnet should be undertaken only with caution, other therapies should be used whenever possible.

8. Data collection plan

Eligibility of patients will be determined during the baseline visit. Followup evaluations may be limited because of a patient's health without disqualifying the patient. The data collection schedule for baseline and followup visits is shown in Table 6. Followup data collection will continue for one year after the trial has been closed for recruitment.

8.1. Ophthalmologic evaluation

Evaluation procedures include ophthalmic history interview; best corrected visual acuity using ETDRS charts; and dilated indirect ophthalmoscopy. Best corrected visual acuity will be assessed using the refraction and acuity assessment procedures described in the SOCA Handbook.

8.2. Visual fields

Peripheral visual fields will be assessed using a Goldmann perimeter with a IV 4 E test object according to the procedures developed for the Diabetic Retinopathy Study (DRS). The procedures for visual field assessment are specified in the SOCA Handbook. Pupils may or may not be dilated for field assessments.

8.3. Fundus photography

CMV lesions will be documented by fundus photography. Photographs of both eyes will be taken with a 60° wide-angle camera (Canon). Procedures for fundus photography are specified in the SOCA Handbook. If a patient is unable to tolerate fundus photography according to the full photography protocol, an abbreviated protocol as outlined in the Handbook should be employed.

8.4. Medical evaluation

An evaluation of a patient's overall health status and AIDS-related disorders will be conducted and recorded on trial forms. The evaluation will consist of a medical history, physical examination and a Karnofsky performance ranking. Specific procedures are outlined below.

- At the baseline visit a medical history interview will be conducted to collect data concerning HIV and non-HIV related health status. Information to be collected includes: health history prior to the onset of AIDS; date of AIDS diagnosis and index disease; occurrence of other opportunistic infections and manifestation of AIDS; and HIV and CMV treatment history. If a patient is unable to provide complete information regarding previous treatment for CMV retinitis or HIV infection, medical records or other physicians will be consulted to obtain data regarding the patient's medical history.

- Concomitant medications including name and dose.

- A physical examination will be conducted. Data concerning vital signs and overall status of major body systems will be collected.

- Karnofsky performance status will be assessed. The Karnofsky performance scale is described in the SOCA Handbook.

8.5. Quality of life assessment

A questionnaire will be used to measure health status and qualitative vision assessment. The questionnaire was developed from the Medical Outcome Study Short-form General Health Survey and includes HIV and vision relevant items [34].

8.6. Laboratory measures

Laboratory measurements should be completed within the 5 days prior to randomization.

- Complete blood count (CBC) with differential and platelet counts. Absolute neutrophil count (ANC) and platelet counts must be at least 500 cells/μl and 20,000 cells/μl, respectively, for a person to be enrolled in the trial.

- Serum electrolytes including calcium, magnesium and phosphate, blood urea nitrogen (BUN), and creatinine. Serum creatinine may not exceed 2.5 mg/dl for a person to be enrolled in the trial.

- Total and percent CD4+ T cell counts [29,30]

- Blood and urine will be cultured for CMV [33]

8.7. Data collection schedule

All evaluations and procedures will be conducted at the baseline visit. Followup visits will be scheduled monthly for 6 months and then every 3 months until death or trial termination. Ophthalmologic and visual acuity examinations, fundus photography, and laboratory assessments will be conducted at all followup visits. Interval medical histories including occurrences of adverse events, drug treatment histories, and concomitant medications will also be collected at all these visits. Visual field assessments, analysis, physical examinations including assessment of Karnofsky score, and quality of life interviews will be conducted every 3 months for 6 months and then every 6 months until death or trial termination.

All patients should undergo trial examinations according to the trial visit schedule outlined in Table 5. The trial visit schedule represents a data collection schedule and should not be seen as a clinical care schedule. More frequent visits for clinical care may be scheduled based on the judgement of the treating physicians.

Audits of patients' vital status will be conducted every three months after the start of the trial. Each clinic will provide information regarding the vital status of patients and the dates of last visit and last contact with patients enrolled in the trial at their clinic.

9. Biostatistical considerations

9.1. Sample size

The sample size of 300 patients for this trial (100 per treatment group) is based largely on pragmatic considerations having to do with patient availability and the total resources of SOCA. Using this sample size of 300 and data from the ganciclovir-assigned patients enrolled in the CMV Retinitis Trial, the estimated pairwise minimum detectable differences are a 60% increase in median time-to-death (6.5 to 11.0 months), a 66% increase in time-to-retinitis progression (44 to 73 days), and a 68% increase in time-to-visual loss of ≥ 2 lines on an EDTRS chart (5.6 to 9.4 months). These estimates are based on logrank tests using a two-sided Type I error level of 0.01, a power level of 0.80, a two year recruitment period, and a one year followup period after the recruitment goal is achieved. Estimates are calculated using a 10% decrease in sample size due to loss to followup, treatment lag and non-compliance [37].

9.2. Data monitoring

A Policy and Data Monitoring Board (PDMB) whose voting members are not involved in the conduct of SOCA trials will be responsible for reviewing the accumulating data related safety and efficacy with treatment groups identified. The PDMB will meet semi-annually, or more often as necessary, throughout the course of the trial.

9.3. Data analysis principles, procedures and interpretation

General analysis principles include analysis by original treatment assignment, counting patients (including ineligible patients) into their assigned treatment once the treatment assignment is revealed to the clinic, and counting all events after randomization. Comparisons will be made among treatment groups both unadjusted and adjusted for baseline covariates including previous anti-CMV and anti-retroviral therapies. P-values will be presented without adjustment for multiple looks, multiple outcomes or multiple comparisons. Other analyses will include comparisons by time-dependent administered treatment when appropriate.

Test statistics for treatment group comparisons will include likelihood ratio tests from Cox regression models and logrank tests from Kaplan-Meier procedures. Mortality, retinitis progression and visual loss will be compared among the three treatment groups.

Additionally, rates of mortality, retinitis progression, and visual loss will be compared between those patients who were switched and those patients who were not switched from their pre-randomization anti-CMV treatment The power to detect an interaction between switching and treatment assignment even of modest size will be low and will depend upon the ratio of patients previously treated with foscarnet to ganciclovir, hence, interpretation of these results may be difficult.

10. Patient rights and responsibilities

10.1. IRB approvals

This protocol will be submitted to the Institutional Review Board (IRB) of participating centers for review and approval. All trial patients must sign an informed consent form and medical record release form.

10.2. Confidentiality of patient data

All patient data will be kept in a secure place. Access to patient identification data will be limited to direct-care clinical personnel and the clinic coordinator. Name, social security number, address and other such personal data will not be used by the Coordinating Center. Data collected from study evaluations and interviews will be identified by trial ID codes only; a patient ID number and name code will be assigned at registration. These data will be released to the patients and the Coordinating Center; it may also be released, without personal identifiers, to the pharmaceutical sponsor or the FDA for monitoring purposes without written consent of the patient. Clinically relevant information may be placed in the patient's medical record. Release of data to any other persons or organizations will require the written consent of the patient.

11. Biohazards

It is probable that blood and urine specimens collected during the trial will be contaminated with CMV, HIV, and other pathogens. All personnel involved in collecting and handling biologic specimens should follow appropriate precautionary procedures as currently recommended by the Centers for Disease Control [32].

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CRRT Protocol — Tables and figures

Table 1. Design summary

Objectives

Primary

- Compare the safety and efficacy of three therapeutic regimens in patients with AIDS-related CMV retinitis previously treated with foscarnet or ganciclovir whose retinitis progresses or recurs

Secondary

- Compare the safety and efficacy of continuing to treat patients with the same anti-CMV drug versus switching to the alternative drug

Type of study

- Multicenter clinical trial
- Fixed sample size: 300

Stratification

- Prior treatment: foscarnet or ganciclovir
- Clinic

Treatment groups

- Foscarnet (Fos-120)
- Ganciclovir (Gcv-10)
- Combination (Cmb-90/5)

Treatment regimens

- Fos-120
  - Step 1: induction with foscarnet at 90 mg/kg/12 hours, maintenance at 120 mg/kg/day
  - Step 2: induction with ganciclovir at 5 mg/kg/12 hours, maintenance at 10 mg/kg/day. Subsequent inductions at 7.5 mg/kg/12 hours

- Gcv-10
  - Step 1: induction with ganciclovir at 5 mg/kg/12 hours maintenance at 10 mg/kg/day. Subsequent inductions at 7.5 mg/kg/12 hours
  - Step 2: induction with foscarnet at 90 mg/kg/12 hours, maintenance at 120mg/kg/day

Table 1. Design summary

- Cmb-90/5
  - Step 1: induction for the foscarnet stratum is ganciclovir at 5 mg/kg/12 hours and foscarnet at 90 mg/kg/day; induction for the ganciclovir stratum is foscarnet at 90 mg/kg/12 hour and ganciclovir at 5 mg/kg/day; maintenance for both strata is foscarnet and 90 mg/kg/day and ganciclovir at 5 mg/kg/day
  - Step 2 (continued progression): induction with foscarnet at 90 mg/kg/12 hours and ganciclovir at 5 mg/kg/12 hours, maintenance with foscarnet at 120 mg/kg/day and ganciclovir of 5 mg/kg/day
  - Step 2 (foscarnet intolerant): induction with ganciclovir at 5 mg/kg/12 hours individual maintenance at 10 mg/kg/day. Subsequent inductions at 7.5 mg/kg/12 hours
  - Step 2 (ganciclovir intolerant): induction with foscarnet at 90 mg/kg/12 hours, individual maintenance at 120 mg/kg/day

Treatment step triggers

Continued progression

- Retinitis progression, persistent activity in safety zone, or extra-ocular CMV infection after two cycles of treatment within 10 weeks

Drug intolerance

- Recurrent toxicity: occurrence of two episodes of any one toxicity (grade 4) requiring interruption of therapy within 28 days
- Persistent drug toxicity: unresolved, serious (grade 4), drug-related toxicity 14 days after stopping drug treatment. Patient may change drug treatment before 14 days if macula or optic nerve are threatened by retinitis
- Drug therapy may be discontinued for any toxicity if, in the judgement of a study physician, continuing therapy represents a significant hazard to a patient

Masking

- Treatment administration not masked
- Masked reading of fundus photographs

Table 1. Design summary

Inclusion criteria

- Diagnosed with CMV retinitis and reactivation of retinitis after therapy with either foscarnet or ganciclovir
- Active CMV retinitis after ≥ 28 days of treatment with either foscarnet or ganciclovir
- At least one-quarter disc area of at least one lesion must be photographable
- Diagnosed with AIDS
- Visual acuity ≥ 3 letters (5/200 Snellen) on ETDRS chart in at least one eye diagnosed with CMV retinitis
- Age 18 or over
- ANC ≥ 500 cells/μl
- Platelet count ≥ 20,000 cells/μl
- Serum creatinine ≤ 2.5 mg/dl
- Karnofsky score ≥ 60
- Informed consent

Exclusion criteria

- History of intolerable toxicity to ganciclovir or foscarnet
- History of combination therapy with foscarnet and ganciclovir
- Pregnancy, lactation, or unwillingness to employ appropriate contraceptive methods
- Active drug or alcohol abuse, sufficient to prevent adequate compliance
- Sufficient media opacity to preclude visualization of both fundi

Outcomes

Major

- Mortality
- CMV retinitis progression
- Loss of visual function

Secondary

- Drug toxicity
- Retinal detachments
- Morbidity measures
- Change in quality of life

Data collection schedule

- Baseline
- Monthly visits for first six months, every 3 months thereafter

Table 1. Design summary

Detectable differences

Assumed event times, minimum detectable increase

- Median time-to-death = 6.5 months, 69%
- Median time-to-progression = 44 days, 66%
- Median time-to-visual loss of $\geq$ 2 lines = 5.6 months, 68%

Parameter assumptions

- Allocation ratio 1:1:1, 100 per treatment regimen group
- α = 0.01, 2-sided, β = 0.20;
- Estimates are calculated using a 10% decrease in sample size due to loss to followup, treatment lag, and non-compliance
- Recruitment rate = 14 participants/clinic/year
- Recruitment period = 2 years
- Followup after recruitment goal achieved = 1 year
- No adjustments for multiple comparisons, multiple looks, or multiple outcomes

Method of calculation

- Logrank test

Data analysis

- Cmb-90/5 vs Fos-120 vs Gcv-10
- Switched Rx at entry vs not switched Rx
- Primary analysis by treatment group assignment
- Other analyses by treatment administered
- All events after randomization will be counted

Data monitoring plan

- Review of data by Policy and Data Monitoring Board (PDMB) at semi-annual meetings
- Recommendations for protocol modifications or early termination of the trial will be made by the PDMB (no formal stopping rules)

Table 2. Foscarnet treatment

Induction therapy

- 90 mg/kg/12 hours for 14 days, adjust for predicted creatinine clearance
- Serum creatinine must be ≤ 2.5 mg/dl to start therapy
- IV administration, peripheral (diluted) or central line by infusion pump only
- Concomitant hydration with 0.50 to 0.75 liter of normal saline, reduce or eliminate if evidence of volume overload or electrolyte abnormalities related to saline load
- Oral hydration acceptable for patients with serum creatinine levels within the normal range, change to IV hydration if serum creatinine level becomes elevated (grade 1)
- Check creatinine, calcium, magnesium, phosphate, potassium, and hemoglobin 2 times per week, adjust dose for creatinine every time and weekly per body weight
- Dose adjustments for predicted creatinine clearance:

CrCl (ml/min/kg)	Fos (mg/kg/12h)
≥1.6	90
1.5	84
1.4	80
1.3	74
1.2	69
1.1	63
1.0	58
0.9	54
0.8	48
0.7	42
0.6	38
0.5	32
0.4	27

- Creatinine clearance (CrCl) is predicted from serum creatinine according to the formula:
  For males: CrCl = (140 - age)/(creatinine x 72)
  For females: CrCl = [(140 - age)/(creatinine x 72)] x 0.85
- Terminate treatment if serum creatinine ≥ 3.0 mg/dl or drug-related grade 4 toxicity develops
- Re-start if serum creatinine ≤ 2.0 mg/dl

Table 2. Foscarnet treatment

Maintenance therapy

- 120 mg/kg/day, adjust for predicted creatinine clearance
- IV administration (central line, indwelling catheter) by infusion pump only
- Concomitant hydration with 1 liter of normal saline, reduce or eliminate for volume overload or electrolyte abnormalities related to saline load
- Oral hydration is acceptable for patients whose serum creatinine levels are within the normal range; change to IV hydration if serum creatinine becomes elevated (grade 1).
- Check creatinine, calcium, magnesium, phosphate, potassium, and hemoglobin weekly, adjust dose for weight
- Dose adjustment for predicted creatinine clearance:

CrCl (ml/min/kg)	Fos (mg/kg/24h)
≥ 1.5	120
1.3-1.4	104
1.1-1.2	100
0.9-1.0	94
0.7-0.8	84
0.4-0.6	76

- Terminate if serum creatinine ≥ 3.0 mg/dl or if other drug-related grade 4 toxicity develops
- Re-start if serum creatinine ≤ 2.0 mg/dl

Table 3. Ganciclovir treatment

Induction therapy

- 5 mg/kg/12 hours for 14 days, adjust for predicted creatinine clearance
- 7.5 mg/kg/12 hours for subsequent inductions
- IV administration, peripheral or central line
- Check CBC and platelet count 2 times per week
- Adjust weekly per body weight and predicted creatinine clearance:

CrCl (ml/min/kg)	Gcv 5 (mg/kg)	Gcv 7.5 (mg/kg)	Dosing interval (hrs)
≥1.1	5.00	7.50	12
0.7-1.0	2.50	3.75	12
0.4-0.6	2.50	3.75	24
≤0.3	1.25	1.88	24

- Creatinine clearance (CrCl) is predicted from serum creatinine according to the following formula:
  For males: CrCl = (140 - age)/(creatinine x 72)
  For females: CrCl= [(140 - age)/(creatinine x 72)] x 0.85
- Institute therapy with filgrastim if ANC ≤ 1,000 cells/μl
- Discontinue Gcv if ANC < 500 cells/μl, re-start therapy when ANC ≥750 cells/μl
- Discontinue Gcv if platelet count < 10,000; re-start therapy when platelet count ≥ 20,000
- Discontinue treatment if other drug-related grade 4 toxicity develops

Maintenance therapy

- 10 mg/kg/day, adjust for predicted creatinine clearance
- IV administration (CVL)
- Check CBC and platelet count weekly
- Adjust weekly per body weight and creatinine clearance:

CrCl (ml/min/kg)	Gcv (mg/kg)
≥1.1	10.00
0.7-1.0	5.00
0.4-0.6	2.50
≤0.3	1.25

- Institute therapy with filgrastim if ANC <1,000 cells/μl
- Discontinue Gcv if ANC < 500 cells/μl, re-start therapy when ANC ≥ 750 cells/μl
- Discontinue Gcv if platelet count < 10,000, re-start therapy when platelet count ≥ 20,000
- Discontinue treatment if other drug-related grade 4 toxicity develops

Table 4. Combination treatment

Induction therapy, ganciclovir stratum

Foscarnet

- 90 mg/kg/12 hours for 14 days, adjust for predicted creatinine clearance
- Serum creatinine must be ≤ 2.5 mg/dl to start therapy
- IV administration, peripheral (diluted) or central line by infusion pump only
- Concomitant hydration with 0.5 liter of normal saline, reduce or eliminate if evidence of volume overload or electrolyte abnormalities related to saline load
- Oral hydration is acceptable for patients with serum creatinine within the normal range; change to IV hydration if serum creatinine becomes elevated (grade 1)
- Check creatinine, calcium, magnesium, phosphate, potassium, and hemoglobin 2 times per week, adjust dose for creatinine every time and weekly per body weight
- Dose adjustments for predicted creatinine clearance:

CrCl (ml/min/kg)	Fos (mg/kg/12h)
≥1.6	90
1.5	84
1.4	80
1.3	74
1.2	69
1.1	63
1.0	58
0.9	54
0.8	48
0.7	42
0.6	38
0.5	32
0.4	27

- Creatinine clearance (CrCl) is predicted from serum creatinine according to the following formula:
  For males: CrCl = (140 - age)/(creatinine x 72)
  For females: CrCl= [(140 - age)/(creatinine x 72)] x 0.85
- Discontinue treatment if serum creatinine ≥ 3.0 mg/dl or drug-related grade 4 toxicity develops
- Re-start if serum creatinine ≤ 2.0 mg/dl

Table 4. Combination treatment

Ganciclovir

- 5 mg/kg/day, adjusted for predicted creatinine clearance
- IV administration (CVL)
- Check CBC and platelet count weekly
- Adjust dose biweekly per body weight
- Dose adjustments for predicted creatinine clearance:

CrCl (ml/min/kg)	Gcv (mg/kg/day)
≥1.1	5.000
0.7-1.0	2.500
0.4-0.6	1.250
≤0.3	0.625

- Institute therapy with filgrastim if ANC <1,000 cells/μl
- Discontinue Gcv if ANC < 500 cells/μl, re-start therapy when ANC ≥ 750 cells/μl
- Discontinue Gcv if platelet count < 10,000 cells/μl, re-start when platelet count ≥ 20,000 cells/μl
- Discontinue treatment if other, drug-related grade 4 toxicity develops

Induction therapy, foscarnet stratum

Foscarnet

- 90 mg/kg/day, adjust for predicted creatinine clearance
- IV administration (central line, indwelling catheter) by infusion pump only
- Concomitant hydration with 1 liter of normal saline, reduce or eliminate if evidence of volume overload or electrolyte abnormalities related to saline load
- Oral hydration is acceptable for patients with serum creatinine within the normal range; change to IV hydration of serum creatinine becomes elevated (grade 1)
- Check creatinine, calcium, magnesium, phosphate, potassium, and hemoglobin weekly
- Adjust dose every week for creatinine and body weight
- Dose adjustment for predicted creatinine clearance:

CrCl (ml/min/kg)	Fos (mg/kg/24h)
≥1.5	90
1.3-1.4	78
1.1-1.2	75
0.9-1.0	71
0.7-0.8	63
0.4-0.6	57

- Discontinue treatment if serum creatinine ≥3.0mg/dl or if other drug-related grade 4 toxicity develop
- Re-start if serum creatinine ≤ 2.0 mg/dl

Table 4. Combination treatment

Ganciclovir

- 5 mg/kg BID for 14 days, adjust for predicted creatinine clearance
- IV administration, peripheral or central line
- Check CBC and platelet count 2 times per week
- Adjust weekly per body weight
- Dose adjustments for predicted creatinine clearance:

CrCl (ml/min/kg)	Gcv (mg/kg)	Dosing interval (hrs)
≥1.1	5.00	12
0.7-1.0	2.50	12
0.4-0.6	2.50	24
≤0.3	1.25	24

- Creatinine clearance (CrCl) is predicted from serum creatinine according to the following formula:
  For males: CrCl = (140 - age)/(creatinine x 72)
  For females: CrCl= [(140 - age)/(creatinine x 72)] x 0.85
- Institute therapy with filgrastim if ANC <1,000 cells/μl
- Discontinue Gcv if ANC < 500 cells/μl, re-start therapy when ANC ≥ 750 cells/μl
- Discontinue Gcv if platelet count < 10,000, re-start therapy when platelet count ≥ 20,000
- Discontinue treatment if other drug-related grade 4 toxicity develops

Maintenance therapy for ganciclovir and foscarnet strata

Foscarnet

- 90 mg/kg/day, adjust for predicted creatinine clearance
- IV administration (central line, indwelling catheter) by infusion pump only
- Concomitant hydration with 1 liter of normal saline, reduce or eliminate if evidence of volume overload or electrolyte abnormalities related to saline load
- Oral hydration acceptable for patients with serum creatinine levels within the normal range, change to IV hydration if serum creatinine level becomes elevated (grade 1)
- Check creatinine, calcium, magnesium, phosphate, potassium, and hemoglobin weekly
- Adjust dose every week for creatinine and body weight
- Dose adjustment for predicted creatinine clearance:

CrCl (ml/min/kg)	Fos (mg/kg/24h)
≥1.5	90
1.3-1.4	78
1.1-1.2	75
0.9-1.0	71
0.7-0.8	63
0.4-0.6	57

- Discontinue if serum creatinine ≥ 3.0 mg/dl or if other drug-related grade 4 toxicity develop

Table 4. Combination treatment

- Re-start if serum creatinine ≤ 2.0 mg/dl

Ganciclovir

- 5 mg/kg/day immediately following reinduction
- IV administration (CVL)
- Check CBC and platelet count weekly
- Adjust dose biweekly per body weight
- Adjust dose for predicted creatinine clearance prescribed below:

CrCl (ml/min/kg)	Gcv (mg/kg/day)
≥1.1	5.000
0.7-1.0	2.500
0.4-0.6	1.250
≤0.3	0.625

- Institute therapy with filgrastim if ANC <1,000 cells/μl
- Discontinue Gcv if ANC < 500 cells/μl, re-start therapy when ANC ≥ 750 cells/μl
- Discontinue Gcv if platelet count < 10,000 cells/μl, re-start when platelet count ≥ 20,000 cells/μl
- Terminate treatment if other, drug-related grade 4 toxicity develops

Table 5. Combination treatment (step 2 for continued progression)

Induction therapy

Foscarnet

- 90 mg/kg/12 hours for 14 days, adjust for predicted creatinine clearance
- Serum creatinine must be ≤ 2.5 mg/dl to start therapy
- IV administration, peripheral (diluted) or central line by infusion pump only
- Concomitant hydration with 0.50 to 0.75 liter of normal saline, reduce or eliminate if evidence of volume overload or electrolyte abnormalities related to saline load
- Oral hydration acceptable for patients with serum creatinine levels within the normal range, change to IV hydration if serum creatinine level becomes elevated (grade 1)
- Check creatinine, calcium, magnesium, phosphate, potassium, and hemoglobin 2 times per week, adjust dose for creatinine every time and weekly per body weight
- Dose adjustments for predicted creatinine clearance:

CrCl (ml/min/kg)	Fos (mg/kg/12h)
≥ 1.6	90
1.5	84
1.4	80
1.3	74
1.2	69
1.1	63
1.0	58
0.9	54
0.8	48
0.7	42
0.6	38
0.5	32
0.4	27

- Creatinine clearance (CrCl) is predicted from serum creatinine according to the formula:
  For males: CrCl = (140 - age)/(creatinine x 72)
  For females: CrCl= [(140 - age)/(creatinine x 72)] x 0.85
- Terminate treatment if serum creatinine ≥ 3.0 mg/dl or drug-related grade 4 toxicity develops
- Re-start if serum creatinine ≤ 2.0 mg/dl

Table 5. Combination treatment (step 2)

Ganciclovir

- 5 mg/kg/12 hours for 14 days, adjust for predicted creatinine clearance
- IV administration, peripheral or central line
- Check CBC and platelet count 2 times per week
- Adjust weekly per body weight
- Dose adjustments for predicted creatinine clearance:

CrCl (ml/min/kg)	Gcv (mg/kg)	Dosing interval (hrs)
≥ 1.1	5.00	12
0.7-1.0	2.50	12
0.4-0.6	2.50	24
≤ 0.3	1.25	24

- Institute therapy with filgrastim if ANC < 1,000 cells/μl

Maintenance therapy

Foscarnet

- 120 mg/kg/day, adjust for predicted creatinine clearance
- IV administration (central line, indwelling catheter) by infusion pump only
- Concomitant hydration with 1 liter of normal saline, reduce or eliminate for volume overload or electrolyte abnormalities related to saline load
- Oral hydration for patients whose serum creatinine levels are within the normal range, change to IV hydraton if serum creatinine level becomes elevated (grade 1)
- Check creatinine, calcium, magnesium, phosphate, potassium, and hemoglobin weekly, adjust dose for weight
- Dose adjustment for predicted creatinine clearance:

CrCl (ml/min/kg)	Fos (mg/kg/24h)
≥ 1.5	120
1.3-1.4	104
1.1-1.2	100
0.9-1.0	94
0.7-0.8	84
0.4-0.6	76

- Terminate if serum creatinine ≥ 3.0 mg/dl or if other drug-related grade 4 toxicity develops
- Re-start if serum creatinine ≤ 2.0 mg/dl

Table 5. Combination treatment (step 2)

Ganciclovir

- 5 mg/kg/day immediately following reinduction
- IV administration (CVL)
- Check CBC and platelet count weekly
- Adjust dose biweekly per body weight
- Adjust dose for predicted creatinine clearance prescribed below:

CrCl (ml/min/kg)	Gcv (mg/kg/day)
≥1.1	5.000
0.7-1.0	2.500
0.4-0.6	1.250
≤0.3	0.625

- Institute therapy with filgrastim if ANC <1,000 cells/μl
- Discontinue Gcv if ANC < 500 cells/μl, re-start therapy when ANC ≥ 750 cells/μl
- Discontinue Gcv if platelet count < 10,000 cells/μl, re-start when platelet count ≥ 20,000 cells/μl
- Terminate treatment if other, drug-related grade 4 toxicity develops

Table 6. Data collection plan

Data	Months									
	0	1	2	3	4	5	6	9	12	15...
Ophthalmic exam	x	x	x	x	x	x	x	x	x	x
Fundus photos	x	x	x	x	x	x	x	x	x	x
Visual acuity	x†	x	x	x†	x	x	x†	x	x†	x
Visual field	x			x			x		x	
Hematology CBC Differential Platelet	x	x	x	x	x	x	x	x	x	x
Chemistries BUN/creatinine Electrolytes	x	x	x	x	x	x	x	x	x	x
Total CD4+	x									
CMV cultures Blood Urine	 x x									
Health history Drug treatment Adverse events AIDS history Other Rx	x	x	x	x	x	x	x	x	x	x
Physical exam	x			x			x		x	
Karnofsky score	x			x			x		x	
Quality of life	x			x			x		x	

†refraction

Figure 1. Design schematic

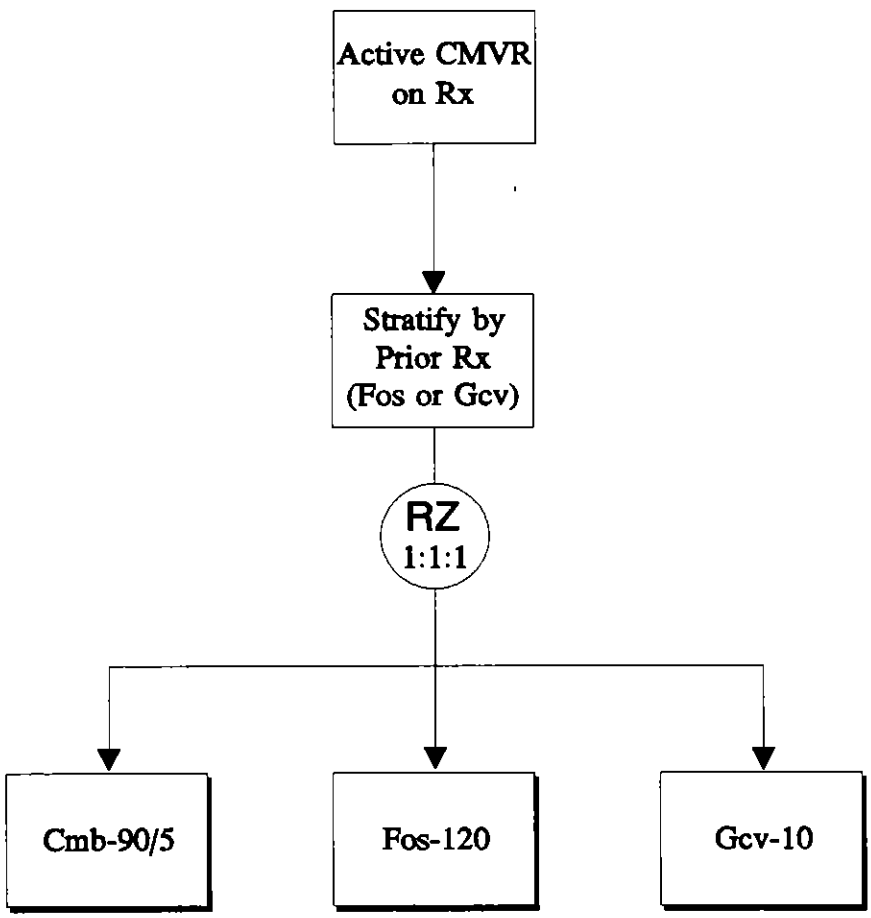
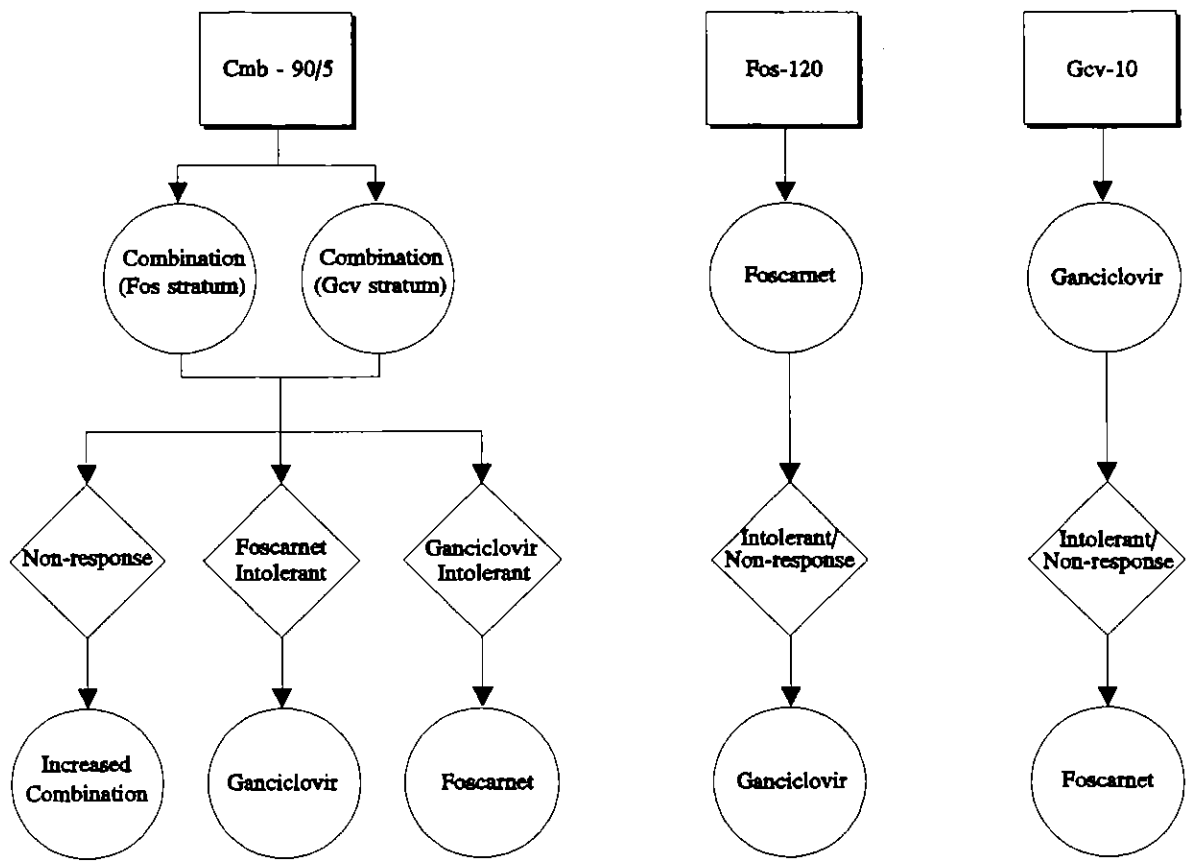


Figure 2. Treatment steps



Consent statement

1. Introduction

Often people with AIDS develop an infection in the eye due to the cytomegalovirus (CMV). The infection -- called CMV retinitis -- involves the retina of the eye and can result in loss of vision.

The two drugs approved by the Food and Drug Administration (FDA) for treatment of CMV retinitis are foscarnet (Foscavir®) and ganciclovir (Cytovene®). Both drugs have been shown to be effective in halting, at least for a time, the progression of the infection. However, neither drug cures CMV retinitis and it is common for the infection to reoccur during treatment.

We evaluated these two drugs in a clinical trial done in 1990 and 1991 involving patients diagnosed with CMV retinitis for the first time. That trial was stopped because those assigned to foscarnet lived about 4 months longer than those assigned to ganciclovir. The reason for the difference is not clear. It may have been due to a beneficial effect of foscarnet in fighting the HIV virus or because people assigned to ganciclovir could not take as much AZT as needed. Drugs available now, but not when the trial was done, such as G-CSF and GM-CSF, make it possible to use ganciclovir and still maintain adequate treatment with AZT or alternate drugs, such as ddI and ddC.

The effect of foscarnet and ganciclovir on retinitis was about the same in that trial. Both drugs stopped the progression of the retinitis temporarily. However, even when people received treatment every day, most people's retinitis reoccurred.

The new trial -- the CMV Retinitis Retreatment Trial (CRRT) -- is designed to evaluate different treatment approaches for people with retinitis that has reoccurred. We are studying the same two drugs as in the previous trial -- foscarnet and ganciclovir -- but this time at higher doses and also in combination. You are being asked to participate because your CMV retinitis has reoccurred.

Treatment for CMV retinitis requires daily doses of either foscarnet or ganciclovir alone, or in combination. A course of treatment usually involves starting by using a fairly high daily dose for the first 14 days (induction) and then continuing use of the drug or drugs at lower levels (maintenance).

2. Study treatments

The treatment regimens to be studied are:

(1) Foscarnet induction at 90 mg/kg twice a day and maintenance at 120 mg/kg once a day. These dosages have been approved by the FDA for induction and maintenance therapy.

(2) Ganciclovir induction at 5 mg/kg twice a day and maintenance 10 mg/kg once a day. If additional courses of ganciclovir induction are needed, the dose will be 7.5 mg/kg twice a day. Induction therapy at 5 mg/kg twice a day has been approved by the FDA. The induction dose of 7.5 mg/kg twice a day and maintenance dose of 10 mg/kg once a day are experimental and have not been approved by the FDA. If treatment with ganciclovir decreases your white blood cell production, we will give you G-CSF (Neupogen®, filgrastim) to stimulate white blood cell production. Using G-CSF to enable people to take higher doses of ganciclovir is experimental and not approved by the FDA.

(3) Combination therapy as follows:

(a) If previously treated with foscarnet, you will receive induction with ganciclovir at 5 mg/kg twice a day and foscarnet at 90 mg/kg once a day, and maintenance with ganciclovir at 5 mg/kg and foscarnet at 90 mg/kg once a day.

(b) If previously treated with ganciclovir, you will receive induction with foscarnet at 90 mg/kg twice a day and ganciclovir at 5 mg/kg once a day, and maintenance with foscarnet at 90 mg/kg and ganciclovir at 5 mg/kg once a day.

Combination therapy is experimental, there are limited data available about the safety and efficacy of combination therapy.

3. Treatment assignment

The treatment you receive will be determined by chance, using a process similar to flipping a coin. A person enrolling in the trial will have an equal chance (33%) of receiving any of one of the three treatment regimens listed above. Treatment will begin as soon after assignment as possible.

4. Treatment administration

As already noted, treatment will begin with high doses of drug given twice a day for up to 14 days (induction). After that, lower doses of drug will be given on a continuing basis (maintenance). Both drugs are given intravenously through an indwelling catheter (tube) placed in a large central vein or blood vessel. Foscarnet and G-CSF will be provided free of charge.

If the retinitis does not respond to treatment or reoccurs after having been halted, you will be given another induction course of treatment, again followed by maintenance. If the retinitis cannot be controlled by the treatment to which you have been assigned, we will try other options as follows:

- If your treatment assignment is to foscarnet, you will receive ganciclovir induction (5 mg/kg twice a day) followed by maintenance with ganciclovir (10 mg/kg once a day)

- If your treatment assignment is to ganciclovir, you will receive foscarnet induction (90 mg/kg twice a day) followed by maintenance with foscarnet (120 mg/kg once a day)

- If your treatment assignment is to the combination of foscarnet and ganciclovir, you will receive induction therapy with both drugs followed by maintenance therapy with both drugs. Induction doses will be 90 mg/kg twice a day for foscarnet and 5 mg/kg twice a day for ganciclovir. Maintenance doses will be 120 mg/kg once a day for foscarnet and 5 mg/kg once a day for ganciclovir

If you cannot tolerate the assigned treatment you will be changed as follows:

- If your treatment assignment is to foscarnet, you will be changed to ganciclovir

- If your treatment assignment is to ganciclovir, you will be changed to foscarnet

- If your treatment assignment is to the combination of foscarnet and ganciclovir, use of the drug that appears to be causing the problem will be stopped and the other drug will be continued

Women and men enrolled in this trial should use birth control procedures. Birth control should continue for at least 90 days after treatment has ended. All women of child-bearing age entering the trial will be given a pregnancy test before treatment is started. Pregnant women will not be enrolled. If a woman becomes pregnant while enrolled in the trial, she and her physician will decide what drug treatment she will receive. She will continue to be seen for scheduled followup visits.

5. Study visits and procedures

You will be expected to come to the clinic for regular visits. Visits will be once a month for the first six months and thereafter every 3 months. Additional visits will be scheduled, if needed, to adjust your treatment or for other reasons.

Each visit will involve fundus photography (photography of the retina) of both eyes, measurement of your visual acuity in both eyes, questions about your general health and medicines your are taking, and collection of 15 to 45 milliliters (1 to 3 tablespoons) of blood for analysis. Some visits will also involve a general physical examination, completion of a questionnaire on how you are feeling, and visual field examinations to measure your ability to see things not directly in front of you.

6. Risks and benefits

There are potential risks and benefits to participation in this trial. The primary risks have to do with the side effects of the treatments as listed below. The treatments to be administered and

examinations to be performed are the best we can deliver in caring for you. The eye examinations and fundus photographs will allow us to watch your disease and may increase the chance of preserving your vision. The results of all tests will be available to you and your primary care physician. The treatments we use may stop the infection from spreading in your eye or to other parts of your body. Beyond that, you will be participating in an effort aimed at improving the treatments available for people with AIDS and CMV retinitis.

Foscarnet

- Kidney function: Decrease in kidney function occurs in as many as 30% of people treated with the drug. (The decrease is detected by changes in blood chemistry and usually does not cause symptoms). If we find that you have seriously reduced kidney function, we will lower the amount of the drug we use or stop it altogether
- Blood electrolytes: Up to half (50%) of the people taking foscarnet have changes in blood levels of certain minerals (calcium, magnesium, and phosphate), but only a small number (5%) have serious changes in blood mineral levels. Symptoms can include tremors, paraesthesia (tingling and numbness of the hands or feet), cramps, and sometimes seizures (convulsions). We will watch your blood mineral level and will prescribe mineral supplements or other kinds of medication if necessary
- Anemia: Decrease in red blood cells (anemia) occurs in about one-third (33%) of the people taking foscarnet. Anemia may cause fatigue (sleepiness). Severe anemia may require blood transfusions
- Thrombophlebitis: Inflammation of veins may occur in a small fraction of people receiving foscarnet (4 to 9%)
- Others: Seizures, penile lesions, nausea, vomiting, headache, and fatigue may occur (10% or fewer of the people treated). In addition, there may be other, as yet, unknown side effects, including the potential for damage to an unborn child

Ganciclovir

- Neutropenia: A serious decrease in white blood cells (neutropenia) occurs in about one-third (33%) of the people taking ganciclovir. Low white blood cell counts reduce one's ability to fight infections. Drugs to stimulate blood cell production will be used to treat neutropenia if it occurs and if severe enough, the use of ganciclovir will be stopped
- Thrombocytopenia: Decreases in blood platelet cells can be expected in about one-fifth (20%) of the people taking ganciclovir. Platelets are needed for blood clotting. Drug treatment will be stopped if the thrombocytopenia is severe
- Neurologic: Serious neurologic side effects have been reported in a few people using ganciclovir (less than 1% of those taking ganciclovir). Symptoms may include dizziness, headaches, mood changes, hallucinations, and seizures
- Liver function: Ganciclovir may reduce liver function (observed in about 2% of the people taking ganciclovir)
- Gastrointestinal (GI): Nausea, vomiting, diarrhea, stomach cramps, anorexia, or bleeding in the gastrointestinal tract may occur in a small number of cases (less than 2% of the those using the drug)

- Others: Anemia, fever, and skin rash can occur (less than 2% of those using the drug). Ganciclovir causes decreased sperm production in animals and may cause infertility in humans. In addition, there may be other, as yet, unknown side effects, including damage to an unborn child.

7. Rights and responsibilities

All participants in this study have certain rights and responsibilities. Your rights are:

- Entry into the study is voluntary
- You may withdraw from the study at any time and still be able to obtain the same quality of medical care at this institution. However, since it is very important to know the status of all patients during and at the end of the trial, we will still want to find out how you are doing even if you do withdraw
- Clinic staff are available to answer any questions or discuss concerns you may have now or in the future

Participants in the study also have certain responsibilities. The success of this trial depends on regular clinic visits and the collection of complete data. If you know now that you will not be able to meet these responsibilities you should not enroll. Your responsibilities include:

- Coming to the clinic for regularly scheduled visits
- Cooperating with clinic staff in relation to trial procedures and in providing information regarding your health
- Informing clinic staff of changes in your address and phone number

8. Privacy and confidentiality

Every effort will be made to protect your privacy and to preserve the confidentiality of the data you provide. Our procedures include:

- Use of only a number to identify your trial study records. We will collect personal information (home and work addresses and corresponding telephone numbers) and the names of two friends or relatives), however, it will not be entered into the data files used for this trial
- Allowing only study personnel access to your data
- Each clinical center participating in this trial has been issued a Certificate of Confidentiality by the Secretary of the US Department of Health and Human Services. These certificates allow clinical personnel to refuse to reveal any identifying information about people participating in the trial in any federal, state, or local civil, criminal, administrative, legislative, or other type of proceeding. The protection is permanent.

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- Release of identifiable information about you to person(s) or organization(s) outside of this study will require your written consent. However, clinical data relevant to your medical care will be placed in your medical record. And data regarding your treatment and followup identified only by study ID codes may be released to outside organizations such as the FDA and the pharmaceutical companies supplying drugs for this trial.
- Not publishing any results in which you are identified

9. Other considerations

Some of the drugs you receive will be provided by the drug manufacturer free of charge to you. Those that are not provided by the drug manufacturer will be billed to you, your insurance company, or Medical Assistance. The drugs that will be provided free of charge are foscarnet, G-CSF, AZT and ddI. All other costs for your care will be billed to you, your insurance company, or Medical Assistance.

Neither this institution nor the Federal Government has insurance to cover costs incurred if you are injured or have other bad effects that are not the fault of the investigators participating in the trial.

10. Consent

Before you agree to enroll, make sure that all your questions concerning the trial have been answered. The principal investigator, Dr. _____ and the clinic staff are available to answer any questions you may have about this study now or later. If you believe that you have been injured by the study or that you are not being treated fairly, you may contact the person named above or you may contact the _____ at _____ (phone number) or The Johns Hopkins University's Office for Research Subjects at (410) 955-3193. Either the principal investigator or the people in the office named above will answer your questions and, if necessary, help you to obtain medical care if you feel you have been injured in the study.

_____

Participant's signature & date

_____

Witness to consent procedure & date

_____

Signature of investigator & date