STUDIES OF THE OCULAR COMPLICATIONS OF AIDS

(SOCA)

CMV Retinitis Trial: Foscarnet Ganciclovir Component

ACTG Protocol 129

Version 3

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Revision history of CMV Retinitis Trial: Foscarnet-Ganciclovir Component Protocol

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Current release:
14 December 1990 (version 3)

Previous releases:
11 April 1990 (version 2)
11 October 1989 (version 1)

Changes incorporated in 14 December 1990 release:

Additions
- Addition of data collection requirements when treatment with the study-assigned drug is discontinued and patient is treated with the alternative drug, i.e., switch administration visits.
- Table 5: Data collection schedule for treatment administration and switch administration visits (page 30)

Modifications
- The maintenance dose of foscarnet for patients who have relapsed after the first course of therapy with foscarnet may be increased to 120 mg/kg/day, adjusted for creatinine clearance, if in the judgement of a study physician, the higher dosage is appropriate.
- Eligibility criterion for minimum platelet counts were reduced from 50K cells/μl to 25K cells/μl. (Policy and Procedure Memorandum 14, effective 6 August 1990)
- Platelet count criteria for modifying ganciclovir therapy were changed. Previously, ganciclovir therapy was discontinued if platelet counts were below 25K cell/μl, and re-instituted if platelet counts were $\geq$50K cells/μl. The discontinuation and reinstitution criteria were changed to less than 10K cells/μl and $\geq$25K cells/μl, respectively. (Policy and Procedure Memorandum 14, August 1990)
- Data collection windows for eligibility (EL) and enrollment (EN) visits, and the first treatment administration visit (TX1) were increased from 3 to 5 days. (Policy and Procedures Memorandum 18, 25 October 1990)

Deletions
- Lymphocyte analyses are no longer required at treatment administration visits. Formerly, lymphocyte analyses were required at two treatment administration (TX1 and TX3) visits. (Policy and Procedure Memorandum 19, 5 November 90)

Changes incorporated in 11 April 1990 release:

Additions
- Treatment preference design for patients with small peripheral lesions was instituted. This design allows eligible patients with a preference to choose immediate or deferred treatment.
- Extra-ocular CMV infections documented by biopsy were added as a criterion for treatment decisions, i.e induction (for deferred patients), re-induction or switching to the other drug.
- Drug treatment should be interrupted in the event of pregnancy and not re-started until the pregnancy is terminated.
- In the event of marrow toxicity, zidovudine should be discontinued entirely.

Additions (cont'd)

- Assessments of serum ionized calcium immediately after completion of infusion therapy with a trial drug if there is evidence of calcium-related abnormalities or other unexplained neurologic events.
- Use of investigational drugs limited to EPO, GMCSF, triazoles, and antiretrovirals available via expanded access programs (currently ddI). The use of other investigational drugs will be considered on a drug by drug basis.
- The confidentiality of patient identifier data are protected by Certificates of Confidentiality issued by the US Department of Health and Human Services.

Modifications

- Eligibility criterion for CMV retinitis was modified to include patients with retinal detachments that require surgical intervention if surgical repair is planned.
- Eligibility criterion for deferred treatment was changed to 25 percent of zones 2 and 3 of the retina affected by retinitis, formerly it was 50 percent of zones 2 and 3.
- Eligibility criterion for age was changed to ≥ 13 years of age; patients ≤ 18 years of age may enroll with the consent of parent or guardian.
- Eligibility criterion for visual acuity was changed to ≥ 3 letters on an ETDRS chart at 1 meter distance; patients with poorer visual acuity may be enrolled if the visual acuity impairment may be reversible (e.g. due to optic disc edema) and at least perceives light. Formerly only 1 letter was required.
- Exclusion criterion for previous treatment for extra-ocular CMV infections was modified to "treatment with anti-CMV drugs currently or within the past 28 days".
- Criterion for considering use of the other drug for persistent drug intolerance was changed to "failure of a toxicity to resolve within 14 days"; previously the time span was 28 days.
- Tables 1, 2 and 3 (drug administration protocols for foscarnet, ganciclovir and zidovudine) have been updated.
- Followup visits associated with induction therapy for deferred patients and additional courses of induction therapy for all patients were defined as treatment administration visits.
- Hematology assessments for safety monitoring are: CBC, differential and platelet count.
- Serum chemistry assessments for safety monitoring are: creatinine, calcium and magnesium.
- Safety assessments results, i.e. hematology and serum chemistries collected every 2 to 3 times per week during induction and weekly during maintenance therapy, are not submitted to the Coordinating Center. These assessments are required for good patient care.
- All patients in all groups should be followed according to the followup schedule. Patients enrolled in the trial beyond 6 months and receiving maintenance therapy or in the deferred treatment groups should have eye examinations every 3 to 4 weeks. These visits should be recorded as Interim visits, but no additional data collection is required unless a change in treatment is required or an adverse event is reported.
- Definitions of retinitis progression and lesion border activity (section 8) were modified.
- The terminology "the center of the macula" replaces "fovea".
- Standard disc diameters and area were added to descriptions of retinal distances and areas.
- Updated table for grading the severity of adverse experiences with the current ACTG table.

Deletions

- Blood drug levels will not be assessed.

Abstract

The objectives of the CMV Retinitis Trial: Foscarnet Ganciclovir Component (CRT) are to: (1) evaluate the relative efficacy and safety of foscarnet and ganciclovir for the treatment of cytomegalovirus (CMV) retinitis in people with AIDS; (2) evaluate the effects of the treatments on survival; and (3) compare the relative benefits of immediate treatment versus deferral of treatment of disease confined to zones 2 and 3 of the retina.

Two-hundred forty patients will be recruited and randomized to the treatment groups. All patients will be randomly assigned to foscarnet or ganciclovir therapy. Prior to randomization, patients will be assigned to one of two strata based on the location and extent of retinitis in the more severely involved eye. The first strata includes patients with retinitis in zone 1 (posterior pole) or extensive retinitis in zones 2 and 3 (peripheral retina); these patients will receive immediate treatment with the randomly assigned drug. The second strata includes patients with retinitis that is confined to less than 25 percent of zones 2 and 3. These patients will be offered the option of participating in the comparison of immediate treatment versus deferral of treatment. Patients opting to participate in this comparison will be randomly assigned to immediate treatment versus deferral. Patients preferring to choose either of these options will have only their drug treatment randomly assigned. Patients in the deferral groups will begin drug treatment when and if their retinitis becomes more sight threatening.

Both drugs are administered in a two step fashion; 14 days of induction followed by lifetime maintenance at lower doses. The design specifies at least two courses of induction and maintenance with the study-assigned drug under most circumstances. If the use of the study-assigned drug is terminated because of efficacy or safety considerations, patients will be treated with the other study drug if appropriate. Patients will be followed until death, study withdrawal or a common study close-out.

The outcome measures are survival, retinitis progression, decrease in visual function (acuity and field), drug toxicity, CMV culture positivity, and morbidity.

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1. Introduction

Cytomegalovirus (CMV) retinitis is the most common intraocular opportunistic infection in patients with the acquired immune deficiency syndrome (AIDS). Estimates of the prevalence of CMV retinitis in AIDS patients have varied from 6 to 38 percent, with an overall estimate of approximately 20 percent [1-9]. The agents currently available for the treatment of CMV retinitis are ganciclovir [9-19] and foscarnet [20-21]. The relative efficacy and safety of these two drugs for the treatment of CMV retinitis is unknown. Also unknown, is the optimum time to implement drug therapy for CMV retinitis confined to the peripheral retina.

Ganciclovir (Cytovene®) is currently the only drug approved by the Food and Drug Administration (FDA) for treatment of CMV retinitis in immunocompromised patients. Approximately 80 to 100 percent of patients respond to ganciclovir with remission rates estimated at 60 to 80 percent [11-13, 16-19]. Ganciclovir suppresses CMV infections, and relapse occurs in virtually all AIDS patients when ganciclovir is discontinued. Data on the efficacy of ganciclovir for the treatment of CMV retinitis has been collected from unmasked, non-randomized, uncontrolled studies.

Currently ganciclovir is used in a two-step fashion as follows: the patient is given a two week induction course, most often at a dose of 5 mg/kg every 12 hours. In people with AIDS, induction is followed by lifetime maintenance therapy at a lower dose of 5 mg/kg every 24 hours. Maintenance therapy is administered via long-term intravenous access such as a Hickman catheter. The major toxicity of ganciclovir is hematologic, with neutropenia occurring in up to 40 percent of patients [9-19]. The neutropenia is generally reversible, but often requires temporary or permanent interruption of ganciclovir. Some patients are unable to tolerate ganciclovir because of recurrent neutropenia.

Because of their similar hematologic toxicities, the concomitant use of high doses of ganciclovir and zidovudine (AZT) is not recommended. Hence, the use of AZT should be discontinued during the induction phase of treatment, but may be initiated or resumed at a dosage of 100 mg per eight hours (see page 27) during maintenance. While zidovudine has no reported direct anti-CMV activity, there have been occasional case reports of patients treated with zidovudine in which the CMV retinitis was arrested [22-24]. The presumption has been that the improvement in the immune function mediated by zidovudine has enabled the host to control the CMV infection [22-26]. However, these reports are isolated and zidovudine is not thought to be efficacious in the majority of patients.

More recently a second anti-CMV agent has become available for investigational use. This drug is foscarnet (tri-sodium phosphonoformate hexahydrate). Experience with foscarnet is more limited than with ganciclovir; initial results suggest that a clinical response can be seen in 94 to 100 percent of patients with a remission in 36 to 77 percent. Again, relapse occurs in virtually 100 percent of patients when foscarnet is discontinued and maintenance therapy is therefore required [20, 21]. The initial studies of foscarnet used continuous infusion as the mode of administration. More recently intermittent infusions have been used and seem to be equally efficacious.

Foscarnet also is given in a two step fashion consisting of an initial induction period followed by lifetime maintenance therapy. Maintenance therapy is also given through long-term intravenous access, such as a Hickman catheter. The induction dose most commonly used is 60 mg/kg every 8 hours for a period of 14 days. The maintenance dose is 90 to 120 mg/kg every 24 hours. Foscarnet is excreted by the kidneys and the dose must be adjusted for renal function.

Nephrotoxicity is the major toxicity of foscarnet and occurs in 10 to 42 percent of patients. The maintenance dose is given over a two hour period in conjunction with hydration in order to minimize nephrotoxicity. When severe nephrotoxicity occurs, the drug must be discontinued. Other reported toxicities include anemia in 0 to 35 percent of patients, electrolyte abnormalities, particularly of calcium, magnesium, and phosphorous (C. Karol, personal communication, 1989), and neurotoxicity. However, no granulocytopenia has been seen, and therefore zidovudine may be used in conjunction with foscarnet.

The management of CMV retinitis confined to peripheral retina (zones 2 and 3) has been controversial. (Posterior retinitis (zone 1) is immediately vision threatening and immediate treatment is generally considered advisable.) Some authors [17] have elected not to treat peripheral retinitis, deferring treatment until lesions become posterior and immediately vision threatening, while other authors [9,18] have chosen to treat all CMV retinitis, including peripheral lesions. Deferring treatment reduces the risk of drug-related toxicity (which may be life-threatening); decreases the risk of catheter-associated sepsis; and allows full dose zidovudine (AZT) therapy, which may prolong life. The effect of deferring treatment of peripheral retinitis on CMV retinitis sequelae, e.g., loss of visual acuity and retinal detachment, are unknown.

Figure 1 on page 22 illustrates the retinal zone definitions to be used in this trial. Zone 1 extends twice the diameter of an average optic disc from the center of the macula in all directions and one average disc

diameter from the edge of optic nerve head in all directions. Zone 3 is the fundus periphery, defined as the area anterior to the ampullae of the vortex veins. Zone 2 is the area between zones 1 and 3.

In summary, the relative efficacy of foscarnet compared with ganciclovir for the immediate control of CMV infections is unknown. Further, the long-term effects of foscarnet or ganciclovir on CMV retinitis, survival and morbidity are unknown. There also are no definitive data on the relative efficacy and safety of deferred versus immediate treatment for CMV retinitis confined to zones 2 and 3.

2. Objectives

The three primary objectives of the trial are:

2.1 Evaluate the relative efficacy and safety of foscarnet versus ganciclovir for the treatment of cytomegalovirus retinitis.

2.2 Evaluate the relative effect on survival of the use of these two anti-CMV agents in the treatment of cytomegalovirus retinitis.

2.3 Compare the relative benefits of immediate treatment with foscarnet or ganciclovir versus deferral of treatment for CMV retinitis limited to less than 25 percent of zones 2 and 3.

3. Trial design

The trial is a multicenter, randomized, clinical trial evaluating the efficacy and safety of therapeutic regimens for the treatment of CMV retinitis in people with AIDS. The design of the trial is summarized in figure 2 page 23. The design includes treatment preference options for individuals with CMV retinitis limited to less than 25 percent of peripheral retina. Treatment administration and clinical followup will be unmasked; reading of fundus photographs and some laboratory analyses will be masked. Outcomes will be survival, decrease in visual function (acuity and field), retinitis progression, drug toxicity, retinal detachment, immunologic and viral laboratory assessments; and morbidity, including CMV disease in other body systems and catheter-related sepsis. If treatment with the randomly assigned drug is terminated because of toxicity or lack of efficacy, the other drug will be used for treatment if appropriate. All patients will be followed until death, withdrawal from study, or a common study close-out.

3.1 Treatment assignment

A maximum of two-hundred forty people will be recruited and enrolled in the trial over a two-year period. Prior to randomization, patients will be assigned to one of two strata depending on the location and extent of retinitis in the more severely involved eye. The strata will be: (1) patients with any retinitis in zone 1 or patients with retinitis involving 25 percent or more of zones 2 and 3; and (2) patients in whom retinitis is confined to less than 25 percent of zones 2 and 3 of the retina. Patients in the first stratum will be randomly assigned to immediate ganciclovir or immediate foscarnet therapy; the allocation ratio will be 1:1. Patients in the second stratum will be randomly assigned to a trial treatment according to their treatment preference option.

Treatment assignments for patients in the second stratum may involve a two step randomization procedure: (1) immediate therapy versus deferral of therapy; and (2) treatment with foscarnet versus treatment with ganciclovir. All patients enrolled in the trial will be randomly assigned to treatment with foscarnet or ganciclovir; the allocation ratio will be 1:1. Patients in the second stratum will have the option of deciding whether they wish to participate in the study of immediate treatment versus deferral, and those who choose to do so will be randomly allocated (in the ratio 1:1:1.5) to immediate foscarnet, immediate ganciclovir and deferral. Patients who elect immediate treatment or deferral will be randomly assigned to foscarnet or ganciclovir; the allocation will be 1:1. For patients in the deferral groups, drug treatment assignments will be revealed when criteria for instituting drug treatment are met. Under this design the only data available for addressing the question of when to initiate treatment for patients with small peripheral lesions (objective 2.3) are data from patients choosing random assignment to immediate treatment versus deferral.

3.2 Treatment administration and followup

Drug treatment administration protocols for foscarnet, ganciclovir, and zidovudine are presented in Tables 1, 2, and 3, respectively, on pages 24 through 27. The schedule of eligibility, enrollment and followup visits for immediate treatment and deferral groups is shown in Table 4 on pages 28 and 29. Treatment of patients assigned to an immediate treatment group should begin as soon as possible after the drug treatment assignment is revealed. Patients receiving drug therapy should have serum creatinine, serum calcium, serum magnesium, CBC with differential, and platelet counts assessed 2 to 3 times per week during induction therapy and weekly during maintenance therapy. Treatment will be

initiated in the deferral groups when and if the following event(s) occur in either eye: (1) retinitis progresses ≥ 0.5 average disc-diameters and extends into zone 1; (2) a new lesion ≥ one-quarter disc in size occurs; (3) >25 percent of zones 2 and 3 of the retina is involved or (4) development of an extra-ocular CMV infection documented by tissue biopsy. The protocols for drug treatment administration are the same as those for immediate treatment.

Evaluations of drug efficacy will begin 28 days after the initiation of induction therapy. If retinitis progression has not been halted, reinduction with the assigned drug will be carried out, if not precluded by drug toxicity. Retinitis progression is defined in section 8 on page 16. The second and subsequent courses of maintenance therapy with foscarnet may be prescribed at a higher dosage, 120mg/kg/day (adjusted for creatinine clearance). If retinitis continues to progress after 2 consecutive courses of induction therapy with the study-assigned drug within 10 weeks, treatment with the alternative study drug should be considered

If appropriate, patients who show signs of drug toxicity will be re-treated with the study-assigned drug. Treatment with the other study drug should be considered for patients with recurrent drug intolerance (2 episodes within 28 days) or persistent drug intolerance (failure of toxicity to resolve within 14 days). Followup will continue on all patient's until death, study withdrawal, or study close-out.

4. Eligibility

4.1 Entry criteria

4.1.1 CMV retinitis diagnosed in one or both eyes by a SOCA-certified ophthalmologist.

4.1.2 At least one-quarter disc area of at least one lesion must be able to be photographed.

4.1.3 Diagnosis of AIDS as defined by the CDC criteria [27] or a documented HIV infection.

4.1.4 Patient must be ≥ 13 years of age; patients ≤ 18 years of age must have the consent of a parent or guardian to enroll.

4.1.5 Visual acuity ≥ 3/200 or able to see 3 or more letters on ETDRS chart at 1 meter distance in at least one eye which has been diagnosed with CMV retinitis. Patients with poorer visual acuity may be enrolled if the visual acuity impairment may be reversible (e.g. due to optic disc edema) and vision is at least light perceptive.

4.1.6 Absolute neutrophil count ≥ 1,000 cells/μl.

4.1.7 Platelet count ≥ 25,000 cells/μl.

4.1.8 Serum creatinine ≤ 2.0 mg/dl.

4.1.9 Karnofsky score of ≥ 60 at entry and the means available for compliance with the followup visits (including a care-giver if necessary).

4.1.10 Willingness to reduce zidovudine dosage or discontinue use of zidovudine, if dictated by treatment assignment.

4.1.11 Willingness to discontinue other systemic treatments for herpesvirus infections while receiving foscarnet or ganciclovir.

4.1.12 Completed consent process and consent statement signed by patient or guardian (patients younger than 18 years of age).

Patients with CMV retinitis and retinal detachments that require surgical intervention are eligible if surgical repair of the detachment is planned. Patients with extra-ocular CMV infection (documented by biopsy) and CMV retinitis are also eligible for the trial. Patients with extra-ocular CMV infections will be assigned treatments as if they had zone 1 disease, regardless of the location and size of their ocular lesion(s).

4.2 Exclusion criteria

4.2.1 Previous treatment of CMV retinitis with foscarnet or ganciclovir.

4.2.2 Treatment with anti-CMV therapy for an extra-ocular CMV infection currently or within the past 28 days.

4.2.3 Known or suspected allergy to foscarnet or ganciclovir.

4.2.4 Pregnant or lactating women.

4.2.5 Unwillingness to practice appropriate birth control.

4.2.6 Subjects who in the investigators' opinion to will not comply with study therapy and followup.

4.2.7 Subjects unable to give consent or unwilling to sign the approved consent form.

4.3 Recruitment

All patients meeting entry criteria will be encouraged to participate in the study. Participants will be drawn from the patient populations seen at SOCA clinical centers. Such centers must have adequate staff trained in infectious disease, ophthalmology, and fundus photography, and appropriate facilities. Prior to participation in the study, all centers must be certified by the coordinating center and fundus photography reading center.

5. Baseline evaluation

Eligibility will be evaluated during a screening visit; in most cases, data collected during the eligibility evaluation may be used as baseline data. Once it has been determined that a patient is potentially eligible for the trial, the specifics of the trial will be explained and discussed with the patient. Patients will be given the consent statement and other informational materials at this time. Patients will be allowed a minimum of 24 hours to make a final decision about participating in the trial; baseline evaluations may be conducted during this time. All baseline evaluations should be conducted within the 5 days prior to randomization.

5.1 Patient registration

A SOCA identification number will be assigned, and initial screening and demographic data will be collected.

5.2 Patient interview

Patients will provide information about where and how they may be contacted; the name and address of two friends or relatives to be contacted if the patient is lost to followup; and some identifying data that could be used to query databases. This information will be kept in a locked file and accessed only by direct-care clinical staff and the clinic coordinator. Registration data will not be transmitted to the Coordinating Center.

5.3 Ophthalmic evaluation

An ophthalmic evaluation will be conducted and recorded on study-specific forms. The evaluation results will be used to assess trial eligibility. Evaluation procedures include ophthalmic history interview; best corrected visual acuity using ETDRS charts; observation of lids and conjunctiva; slit lamp examination; intraocular pressure; and dilated indirect ophthalmoscopy. Best corrected visual acuity will be assessed using the refraction and acuity assessment procedures described in the CMV Retinitis Trial Handbook. Clinical evaluations of CMV lesions will be documented by retinal drawings. Patients unable to complete the baseline ophthalmic exam will not be eligible for participation in the trial. However, subsequent ophthalmic examinations may be limited because of a patient's health without disqualifying the patient.

5.4 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 CMV Retinitis Trial Handbook. If a patient is unable to tolerate the full fundus photography protocol, the abbreviated protocol outlined in the Handbook should be employed.

5.5 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), and results recorded on study-specific forms. The procedures for visual field assessment are specified in CMV Retinitis Trial Handbook. Pupils may or may not be dilated for field assessments.

5.6 Medical evaluation

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

5.6.1 A medical history interview will be conducted for the collection of information 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 AIDS treatment history. Interviewers will probe for occurrence of previous CMV infections in other organs as well as the eye. If the patient indicates that he or she has had previous CMV infections and can not provide complete information about the course of the infection, other sources will be used to investigate the patient's history. These sources may include the treating physician or medical records.

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

5.6.3 Karnofsky performance status will be assessed. The Karnofsky performance scale is described in the CMV Retinitis Trial Handbook.

5.6.4 A Trail Making test of psychomotor speed will be conducted for assessment of gross neurologic function. Test procedures are described in the CMV Retinitis Trial Handbook.

5.7 Laboratory studies

Most laboratory measurements should be completed within the 5 days prior to the initiation of treatment.

5.7.1 Complete blood count (CBC) with differential and platelet counts. Absolute neutrophil count (ANC) and platelet counts must be at least 1,000 cells/μl and 25,000 cells/μl, respectively, for a patient to be enrolled in the trial.

5.7.2 Serum chemistries including electrolytes (calcium, magnesium, phosphate, sodium, potassium, and bicarbonate), blood urea nitrogen (BUN), creatinine, and liver function tests (aspartate transaminase, alanine transaminase, and alkaline phosphatase) will be performed. Serum creatinine may not exceed 2.0 mg/dl for a patient to be enrolled in the trial.

5.7.3 Total and percent CD4+ T cell counts.

5.7.4 Blood and urine will be cultured for CMV. Positive isolates will be sent to central freezer facility for storage.

5.7.5 Serum for subsequent analyses (e.g. p24 antigen) will be sent to a central repository for storage.

6. Study medications

Treatment should be started as soon as possible after randomization. The procedures for drug administration are similar for foscarnet and ganciclovir (Tables 1 and 2 on pages 24 through 26). Drugs are administered intravenously and an indwelling catheter will be used for long-term administration. Both administration protocols call for 14 days of induction followed by lifetime maintenance therapy. Guidelines for concomitant zidovudine therapy are presented in section 6.3 and Table 3 (page 27).

6.1 Foscarnet

The induction dose for foscarnet is 60 mg/kg every 8 hours. Serum creatinine levels should be ≤ 2.0 mg/dl for the initiation of induction therapy; induction dosage will be reduced if creatinine clearance is below normal (Table 1). Induction will be continued for 14 days; hematology (CBC with differential and platelet counts) and serum chemistries (creatinine, calcium, magnesium) will be monitored 2 to 3 times per week during induction therapy.

Maintenance therapy should begin immediately after completion of induction therapy. Full dose maintenance therapy for foscarnet is 90 mg/kg/day adjusted for creatinine clearance accompanied by 1 liter of a 0.9N saline solution, 7 days a week. Hydration volume can be adjusted to prevent fluid overload. Hematology and serum chemistries will be monitored weekly during maintenance therapy. If retinitis progresses and a second course of induction therapy of foscarnet is administered, the subsequent maintenance dose of foscarnet may be increased to 120 mg/kg/day, adjusted for creatinine clearance, at the discretion of study physicians.

The most significant documented side-effects of foscarnet are impairment of renal function, serum electrolyte abnormalities and neurotoxicity. If serum creatinine is ≥ 2.9 mg/dl, foscarnet therapy will be interrupted. Foscarnet should not be re-started until serum creatinine ≤ 2.0 mg/dl. If serum calcium, phosphate or magnesium are significantly lowered (grade 2 or 3) institution of oral or intravenous supplementation or other therapy should be considered. If a patient develops symptoms of calcium abnormalities (e.g. muscle irritability, paresthesia, tetany) or other unexplained neurologic events including seizures, blood should be collected for assessment of serum ionized calcium immediately after the completion of the next dose of foscarnet. Foscarnet therapy will be interrupted if grade 4 abnormalities of serum calcium or magnesium, or other drug-related grade 4 toxicity develops.

6.2 Ganciclovir

The induction dose for ganciclovir is 5 mg/kg every 12 hours. Absolute neutrophil counts (ANC) and platelet counts must exceed 1,000 cells/μl and 25,000 cells/μl, respectively, for induction therapy to be initiated. Dosage will be reduced if creatinine clearance is below 1.1 ml/min/kg (Table 2). Induction will be continued for 14 days; hematology (CBC with differential and platelet count) and serum chemistries (creatinine, calcium and magnesium) will be monitored 2 to 3 times per week during induction therapy.

Maintenance therapy should begin immediately after completion of induction therapy. Full dose maintenance therapy for ganciclovir is 5 mg/kg every 24 hours, 7 days a week. Dose levels will be reduced if creatinine clearance is below 1.1 ml/min/kg (Table 2). Hematology and serum chemistries will be monitored weekly during maintenance therapy.

The most significant documented side-effects of ganciclovir are neutropenia and thrombocytopenia. If ANC falls below 500 cells/μl therapy should be interrupted. Therapy can be re-started after ANC recovers to $\geq$ 750 cells/μl. Therapy also should be interrupted if platelet counts are $\leq$ 10,000 cells/μl; therapy can be re-started when platelet count recovers to $\geq$ 25,000 cells/μl. Drug therapy will be interrupted if drug-related grade 4 toxicity develop.

6.3 Zidovudine

For patients in the deferral or foscarnet treatment groups, the initial dose of zidovudine will be 100 mg every 4 hours (Table 3, page 27). Both ganciclovir and zidovudine are myelosuppressive. Therefore, a patient treated with ganciclovir should discontinue use of zidovudine during induction therapy and a reduced dosages of zidovudine, 100 mg every 8 hours, may be prescribed at the start of maintenance therapy (Table 3, page 27). If a patient tolerates the combination of reduced dose zidovudine and ganciclovir, zidovudine dosage may be increased to 600 mg per day. Reduced dose zidovudine has not been demonstrated to be an efficacious anti-HIV therapy. In the event of marrow toxicity, zidovudine dosage should be reduced or discontinued (Table 3, page 27). Foscarnet or ganciclovir dosage should not be modified unless toxicity persists after zidovudine has been discontinued.

6.4 Other medications

Patients participating in this trial should not take other systemic anti-herpesvirus agents, e.g. IV or PO acyclovir. Topical anti-herpesvirus agents may be used. Use of marrow toxic agents with ganciclovir and nephrotoxic agents with foscarnet should be carefully considered, alternative treatments should be used whenever possible.

Patients who cannot tolerate zidovudine, should be encouraged to use ddI on an appropriate protocol. Similarly, the use of other antiretrovirals available via expanded access programs are allowed. The use of investigational triazoles (itracmazole-R51211), granulocyte-macrophage colony stimulating factor (GM-CSF) or erythropoietin (EPO) to treat marrow toxicity is allowed. The use of other investigational drugs will be considered on a drug by drug basis. Participation in other clinical trials also will be considered on a case by case basis. Inquiries about the use of other investigational drugs and participation in other trials should be directed to the Coordinating Center.

7. Followup evaluations

All patients enrolled in the trial will be followed until death, withdrawal from the study, or study close-out. The schedule for followup evaluations is presented in Table 4 on pages 28 and 29. At baseline, weeks 4, 12 and 26, and every 6 months thereafter, evaluations will be conducted that include ophthalmic examinations, physical examinations, fundus photography, measurement of visual fields, trail making test, and all laboratory assessments. At all other followup visits evaluations will include ophthalmic examinations, fundus photography, physical examinations, clinical chemistry and hematology assessments.

Patients in the deferral groups who show progression mandating treatment and patients receiving maintenance therapy who require reinduction will undergo evaluations (treatment administration visits) just prior to initiation of induction therapy and every 2 weeks thereafter for 8 weeks, 5 visits in all. Data collected at the first treatment administration visit (TX1) are similar to baseline data and should be collected within the 5 days prior to initiation of induction therapy (Table 5, page 30). Treatment administration visits include ophthalmic examinations, fundus photography, physical examinations, clinical chemistry and hematology assessments. In addition, prior to the start of and at the completion of a course of induction therapy, blood and urine specimens should be collected for CMV culture assays.

If during the course of a series of TX visits retinitis progresses and induction therapy is re-initiated, a new series of TX visits is started and the remaining TX visits from the first series are not completed. For example, if a second episode of progression is noted at a TX3 visit and another course of re-induction therapy is prescribed, that visit becomes a TX1 visit and the TX3 and subsequent visits associated with the first re-induction are not completed.

A patient who discontinues treatment with the study-assigned drug and begins treatment with the alternative drug without requiring a new course of induction therapy will undergo an evaluation prior to receiving the alternative drug. This type of evaluations is designated as a switch administration visit (SX visit). For example, a patient who is switched from maintenance therapy with the study-assigned drug to maintenance therapy with the alternative drug will undergo a switch administration visit. A second example is a patient who completes a course of re/induction therapy with the study-assigned drug but can not continue receiving that drug for safety reason and is therefore switched to the alternative drug. Such a patient will complete a SX visit prior to starting maintenance therapy with the alternative drug. Data collected at the switch administration visit are similar to baseline data and should be collected in the 5 days prior to initiation of therapy with the alternative drug (Table 5, page 30). Switch administration visits include ophthalmic examinations, fundus photography, physical examinations, CMV cultures, clinical chemistry and hematology assessments. Patients should resume their followup visit schedule or treatment administration visit schedule after the SX visit.

All patients should undergo study examinations according to the study visit schedule outlined in Table 4. However, the study 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. It is recommended that after the initial 6 months of followup patients in the deferral groups and patients receiving maintenance therapy undergo eye exam every 3 to 4 weeks. Limited data collection is required for these patient care visits. In order to know whether trial results are biased by differences in the frequency of followup, any visit by a trial patient to a study physician should be recorded on the patient's Medical File Contents form and an Interim Visit form briefly summarizing the reason for the visit should be completed. If an interim visit leads to induction therapy, a series of treatment administration visits should be scheduled. If other changes in drug treatment are prescribed or evidence of drug toxicity is reported at such a visit, a Drug Treatment Report form or an Adverse Event Report form, respectively, should be completed.

7.1 Followup procedures

Evaluation procedures for followup, treatment administration, and switch administration visits are essentially the same as those specified for the baseline visits (see sections 5.3 to 5.7). Ophthalmic and medical histories will pertain to the interval since the last followup visit and evaluation of treatment response and drug toxicity and their implications for management will be emphasized. Blood specimens for laboratory analysis should be drawn on the same day as other followup procedures are scheduled.

7.2 Trial withdrawal

Limited followup will be conducted on patients who no longer wish to participate in the trial. This will include telephone interviews and possibly some clinical assessments in order to obtain data on primary outcomes.

8. Evaluation of response

The objectives of the trial are to compare the efficacy and safety of foscarnet and ganciclovir for the treatment of CMV retinitis; to evaluate each drug's effect on survival and morbidity; and to compare the benefits of immediate treatment versus deferral for both drugs. The primary outcomes to be assessed are survival; visual function (visual acuity and field); retinitis progression; and drug toxicity. Other outcome include retinal detachment; CMV culture positivity (blood and urine); and morbidity. The definitions of survival, retinitis progression, lesion border activity, and retinitis remission established for this trial of are listed.

Survival: The duration of life after study entry. Survival will be measured as the time interval between study entry and death or the end of followup. Time since the development of AIDS will be included as a covariate in the analysis.

Retinitis progression: (1) advancement of the edge of an existing lesion by one-half the diameter of the optic disc in an average eye (designated here as 750μ[1]) perpendicularly from the edge and along ≥ 750μ of it; or (2) occurrence of new lesion ≥ one-quarter disc area in size (a circle, ≥ 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. Time-to-progression is the time interval between study entry and first progression.

Lesion border activity: The border of a CMV lesion is defined as a zone 1,000μ wide 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. Lesions which cannot be classified as either active or inactive will be classified as indeterminate.

Retinitis remission: Non-progressive lesions with inactive borders.

9. Patient care

Treatment decisions will be dictated by retinitis status in the more severely involved eye, the presence of documented extra-ocular CMV infection, or safety considerations. An extra-ocular CMV infection should be documented by a tissue biopsy; positive culture alone is not sufficient documentation. Patients in the immediate treatment group should begin their study-assigned treatment as soon as possible. Patients will require surgery for the placement of an indwelling catheter. It will be left to the discretion of the study ophthalmologist and internist as to whether admission to a hospital will be necessary for induction therapy.

[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.

Ganciclovir

- Neutropenia: serious decreases in white blood cells (neutropenia) occurs in about 33 percent of people taking ganciclovir. Neutropenia reduces your ability to fight infections. Drug treatment will be interrupted if there is severe neutropenia. About 15 percent of people are unable to tolerate ganciclovir because of recurrent neutropenia.

- Thrombocytopenia: serious decreases in blood platelet cells occurred in 20 percent of people studied. Platelets are important for blood clotting, and very low platelet counts are associated with an increased risk of bleeding. Drug treatment will be interrupted if severe thrombocytopenia occurs.

- Neurologic: central nervous system disorders have occurred in 5 percent of people studied. Serious neurologic side effects occur in less than 1 percent of people. Symptoms include dizziness, headaches, mood changes, hallucinations, and seizures.

- Liver function: abnormal blood tests related to liver function have been observed in 2 percent of people studied, but generally have not been serious enough to warrant stopping ganciclovir.

- Gastrointestinal (GI): nausea, vomiting, diarrhea, stomach cramps, anorexia, or bleeding in the gastrointestinal tract have occurred in less than 2 percent of people studied.

- Other: anemia, fever and skin rash has occurred in less than 2 percent of people studied. Ganciclovir causes decreased sperm production in animals and may cause infertility in humans. There may be other, unknown side effects, including damage to an unborn child.

Study Procedures

- Tissue around the catheter (tube for giving drug directly into your blood) may become irritated or infected. You could develop a blood infection (bacteremia) because of the catheter. Blood infections occur in about 5 to 30 percent of people with AIDS that have catheters. These infections can range from mild to severe. Severe bacteremia (sepsis) can cause death.

- Drawing of blood samples occasionally leaves a bruise. A few people feel faint or light-headed for a short time after a blood sample has been drawn.

The benefits from enrolling in this trial include expert care and monitoring of your eye infection. The regular eye exams and fundus photographs will allow us to watch your disease closely and may increase the chances of preserving your vision. The results of all tests conducted on you will be available to you and your primary care physician. The drugs used in the trial may stop the disease from spreading in your eye or other organs. In addition, you will be participating in an important effort to provide information on the most effective way to preserve sight and overall health in people with AIDS.

7. Alternative Care

Refusal to participate in this study will not prohibit you from getting medical care at this institution. Ganciclovir was approved by the Food and Drug Administration (FDA) on June 26, 1989, for treatment of CMV retinitis. You can receive that drug without enrolling in a study. Foscarnet has not been approved by the FDA yet. Therefore you may not be able to be treated with foscarnet outside of this study.

8. Rights and Responsibilities

- Your entry into the study is voluntary.
- You may chose to withdraw from the study at any time and still be able to obtain care at this institution. However, since it is very important to know the status of all patients at the end of the trial, we may try to find out how you are doing periodically even after you withdraw.
- Clinic staff are available to answer any questions or discuss concerns you may have now or in the future.
- The success of this trial depends on regular and complete data collection. If you know now that you will be unable to come to the clinic for regularly scheduled visits, do not enroll.
- You are responsible for informing clinic staff of changes in your address and phone number.
- This institution and the Federal Government do not have any insurance program to provide compensation (money) to you if you experience any injury or bad effects that are not the fault of the investigators.

9. Confidentiality

The people working in this trial know that confidentiality of participant data is important. Every effort will be made to insure that your records are maintained in a confidential manner. Our procedures are:

- Only study ID codes will be used to identify participant records. You will be asked to provide personal data (home and work address and telephone number, and the names of two friends or relatives). However, these data will not be sent to the study coordinating center. Only direct-care clinic staff will see or use that data. Personal data will be kept in a secure place, separate from other study data.

- Other study data, identified by study ID codes only, also will be kept in a secure place. Only people working on the study will be allowed access to study 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 center 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.

- 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.

- When the results of this study are published, the data will never be displayed by your name or study ID number.

10. Consent Statement

Before you agree to enroll in this trial, make sure that all your question concerning the study have been answered. The principal investigator, Dr. _____ and the clinic staff are available to answer any questions you may have about this research study now and in the future. In the event you believe that participation in the study led to an injury or that you are not being treated fairly, you also may contact the _____ (institution's IRB) at _____ (phone number) or The Johns Hopkins University's Committee on Human Volunteers at (301) 955-3795.

_____
Participant's signature & date

_____
Witness to consent procedure & date

_____
Signature of investigator & date

Adequate induction therapy is defined as completion of 10 or more days of therapy at induction levels within 14 days. Induction therapy will only be instituted for treatment of active CMV retinitis or active extra-ocular CMV infections. Maintenance therapy should begin immediately after induction therapy has been completed and ordinarily will be administered on an outpatient basis.

Patients in the deferral groups who show progression mandating drug treatment and patients undergoing additional courses of induction therapy will be scheduled for treatment administration visits every 2 weeks for 8 weeks and then resume their former follow-up schedule. The first treatment administration visit should occur just prior to the initiation of induction therapy.

9.1 Efficacy considerations

Patients will undergo at least two induction-maintenance cycles with the study-assigned drug before the use of the other drug is considered. For most patients, the event which triggers re-induction is retinitis progression as defined in section 8 on page 16, and the first time point for evaluating retinitis progression is 28 days after the initiation of induction therapy. If retinitis continues to progress or there is no clinical response after 2 consecutive induction courses within a 10 week period, use of the other drug will be considered.

In situations where progression of 750μ may lead to irreversible damage to the center of the macula or the optic nerve, the re-induction criterion at 28 days is a lack of clinical response, i.e. persistent or increased border activity. Persistent activity refers to retinitis that is as active or more active than at the start of therapy presenting clear evidence of a failure of the drug to control disease. If drug therapy is interrupted because of toxicity and the center of the macula or the optic nerve is threatened, the other drug may be used before persistent or recurrent intolerable drug toxicity is established.

Patient's whose retinitis progresses after a period of remission will undergo another course of induction with the assigned drug. If in the judgment of a study physician the higher dosage of foscarnet is appropriate, the maintenance dose for a second and subsequent courses of foscarnet therapy may be increased 120 mg/kg/day.

For patients in the deferral groups, treatment will be initiated when and if the following event(s) occur in either eye: (1) retinitis progresses ≥ 750μ and into zone 1; (2) a new lesion ≥ one-quarter disc area in size (a circle, ≥ 750μ in diameter) develops; or (3) retinitis progresses to involve > 25 percent of zones 2 and 3 of the retina.

The development of extra-ocular CMV disease confirmed by tissue biopsy will be equivalent to retinitis progression in terms of treatment action. Hence, a patient in a deferral group who develops a confirmed extra-ocular CMV infection will receive induction therapy with the assigned drug. Confirmed extra-ocular CMV disease in patients receiving study drugs will trigger either re-induction or therapy with the alternative drug.

All patients will be instructed to contact the clinic if they experience any problems with their eyes; noticeable changes in their vision; or other symptoms. If appropriate, an interim visit will be scheduled as soon as possible.

9.2 Safety consideration

Drug therapy also may be altered or interrupted because of safety considerations. Foscarnet and ganciclovir dosage will be modified if creatinine clearance is low (Tables 1 & 2). Foscarnet therapy will be interrupted if serum creatinine is ≥ 2.9 mg/dl. Ganciclovir therapy will be interrupted if ANC is less than 500 cells/μl or platelet count is less than 10,000 cells/μl. Drug therapy also will be interrupted for grade 4 drug-related toxicity; toxicity definitions are listed in the SOCA CMV Retinitis Trial Handbook. If a drug-related grade 4 abnormality develops in a laboratory measure and is asymptomatic, drug therapy will only be interrupted if the abnormality also represents an increase in severity of ≥ 2 grades from the baseline measurement. Drug therapy may be discontinued for a grade 2 or 3 toxicity if, in the judgement of a study physician, continuing therapy is a significant hazard to a patient. In most cases, a patient will be re-treated at least once with the study-assigned drug after a drug-interrupting toxicity is resolved or controlled. If drug was discontinued during maintenance therapy, drug treatment should be re-started at maintenance levels unless retinitis has progressed or there is evidence of extra-ocular CMV infection. However, if a study physician considers re-treatment to be inappropriate medical care, drug treatment will not be re-instituted and use of the alternative drug will be considered. Drug treatment will be terminated if a patient becomes pregnant and not re-started until the pregnancy is terminated.

Recurrent drug toxicity is defined as the occurrence of two episodes of any one toxicity requiring interruption of drug therapy within 28 days. Persistent drug toxicity is defined as the failure of a toxicity presumed to be related to the study drug to be resolved or controlled, with or without treatment, within 14 days of stopping the study drug. The use of the alternative drug will be considered for patients with recurrent or persistent drug toxicity. If CMV lesions threaten the optic nerve or the center of the macula, patients with toxicity may be switched to the other drug before 14 days have elapsed.

10. Biostatistical considerations

The statistical design of this trial was based on a pragmatic power analysis. That is to say, minimal detectable differences for three outcomes (mortality, visual loss and retinitis progression) were calculated for a fixed sample size and power level; expected outcomes rates for treated patients, expected sampling fractions, and budgetary limitations also were taken into consideration. The estimated event rates for these outcomes after one year of followup in ganciclovir treated patients are 70 percent for mortality; 34 percent for visual loss in a treated eye; and 39 percent for retinitis progression. The expected sampling fractions are that two-thirds of the eligible patients will present with zone 1 CMV retinitis and the remaining one-third will present with zone 2 or 3 CMV retinitis. Retinitis progression was the only outcome considered for the sample size calculations regarding the comparison of immediate treatment and deferral. Visual loss is of greater importance and will be carefully monitored, however, the power to detect a difference in the outcome is low.

Patients with zone 1 disease, patients with extensive disease in zones 2 and 3, or patients with small peripheral lesions who elect immediate treatment will be randomized equally into the two drug treatment groups. Patients who elect randomization between immediate treatment and deferral will be randomized 1:1:1.5 into the immediate ganciclovir, immediate foscarnet or deferral groups, respectively. Those randomized to the deferral and those choosing deferral will be assigned equally to the foscarnet and ganciclovir treatment groups (with disclosure only when progression mandates treatment).

The treatment preference option for patients with small peripheral lesions does not in anyway compromise the drug comparison. All patients enrolled in this trial will have their drug treatment randomly assigned. The treatment preference option may influence the evaluation of immediate treatment versus deferral for small peripheral lesions. Data from patients who accept random assignment to immediate treatment or deferral will be used to address that trial objective (objective 2.3).

The assumptions mentioned above concerning outcomes and sampling fraction, a Type I error level of 0.05 (two-sided), a power level of 0.90, and an estimated recruitment of 240 patients were used to calculate minimum detectable arithmetic differences between treatment groups. The minimum detectable drug treatment difference for survival is 23 percent; for visual loss (<20/200) 20 percent, and for arrest of retinitis progression 21 percent. For patients electing randomization between immediate treatment and deferral, the minimum detectable difference for the arrest of retinitis progression is 43 percent (between immediate ganciclovir versus deferred induction or between immediate foscarnet versus deferred induction). These calculations include a 10 percent allowance for dropouts, noncompliance or treatment lag effects. There are no adjustments for multiple comparisons, multiple looks or multiple outcomes.

Cox regression and Kaplan-Meier procedures will be used to assess treatment group differences. All patients will be analyzed according to the treatment group into which they were originally randomized. Analyses will include estimation of drug effects, immediate ganciclovir and immediate foscarnet treatment versus deferral effects, zone effects, clinic effects and interaction effects along with adjustment for confounders.

11. Patient rights and responsibilities

11.1 IRB approval

This protocol must receive approval from the Institutional Review Board (IRB's) of participating clinical centers. All trial participants must sign an informed consent form and medical record release form.

11.2 Patient confidentiality

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. Patient identification data will not be transmitted to the Coordinating Center. Other patient data will be identified by study ID codes only; a patient ID number and name code will be assigned at registration. Clinical data will be released

to the patients, the Coordinating Center, and may 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 organization will require the written consent of the patient.

The clinical centers and Coordinating Center participating in this trial have been issued a Certificate of Confidentiality by the Secretary of the US Department of Health and Human Services. The certificate protects investigators from compulsory disclosure of research data that identifies research subjects. These certificates allows clinical center personnel to refuse to reveal any information regarding the identity of trial patients in any Federal, State, or local proceedings. The certificate does not govern voluntary disclosure of data. Nor does it authorize refusal if: subject consents in writing to disclosure of identifying information; the US Department of Health and Human Services requests information for an audit, program evaluation, or investigation; or data release is required by the Federal Food, Drug, and Cosmetic Act. The certificates are valid for all patients enrolled between January 2, 1990 and August 1, 1992. The protection offered by the certificate is permanent.

12. Biohazard

It is extremely probable that blood and urine specimens collected during the trial will be contaminated with pathogens, CMV, HIV, and others. All personnel involved in collecting and handling biologic specimens should follow appropriate precautionary procedures as currently recommended by the Center for Disease Control [28]. Specimens that need to be shipped will be packaged and labeled in compliance with regulations for transportation of etiologic agents.

Figure 1: Retinal Map

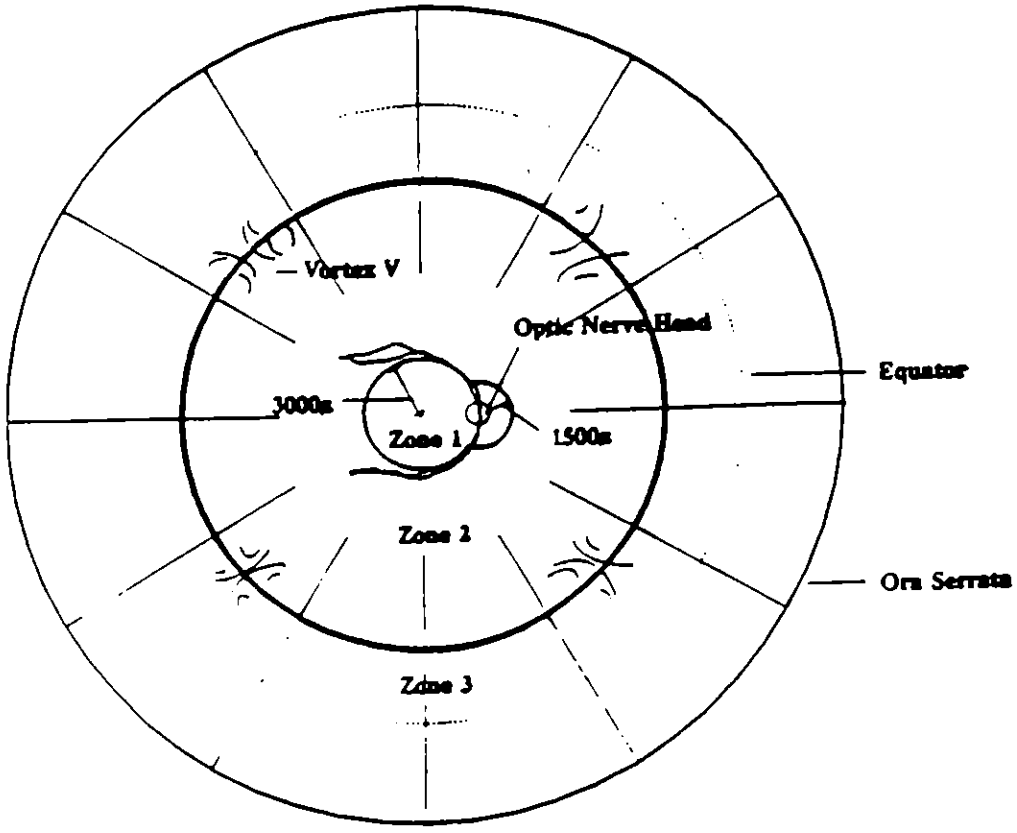

Figure 2: Design schematic

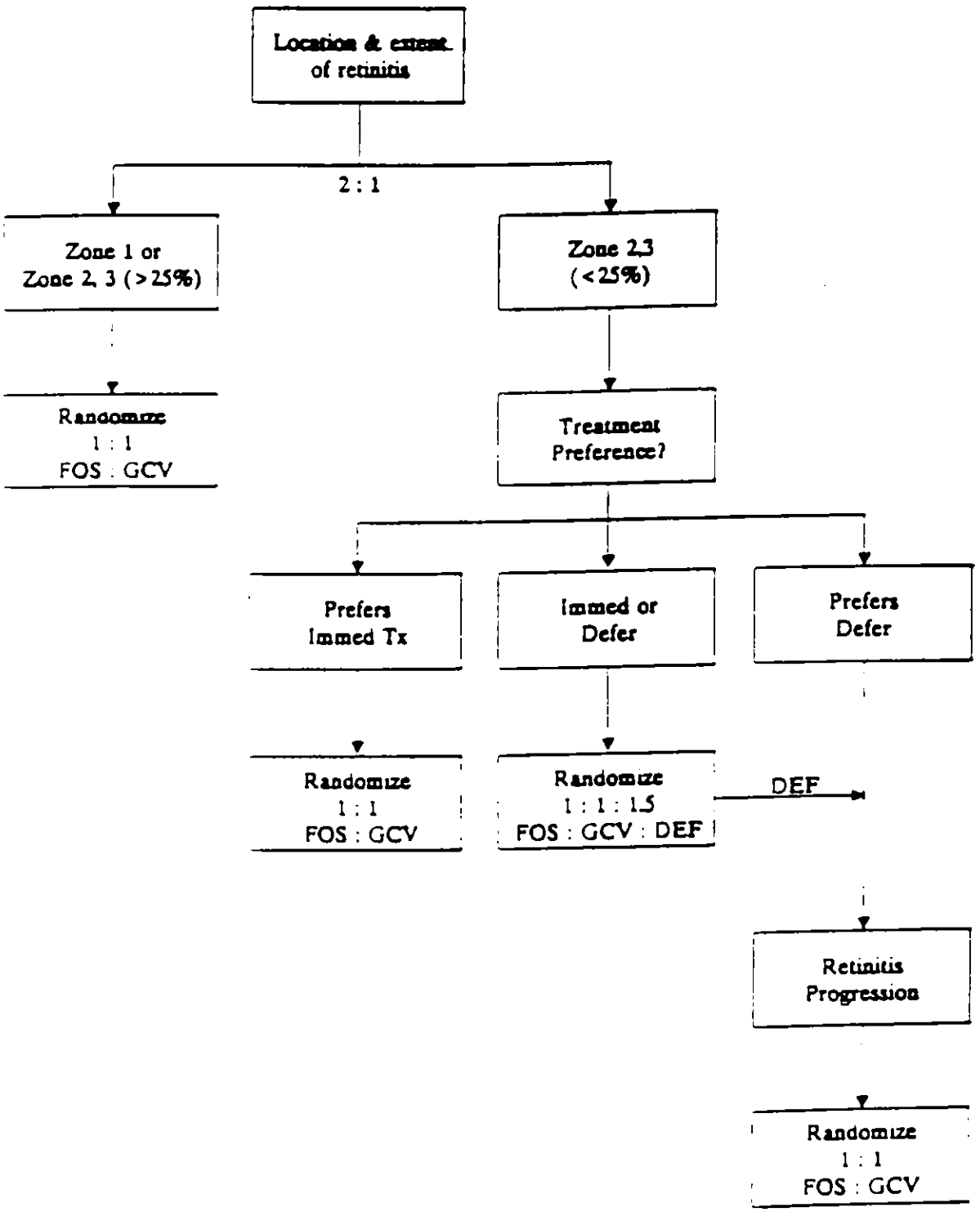

Table 1: Foscarnet administration protocol

Induction therapy

- 60 mg/kg/8h for 14 days
- Serum creatinine must be ≤ 2.0 mg/dl to start therapy
- IV administration, peripheral (diluted) or central line by infusion pump only
- Check creatinine, calcium, magnesium, and hemoglobin 2 to 3 times per week
- Adjust dose each time creatinine is checked and weekly per body weight
- Adjust dose for impaired renal function as prescribed below:

CrCl (ml/min/kg)	Fos (mg/kg/8h)
≥1.6	60.0
1.5	56.5
1.4	53.0
1.3	49.4
1.2	45.9
1.1	42.4
1.0	38.9
0.9	35.3
0.8	31.8
0.7	28.3
0.6	24.8
0.5	21.2
0.4	17.7

- Creatine clearance (CrCl) is estimated 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
- Terminate treatment if serum creatinine ≥ 2.9 mg/dl or non-renal, drug-related grade 4 toxicity develops
- Re-start if serum creatinine ≤ 2.0 mg/dl

Maintenance therapy

- 90 mg/kg/day immediately following induction the first course of induction therapy with foscarnet
- may increase to 120 mg/kg/day following the second and subsequent courses of induction therapy with foscarnet
- IV administration (central line, indwelling catheter) by infusion pump only
- Hydration with 1 liter of normal saline, reduce or eliminate if evidence of volume overload or electrolyte abnormalities related to saline load
- Check creatinine, calcium, magnesium, and hemoglobin weekly
- Adjust dose every week for creatinine and body weight
- Adjust dose for impaired renal function as prescribed below:

CrCl (ml/min/kg)	Fos (mg/kg/24h)	Fos (mg/kg/24h)
≥1.4	90	120
1.2-1.4	78	104
1.0-1.2	75	100
0.8-1.0	71	94
0.6-0.8	63	84
0.4-0.6	57	76

- Terminate if serum creatinine ≥ 2.9 mg/dl or if other drug-related grade 4 toxicity develop
- Re-start if serum creatinine ≤ 2.0 mg/dl

Table 1: Foscarnet administration protocol (cont'd)

Drug toxicities:indices

- Renal function: serum creatinine, creatinine clearance
- Anemia: hemoglobin & hematocrit
- Abnormalities in serum Ca^{2+}, Mg^{2+}, & phosphate: serum Ca^{2+}, Mg^{2+}, & phosphate
- Neurotoxicity, seizure, paresthesia: serum free-ionized Ca^{2+} & Mg^{2+}
- Nausea, vomiting, headache, irritability, sleep disruption: serum free-ionized Ca^{2+} & Mg^{2+}
- Penile ulcerations
- Specimens for assessments of serum free-ionized Ca^{2+} should be obtained immediately after infusion

Concomitant drug use

- No IV or PO anti-herpesvirus agents
- Zidovudine (AZT) allowed
- Use of other nephrotoxic agents should be weighed carefully, alternative treatments should be used if possible
- Best medical judgement for the use of other licensed and experimental pharmaceutical agents

Table 2: Ganciclovir administration protocol

Induction therapy

- 5 mg/kg/12h for 14 days
- IV administration, peripheral or central line
- Check CBC and platelet count 2 to 3 times per week
- Adjust weekly per body weight
- Adjust dose for impaired renal function as prescribed below:

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

- Creatine clearance (CrCl) is estimated 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
- ANC ≥ 1,000 cells/μl and platelet count ≥ 25K cells/μl to start therapy
- Discontinue Gcv if ANC < 500 cells/μl, re-start therapy when ANC > 750 cells/μl
- Discontinue Gcv if platelet count < 10K, re-start therapy when platelet count ≥ 25K
- Terminate treatment if other drug-related grade 4 toxicity develops

Maintenance therapy

- 5 mg/kg/day, immediately following induction
- IV administration (central line, in-dwelling catheter)
- Check CBC and platelet count weekly
- Adjust dose biweekly per body weight
- Adjust dose for impaired renal function as 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

- Discontinue Gcv if ANC <500 cells/μl, re-start therapy when ANC ≥ 750 cells/μl
- Discontinue Gcv if platelet count <10K cells/μl, re-start when platelet count ≥ 25K cells/μl
- Terminate treatment if non-hematologic, drug-related grade 4 toxicity develops

Drug toxicities:indices

- Neutropenia: ANC
- Thrombocytopenia: platelet count
- Anemia: hemoglobin & hematocrit
- Nausea, vomiting, headache, irritability, sleep disruption

Concomitant drug use

- No IV or PO anti-herpesvirus agents
- No zidovudine allowed during induction therapy
- Reduced dose zidovudine during maintenance therapy, see Table 3
- Use of other marrow toxic agents is discouraged, alternative treatments should be used if possible
- Best medical judgement for the use of other licensed pharmaceutical agents

Table 3: Zidovudine (AZT) administration protocol

Contraindications
- Hemoglobin (Hgb) ≤ 8 g/dl
- Absolute neutrophil count (ANC) ≤ 500 cells/μl

Dosage (deferral or foscarnet patients)
- PO
- 100 mg every 4 hours (600 mg/day)
- Start with half dose (100 mg every 8 hours) if:
  - Hepatic failure (ascites jaundice, acute hepatitis)
  - Renal function impairment (serum creatinine ≥ 2.9 mg/dl)
  - Grade 2 toxicity other than hematologic

Dose adjustments (foscarnet and deferral patients)
- Half dose, 100 mg every 8 hours (300 mg/day) if:
  - Hgb ≤ 7.5 g/dl, transfuse if symptomatic for anemia
  - ANC ≤ 750 cells/μl
  - other grade 3 drug-related toxicity
- Restart full dose if:
  - Hgb ≥ 8.5 g/dl
  - ANC > 750 cells/μl
  - If patient tolerates half dose for 1 month without hematologic support

Dose interruption (foscarnet and deferral patients)
- ANC < 500 cells/μl
- Hgb ≤ 6.5 g/dl, may transfuse to return Hgb to > 8.5 g/dl
- Other grade 4 drug-related toxicity
- Restart half dose (100 mg q 8h) if:
  - Hgb ≥ 7.5 g/dl
  - ANC ≥ 750 cells/μl

Dosage (ganciclovir patients)
- Discontinue during induction therapy
- ANC ≥ 750 cells/μl to start
- 100 mg every 8 hours; may increase to 600 mg/day if tolerated

Dose interruption (ganciclovir patients)
- ANC ≤ 750 cells/μl
- Hgb ≤ 6.5 g/dl, may transfuse to return Hgb to > 8.5 g/dl
- Other grade 4 drug-related toxicity

Drug toxicities:indices
- Macrocytic anemia: Hgb
- Neutropenia: ANC
- Gastrointestinal: nausea, vomiting, anorexia
- CNS: headache, somnolence, dizziness, insomnia, confusion, cerebellar, ataxia, stupor, seizures
- Myopathy: CPK elevation
- Other: fever, rash, nail pigmentation

Table 4: Data collection schedule (baseline to 26 weeks)

Data	Visit/weeks EL 0	EN 0	F1 2	F2 4	F3 6	F4 8	F5 12	F6 16	F7 20	F8 26
Registration	x									
Visual acuity	x		x	x	x	x	x	x	x	x
Slit lamp exam	x		x	x	x	x	x	x	x	x
Intraocular pressure	x									
Ophthalmic exam	x		x	x	x	x	x	x	x	x
Fundus photographs	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
Chemistries BUN/creatinine† Serum Ca^{2+} & Mg^{2+}† Electrolytes/albumin Liver function tests (AST, ALT, alk phos)	x		x	x	x	x	x	x	x	x
Total and percent CD4+		x		x			x			x
CMV viral cultures Blood & urine		x	x	x			x			x
Serum bank		x		x			x			x
Health interview AIDS history Concomitant medicine Symptoms		x	x	x	x	x	x	x	x	x
Physical exam		x	x	x	x	x	x	x	x	x
Trail making test		x		x			x			x

†Creatinine, serum calcium and magnesium, CBC with differential and platelet count should be assessed 2 to 3 times per week during induction and weekly during maintenance.

Table 4: Data collection schedule (8 to 26 months) cont'd

Data	Visit/months F10 8	F11 10	F12 12	F13 14	F14 16	F15 18	F16 20	F17 22	F18 24	F19 26
Visual acuity	x	x	x	x	x	x	x	x	x	x
Slit lamp	x	x	x	x	x	x	x	x	x	x
Ophthalmic exam	x	x	x	x	x	x	x	x	x	x
Fundus photographs	x	x	x	x	x	x	x	x	x	x
Visual field			x			x			x	
Hematology CBC† Differential† Platelet†	x	x	x	x	x	x	x	x	x	x
Chemistries BUN/creatinine† Serum Ca^{2+} & Mg^{2+}† Electrolytes/albumin Liver function tests (AST, ALT, alk phos)	x	x	x	x	x	x	x	x	x	x
Total and percent CD4+			x			x			x	
CMV viral cultures blood & urine			x			x			x	
Serum bank			x			x			x	
Health interview AIDS history Concomitant medicine Symptoms	x	x	x	x	x	x	x	x	x	x
Physical exam	x	x	x	x	x	x	x	x	x	x
Trail making test			x			x			x	

†Creatinine, serum calcium and magnesium, CBC with differential and platelet count should be assessed 2 to 3 times per week during induction and weekly during maintenance.

Table 5: Data collection schedule for treatment administration (TX1-TX5) and switch administration (SX) visits

Data	Visit/weeks TX1 0*	TX2 2	TX3 4	TX4 6	TX5 8	SX 0†
Visual acuity	x	x	x	x	x	x
Slit lamp exam	x	x	x	x	x	x
Ophthalmic exam	x	x	x	x	x	x
Fundus photographs	x	x	x	x	x	x
Visual field	x		x			x
Hematology CBC‡ Differential‡ Platelet‡	x	x	x	x	x	x
Chemistries BUN/creatinine‡ Serum Ca^{2+} & Mg^{2+}‡ Electrolytes/albumin Liver function tests (AST, ALT, alk phos)	x	x	x	x	x	x
CMV viral cultures Blood & urine	x	x	x			x
Serum bank	x		x			x
Health interview AIDS history Concomitant medicine Symptoms	x	x	x	x	x	x
Physical exam	x	x	x	x	x	x
Trail making test	x		x			x

*Day 0 to -5 from start of induction therapy
†Day 0 to -5 from start of alternative drug
‡Creatinine, serum calcium and magnesium, CBC with differential and platelet count should be assessed 2 to 3 times per week during induction and weekly during maintenance.

13. References

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CMV Retinitis Trial: Foscarnet Ganciclovir

Consent Statement

1. Introduction

Often people with AIDS develop a virus infection in the eye. The virus infection involves the part of the eye called the retina, the nerve layer in the eye. The retina acts like film in a camera: it detects the picture. The virus is called cytomegalovirus (CMV), and the eye infection is called CMV retinitis. The CMV Retinitis Trial: Foscarnet Ganciclovir (CRT) is a research study to determine the best treatment for this eye infection. You are being asked to participate in this trial because you have been diagnosed as having CMV retinitis.

CMV retinitis may result in partial or total loss of vision in the affected eye(s). The amount of vision lost depends on what part of the retina is infected. If only peripheral retina is infected, some side vision may be lost. If the infection involves the central part of the retina (macula) or the optic nerve, central vision, which is important for good sight, may be decreased or lost. The location of your particular infection will affect which treatments you may receive in this trial. Your doctor has told you where your infection is located.

Currently, there are only two drugs that appear to be effective for treating CMV retinitis: foscarnet and ganciclovir. Ganciclovir (Cytovene®) is approved by the Food and Drug Administration (FDA) for treatment of CMV retinitis. Foscarnet appears to be effective, but is still being tested as an investigational drug. Neither drug will cure CMV retinitis, but each drug may stop the infection from spreading. Life-time treatment is required to keep the infection under control.

2. Purpose

The goal of retinitis treatment is to maintain good vision without causing a decrease in the length or quality of life. However, the long-term effects of foscarnet or ganciclovir on CMV retinitis or on length and quality of life are not known. Each of the two drugs has benefits and risks; both drugs appear to be equally effective for treatment of CMV retinitis, and both drugs have side effects. In order to determine which of the drug treatments is better, you are being asked to participate in a clinical trial.

In this trial, one group of patients receiving foscarnet will be compared with another group receiving ganciclovir. As soon as it is determined which drug treatment is better, you will be informed and offered that treatment, if medically indicated.

In addition to questions about which drug is more effective, there is also uncertainty about when to start drug treatment for peripheral retinitis. It may be better to wait and begin drug treatment only if the infection spreads and threatens the macula or the optic nerve. Waiting has some advantages. The risk of toxicity due to foscarnet, ganciclovir, or of mixing these drugs with other medications is reduced. Also, a central intravenous catheter does not need to be inserted immediately. However, immediate treatment of small peripheral retinitis lesions may limit the area affected by infection and thereby limit the amount of vision lost.

In one part of this trial, people receiving immediate treatment for small peripheral lesions will be compared to those receiving drug therapy when and if their infections progress.

3. Treatment Assignment

The trial treatments available to you depend on the location of your retinitis. It is the collective judgement of the ophthalmologists working on this trial that people with infections threatening the macula or optic nerve, or involving more than 25% of the peripheral retina, should receive immediate drug treatment in order to preserve vision. The two trial treatments available to these people are immediate treatment with foscarnet or ganciclovir. The treatment will be selected by random chance; the process is similar to flipping a coin. Thus a person enrolling in this part of the trial will have a 50% chance of receiving foscarnet and a 50% chance of receiving ganciclovir, and treatment will begin as soon as possible.

For people with small peripheral lesions only (lesions involving less than 25% of the peripheral retina) it is not known whether immediate treatment or waiting (deferral of treatment) is better. For those people, we will recommend entry into another part of this trial, in which patients will be randomly assigned to either immediate treatment or deferral of treatment (waiting and starting treatment only if infection spreads to threaten the macula or optic nerve, or to involve more than 25% of the peripheral retina). If you enter, the chance of receiving immediate treatment with foscarnet is 30%; the chance of receiving immediate treatment with ganciclovir is 30%; and the chance of being assigned to deferral of treatment is 40%. Randomly assigning people to treatment regimens is the best way to compare these regimens.

However, we recognize that some people with small peripheral retinitis lesions may prefer to choose either immediate treatment or deferral, and they may do so and still participate in this study, provided they agree to random assignment of the drug to be used. A person with a small peripheral lesion who chooses to receive immediate treatment will have a 50% change of receiving foscarnet and a 50% chance of receiving ganciclovir. People choosing deferral of treatment will come to the clinic for regular eye exams and will begin drug treatment when and if their infections progress to threaten the macula or optic nerve or to involve more than 25% of the peripheral retina; or an extra-ocular CMV infection develops. At that time they will be randomly assigned to foscarnet (50%) or ganciclovir (50%).

4. Treatment Administration

Both foscarnet and ganciclovir treatments begin with relatively high doses of drug given for up to 14 days. After that, lower doses of drug will be given daily indefinitely. However, if the infection does not respond to treatment or flares up again, dosage of drug will be increased for up to 14 days. If we can not control your infection with the drug assigned to you, we will try using the other drug.

Both of these drugs are given directly into the blood stream (intravenously). Drug treatment may be started with an intravenous tube in a small vein (blood vessel), most commonly in a vein in your arm. However, long-term treatment will require placement of a catheter (tube) in a large central vein, usually the catheter is placed in a vein in your chest wall. Placing a catheter into a central vein is a surgical procedure that requires local anesthesia. The catheter will not limit your ability to move around or do normal tasks. The catheter can be removed if it causes serious problems, such as an infection.

In general you will be able to continue taking most other drugs while receiving foscarnet or ganciclovir. However, oral or intravenous drug treatments for herpes infections should not be continued. CMV virus is a herpes virus, so the drug you are being given to treat your CMV infection will also treat other herpes infections. Therefore it is not necessary for people taking foscarnet or ganciclovir to take acyclovir (Zovirax®) or other herpes treatments. (Acyclovir is not an effective treatment for CMV retinitis). Some drugs that are toxic to the kidneys can not be taken in combination with foscarnet. These are amphotericin B, aminoglycosides and intravenous pentamidine. You may or may not be able to continue taking AZT (zidovudine). Both AZT and ganciclovir decrease blood cell production and taking both drugs together may cause severe, life-threatening toxicity. If you are taking ganciclovir we will recommend a reduced dosage regimen for AZT and discontinuation of AZT if blood cell production decreases.

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 in the trial. Women participants should use some form of birth-control method to avoid getting pregnant while they are taking ganciclovir or foscarnet. If a women becomes pregnant, drug treatment will be stopped. Men enrolled in this trial should also use condoms for birth-control. Women and men should continue to use birth control for at least 90 days after drug treatment has ended.

5. Study Exams and Sample Collection

Study participants will have regularly scheduled clinic visits. There are nine visits scheduled for the first six months, visits are scheduled less frequently after that. At each visit there will be an eye exam, photos of the retina (fundus photography), blood and urine collections, and a physical exam. The eye exams will be similar to regular eye exams but include more visual function testing than you may have had before. The fundus photographs will allow us to monitor your eye infection. Depending on the visit, 15 to 45 milliliters (1 to 3 tablespoons) of blood will be collected. When necessary, we may obtain information about AIDS-related diagnoses or treatments from your medical records or physician. You may be asked to return to clinic between study visits to have your eyes checked.

6. Risks & Benefits

CMV retinitis is a serious disease that is difficult to treat. Enrolling in this trial will expose you to certain risk; most of these risks are associated with the drugs used and how the drugs are given. However, the risks are no greater than the risks associated with being treated for CMV retinitis outside of this trial. The benefits to you are receiving expert care directed by leaders in the field of AIDS-related eye infections under protocols that give you an equal chance of receiving ganciclovir or foscarnet initially, and includes a switch to the second drug if your infection does not respond to the assigned drug, or if you cannot tolerate it.

All drugs have side effects. The possible side effects from taking foscarnet or ganciclovir range from mild to severe, life-threatening ones. You will be monitored for the development of side effects. If side effects develop, we will decrease the dose of the drug, stop using the drug, or treat the side effect. The known side effects associated with foscarnet and ganciclovir and the risks associated with study procedures are listed below.

Foscarnet

- Kidney function: small decreases in kidney function occur in up to 30 percent of people studied. Large decreases requiring an interruption of therapy occur in about 10 percent. Decreased kidney function is detected by changes in blood chemistry and usually does not cause any symptoms. In the event of serious decreases in renal function, the drug dose will be lowered or the drug stopped.

- Blood electrolytes: changes in blood levels of certain minerals (calcium, magnesium, and phosphate) occurred in up to 50 percent of people studied. However, significant abnormalities requiring therapy only occurred in about 5 percent. When severe, these abnormalities can produce symptoms. Symptoms included tremors, paraesthesia (tingling and numbness in the extremities), and cramps. Rarely, approximately 5 percent, extreme abnormalities can cause more severe symptoms such as seizures (convulsions). Because of this your blood levels of these minerals will be monitored and oral mineral supplements or other medication will be used if needed.

- Anemia: significant decreases in red blood cells (anemia) occurred in approximately 33 percent of people taking foscarnet. Anemia sometimes may cause fatigue (sleepiness), severe anemia is treated with blood transfusions.

- Thrombophlebitis: inflammation of veins occurred in 4 to 9 percent of people studied.

- Non-specific: seizures, nausea, vomiting, headache, and fatigue occurred in less than 10 percent of people studied and generally is easily treated.

- Other: there may be other, unknown side effects, including damage to an unborn child.

Studies of the Ocular Complications of AIDS

SOCA

Procedures for Preparing

and

Shipping Specimens

Revision 1.0
9 October 1990

Prepared by:
SOCA Coordinating Center
Department of Epidemiology
School of Hygiene and Public Health
Johns Hopkins University
615 North Wolfe Street
Baltimore, Maryland 21205
(301) 955-8176

Procedures for Preparing and Shipping Specimens

Table of contents

Procedures for Preparing and Shipping Specimens

Central repository personnel and address

Director:	James Leef, PhD
Project manager:	Sandy Palmer
Address:	Biomedical Research Institute 12111 Parklawn Drive Rockville, Maryland 20852
Telephone:	(301) 881-3300 (301) 881-7640 (FAX)

Procedures for Preparing and Shipping Specimens

Specimen shipment procedures

Purpose
- Send CMV isolates and serum to central repository (BRI)

When
- CMV cultures show ≥ 30% CPE, **Mondays only for CMV cultures**
- Within 12 hours of collecting blood for serum repository, or
- Monthly for shipment of frozen serum (clinic preference)
- Notify Sandy Palmer at BRI on the day of shipment of all shipments

By whom
- Clinic coordinator
- BRI personnel

Forms
- Specimen Shipment Log (SS)
- Federal Express Shipper's Certification for Restricted Articles/Dangerous Good form

Equipment
- Specimen tube labels (supplied by Coordinating Center)
- Culture tubes, maximum size 12.5 cm by 1.5 cm
- Serum tubes, 5 to 15 ml vacutainers tube
- Parafilm
- Aluminum cans with preformed tube inserts (supplied by BRI)
- Cardboard cans (supplied by BRI)
- Polyfoam tube holders (supplied by BRI)
- Yellow Powersorb™ sheets (supplied by BRI)
- Rubber bands
- Spill pillows (supplied by BRI)
- Zip-lock plastic bags (supplied by BRI)
- Shippers, polyfoam box within a fiberboard box - do not separate boxes (supplied by BRI)
- Strapping tape
- Packing labels (supplied by BRI)
  - Danger, Do Not Load in Passenger Aircraft
  - Infectious Substance Affecting Humans: (HIV) UN2814
  - Infectious Substance Affecting Humans: (CMV) UN2814
  - Infectious Substance, #6
  - Dry Ice UN1845, ice in _____ kilograms
  - White diamond with vertical lines and #9 (dry ice label)

Procedures for Preparing and Shipping Specimens

Specimen shipment procedures (cont'd)

- Plastic sleeve for Federal Express airbill and hazardous materials form
- Address label: shipper and consignee (supplied by Coordinating Center)

Procedures for labeling specimens

- Complete SOCA specimen tube labels and affix to tubes
- Labels should contain the following information:
  - clinic ID code, patient ID number, and visit ID
  - date of collection
  - types of specimen: serum or CMV-tissue (e.g. CMV-blood, CMV-urine, or CMV-colon, etc.)
- For CMV cultures, wrap label around tube just below tube cap to avoid obscuring monolayer
- Note: if freezing serum at clinical center use freezer compatible labels

Packing CMV culture isolates

- Only ship cultures with at least 30% CPE
- Fill tube with medium
- Wrap top of sealed culture tube(s) with parafilm
- Place tube(s) in aluminum can (maximum of 6 tubes per can)
- Place aluminum can in cardboard can
- Place cardboard can(s) upright in shipper (maximum 2 per shipper)
- Ship CMV cultures on Monday for Tuesday delivery
- CMV isolates are shipped without refrigeration (do not ship CMV isolates with frozen serum)
- Place minimum of one spill pillow in bottom of polyfoam box; additional spill pillows may be used to secure and cushion specimens
- Total volume of specimens per shipment should not exceed 4 liters
- Place a copy of Specimen Shipment Log form enclosed in a separate zip-lock bag into shipper; the original Specimen Shipment form should be kept in a Specimen Shipment notebook or file at clinic
- Place lid on interior polyfoam box (do not tape interior polyfoam box) and close exterior fiberboard box of shipper and secure exterior box with strapping tape

Packing serum specimens

- May ship fresh serum without refrigerationon if shipping on the day serum collected, or
- Store serum at -70°C locally and ship frozen serum on dry ice
- Use 5 ml or larger tubes
- Place specimen tubes in a polyfoam tube holder
- Wrap each tube holder in Powersorb™ sheet and secure with rubberband
- Place wrapped tube holder in zip-lock plastic bag
- Place upright in shipper

Procedures for Preparing and Shipping Specimens

Specimen shipment procedures (cont'd)

Packing serum specimens (cont'd)

- Place minimum of one spill pillow in bottom of polyfoam box; additional spill pillows may be used to secure and cushion specimens
- For frozen serum specimen, surround tube holders with dry ice if shipping frozen serum
- Total volume of specimens per shipment should not exceed 4 liters
- Place a copy of Specimen Shipment Log form enclosed in a separate zip-lock bag into shipper; the original Specimen Shipment Log form should be kept in a Specimen Shipment notebook or file at clinic
- Place lid on interior polyfoam box (do not tape interior polyfoam box) and close exterior fiberboard box of shipper and secure exterior box with strapping tape

Labeling Shipper (see illustration on page 9)

- All labels are easily removed so that shipper's can be re-used for different specimens
- **Do not write on the shipper box**
- For shipment of CMV; place following labels on **one side** of shipper box:
  - Infectious Substance, 6
  - Danger, Do Not Load in Passenger Aircraft
  - Infectious Substance Affecting Humans: (CMV) UN2814
- For shipment of fresh of serum (no refrigeration; place following labels on **one side** of shipper box:
  - Infectious Substance, 6
  - Danger, Do Not Load in Passenger Aircraft
  - Infectious Substance Affecting Humans: (HIV) UN2814
- For shipment of CMV and fresh serum (no refrigeration); place following labels on **one side** of shipper box:
  - Infectious Substance, 6
  - Danger, Do Not Load in Passenger Aircraft
  - Infectious Substance Affecting Humans: (HIV) UN2814
  - Infectious Substance Affecting Humans: (CMV) UN2814
- For shipment of frozen serum on dry ice; place following labels on **one side** of shipper box:
  - Infectious Substance, 6
  - Danger, Do Not Load in Passenger Aircraft
  - Infectious Substance Affecting Humans: (HIV) UN2814
  - Diamond shaped with vertical lines, 9
  - Dry Ice UN1845, ice in ____ kilograms (record weight of ice in kg)
- Attach address labels (shipper and consignee) on **top** of box
- Complete Federal Express Shipper's Certification for Restricted Articles/Dangerous Goods form (see instructions and sample form on pages 6 through 8)
- Place completed Federal Express airbill Shipper's Certification for Restricted Articles/Dangerous Goods form in sleeve and attach to front of box
- Arrange for priority shipment next day delivery via Federal Express no later than 5:00 p.m. local time
- Notify Sandy Palmer at BRI (301) 881-3300

Procedures for Preparing and Shipping Specimens

Specimen shipment procedures (cont'd)

Receipt of specimen notification

- Upon receipt of specimens, BRI personnel completes a Patient Specimen Receipt form (Form SR) and sends the completed form to clinic
- Form items
  - patient-specific form identifying specimens received and condition of specimen
  - clinic ID code, patient ID number, and visit code
  - sequential shipment number
  - date of receipt
  - condition of specimen seceived
- If CMV isolate is not viable, BRI will notify and instruct clinic to retrieve CMV aliquot and send to BRI
- Clinic center personnel enters data from Patient Specimen Receipt form into database

Shipping materials list

Items	Description
Shipper	Polyfoam insulated box within a fiberboard box
Tube holder	Polyform container with depressions
Powersorb pads	Yellow cloth
Spill pillows	White bag filled with absorbent material
Cans	Small aluminum can with lid
Inserts	Preformed foam inserts with six depressions
Cylinders	Large cardboard cylinders with lid
Zip-lock bags	Plastic bag
Federal Express airbill	Airbill with a Shipper's Certification for Restricted Articles/Dangerous Goods section, pre-printed with consignee information and third-party account number
Airbill sleeve	Clear plastic sleeve with adhesive back
Labels	Infectious substance affecting humans: HIV (white rectangle) Infectious substance affecting humans: CMV (white rectangle) Infectious substance, 6 (white diamond) Danger, do not load on passenger aircraft (orange and black square) Dry ice UN1845, ice in ___ kilogram (white rectangle) White diamond with vertical lines, 9 (dry ice label) Clinical center address label (white rectangle) BRI address label (white rectangle) Specimen tube label (white rectangle)

Note: BRI will supply clinics with bulk supply of shipping labels and plastic sleeves
The Coordinating Center will supply clinics with address labels (shipper and consignee)

Procedures for Preparing and Shipping Specimens

Instructions* for completing Federal Express Dangerous Goods form

---

Date: *record date of shipment*

Sender's Federal Express Account Number: *leave blank*

Airbill number: *shipment number from the Federal Express air bill*

Shipper: *Record Clinic coordinator name, clinic name, clinic street address, City, State, zip code, and telephone number*

Consignee (*printed on form*):
Sandy Palmer
Biomedical Research Institute
12111 Parklawn Drive
Rockville, Maryland 20852
1-301-881-3300

Billing Reference Information: *already printed on form*

Payment (*already printed*): third party Federal Express account number
for shipments on dry ice only, write "Dry Ice, 9, UN1845 1 pkg. ___ kilograms of dry ice, III" *in space by account number*

Services: *check* Priority Overnight Service, Cargo Aircraft only, Dangerous goods.

Delivery and Special Handling: *for shipments of serum on dry check* **dry ice service** *and fill in the # of lbs of dry ice used*

Dangerous Goods Identification

Check one: *check* IATA/ICAO
Proper Shipping Name: *write in* "infectious substance affecting humans (HIV and CMV)" *for serum and culture shipments) ; or* "infectious substance affecting humans (HIV)" *for serum shipments; or* "infectious substance affecting humans (CMV)" *for CMV cultures shipments*
Class or Division: *write in* 6.2 (Etiologic agent)
UN or ID no.: *write in* UN2814
Subsidiary Risk: *leave blank*
Quantity & type of packing: *write in* 1 fiberboard box, __ milliliters of specimen
Packing instructions: *write in* 602
Authorization: *leave blank*

Additional handling: *leave blank*

Instructions* for completing Federal Express Dangerous Goods form (cont'd)

Transport details: *cross out box* "Passenger aircraft"

Airport of Departure: *record clinic location (city)*

Airport of Destination: *write in* Washington, DC

Shipment type: *cross out box* "Radioactive"

Name/title of shipper: *type or print name and title of person signing form*

Place and date: *record city, State and date signed*

Emergency telephone number: *print or type* (301) 881-3300, Biomedical Research Institute

Signature: *Signature of person listed as signatory*

---

*Form heading are in bold fonts
Instructions are in italic fonts
Items to be copied onto the form without modifications are in normal font

Procedures for Preparing and Shipping Specimens

Sample Federal Express Shipper's Certification for Dangerous Goods form

FEDERAL EXPRESS

QUESTIONS? CALL 800-238-5355 TOLL FREE.

AIRBILL PACKAGE TRACKING NUMBER 8750428083

1 259R 8750428083

Sender's Federal Express Account Number — Date

From (Your Name) Please Print — Your Phone Number (Very Important)

Company — Department/Floor No.

Street Address

City — State — ZIP Required

To (Recipient's Name) Please Print: SANDY PALMER — Recipient's Phone Number (Very Important): 301-881-3300

Company: BIOMEDICAL RESEARCH INSTITUTE — Department/Floor No.

Exact Street Address: 12111 PARKLAWN DR.

City: ROCKVILLE, State: MD, ZIP Required: 20852

YOUR INTERNAL BILLING REFERENCE INFORMATION: H3465

IF HOLD FOR PICK-UP, Print FEDEX Address Here — Street Address — City — State — ZIP Required

PAYMENT: Bill Sender / Bill Recipient's FedEx Acct No. / [X] Bill 3rd Party FedEx Acct No. / Bill Credit Card — 1489-5550-6

SERVICES (Check only one box) — DELIVERY AND SPECIAL HANDLING (Check services required)

- HOLD FOR PICK-UP
- DELIVER WEEKDAY
- DELIVER SATURDAY
- [X] DANGEROUS GOODS
- DRY ICE
- OTHER SPECIAL SERVICE
- HOLIDAY DELIVERY

INSTRUCTIONS (Check only one box)

SERVICE CONDITIONS, DECLARED VALUE AND LIMIT OF LIABILITY

SIGNATURE RELEASE UNAVAILABLE 017

ORIGIN COPY

8750428083 AIRBILL NUMBER

SHIPPER'S CERTIFICATION FOR RESTRICTED ARTICLES/DANGEROUS GOODS (TYPE OR PRINT)

CHECK ONE ➡ ☐ 49 CFR ☐ IATA/ICAO

DANGEROUS GOODS IDENTIFICATION						
PROPER SHIPPING NAME	CLASS OR DIVISION	UN OR ID NO	SUBSIDIARY RISK	QUANTITY AND TYPE OF PACKING	PACKING INST	AUTHORIZATION

ADDITIONAL HANDLING INFORMATION

TRANSPORT DETAILS — THIS SHIPMENT IS WITHIN THE LIMITATIONS PRESCRIBED FOR ▶ PASSENGER AIRCRAFT — CARGO AIRCRAFT ONLY — (DELETE NONAPPLICABLE)

AIRPORT OF DEPARTURE — AIRPORT OF DESTINATION — SHIPMENT TYPE ▶ NON RADIOACTIVE — RADIOACTIVE — (DELETE NONAPPLICABLE)

ACCEPTABLE FOR PASSENGER AIRCRAFT. THIS SHIPMENT CONTAINS RADIOACTIVE MATERIAL INTENDED FOR USE IN, OR INCIDENT TO, RESEARCH, MEDICAL DIAGNOSIS OR TREATMENT

I HEREBY DECLARE THAT THE CONTENTS OF THIS CONSIGNMENT ARE FULLY AND ACCURATELY DESCRIBED ABOVE BY PROPER SHIPPING NAME AND ARE CLASSIFIED, PACKED, MARKED, AND LABELED, AND ARE IN ALL RESPECTS IN PROPER CONDITION FOR TRANSPORT BY AIR ACCORDING TO THE APPLICABLE INTERNATIONAL AND NATIONAL GOVERNMENT REGULATIONS.

NAME AND TITLE OF SHIPPER — PLACE AND DATE

EMERGENCY TELEPHONE NUMBER — SIGNATURE OF SHIPPER

SEE WARNING ON BACK

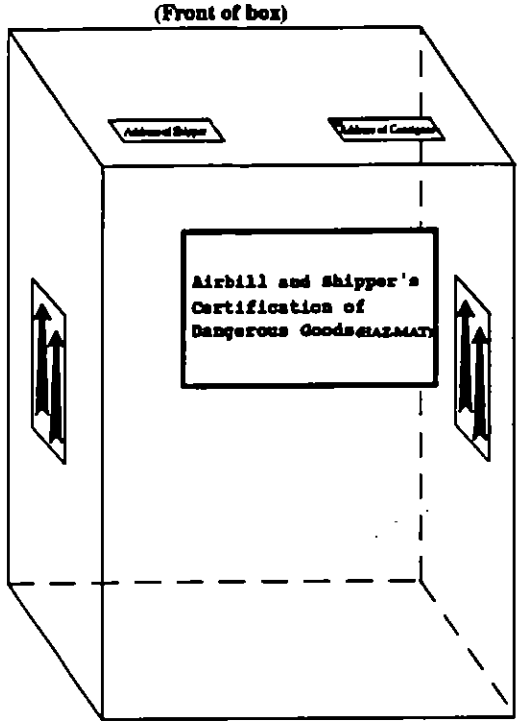
ShipD.Pro

Procedures for Preparing and Shipping Specimens

Illustration of placement of airbill and labels on shipper

Placement of plastic sleeve and airbill

(Front of box)



Labeling for shipment of serum and CMV

(Back of box)

Labeling for shipment of CMV only

(Back of box)

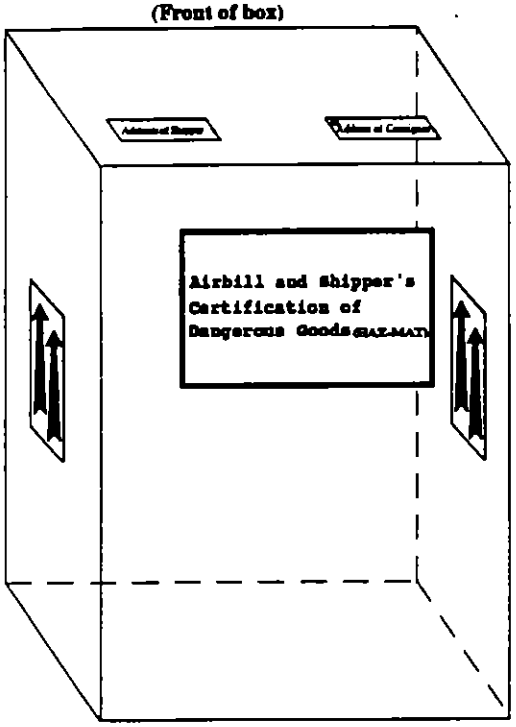
* consignee phone number must appear on address label

Procedures for Preparing and Shipping Specimens

Illustration of placement of airbill and labels on shipper for dry ice shipments

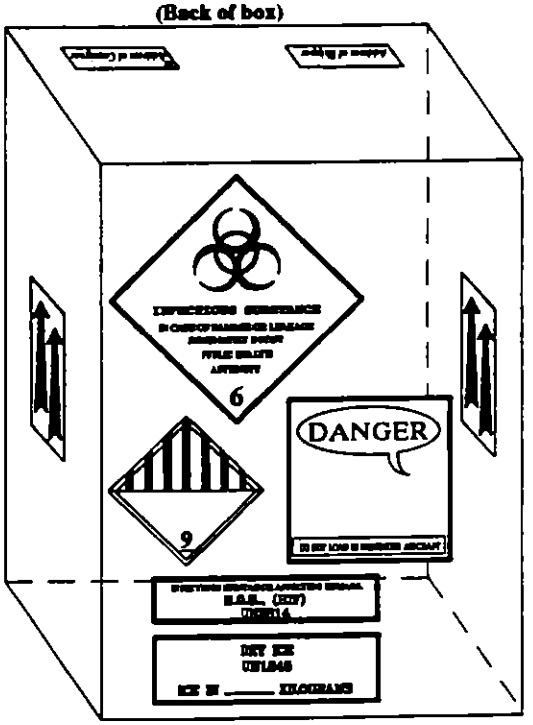
Placement of plastic sleeve and airbill

(Front of box)



Labeling for shipment of frozen serum with Dry Ice

(Back of box)



* consignee phone number must appear on address label

Procedures for Preparing and Shipping Specimens

Sample Specimen Shipment Log

Studies of the Ocular Complications of AIDS

CMV Retinitis Trial
Foscarnet / Ganciclovir

Specimen Shipment Log

Purpose: Record information about specimens sent to BRI.

When: Eligibility, followup, treatment administration visits when serum is collected for banking or when shipping CMV culture isolates.

By whom: Clinic coordinator or laboratory personnel and BRI personnel.

Instructions: Complete one SS Log for each shipper box sent to BRI. CMV isolates and serum can be shipped together without refrigeration, or frozen serum can be shipped separately on dry ice (clinic preference). Ship all specimens via Federal Express priority service (next day, am delivery).

Packing instructions:

For CMV isolates (no refrigeration):
Wrap top of culture sealed tube with parafilm.
Place tubes in small aluminum can (maximum of 6 tubes per can).
Place aluminum can in cardboard can.
Place cardboard cans upright in shipper box (maximum of 2 per box).

For fresh serum (no refrigeration):
Place serum tubes in tubeholders and secure with tape.
Wrap each tubeholder in Powersorb® sheet and secure with rubberband.
Place each wrapped tubeholder in a ziplock bag and place in an upright position in shipper box.

For frozen serum on dry ice:
Follow above packing instructions and surround tube holders with dry ice.
Attach both dry ice labels to front of package and record weight of ice in kilograms. Attach other required labels as well.

For all shipments:
Place 1 pillow in bottom of shipper box; place extra pillows in shipper, if necessary, for small shipments.
Place a copy of this form in a separate ziplock bag and place in shipper box.
Close polyform container and exterior shipper box and secure exterior box with strapping tape.
Place appropriate content, warning and address labels on exterior of box.
Place completed Federal Express Shipper's Certification of Goods, in plastic sleeve and attach to front of box.
Notify Sandy Palmer of shipment: 301-881-3300 (office) or 301-881-7640 (fax)

A. Clinic ID and shipment information

1. Clinic ID code: ___ ___ ___ ___

2. Sequential shipment number: ___ ___ ___

3. Date specimens shipped: ___ ___ – ___ ___ – ___ ___ (month – day – year)

4. Total number of specimens sent: ___ ___

   a. # serum specimens: ___ ___

   b. # CMV isolates: ___ ___

   c. # other specimens sent: ___ ___

B. Clinic administrative information

5. Signature of person preparing shipment:

_____

C. BRI administrative information

6. Date received: ___ ___ – ___ ___ – ___ ___ (month – day – year)

7. BRI signature:

_____

Procedures for Preparing and Shipping Specimens

Sample Specimen Shipment Log (cont'd)

Studies of the Ocular Complications of AIDS

Clinic ID code: __ __ __ __
CMV Retinitis Trial
Foscarnet / Ganciclovir

D. Specimen shipment information

Record specified information about each specimen shipped in items 8 thru 23. If more than 16 specimens are shipped at one time, fill out a second Specimen Shipment Log. Indicate type of specimen as serum, CMV-blood, CMV-urine, CMV-(specify other site), or other (specify other). For frozen serum only, record the total number of times serum was frozen in column f. BRI will fill-in the Receipt code column with a code indicating the condition of the specimen upon arrival.

	a. Patient ID#	b. Name code	c. Visit ID	d. Collection date mm–dd–yy	e. Type of specimen	f. #times frozen	g. Receipt code
8.	_ _ _ _	_ _ _ _ _ _	_ _ _	_ _–_ _–_ _	_____	____	_ _
9.	_ _ _ _	_ _ _ _ _ _	_ _ _	_ _–_ _–_ _	_____	____	_ _
10.	_ _ _ _	_ _ _ _ _ _	_ _ _	_ _–_ _–_ _	_____	____	_ _
11.	_ _ _ _	_ _ _ _ _ _	_ _ _	_ _–_ _–_ _	_____	____	_ _
12.	_ _ _ _	_ _ _ _ _ _	_ _ _	_ _–_ _–_ _	_____	____	_ _
13.	_ _ _ _	_ _ _ _ _ _	_ _ _	_ _–_ _–_ _	_____	____	_ _
14.	_ _ _ _	_ _ _ _ _ _	_ _ _	_ _–_ _–_ _	_____	____	_ _
15.	_ _ _ _	_ _ _ _ _ _	_ _ _	_ _–_ _–_ _	_____	____	_ _
16.	_ _ _ _	_ _ _ _ _ _	_ _ _	_ _–_ _–_ _	_____	____	_ _
17.	_ _ _ _	_ _ _ _ _ _	_ _ _	_ _–_ _–_ _	_____	____	_ _
18.	_ _ _ _	_ _ _ _ _ _	_ _ _	_ _–_ _–_ _	_____	____	_ _
19.	_ _ _ _	_ _ _ _ _ _	_ _ _	_ _–_ _–_ _	_____	____	_ _
20.	_ _ _ _	_ _ _ _ _ _	_ _ _	_ _–_ _–_ _	_____	____	_ _
21.	_ _ _ _	_ _ _ _ _ _	_ _ _	_ _–_ _–_ _	_____	____	_ _
22.	_ _ _ _	_ _ _ _ _ _	_ _ _	_ _–_ _–_ _	_____	____	_ _
23.	_ _ _ _	_ _ _ _ _ _	_ _ _	_ _–_ _–_ _	_____	____	_ _

Procedures for Preparing and Shipping Specimens

Sample Patient Specimen Receipt form

Studies of the Ocular Complications of AIDS

CMV Retinitis Trial
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Patient Specimen Receipt

Purpose: Document receipt of specimens at Central Laboratory and Repository (BRI).

When: Upon receipt of specimens at BRI.

By whom: BRI personnel, clinic coordinator.

Instructions: BRI personnel should complete form as soon as shipment is received and send a copy to clinic. Upon receipt at clinic, the clinic coordinator should file copy with patient forms.

A. Clinic, patient and visit identification

1. Clinic ID code: ___ ___ ___ ___
2. Patient ID#: ___ ___ ___ ___
3. Patient namecode: ___ ___ ___ ___ ___
4. Visit ID code: ___ ___ ___
5. Date specimens received: ___ ___-___ ___-___ ___ (month / day / year)
6. Specimen shipment #: ___ ___ ___

B. Administrative information

7. BRI signature: _____
8. Date completed: ___ ___-___ ___-___ ___ (month / day / year)

C. Specimens received

List all specimens received in a single shipment (item 6) for one patient (item 2) at a particular visit (item 5). If there are any discrepancies between the shipment and the shipment log, note them in the additional comments.

	a. Type of specimen	b. Date collected (mm-dd-yy)	c. Receipt condition / Remarks
9.	_____	___ ___-___ ___-___ ___	_____
10.	_____	___ ___-___ ___-___ ___	_____
11.	_____	___ ___-___ ___-___ ___	_____
12.	_____	___ ___-___ ___-___ ___	_____
13.	_____	___ ___-___ ___-___ ___	_____

Additional comments:

_____

_____

_____

Procedures for Preparing and Shipping Specimens

Clinical center CMV assay procedures

Purpose
- Collect data on CMV viremia and viruria, freeze CMV isolates for future analyses

When
- Eligibility or Enrollment visit (EL or EN)
- Week 2 visit (F1)
- Week 4 visit (F2)
- Week 12 visit (F5)
- Week 26 visit (F8)
- Month 12 (F11)
- Month 18 (F14)
- Month 24 (F17)
- Treatment administration visit
  - Prior to initiation of induction therapy (TX1)
  - Week 2 visit (TX2)
  - Week 4 visit (TX3)

By Whom
- Local virology laboratory
- Clinic coordinator

Forms
- Specimen Collection (SC)
- CMV Assay Report (CA)

Equipment
- Sterile urine collection container
- Heparinized 3 to 10 ml blood collection tube

Specimen Collection
- 3-10 cc heparinized peripheral blood
- 10 cc urine
- Specimen must be delivered and assay begun within one hour of specimen collection
- Record time specimen is collected, delivered to lab, and assay begun

- Urine specimens should be adjusted to ph7, centrifuged and supernatant and pellet cultured
- Leucocytes should be separated from whole blood by buffy coat isolation (room temperature sedimentation or moderate centrifugation or Ficoll isolation with cultures of both mononuclear and polymorphonuclear portions

Procedures for Preparing and Shipping Specimens

Clinical center CMV Assay procedures (cont'd)

Isolation of CMV

- May use tube culture and/or shell vial techniques
- Regardless of the type of CMV assay performed (tube culture or shell vial), multiple cell cultures must be inoculated to provide CMV isolates for central storage
- Routine tube culture techniques
  - hold cultures for at least six weeks
  - confirm isolation by CMV specific monoclonal antibody or shell vial
  - confirm culture with 30% CPE with CMV monoclonal antibody if shell vial negative
  - multiple tube cultures should be processed simultaneously to ensure virus available for central storage
- If only one culture has CPE, subculture this isolate and maintain both cultures.
- Ship one CMV isolate from each tissue source to central repository
- Maintain one culture showing CPE from each specimen for one week after shipment to central repository

Procedures for Preparing and Shipping Specimens

Clinical center serum collection procedures

Purpose
- To collect serum to be stored at the central repository (BRI) for future analyses

When
- Enrollment
- Week 4 (F2)
- Week 12 (F5)
- Week 26 (F8)
- Month 12 (F11)
- Month 18 (F14)
- Month 24 (F17)
- Treatment administration visits
  - Prior to initiation of induction therapy (TX1)
  - Week 4 (TX3)

By whom
- Phlebotomist
- Clinic Coordinator

Form
- Specimen Collection (SC)

Equipment
- 10-15 ml untreated tube

Procedures
- Collect 10 to 15 ml of blood
- Separate serum and place in 5 to 10 ml tube
- Label tube with:
  - clinic ID code
  - patient ID number
  - visit ID
  - collection date
  - specimen type, i.e. serum
- Ship fresh serum without refrigeration to BRI within 12 hours of blood collection, or
- Freeze serum locally and ship with dry ice to BRI monthly
- Store serum locally at -70°C, ship frozen serum to BRI once a month or more frequently

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By whom: Clinic coordinator or laboratory personnel.

Instructions: Complete one SS Log for each shipper box sent to BRI. CMV isolates and serum can be shipped together without refrigeration, or frozen serum can be shipped separately on dry ice (clinic preference). Ship all specimens via Federal Express priority service (next day, am delivery).

Packing instructions:

For CMV isolates (no refrigeration):
- Wrap top of culture sealed tube with parafilm.
- Place tubes in small aluminum can (maximum of 6 tubes per can).
- Place aluminum can in cardboard can.
- Place cardboard cans upright in shipper box (maximum of 2 per box).

For fresh serum (no refrigeration):
- Place serum tubes in tubeholders and secure with tape.
- Wrap each tubeholder in Powersorb® sheet and secure with rubberband.
- Place each wrapped tubeholder in a ziplock bag and place in an upright position in shipper box.

For frozen serum on dry ice:
- Follow above packing instructions and surround tube holders with dry ice.
- Attach dry ice label to front of package along with other required labels.
- With magic marker, write the following: DRY ICE, UN 1845, and record weight of ice in kilograms.

For all shipments:
- Place 1 pillow in bottom of shipper box; place extra pillows in shipper, if necessary, for small shipments.
- Place a copy of this form in a separate ziplock bag and place in shipper box.
- Close polyform container and exterior shipper box and secure exterior box with strapping tape.
- Place appropriate content, warning and address labels on exterior of box.
- Place completed Federal Express Shipper's Certification of Goods, in plastic sleeve and attach to front of box.
- Notify Sandy Palmer of shipment; 301-881-3300 (office) or 301-881-7640 (fax)

A. Clinic ID and shipment information

1. Clinic ID code: ___ ___ ___ ___
2. Sequential shipment number: ___ ___ ___
3. Date specimens shipped: ___ ___ – ___ ___ – ___ ___ (month – day – year)
4. Total number of specimens sent: ___ ___
   - a. # serum specimens: ___ ___
   - b. # CMV isolates: ___ ___
   - c. # other specimens sent: ___ ___

B. Clinic administrative information

5. Signature of person preparing shipment: _____

C. BRI administrative information

6. Date received: ___ ___ – ___ ___ – ___ ___ (month – day – year)
7. BRI signature: _____

C. Specimen shipment information

Record specified information about each specimen shipped in items 10 thru 26. If more than 17 specimens are shipped at one time, fill out a second Specimen Shipment Log. Indicate type of specimen as serum, CMV–blood, CMV–urine, CMV–(specify other site), or other (specify other). BRI will fill–in the Receipt code column with a code indicating the condition of the specimen upon arrival.

	a. Patient ID#	b. Name code	c. Visit ID	d. Collection date mm–dd–yy	e. Type of specimen	f. Receipt code
8.	_ _ _ _	_ _ _ _ _	_ _ _	_ _–_ _–_ _	_____	_ _
9.	_ _ _ _	_ _ _ _ _	_ _ _	_ _–_ _–_ _	_____	_ _
10.	_ _ _ _	_ _ _ _ _	_ _ _	_ _–_ _–_ _	_____	_ _
11.	_ _ _ _	_ _ _ _ _	_ _ _	_ _–_ _–_ _	_____	_ _
12.	_ _ _ _	_ _ _ _ _	_ _ _	_ _–_ _–_ _	_____	_ _
13.	_ _ _ _	_ _ _ _ _	_ _ _	_ _–_ _–_ _	_____	_ _
14.	_ _ _ _	_ _ _ _ _	_ _ _	_ _–_ _–_ _	_____	_ _
15.	_ _ _ _	_ _ _ _ _	_ _ _	_ _–_ _–_ _	_____	_ _
16.	_ _ _ _	_ _ _ _ _	_ _ _	_ _–_ _–_ _	_____	_ _
17.	_ _ _ _	_ _ _ _ _	_ _ _	_ _–_ _–_ _	_____	_ _
18.	_ _ _ _	_ _ _ _ _	_ _ _	_ _–_ _–_ _	_____	_ _
19.	_ _ _ _	_ _ _ _ _	_ _ _	_ _–_ _–_ _	_____	_ _
20.	_ _ _ _	_ _ _ _ _	_ _ _	_ _–_ _–_ _	_____	_ _
21.	_ _ _ _	_ _ _ _ _	_ _ _	_ _–_ _–_ _	_____	_ _
22.	_ _ _ _	_ _ _ _ _	_ _ _	_ _–_ _–_ _	_____	_ _
23.	_ _ _ _	_ _ _ _ _	_ _ _	_ _–_ _–_ _	_____	_ _
24.	_ _ _ _	_ _ _ _ _	_ _ _	_ _–_ _–_ _	_____	_ _