LSOCA Protocol Version 6.0

Document History

Version 0 (1 December 1997): Draft protocol distributed to protocol committee

Version 1.0 (6 February 1998): Protocol revised and distributed to protocol committee following protocol committee conference call on 5 December 1997

Version 1.0 (30 March 1998): Protocol revised and distributed to protocol committee and research group following protocol committee conference call on 25 February 1998

§4.1 Ophthalmologic evaluation: for patients without major ocular complications, visual field will be performed only at baseline and at the time of a diagnosis of a major ocular complication. For patients with major ocular complications, visual field will be performed at baseline and every 3 months thereafter

§4.2 Fundus photography: fundus photographs will be taken at baseline for all patients enrolled, with or without ocular complications. Followup fundus photographs are required only for patients with selected major ocular complications, such as those with retinal involvement. Followup fundus photographs will be taken at the time of diagnosis and every 3 months

§4.3 Medical history: ACTG diagnostic criteria and coding scheme will be used to define opportunistic infections (OI's). Confirmatory data on OI's will be collected

§4.4 Quality of life: quality of life measures will be collected at every study visit, ie, every 6 months for patients without major ocular complications and every 3 months for patients with major ocular complications. Quality of life questionnaire is recommended to be administered at the beginning of the visit to avoid events at visit influencing responses to the questionnaire

§4.5 Laboratory studies: laboratory studies will be conducted at baseline and at every study visit, ie, every 6 months for patients without major ocular complications and every 3 months for patients with major ocular complications. Serum chemistry will be conducted for patients with major ocular complications only

§4.6 Specimen banking: specimen will be collected for banking at baseline and at every study visit, ie, every 6 months for patients without major ocular complications and every 3 months for patients with major ocular complications

§4.7 Interim visits: data will be collected at an interim visit only if patient is diagnosed with a major ocular complication. All baseline evaluations for a major ocular complication will be performed. These include eye examination, visual field, fundus photography, medical and treatment history, laboratory studies, specimen collection and quality of life assessment. Patients diagnosed with major ocular complications will be scheduled to be seen every 3 months from the time of diagnosis

§4.8 Missed visits: a section on missed visits has been added. Patients will be contacted by phone for missed visits to ascertain vital status and to obtain medical history interview and quality of life assessment

§6.2 Sample size consideration: the order for sample size justification for patients with and without CMV retinitis has been reversed. The planned sample size is adequate to detect reasonable relative risks (ie, a relative risk of 2) even if event rate is low. The Coordinating Center and the SOCA Policy and Data Monitoring Board will monitor event rates and patient characteristics to adjust sample size as necessary

Version 1.0 (27 May 1998): Protocol revised and distributed to SOCA research group following the Research Group Meeting on 20 April 1998

§3.1 Inclusion criteria: the inclusion criterion of best corrected visual acuity of 20/100 or better in at least one eye has been eliminated. The inclusion criteria of ability to visualize and photograph fundus in at least one eye with best corrected visual acuity of 20/100 or better also has been eliminated.

§3.2 Exclusion criteria: the exclusion criterion of untreatable media opacities that preclude visualization of the fundus in both eyes has been eliminated.

§4.1 Ophthalmologic evaluations: evaluations for contrast sensitivity and automated perimetry have been added. Contrast sensitivity test will be performed at baseline and every 6 months on all patients with and without major ocular complications. Automated perimetry will be performed at baseline and annually on all patients with and without major ocular complications.

§4.5 Laboratory studies: collection of local determinations of HIV viral load has been added.

Version 1.1 (7 August 1998): Protocol revised and distributed to SOCA Research Group.

§4.1 Telephone visit: a section on telephone visit has been added. Patients without a major ocular complication will be contacted by telephone or mail at the halfway point (3 months) between followup visits at the clinic to ascertain vital status and screen for eye conditions developed during the interval. These contacts are considered scheduled followup visits. Patients reporting eye problems will be scheduled for an eye exam by a study ophthalmologist.

§4.2 Ophthalmologic evaluation: the schedule for contrast sensitivity testing for patients with a major ocular complication has been changed from every 6 months to perimetry are specified: contrast sensitivity will be assessed with the Pelli-Robson chart and automated perimetry will be performed with Humphrey field analyzer. Also, a sentence has been added to state the recommended order for ophthalmic procedures: best corrected visual acuity with refraction first, followed by contrast sensitivity, Humphrey field, Goldmann field, and then ophthalmologic exam and fundus photography.

§4.6 Laboratory studies: this section has been revised to specify that laboratory data collected in the context of another study may be used for LSOCA if the data were collected within two weeks of the study visit, and within the visit time window. In addition, no blood collection for the local HIV viral load determination is required by the study, as HIV viral load analysis is expected to be part of standard care for patients infected with HIV. Data existing on HIV viral load analysis at the clinic will be collected.

§4.7 Specimen banking: this section has been revised to specify the amount of blood required for plasma and leukocytes specimens. Blood will be collected into two 10-mL yellow-top ACD tubes. Blood will be processed locally to obtain aliquots of plasma and 5 x 10^6 cell aliquots for banking.

§4.8 Interim visits: data to be collected at an interim visit has been revised. If the patient is diagnosed with a major ocular complication at an interim visit, data to be collected include eye history, eye examination, contrast sensitivity, Humphrey and Goldmann visual field, and fundus photography.

§5.1.1 Major ocular complications: this section has been added to provide a list of major ocular complications for purposes of LSOCA. Syphilitic chorioretinitis or papillitis is no longer considered a major ocular complication. On the other hand, optic nerve abnormalities associated with risk of substantial visual loss, such as papilledema, optic nerve disease associated with cryptococcal meningitis, or other serious optic neuropathy, will be considered major ocular complications.

§5.1.2 Other ocular complications: this section has been added to provide a list of other non-major ocular complications for purposes of LSOCA.

§5.3.2 Contrast sensitivity: outcome measures for contrast sensitivity have been added. The threshold contrast sensitivity value as well as the "by letter" contrast sensitivity score will be used to assess change in contrast sensitivity and rate of change over time.

§5.3.3 Visual field: outcome measures for Humphrey field have been added. Patient reliability will be assessed by fixation losses, false-negative responses, and false-positive responses. Four global indices: mean deviation (MD), pattern standard deviation (PSD), short-term fluctuation (SF) and corrected pattern standard deviation (CPSD), which summarize the point-by-point field data into single numbers will be used to assess field deficit and intra-test reliability. Field change and rate of change will be evaluated. Additionally, the glaucoma hemifield test (GHT) will be used to assess for asymmetric visual thresholds. Proportion of patients with normal, borderline, and abnormal GHT will be estimated.

Appendix 1 Data collection schedule: separate schedules are provided for patients with, and for patients without a major ocular complication. The schedule for patients without a major ocular complication has been revised to reflect telephone visits between followup visits at the clinic.

Appendix 2 Definitions for ocular complications have been revised.

Version 1.2 (8 January 1999)

Appendix 6 Addition of Patient Assent Statement approved by JHU CHR and distributed to SOCA Research Group

Version 2.0 (2 August 2001)

Appendix 5 and 6 Certificate of Confidentiality added to the Patient Consent and Assent Statements in Appendix 5 and 6; revision to Patient Consent form regarding no charge for examinations and tests for the study.

Version 3.0 (4 August 2004)

Blood collection for HIV viral load analysis to be obtained if HIV data are not available within the visit time window

Version 4.0 (21 April 2005)

Fundus photographs to be taken at five years and five year intervals thereafter for all patients. Serum chemistry data collected for all patients.

Version 5.0 (21 December 2005)

Upper limit for enrollment revised to 2,300 patients.

Version 6.0 (01 Sept 2008)

Abstract; §2.2	Upper limit for enrollment revised to 2,800 patients
§3.1	Eligibility criteria revised to include enrollment of either patients diagnosed with AIDS on or after January 2001 or patients with newly diagnosed ocular opportunistic infections
§3.3	Nomenclature changed from Major Ocular Complications (MOC) and No Major Ocular Complications (NoMOC) to Ocular Opportunistic Infections (No OOI)
§4.0	Visit schedule for OOI patients will be every six months with a telephone contact between clinic visits

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Abstract

The Longitudinal Study of Ocular Complications of AIDS (LSOCA) is a multicenter, prospective, observational study of patients with AIDS. Patients with a diagnosis of AIDS according to the 1993 CDC criteria, with or without ocular opportunistic infections, will be enrolled. The objectives of the study are:

- To monitor secular trends in the incidence of CMV retinitis and other ocular complications of AIDS.
- To determine the effect of HAART-induced changes in immune status on the risk of CMV retinitis and other ocular complications of AIDS.
- To determine the characteristics (clinical, virologic, hematologic, and biochemical) of populations at high risk for CMV retinitis and other ocular complications of AIDS.

Approximately 2,800 patients will be enrolled in the study. Enrollment of patients with CMV retinitis at baseline will be between 300 and 600 patients. All patients will be on a 6-month followup schedule; and have telephone contacts at the 3-month time point between visits. Data will be collected from eye examinations, fundus photographs, visual function testing, medical history, quality of life assessment, laboratory studies, and collection of plasma and blood cells for banking. Banked specimens will be analyzed for HIV RNA levels and CMV DNA levels. Outcomes of primary interest are incidence of CMV retinitis, incidence of other ocular complications, and mortality. Other outcomes of interest include incidence of extra-ocular CMV disease, sequelae of AIDS-related eye disease (e.g., retinal detachment), visual function, quality of life, and incidence of complications of therapies for ocular complications.

1. Introduction

1.1. Ocular complications of AIDS

Ocular abnormalities in patients with AIDS were first reported by Holland et. al in 1982[17]. The most common ocular finding is non-infectious "HIV retinopathy", characterized by cotton wool spots, intraretinal hemorrhages, and/or microaneurysms. These changes occur in approximately 50% of patients with AIDS[21]. HIV retinopathy alone is not typically associated with clinical loss of vision, but it has been proposed that functional deficits in patients with AIDS without other ocular complications measurable by contrast sensitivity and color vision testing may be due to a cumulative insult from this microangiopathy[33].

CMV retinitis, a condition that is common in late-stage AIDS, is the ocular complication that has had the most clinical importance. CMV retinitis, even when treated, has the potential to cause substantial loss of vision. In patients treated with intravenous ganciclovir and/or foscarnet, the median time until visual acuity is 20/200 or worse in both eyes (legal "blindness") has been reported to be 21 months[21]. In addition, CMV retinitis is the most costly AIDS-related opportunistic infection; the mean monthly cost of treatment for an AIDS patient with CMV retinitis has been estimated as $7,825[29].

Estimates of the risk for CMV retinitis have varied with changes in the therapeutic and prophylactic strategies for AIDS and its complications. By 1996, the incidence of CMV retinitis declined to about half from its peak in 1994 and 1995[20]. The decline is thought to be due to the increasing use of highly active anti-retroviral therapy (HAART), a combination of anti-HIV drugs that includes one or more protease inhibitors.

Ocular complications other than HIV retinopathy and CMV retinitis occur less frequently. Ocular toxoplasmosis, herpes zoster retinitis, and pneumocystis choroidopathy have been reported to occur in less than 1% of patients[21]. A rapidly progressing form of herpes zoster retinitis that responds poorly to treatment also has been reported in patients with AIDS[8,23,27,30]. The frequency of these infections, like that of CMV retinitis, has changed over the course of the AIDS epidemic. For example, the incidence of pneumocystis choroidopathy increased with the use of aerosolized pentamidine for PCP prophylaxis but decreased with the use of systemic prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX). The incidence of ocular toxoplasmosis also seems to have decreased with systemic PCP prophylaxis with TMP-SMX.

A survey of the number of HIV-positive patients followed or screened for ocular complications during the first 6 months of 1997 at SOCA clinical centers was conducted. During the 6-month period, 4,292 patients with HIV were screened. Of the screened patients, 83% were male, 58% were

white, 73% were bisexual or homosexual, and 41% had CD4+ T cell counts 100 cells/μL or less. Extrapolating from the survey, the estimated annual total number of patients screened at 19 SOCA clinics is 8,584 with 724 newly diagnosed cases of ocular complications (excluding HIV retinopathy) and 1,398 prevalent cases of ocular complications (excluding HIV retinopathy). Among the newly diagnosed patients, 52% had CMV retinitis, 18% had neuro-ophthalmic lesions, 7% had herpes zoster ophthalmicus, 10% had drug-induced lesions, and 13% had other types of complications (excluding HIV retinopathy). The distribution of complications for prevalent patients – HIV patients with diagnosed ocular complications – was: 83% CMV retinitis, 5% neuro-ophthalmic lesions, 4% herpes zoster ophthalmicus, 2% drug-induced lesions, and 6% other types of complications (excluding HIV retinopathy). These results indicate that CMV retinitis remains the major ocular complication of AIDS even in the era of HAART.

1.2. Rationale

Because the epidemiology of AIDS is rapidly evolving, with HIV becoming more like a chronic disease, new information is needed on the incidence and course of ocular complications. The Longitudinal Study of Ocular Complications of AIDS (LSOCA) is a prospective, observational, multicenter study that will provide such information by collecting data on the incidence of and risk factors for ocular complications of patients with AIDS. The study also will supplement information from treatment trials by collecting data from a large, diverse patient population. These data will allow us to examine the clinical course of ocular complications and to assess the effectiveness of treatments with regard to visual function, quality of life, and survival.

One objective of LSOCA is to characterize the effect of HAART-induced changes in immune status on the risk of CMV retinitis and other ocular complications of AIDS over time. Although the decline in CMV retinitis has been marked, we do not expect this or other complications of AIDS to disappear. Evidence suggests that HAART may not prevent CMV retinitis in patients who are severely immunocompromised at the time this therapy is begun[22]. Furthermore, although HAART may help to restore immune functioning in many people, it may simply delay the onset of severe immunosuppression. With time, there may exist a large population of severely immunocompromised patients who do not, or no longer, respond to HAART. The long-term effect of the changing epidemiology and clinical course of AIDS on the incidence of CMV retinitis remains to be determined, but the nadir may have been reached. Figures from the first half of 1997 suggest an incidence similar to or slightly greater than that of 1996[20]. LSOCA will monitor the incidence of CMV retinitis and other ocular complications of AIDS over time. Secular trends will be examined by observing changes in annual incidence in the longitudinally followed cohort. The trends will be evaluated among subgroups of patients.

LSOCA aims to determine the characteristics (clinical, virologic, hematologic, and biochemical) of populations at high risk for CMV retinitis and other ocular complications of AIDS. Knowledge of incidence rates and risk factors is crucial for the design and implementation of screening and primary prevention programs for ocular complications. Screening and primary prophylaxis interventions are most effective and cost-efficient when patients at high risk can be identified. Given the high risk of AIDS patients for CMV retinitis and consequent vision loss, as well as the cost and morbidity of treatment, effective screening and primary prophylaxis strategies for this complication are needed.

Low CD4+ T cell count has been a major predictor of risk for CMV retinitis[18,21,36] but in the era of HAART, we do not know the level of CD4+ T cell count at which patients should be considered at "high risk."[22] We also do not know whether current or nadir CD4+ T cell counts are more predictive of risk. In addition, measures other than CD4+ T cell counts may also be predictive of risk. CMV viremia has been identified as a predictor of CMV disease in patients infected with HIV[2,6,14,24,36,37]. The sensitivities of blood and urine cultures have been reported to be 38% and 85%, respectively, and the specificities 74% and 29%, respectively[37]. Plasma CMV PCR assays, either qualitative or quantitative, may be a better predictor of risk for CMV disease than cultures. The sensitivity of qualitative PCR has been reported as 84% and 89%, and the specificity as 89% and 75%[2,37]. Quantitative CMV PCR assays[1] performed serially may provide additional predictive ability beyond that of qualitative PCR[11]. Further research is needed to determine the value of their clinical use. Measurement of CMV viremia may supplement or replace CD4+ T cell counts as the major predictor of CMV disease. Analyses involving CMV viremia have shown that CD4+ T cell count did not add significantly to the ability to predict risk[14,37].

The collection of virologic data in LSOCA will allow examination of the biological interaction of HIV and CMV. CMV has been proposed as a cofactor in the pathogenesis of HIV disease[3,16,28,38]. Epidemiological evidence from hemophiliac patients suggests that CMV seropositivity is associated with an increased risk for the progression of HIV infection to AIDS[34,35,40,41]. Preliminary *in vitro* evidence suggests a role of CMV as a cofactor in AIDS. One study reported that cells infected with CMV produced receptors similar to those that bind HIV[32]. Because HIV and CMV may transactivate each other, it also may be true that HIV RNA level is predictive of the development and course of clinical CMV disease.

Relationships between the clinical course of ocular complications of AIDS and treatment strategies will be examined. Although randomized, controlled clinical trials provide the best mechanism for the estimation of treatment efficacy, longitudinal studies provide "real world" effectiveness data in the absence of trials, and also assist in the interpretation of data from clinical trials. Such studies also allow for collection of data from a larger number and wider spectrum of patients than is typically available from clinical trials. The proposed longitudinal study design, with active, direct followup — which is the strongest type of observational study to use for the estimation of treatment effects[12] — will help elucidate the long-term impact of CMV and HIV therapies on visual function, quality of life, and survival.

2. Objectives

2.1. Objectives

The Longitudinal Study of Ocular Complications of AIDS (LSOCA) is a prospective, observational study designed to provide information on the incidence and course of ocular complications of AIDS in the face of changing anti-HIV and anti-CMV therapies. The objectives are:

- To monitor secular trends in the incidence of CMV retinitis and other ocular complications of AIDS.
- To determine the effect of HAART-induced changes in immune status on the risk of CMV retinitis and other ocular complications of AIDS.
- To determine the characteristics (clinical, virologic, hematologic, and biochemical) of populations at high risk for CMV retinitis and other ocular complications of AIDS.
- To evaluate the effects of treatments for CMV retinitis and other ocular complications on visual function, quality of life, and survival.

2.2. Design

The study is a multicenter, prospective study design to enroll 2,800 patients with AIDS. Patients with a diagnosis of AIDS according to the 1993 CDC diagnostic criteria for AIDS and diagnosed on or after 01 January 2001 will be eligible for enrollment. The outcomes of primary interest are incidence of CMV retinitis and other ocular complications, and mortality. Outcomes of secondary interest include incidence of sequelae of AIDS-related eye disease (e.g., retinal detachments), incidence of complications of therapy, and long-term outcomes of ocular complications (e.g., visual function, quality of life).

3. Patient enrollment

Recruitment, assessment of eligibility, and enrollment will be performed at participating SOCA clinical centers (Appendix 3, page 38). Patients considering participating in the study will be given the consent statement; the study and any questions about it will be discussed before they decide whether to enroll in the study.

3.1. Inclusion criteria

- A diagnosis of AIDS according to the 1993 Centers for Disease Control and Prevention (CDC) definition (with or without clinical symptoms of CMV retinitis or other ocular complications of AIDS)
- Age 13 years or older
- Signed consent statement
- Patients with newly diagnosed (within 45 days of enrollment) Ocular Opportunistic Infections (OOIs)
- Patients without a newly diagnosed Ocular Opportunistic Infection (OOI) diagnosed with AIDS after 1 Jan 2001

3.2. Exclusion criteria

None.

3.3. Enrollment of patients with Ocular Opportunistic Infection (OOI)

As stated in section 3.1, patients with existing CMV retinitis or other ocular complications diagnosed on or after 1 Jan 2001 are eligible for enrollment. In order to have sufficient power to detect differences in visual outcomes or mortality associated with treatments or other factors in this group of patients, at least 300 patients will be enrolled. The maximum number of such patients to be enrolled will be 600.

3.4. Participation in other studies

Patients enrolled in LSOCA may be enrolled in other studies including treatment trials, and vice versa. Consolidation of study visits between LSOCA and other studies is encouraged when possible to avoid duplicate tests done on patients.

3.5. Monitoring

Characteristics of patients enrolled, such as the proportion of the cohort with prevalent CMV retinitis, will be monitored by the Coordinating Center and the SOCA Policy and Data Monitoring Board. If the characteristics of the patient population enrolled or the rate of enrollment are such as to jeopardize the goals of the study, the eligibility criteria and enrollment guidelines may be modified.

3.6. Consent

Once it has been determined that a patient is eligible for the study, the specifics of the study will be explained and discussed with the patient. Patients considering participating in the study will be given the consent statement and should be allowed sufficient time to decide whether to enroll. Patients 13-17 years old will be provided an Assent Statement, which should be reviewed and signed by both the patient and his/her parent or guardian. The Consent Statement should be reviewed and signed by the parent/guardian as well. It is important to give patients the time they need to ensure informed consent.

4. Data collection plan

All patients will be on a 6-month followup schedule. All followup visits will be clinic visits (Appendix 1A, page 26) with telephone contact in between clinic visits (Appendix 1B, page 27). Patients who enrolled in the study with No Ocular Opportunistic Infection (No OOI) and develop one during followup will be switched to the same data collection schedule as patients who enrolled with an Ocular Opportunistic Infection (OOI) (Appendix 1A, page 26). Data will be collected at every clinic visit, at the time of diagnosis of, an Ocular Opportunistic Infection (OOI) or at the time of death. These are data collection schedules, not patient care schedules. All patients will be followed until death or a common study closeout. Study closeout is expected to occur one year after enrollment of the last patient.

Data collection will include ophthalmologic examination, fundus photographs as appropriate, medical history, treatment history for AIDS and CMV diseases, and quality of life assessment. Laboratory studies and blood specimens for banking also will be obtained.

4.1. Telephone visits

Patients will be contacted by telephone or mail at the halfway point (3 months) between followup visits at the clinic to ascertain vital status and screen for eye conditions developed during the interval. These contacts are considered scheduled followup visits. Patients reporting eye problems will be scheduled for an eye examination by a study ophthalmologist.

4.2. Ophthalmologic evaluations

The recommended order for ophthalmologic procedures is as follows: assessment of best corrected visual acuity with refraction first, followed by assessment of contrast sensitivity, Humphrey field, Goldmann field, and then ophthalmologic exam and fundus photography.

Ophthalmologic examinations will be conducted at baseline, at the time of diagnosis of an Ocular Opportunistic Infection (OOI), and at every clinic followup visit. Examinations will include assessment of best corrected visual acuity with refraction, Pelli-Robson contrast sensitivity test, ~~biomicroscopy~~, measurement of intraocular pressure (IOP), evaluation of pupils, assessment of motility and alignment, and dilated indirect ophthalmoscopy.

Visual field testing will be conducted using Humphrey field analyzer and Goldmann perimeter. Automated perimetry with the Humphrey field analyzer using the 24-2 program for threshold testing will be performed at baseline and annually on all patients, with or without an Ocular Opportunistic Infection (OOI). Humphrey field testing also will be conducted at the time of diagnosis of an Ocular

Opportunistic Infection (OOI).

Visual field with Goldmann perimeter will be performed only at baseline for patients without an Ocular Opportunistic Infection (OOI). For patients who enrolled in the study without an Ocular Opportunistic Infection (OOI) and develop one during followup, Goldmann field testing will be performed at the time of diagnosis of Ocular Opportunistic Infection (OOI), and at every followup visit thereafter. For patients who enrolled in the study with an Ocular Opportunistic Infection (OOI) , Goldmann field testing will be performed at baseline, at the time of diagnosis of an Ocular Opportunistic Infection (OOI), and at every followup visit.

Procedures for visual acuity, refraction, and Goldmann visual fields are described in the SOCA General Handbook. Procedures for contrast sensitivity and automated perimetry are described in the LSOCA Handbook.

4.3. Fundus photography

Fundus photographs will be taken at baseline and every 5 years for patients without an Ocular Opportunistic Infection (OOI). If a patient has already completed a five year visit (e.g., Followup Visit 20), then the fundus photographs should be obtained at the next scheduled visit. For patients who enrolled in the study without an Ocular Opportunistic Infection (OOI) and develop one during followup, fundus photographs will be taken at the time of diagnosis of an Ocular Opportunistic Infection (OOI), and at every followup visit thereafter. For patients who enrolled in the study with an Ocular Opportunistic Infection (OOI), fundus photographs will be taken at baseline, at the time of diagnosis of an Ocular Opportunistic Infection (OOI), and at every followup visit.

Photographs will be taken as described in the Fundus Photograph Reading Center (FPRC) protocol located in the SOCA General Handbook.

4.4. Medical history

Medical history will be obtained via patient interview. Interviews will be conducted at baseline and at every clinic followup visit. Medical history will include ophthalmic history, health history, date of AIDS diagnosis, basis for AIDS diagnosis, occurrence of opportunistic infections and other manifestations of AIDS, and treatment history for HIV and CMV. ACTG diagnostic criteria and coding scheme will be used to define opportunistic infections (OI's). A questionnaire regarding symptoms of CMV disease will be administered as part of the medical history review. Information regarding the patient’s insurance status, and changes in insurance status also will be collected.

4.5. Quality of life

Quality of life measures will be collected at baseline and at every clinic followup visit. A questionnaire will be used to collect information regarding health-related quality of life, a subjective assessment of vision and overall quality of life (utility). It is recommended that the quality of life questionnaire be administered at the beginning of the visit to avoid events during the visit from influencing responses to the questionnaire.

4.6. Laboratory studies

Laboratory studies will be conducted at baseline and at every clinic followup visit. Laboratory data collected in the context of another study may be used for LSOCA if the data were collected within the visit time window.

Laboratory studies will include hematology serum chemistry and lymphocyte subset analysis for all patients. The amount of blood for hematology, serum chemistry, and lymphocyte subset analysis is restricted to no more than a total of 17 mL per draw. Data existing on HIV viral load analysis at the clinic will be collected. If HIV data are not available from medical records within the visit time window, blood should be collected for local HIV viral load determination.

4.7. Specimen banking

Plasma and leukocytes will be collected for banking at baseline and at every clinic followup visit. Blood (15 mL) will be collected into two 8.5 mL yellow-top ACD tubes and processed locally to obtain aliquots of plasma and 5 x 10^6 cell aliquots for banking. Procedures for collection and shipment of blood specimens for banking are described in the LSOCA Handbook. Other virologic and immunologic measurements will be made based on the advice of the SOCA Study Officers and other experts.

4.8. Interim visits

Patients will be instructed to notify the clinic and schedule a clinic visit whenever they experience a problem with their eyes or vision or are informed of a diagnosis of an Ocular Opportunistic Infection (OOI) If a study visit at the clinic for that visit window has already occurred, such a visit will be deemed an "interim visit." Data will be collected at an interim visit only if the patient is diagnosed with an Ocular Opportunistic Infection (OOI). Data to be collected at an interim visit include eye history, eye examination, visual acuity, contrast sensitivity, Humphrey and Goldmann visual field, contrast sensitivity, and fundus photography.

If the patient is diagnosed with an Ocular Opportunistic Infection (OOI) at a clinic visit that is not an interim visit, all evaluations and procedures for an Ocular Opportunistic Infection (OOI) for that visit will be performed. Patients diagnosed with an Ocular Opportunistic Infection (OOI) either at an interim visit or at a scheduled followup visit will be seen at the clinic for all subsequent followup visits.

4.9. Missed visits

Patients will be contacted by phone for missed visits to ascertain vital status, to obtain information on eye problems, and to conduct quality of life assessment.

5. Outcome measures

The outcomes of primary interest are incidence of CMV retinitis, incidence of other ocular complications, and mortality. Additional outcomes of interest include incidence of sequelae of AIDS-related eye disease (e.g., rhegmatogenous retinal detachment, macular edema), incidence of complications of treatment, visual function and quality of life.

5.1. Incidence of AIDS-related eye diseases and ocular complications

Incidence of CMV retinitis and other AIDS-related eye diseases and ocular complications, such as retinal detachments, will be defined as the number of newly diagnosed cases out of the total number of person-years of followup at risk from patients without the complication of interest. Methods to estimate net incidence and time with CMV retinitis will take into account patients' high risk for death.

Data will be collected on the incidence and characteristics of ocular complications that are a direct result of HIV disease, opportunistic infections, or a complication of ocular disease or their treatment. Definitions of ocular complications are provided in Appendix 2 (page 28).

5.1.1. Ocular Opportunistic Infection (OOI) ~~Major ocular complications~~

For purposes of LSOCA, major ocular complications are defined as those that are chronic and place a patient at significant risk for prolonged or permanent vision loss. These include:

- CMV retinitis,
- Herpetic retinitis,
- Toxoplasmic retinitis,
- Cryptococcal choroidopathy,
- Pneumocystic choroidopathy,

5.1.2. No Ocular Opportunistic Infection (OOI)

Other ocular complications of interest include: large vessel vaso-occlusive disease, and optic nerve abnormalities: papilledema, optic nerve disease associated with cryptococcal meningitis, or other serious optic neuropathy, HIV retinopathy, syphilitic retinitis, macular edema, epiretinal membrane, cranial nerve lesions, keratitis/conjunctivitis, Kaposi's sarcoma of the ocular adnexae, lymphoma, molluscum contagiosum, cataract, and complications of infections or their treatment such as retinal detachment, uveitis, and hypotony.

5.2. Mortality

Time to death will be measured from the date of enrollment to date of death and will be censored at study closeout for patients still living.

5.3. Visual function

Outcome measures for visual function in patients with AIDS-related eye diseases will include change in best corrected visual acuity from baseline, incidence of significant vision loss (e.g., < 20/200), change in visual field from baseline, and change in contrast sensitivity from baseline.

5.3.1. Visual acuity

Best corrected visual acuity will be measured using logarithmic visual acuity charts according the protocol developed for the Early Treatment Diabetic Retinopathy Study (ETDRS)[10]. Visual acuity will be expressed as the number of letters read correctly (visual acuity score). Change in visual acuity will be expressed as the decrease in the number of total letters read in best corrected vision from baseline or from the time of diagnosis for patients without AIDS-related eye diseases at enrollment. Visual acuity events will be defined as loss of 15 letters of vision, a doubling of the visual angle, or visual acuity 20/200 or worse.

5.3.2. Contrast sensitivity

Contrast sensitivity will be measured with the Pelli-Robson chart. The threshold contrast sensitivity value (the lowest contrast level at which at least 2 of the 3 letters were reported correctly),[31] as well as the "by-letter" contrast sensitivity score (giving credit for each individual letter read correctly)[7] will be used to assess change in contrast sensitivity and rate of change over time.

5.3.3. Visual field

Visual field with Goldmann perimeter will be measured using the Diabetic Retinopathy Study visual field protocol[5]. A visual field score is computed by summing the degrees of field along 12 meridians. Change in visual field will be expressed as the decrease in the number of total degrees of field from baseline or from the time of diagnosis for patients without AIDS-related eye diseases at enrollment. Rate of visual field loss per month also will be evaluated.

Visual field with Humphrey field analyzer using the 24-2 program for threshold testing will be measured according to the Humphrey Field Analyzer User's Guide[4]. Patient reliability will be assessed by fixation losses, false-negative responses, and false-positive responses. Four global indices: mean deviation (MD), pattern standard deviation (PSD), short-term fluctuation (SF) and corrected pattern standard deviation (CPSD), which summarize the point-by-point field data into single numbers will be used to assess deficits and intra-test reliability. Field change and rate of

change will be evaluated. Additionally, the glaucoma hemifield test (GHT) will be used to assess for asymmetric visual thresholds. The proportion of patients with normal, borderline, and abnormal GHT will be estimated.

5.4. Quality of life

A questionnaire will be used to measure health status and subjective visual function. The questionnaire includes the SOCA vision-related instrument[43], the Medical Outcome Study Short-form General Health (MOS-HIV) Survey[44], and the EuroQoL[9]. The vision-related instrument and the MOS-HIV will provide data on self-evaluated ability to see, ability to perform functions of daily life, and overall health status. The EuroQoL provides utility scores which allow estimation of quality-adjusted life years. Quality-adjusted life years incorporate both quality and length of survival time into a single measure[13,15,39]. These data will be used separately and in combination to evaluate visual function and its relationship to overall quality of life.

5.5. Other morbidity

The incidence of extraocular CMV disease and other opportunistic infections will be compared among subgroups of patients. ACTG diagnosis codes will be used to define opportunistic infections.

6. Biostatistics

6.1. Data analysis

Secular trends in the rates of ocular complications of AIDS will be examined by observing changes in annual incidence in the longitudinally followed cohort. These trends also will be evaluated among subgroups of patients. Incidence will be defined as the number of newly diagnosed cases of specific ocular complications out of the total number of person-years of followup from patients without the complication in question. In addition, methods to estimate net incidence and time with CMV retinitis in patients at high risk for death will be employed. These methods allow for the incorporation of death as a censoring event but do not require the usual assumption of an equivalent experience among censored individuals as those who remain under followup[18]. Estimates of probabilities of events are usually lower using these methods because once patients are censored due to death they are not assumed to have any events.

Relationships between clinical course of ocular complications of AIDS and treatment strategies will be examined. Comparisons of disease progression, visual outcomes, and survival among subgroups of patients defined by demographic and clinical characteristics and by treatment history will be conducted adjusting for potential confounders with proportional hazards regression techniques. Of particular interest are the long-term effects associated with discontinuation of secondary prophylaxis (maintenance therapy) among patients with CMV retinitis who respond to HAART. For this analysis, HAART response will be explored in terms of an increase in CD4+ T cell counts and/or a decrease in HIV RNA viral load. Since a major risk factor identified for CMV retinitis is low CD4+ T cell counts[19,21,36], we will explore using change in CD4+ T cell counts as one way to gauge HAART response. For example, HAART response may be defined as an increase in CD4+ T cell counts from $\leq$ 50 cells/μL to $\geq$ 100 cells/μL. The duration of HAART use, time of first use, and use of HAART as a time-dependent covariate also will be explored.

The effect of HAART response and other factors on the incidence of ocular complications of AIDS, particularly CMV retinitis, will be addressed by estimating the relative risk of ocular complications among different subgroups. Baseline and time-dependent risk factors for development of ocular complications, including demographic characteristics, HIV treatment, CMV prophylaxis, HIV and CMV viral load, and CD4+ T cell counts (current and nadir levels), will be explored using Cox regression models for incident and recurrent CMV retinitis and other ocular complications[25,26]. Predictive models estimating risk of developing CMV retinitis and other ocular complications will be explored using logistic regression and parametric survival models such as lognormal and Weibull. The interrelationship of HIV viral load, CMV viral load, and CD4+ T cell counts over time will be explored. The bidirectional effect of HIV load on CMV disease and CMV viremia also will be explored.

Use of HIV viral load has proved to be an important tool for management of HIV-infected patients. Similarly, the measurement of CMV viral load along with CD4+ T cell counts is likely to improve our ability to identify patients at high risk of CMV retinitis, which currently is based only on CD4+ T cell counts. Even if the use of both tests together proves no better than the use of either test alone at identifying populations at high risk for CMV disease, it will still be important to determine an optimal algorithm for the clinical use of these tests.

The results of these analyses will be used to identify populations at high risk for ocular complications, who might be targeted for screening or primary prophylaxis.

6.2. Sample size consideration

We anticipate enrolling a cohort of 2,800 patients with AIDS for additional followup. At least 300 patients but no more than 600 patients with existing CMV retinitis will be enrolled. The overall sample size and the minimum and maximum number of patients enrolled with existing CMV retinitis are determined based on the ability to meet study objectives and on the basis of resource availability.

Data analysis for LSOCA will be largely exploratory, ie, hypothesis generating, rather than hypothesis testing. However, the planned sample has sufficient power to test certain specific hypotheses, eg, response to HAART therapy and the development of CMV retinitis. It is large enough to detect reasonable relative risks (ie, a relative risk of 2) for other unspecified hypotheses, even for rare events.

Table 1. Minimum detectable relative risk* of development of CMV retinitis

CMV retinitis rate† in HAART responders	% with nadir CD4 ≤ 50 cells/μL	
	50%	30%
2.5%	1.98	2.32
5%	1.68	1.91
10%	1.48	1.64
15%	1.40	1.53

*Specifications for calculations: total number of patients enrolled free of CMV retinitis = 1,400; type I error = 0.05; power = 80%; exponential survival function and proportional hazards; accrual = 4 years; followup after sample size is achieved = 1 year; loss to followup = 10%; and proportion respond to HAART = 50%.
†Annual rate in patients with nadir CD4+ T cell counts ≤ 50 cells/μL who respond to HAART.

Table 1 provides estimates of the minimum detectable relative risk of developing CMV retinitis in patients with a nadir CD4+ T cell counts ≤ 50 cells/μL in relation to HAART response if 1,400 patients initially free of CMV retinitis are enrolled in the study, assuming that 50% of the patients are HAART responders (the hypothesized proportion of patients who respond to HAART therapy has little effect on these estimates). Each row corresponds to a hypothesized CMV retinitis rate among patients initially free of CMV retinitis who respond to HAART; each column corresponds to a hypothesized proportion of patients enrolled with a nadir CD4+ T-cell counts ≤ 50 cells/μL. (A review of medical records for a subset of AIDS patients seen at the Johns Hopkins SOCA clinical center in the first 6 months of 1997 revealed that about 50% of the patients seen had a nadir CD4+ T cell count ≤ 50 cells/μL.) Because some patients with a nadir CD4+ T cell count > 50 cells/μL at enrollment will move into a higher risk group during followup, an even smaller relative risk may be detected. However, the clinical course for these patients on HAART therapy cannot be anticipated at this time. In addition, these calculations are based on patients with nadir CD4+ T cell counts ≤ 50 cells/μL only. Patients with CD4+ T cell counts > 50 cells/μL have a lesser, but real, risk of CMV retinitis. When these patients are included in the calculations, the detectable relative risks are smaller than those presented in the table.

The study needs to enroll a minimum sample size of 300 patients with existing CMV retinitis to allow detection of a relative risk (RR) of 2 for pairwise comparisons among three equally sized risk groups (eg, by treatment regimen or viral load) if the one–year event rate (eg, vision loss or mortality) in the referent (low risk) group is 10%. A larger sample size is needed if the event rate is less than 10%.

Table 2. Minimum detectable relative risk for vision loss greater than three lines in patients with CMV retinitis*

Rate† of vision loss > 3 lines in the referent group	Sample size	
	300	600
5%	2.40	1.93
10%	1.99	1.66
15%	1.82	1.55
20%	1.72	1.48

*Specifications for calculations: type I error = 0.05; power = 80%; exponential survival function and proportional hazards; accrual = 4 years; followup after sample size is achieved = 1 year; loss to followup = 10%; three equally sized groups.
†Annual rate in patients with CMV retinitis in the referent group.

Table 2 provides estimates of the minimum detectable relative risk for vision loss greater than three lines in patients with CMV retinitis. Each row corresponds to a hypothesized proportion of patients with vision loss greater than three lines in one year in the referent group (In the Monoclonal Antibody Cytomegalovirus Retinitis Trial, about 50% of the patients had vision loss greater than three lines at one year); each column corresponds to the proposed minimum and maximum number (the maximum number is limited by the number of patients enrolled free of CMV retinitis and the total resource availability) of patients enrolled with existing CMV retinitis. These estimates are conservative as patients who develop CMV retinitis during followup also will be included in the analysis.

The Coordinating Center and the SOCA Policy and Data Monitoring Board will review event rates and patient characteristics (eg, proportion of patients with a nadir CD4+ T cell counts $\leq$ 50, proportion of patients respond to HAART) periodically. The proposed sample size will be adjusted as necessary to maintain adequate power for analysis.

7. Rights and responsibilities

7.1. IRB approval

This protocol will be submitted to the Institutional Review Board (IRB) of participating centers for review and approval. Clinics may not start recruiting patients into the study prior to approval of this protocol by their local IRB. All study patients must sign a consent statement and medical record release form.

7.2. Confidentiality of patient data

All patient data will be kept in a secure place. Name, social security number, address and other such personal data will not be used by the Coordinating Center. Data collected from study evaluations and interviews will be identified by study ID codes only; a patient ID number and name code will be assigned at registration. Clinically relevant information may be placed in the patient's medical record. Release of data to any other persons or organizations will require the written consent of the patient.

8. Biohazards

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

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Appendix

Appendix 1.A: Data collection schedule for patients with an Ocular Opportunistic Infection (OOI)

	Visit code/Target month from enrollment								
Month	BL 0	F1 3	F2 6	F3 9	F4 12	F5 15	F6 18	F7 21	F8 ... 24 ...
Eligibility review	X								
Telephone interview		**X**		**X**		**X**		**X**	
Ophthalmologic Visual acuity with refraction Contrast sensitivity Slit lamp exam Intraocular pressure Dilated indirect ophthalmoscopy	X		X		X		X		X
Humphrey visual field	X				X				X
Goldmann visual field	X		X		X		X		X
Fundus photographs	X		X		X		X		X
Health history AIDS history Treatment history for HIV/CMV Other treatments	X		X		X		X		X
Laboratory studies Hematology Serum chemistry T-cell subsets HIV viral load*	X		X		X		X		X
Specimen collection Plasma Leukocytes	X		X		X		X		X
Quality of Life	X		X		X		X		X

*Blood collection for local HIV viral load analysis should be obtained if HIV data are not available from medical records within the visit time window

Appendix 1.B: Data collection schedule for patients without an Ocular Opportunistic Infection (OOI)

	Visit code/Target month from enrollment									
Month	BL 0	F1 3	F2 6	F3 9	F4 12	F5 15	F6 18	F7 21	F8 ... 24 ...	~~F20~~ ~~60~~
Eligibility review	X									
Telephone visit*		X		X		X		X		
Ophthalmologic Visual acuity with refraction Contrast sensitivity Slit lamp exam Intraocular pressure Dilated indirect ophthalmoscopy	X		X		X		X		X	
Humphrey visual field	X				X				X	
Goldmann visual field	X									
Fundus photographs‡	X									~~X~~
Health history AIDS history Treatment history for HIV/CMV Other treatments	X		X		X		X		X	
Laboratory studies Hematology serum chemistry T-cell subsets HIV viral load‡	X		X		X		X		X	
Specimen collection Plasma Leukocytes	X		X		X		X		X	
Quality of Life	X		X		X		X		X	

*Patients without **an Ocular Opportunistic Infection (OOI)** ~~a major ocular complications~~ will be contacted by telephone or mail between followup visits at the clinic to ascertain vital status and screen for eye conditions developed during the interval. Patient reporting eye problems will be scheduled for an eye exam by study ophthalmologists

†Blood collection for local HIV viral load analysis should be obtained if HIV data are not available from medical records within the visit time window

‡Fundus photographs will be taken at Baseline and every five years, or if patients' five year visit has passed, photographs to be obtained at the next schedule visit.

Appendix 2: Definitions of ocular complications (OOI and other complications)

A. Posterior segment syndromes

1. Infectious retinitis

Cytomegalovirus (CMV) retinitis: Caused by CMV, a type of herpesvirus, this necrotizing retinitis presents with lesions that have either edematous or granular white borders. Lesions typically extend slowly into the remaining normal retina over time. Hemorrhages are frequently present. Diagnosis may be made based on the characteristic clinical picture.

Herpetic (non-CMV) retinitis: For purposes of LSOCA, herpetic retinitis other than CMV retinitis will be grouped together. These include varicella zoster (VZV) and herpes simplex (HSV) retinitis. These present with two major syndromes: acute retinal necrosis, and progressive outer retinal necrosis. Which agent is the cause of either of these syndromes cannot typically be determined without testing of vitreous samples.

Acute retinal necrosis is characterized by confluent, full-thickness, yellow necrotizing retinitis with little or minimal hemorrhage, with or without overlying vitritis. It usually begins in the far retinal periphery, extends circumferentially, and rapidly progresses posteriorly. Diagnosis may be made based on the characteristic clinical picture.

Progressive outer retinal necrosis is characterized by a multifocal rapidly progressive yellow necrotizing retinitis with early posterior pole involvement, which clinically appears to affect primarily the outer retina. However, histologically this is a full-thickness retinitis. Diagnosis may be made based on the characteristic clinical picture.

Toxoplasmic retinitis: Caused by the parasite Toxoplasma, this retinitis is characterized by focal yellow-white necrotizing retinal lesion(s) with fluffy borders and no or few scattered intraretinal hemorrhages. It is usually associated with an overlying vitritis, which may be profound. In AIDS, the condition may result from new infection, or a reactivation of prior infection, in which case the lesion usually occurs adjacent to typical fundus scars with focal atrophy of the retina and choroid with RPE clumping. Diagnosis may be made by clinical examination in many cases, though in some cases further data and/or a therapeutic trial are needed to establish the diagnosis.

Syphilitic retinitis (or chorioretinitis): Caused by infection with a spirochete, syphilis may cause several ocular inflammatory syndromes including retinitis or chorioretinitis. Syphilitic retinitis does not have as characteristic of a presentation as the complications listed above, and may have various patterns. Diagnosis requires a positive specific serologic test for syphilis, a clinically compatible retinitis picture, and usually evidence of resolution with specific anti-syphilis therapy.

2. Non-infectious retinal disease

Non-infectious HIV retinopathy: Presumed to be caused by the effects of HIV infection without other supervening opportunistic infection, this is an occlusive microangiopathy characterized by microinfarctions of the retinal nerve fiber layer ("cotton-wool spots"). In some cases intraretinal blot hemorrhages are present. Diagnosis is based on the typical clinical appearance in an HIV-infected patient after excluding other possible causes of a similar syndrome, such as diabetes and hypertension.

3. Choroidopathy

Infectious choroidopathies occur infrequently in AIDS, and may result from Pneumocystosis (most commonly classified as a parasite), Cryptococcosis or other fungal infections, Mycobacterial infections, and perhaps other causes. Methods of defining the causal agent are not uniform; they may rely upon systemic disease status, response to therapy, clinical appearance, and/or biopsy. Pneumocystis choroidopathy often presents with multiple pale 1-3 mm lesions with minimal retinal dysfunction or other inflammation. Other choroidopathies have not been observed frequently, making it difficult to define a "typical" clinical presentation. For purposes of LSOCA, diagnosis of choroidopathy will be based on compatible choroidal lesions, with characterization of the most likely etiology based on the above as interpreted by best ophthalmologic judgment.

4. Large vessel vaso-occlusive disease

Central retinal vein occlusion: Obstruction/reduction of blood flow through the central retinal artery, typically resulting in diffuse superficial hemorrhages and retinal swelling in all four quadrants of the retina, often with cotton-wool spots, and thickening/tortuosity of the retinal veins. Diagnosed by clinical presentation, sometimes supplemented by fluorescein angiography. "Ischemic" and "non-ischemic" subtypes exist, which may be differentiated by clinical presentation and/or fluorescein angiography.

Branch retinal vein occlusion: Obstruction/reduction of blood flow through a branch retinal artery focal, typically resulting in an area of retina with superficial hemorrhages and retinal swelling often with cotton-wool spots, and often associated with thickening and tortuosity of the vein in that segment of retina. Diagnosed by clinical presentation, sometimes supplemented by fluorescein angiography.

Central retinal artery occlusion: Obstruction of blood flow through the central retinal artery, usually with near immediate profound vision loss. Within hours edematous opacification and thickening of the retina occurs, typically with eventual appearance of a "cherry red spot" in the center of the macula. Diagnosed by clinical presentation, sometimes supplemented by fluorescein angiography.

A. Posterior segment syndromes

Branch retinal artery occlusion: Obstruction of blood flow through a branch retinal artery, usually with near immediate visual dysfunction. Edematous opacification and thickening of the retina follows in hours. Diagnosed by clinical presentation, sometimes supplemented by fluorescein angiography.

5. Secondary retinal lesions

Macular edema: Swelling of the macula diagnosed by clinical examination, fluorescein angiography, or other accessory studies.

Epiretinal membrane: A preretinal proliferation of cells causing traction on the retina. Diagnosed by clinical presentation.

B. Neuro-ophthalmologic lesions

1. Optic nerve lesions

Optic neuritis: Optic neuritis is an acute inflammatory demyelinating disease of the optic nerve. The clinical syndrome is similar whether or not multiple sclerosis is present. Visual loss in optic neuritis is usually sudden and often accompanied by pain. The degree of visual loss varies widely from a mild visual field deficit to no light perception. Patients with acute optic neuritis virtually always have abnormalities in color vision, visual field, contrast sensitivity, light brightness sense, and pupillary reaction. The optic disc may be edematous ("papillitis") or normal ("retrobulbar neuritis") in appearance.

Optic neuropathy: Optic nerve dysfunction as manifested by dyschromatopsia, visual field defects, and/or reduced visual acuity; not meeting criteria for Optic neuritis (above). Diagnosed by clinical findings.

Papillaedema/Optic nerve swelling: Optic nerve edema diagnosed by clinical examination without optic neuropathy, and associated with intracranial pressure.

Non-glaucomatous optic atrophy: Atrophy of the optic nerve, as demonstrated by pallor of the optic nerve with reduced thickness of the nerve fiber layer. Potential etiologies include infection, toxicity, malnutrition and others. Diagnosed by clinical presentation.

Glaucomatous optic atrophy: Loss of optic nerve tissue with typical changes in the morphology of the optic nerve head (cupping/excavation, notching, undercutting of the retinal vessels), associated with visual field defects with a consistent pattern. Usually associated with elevated intraocular pressure. Diagnosed by clinical presentation. Many subtypes exist. Note: elevated intraocular pressure without optic nerve damage should not be diagnosed as glaucomatous optic atrophy.

A. Posterior segment syndromes

2. Cranial nerve lesions, and central disorders of eye movements

Oculomotor nerve lesions: Hypo- or non-function of part or all of the oculomotor nerve, typically resulting in ipsilateral eye movement, upper eyelid movement and pupillary abnormalities. Diagnosed by clinical presentation.

Trochlear nerve lesions: Hypo- or non-function of the trochlear nerve, resulting in ipsilateral superior oblique dysfunction, usually with a vertical deviation. Diagnosed by clinical presentation.

Abducens nerve lesions: Hypo- or non-function of the abducens nerve, resulting in ipsilateral lateral rectus dysfunction, and resultant ipsilateral eye movement abnormalities. Diagnosed by clinical presentation.

Central lesions causing eye movement disorders: Eye movement abnormalities attributable to specific brain lesions/disorders at a level "higher" than the cranial nerve nuclei. Many disorders exist (refer to neuro-ophthalmology texts). Diagnosed by clinical presentation, often supplemented by imaging or other studies.

Trigeminal Nerve Lesions: Dysfunction of the trigeminal nerve, with ipsilateral reduction of facial sensation and/or strength of the masticatory muscles. Diagnosed by clinical presentation.

Facial Nerve Lesions: Dysfunction of the facial nerve, resulting in ipsilateral reduction of facial strength, and other dysfunctions depending on the location of the lesion within the course of the facial nerve. Diagnosed by clinical presentation.

Strabismus (non-paralytic): A non-alignment of the eyes not of specific neurologic etiology, diagnosed by clinical presentation.

C. Anterior segment lesions

Keratitis: Inflammation of the cornea, not including cases with keratic precipitates and no other corneal inflammation. Etiology may be infectious or autoimmune. Diagnosis is based on clinical examination, supplemented by cultures, scrapings, and/or biopsy when appropriate. Specific infectious agents include bacteria, viruses, microsporidia, and fungi.

Conjunctivitis: Inflammation of the conjunctiva, of infectious or inflammatory (non-infectious) etiology. Diagnosis is based on clinical examination, supplemented by cultures, conjunctival scrapings, and/or biopsy where appropriate. Infectious organisms causing conjunctivitis include viruses, chlamydiae, bacteria, and other pathogens-laboratory studies are typically required to implicate a specific infectious organism.

Cataract: An opacity of the lens diagnosed by ophthalmologic examination.

A. Posterior segment syndromes

D. Uveitic syndromes (not elsewhere specified)

Non-infectious uveitis: For purposes of LSOCA, uveitic syndromes without a specific infectious etiology are grouped under this heading, including autoimmune and idiopathic uveitis. Diagnoses are made according best ophthalmologic judgment. Clinicians should be able to provide the appropriate DRG code for these syndromes. Syndromes may be classified as anterior, intermediate, posterior, or pan- uveitic syndromes, based on the predominant location(s) of the inflammation in the eye, as well as the clinical presentation.

Immune reconstitution vitritis: Is the occurrence of intermediate uveitis in patients with CMV retinitis who have evidence of immune reconstitution, as shown by a rise in CD4+ T cell counts after the institution of highly active anti-retroviral therapy (HAART). Other causes of uveitis, e.g., syphilitic or other infections must be excluded.

E. Lesions of the ocular adnexae

Kaposi's sarcoma: A vascular tumor characterized as a malignant sarcoma, which may affect skin, mucosa, and internal organs. The lids, conjunctivae, and orbit may be affected. The tumor is typically multifocal. The tumor may be diagnosed by its characteristic clinical appearance or by histologic characteristics.

Lymphoma: Tumors consisting of a pathologic proliferation of lymphoid cells. Diagnosed by histologic characteristics.

Molluscum contagiosum: A viral infection of the skin periocular skin caused by a specific virus, creating a characteristic umbilicated, raised lesion. Diagnosed by clinical presentation or biopsy.

F. Complications of HIV-related diseases of the eye and of therapy (not described elsewhere)

Retinal Detachment: Separation of the neurosensory retina from the underlying pigment epithelium as a result of retinal holed ("rhegmatogenous"), an effusion of fluid ("serous"), or traction on the retina ("tractional"). Diagnosed by ophthalmologic examination and/or ultrasonography.

Hypotony: Persistently low intraocular pressure other than in the immediate post-operative period. Diagnosed by tonometry. Toxicity scale: mild: < 50% reduction from baseline intraocular pressure (IOP) or IOP > 10 mm Hg; moderate: ≥ 50% reduction from baseline IOP to an IOP between 5 and 10 mm Hg; severe: ≥ 50% reduction from baseline IOP to an IOP < 5 mm Hg with no structural changes; severe: occurrence of ocular chagnes indicative of hypotony such as retinal or choroidal folds, elevation of optic nerve head, suprachoroidal effusions or hemorrhage, or corneal striate associated with an IOP ≤ 5 mm Hg.

Appendix 3: SOCA Centers

SOCA ID	Institution	Director
Clinical centers		
BCM	Cullen Eye Institute Baylor College of Medicine Houston, TX	Richard A. Lewis, MD
EU	Eye Center Emory University Atlanta, GA	Daniel F. Martin, MD
JHU	Wilmer Ophthalmological Institute Johns Hopkins University Baltimore, MD	James P. Dunn, MD
LSU	LSU Eye Center Louisiana State University New Orleans, LA	Donald Bergsma, MD
MSK	Memorial Sloan Kettering Cancer Center Cornell Medical Center New York, NY	Murk-Hein Heinemann, MD
NJMS	Department of Ophthalmology University of Medicine and Dentistry, New Jersey Newark, NJ	Ronald Rescigno, MD
NYU	Department of Ophthalmology New York University Medical Center New York, NY	Dorothy Friedberg, MD
NU	Northwestern University Chicago, IL	Alice Lyon, MD
PENN	Department of Ophthalmology Hospital of the University of Pennsylvania Philadelphia, PA	Charles Nichols, MD

Appendix 3: SOCA Centers

SOCA ID	Institution	Director
RUSH	Department of Ophthalmology Rush-Presbyterian - St. Luke's Medical Center Chicago, IL	Mathew MacCumber, MD
UC Irvine	Department of Ophthalmology University of California, Irvine Irvine, CA	Baruch Kupperman, MD, PhD
UCLA	Jules Stein Eye Institute University of California Los Angeles, CA	Gary Holland, MD
UCSD	Department of Ophthalmology University of California San Diego, CA	William Freeman, MD
UCSF	Beckman Vision Center University of California San Francisco San Francisco General Hospital San Francisco, CA	Jacque Duncan, MD
UNC	Department of Ophthalmology University of North Carolina Chapel Hill, NC	Travis Meredith, MD
USF	Department of Ophthalmology University of South Florida Tampa, FL	Peter Reed Pavan, MD
UTMB	University of Texas Medical Branch Galveston, TX	**Garvin Davis, MD**

Appendix 3: SOCA Centers

SOCA ID	Institution	Director
Resource centers		
CO	Chairman's Office Department of Ophthalmology Mount Sinai School of Medicine Mount Sinai Hospital One Gustave L. Levy Place Box 1183 New York, NY 10029-6574	Douglas A. Jabs, MBA
CC	Coordinating Center Center for Clinical Trials Johns Hopkins University Baltimore, MD	Curtis Meinert, PhD
FPRC	Fundus Photography Reading Center Department of Ophthalmology University of Wisconsin Madison, WI	Ronald Davis, MD
NEI	Project Office National Eye Institute Bethesda, MD	Natalie Kurinij, PhD
Support centers		
ThermoFisher Bioservices	Central Laboratory	Kathy Sease

Appendix 4: Design summary

Type of study

- Prospective, observational study
- Multicenter
- Sample size: approximately 2,800 patients

Inclusion criteria

- Diagnosis of AIDS according to the 1993 CDC diagnostic criteria (with or without clinical symptoms of CMV retinitis or other ocular complications of AIDS)
- Age 13 years old or older
- Signed consent statement
- Patients diagnosed with AIDS on or after 1 January 2001; or patients with newly diagnosed (within 45 days of enrollment) Ocular Opportunistic Infection (OOI)
- For minors, ages 13-17, signed Consent Statement (by parent/guardian) and Assent Statement (by adolescent and parent/guardian)

Exclusion criteria

None

Outcomes

- Primary outcomes
  - Incidence of ocular complications
  - Mortality
- Secondary outcomes
  - Incidence of sequelae of AIDS-related eye disease (eg, retinal detachment)
  - Incidence of complications of therapy
  - Long-term outcome of ocular complications (eg, incidence of blindness)
  - Incidence of extra-ocular CMV disease

Data collection schedule

- Baseline
- Every 6 months: clinic visits for patients with and without an Ocular Opportunistic Infection (OOI); alternating with telephone contact in between the clinic visits
- Interim visits only when diagnosis of a major ocular complication of AIDS is made
- Missed visits

Appendix 4: Design Summary

Data collection

- Demographic data
- Medical histories: medications and diagnosis
- Ophthalmologic data: status, diagnosis, and disease followup
- Fundus photographs
- Quality of life questionnaire
- Hematology, lymphocyte subset analysis, and serum chemistry
- Plasma HIV viral load
- Plasma and polymorphonuclear blood leukocytes specimens banked for future analysis

Analysis plan

- Examine secular trends of ocular complications
  - Changes in annual incidence in the longitudinally followed cohort
  - By subgroups
- Estimate relative risks of development of ocular complications among subgroups of patients, eg, by
  - Demographic characteristics
  - HIV treatment
  - HAART response
  - Use of CMV prophylaxis
  - HIV and CMV viral load
  - CD4+ T cell counts (current and nadir levels)
- Explore interrelationship of HIV viral load, CMV viral load, and CD4+ T cell counts over time
- Examine clinical course (disease progression, survival and visual outcomes) of ocular complications by patient characteristics and treatment strategies, eg,
  - Long-term effects of discontinuation of secondary prophylaxis among patients with CMV retinitis who respond to HAART
  - Local versus systemic therapies as primary treatments for ocular complications

Appendix 5: Consent statement

Purpose of study

You are being asked to take part in this research study, The Longitudinal Study of Ocular Complications of AIDS (LSOCA) because you have been diagnosed with AIDS, the condition caused by the human immunodeficiency virus (HIV). The purpose of the study is to learn how HIV infections and its treatments affect people's eyes and their sight. The study is being conducted at several clinics around the country. We plan to enroll approximately 2,800 patients and follow them for 4 years or longer. Your participation in the study is voluntary. If you decide not to take part in the study, it will not affect the quality of the medical care you receive at this institution.

Whether or not you decide to enroll in the study, you will continue to receive whatever treatments you and your doctor have chosen to treat your condition. This study does not pay for any medical treatments or any costs of your care. You will not receive drugs or treatment as part of LSOCA. If you want, you can take part in any other research study that you are eligible for, including other SOCA studies.

Procedures

If you enroll in the study, you will be asked to come to the clinic for study visits. The study visits will be every 6 months , and we will call you between the study visits to ask you a few questions about your eyes.

At all study visits, your eyes will be examined. We will test how well you can see by asking you to read letters on a chart. We will also test how well you can see things to the side. If you have or if you develop serious eye problems, we will take photographs of the inside of your eyes (fundus photographs). Fundus photographs will be taken at the Baseline visit and every five years thereafter for patients without serious eye problems. You will be asked questions about your medical history, any illness you have and any medications that you take. We will also ask you questions about how you are feeling and about the quality of your life.

Blood tests will be performed every study visit. One to three tablespoons of blood will be drawn from a vein, usually in your arm. This may cause some pain, bruising, swelling and the chance of infection. These blood tests are not being done to manage your treatment. Blood will be stored at a central facility for future analysis. Near the end of the study, the blood will be tested for things related to eye disease and HIV diseases (such as HIV viral load and CMV viral load).

Specimen Banking and Use

If you agree to participate in LSOCA, some of your blood will be stored and may be used for AIDS-related research in the future including possibly genetic tests related to HIV/AIDS. It is possible that the use of your blood may result in the development of new products or tests, some of which may have commercial value. You will not receive any payment or financial benefits from such products or tests.

Appendix 5: Consent statement

We regard the banking of blood as an essential part of LSOCA. Therefore, blood once collected cannot be withdrawn by you from the study. Study data and blood samples collected, including blood for banking, are considered the property of LSOCA. If you are uncomfortable with having a portion of your blood banked for future research, you might want to consider not enrolling in the study.

Your blood will be stored with an assigned patient number-code at the specimen bank such that you will not be identified by name from your blood specimen. We will not inform you or anyone else about the results of tests done with your banked blood. These tests are done for research purposes only and are not conducted to manage your care or treatment.

Risks and benefits

The risks involved in participating in this study are minimal. Before doing an eye exam and taking photographs, we need to put drops in your eyes to dilate your pupils. Afterwards, your vision may be blurred for about two hours, sometimes longer. You may need to have someone drive you home after a visit.

You may benefit by having regular eye exams. If we detect a problem with your eyes, we will let you know. By participating in the study, you will help us to better understand how HIV disease and its treatment affect vision.

Rights and responsibilities

All people who take part in part in this study have rights and responsibilities that include:

- The choice to enter the study is up to you.
- You can leave the study at any time. Leaving the study will not affect the care that you receive at this institution. If you decide to leave the study, we would still like to contact you to find out how you are doing, but you can choose not to be contacted if you so indicate.
- Clinic staff will be prepared to answer questions or discuss any concerns about the study you may have now or in the future.
- The success of the study depends on coming to the clinic for regularly scheduled follow up visits. If you enroll we expect you to:
- Come to clinic for the study visits, and possibly answer questions about your health over the telephone.
- Work with the clinic staff to complete the examinations and give information about your medical history and quality of life.
- Tell the clinic staff about any changes in your address or phone number.

If you do not think you will be able to do these things, you should not enroll in LSOCA.

Appendix 5: Consent statement

Privacy and confidentiality

We are collecting data for the purpose of this study. We will keep the data at the SOCA clinic and at the SOCA Coordinating Center in Baltimore, Maryland. We will keep your records confidential to the extent possible within the limits of the law. To make sure that your identity and the data we collect about you are confidential, we will do the following:

- We will not use your name or address on study records. A number and a letter-code will be used for identification.
- The personal identifying information that we need will be kept in a secure location apart from the study records.
- With your written permission, we may read your medical record or speak with your doctor to get information about your health and what medications you are taking.
- We will not publish or present any of the results of this study in such a way that you could be identified as participating in this study.

It is important for you to know that we have gotten a Certificate of Confidentiality from the Federal Government for this study, to make sure we can best protect your privacy. This certificate means that researchers cannot be forced to tell people who are not connected with the study about your participation. This includes courts and the police. However, if you request disclosure, the researchers will release information.

There are some limits to the researchers' ability to maintain your confidentiality. If we learn that keeping information private would immediately put you in danger, or put in danger someone else we know about, then we will have to tell the appropriate agencies to protect you or another person.

Other things to consider

Examinations and tests performed for the study which you would not normally have done for your clinical care will be performed at no charge to you. Neither this institution nor the Federal Government has insurance to cover any costs if you are injured or have any bad effects that are not the fault of the investigator taking part in this study.

Consent

Before you agree to enroll, be sure that you have answers for all your questions about the study. Dr. *(name of doctor)* and the clinic staff will answer questions you may have. They can be reached at *(phone number)*. Once you have enrolled, if you believe that you have been injured or harmed by being in the study or are not being treated fairly, you may contact the clinic or the institutional review board to discuss your concerns. The phone number is *(institution and phone number)*. The study is being coordinated by The Johns Hopkins University. You may also contact The Johns Hopkins University's Office for Research Subjects at (410) 955-3193.

Appendix 5: Consent statement

To be completed by the patient

The purpose of the study has been explained to me. I have had my questions answered. I understand that if I have questions later on, the clinic staff will answer them. If I sign below, it shows that I agree to participate in the study. *(Record date)*

_____ _____

_____ _____

To be completed by SOCA certified personnel *(witness the patient's signature, sign below and record date.)*

_____ _____

_____ _____

SOCA personnel signature *date*

Clinic ID code: ____ ____ ____ ____

Patient ID#: ____ ____ ____ ____

Patient name code: ____ ____ ____ ____ ____

Appendix 6: Assent statement

The purpose of the Longitudinal Study of Ocular Complications of AIDS (LSOCA) is to help us learn how HIV infections and its treatments affect people's eyes and their sight. We will follow people with this condition for a period of several years.

If you agree to be in this study, you will continue to receive whatever treatments you and your doctor have chosen. You can take part in any other research study for which you are eligible. You will not receive any drugs or treatments as part of this study.

Participation in the study requires that you come to the clinic for study visits, and possibly answer questions about your health over the telephone. We will see you every 6 months. At each visit, your eyes will be examined. We will ask you to read letters on a chart. We also will test how well you can see to the side. If you have eye problems, we will take photographs of the inside of your eyes (pictures of your retina). If you do not have eye problems we will take photographs of the inside of your eye at Baseline and every five years. We will ask you questions about your medical history, illness that you have and medicines that you take. We will ask you questions about how you are feeling and about your activities you do in a day.

You will have blood drawn at every study visit. The amount of blood that will be drawn is about three tablespoons. We will take the blood from a vein, usually in your arm. This may cause some pain, bruising, swelling and the chance of infection.

You may choose not to be in this study. You also may leave the study at any time. If you decide to leave the study, we would still like to contact you to find out how you are doing, but you can choose not to be contacted if you so indicate. Also, if you decide not to be in this study, it will not affect your medical care. No one in the study will be upset with you. You should ask the doctors and nurses questions that you may have about the study. We would like you to talk this over with other people if you need to before giving your answer. If you want to, you can read more about this study in the Consent Statement for LSOCA. If you have any questions you can ask Dr._____ at _____.

It is important for you to know that we have gotten a Certificate of Confidentiality from the Federal Government for this study. This certificate means that the people doing the study cannot be forced to tell people who are not connected with the study about your participation. This includes courts and the police. If you ask them to, the study doctor or nurse will give information about you to others.

There are some limits to the researchers' ability to maintain your confidentiality. If we learn that keeping information private would immediately put you in danger, or put in danger someone else we know about, then we will have to tell the appropriate agencies to protect you or another person.

Appendix 5: Consent statement

If you agree to be in this study, please sign below.

To be completed by the patient

The purpose of the study has been explained to me. My questions about it have been answered. If I sign below, it shows that I agree to be in the study.

_____ _____

patient signature date of signature

To be completed by the parent/guardian *(please sign below)*

_____ _____

guardian/parent signature date of signature

To be completed by SOCA certified personnel (witness the patient's signature, sign below and record date.)

_____ _____

witness signature date of signature

Clinic ID code: ____ ____ ____ ____
Patient ID#: ____ ____ ____ ____
Patient name code: ____ ____ ____ ____ ___

A parent or guardian should review and sign a Consent Statement