Chapter 1. The different phases of the natural course of HIV infection is briefly depicted in the background section. Immune incompetence resulting from advanced HIV infection leads to an enhanced susceptibility of certain malignancies and infections with a spectrum of pathogens that changes with ongoing decline of immunity. In the era preceding the advent of modern antiretroviral combination therapy (cART), HIV replication could not be controlled by the available therapeutic arsenal, and HIV infection was characterized by ongoing destruction of the immune system. Serious ocular involvement was common in advanced immune compromised individuals. Although CMV retinitis is the best known representative of these disorders, numerous clinical case reports have documented a wide variety of other ocular manifestations in AIDS. Patients often presented relatively late with serious infections due to the relative paucity of symptoms as a consequence of their inability to mount inflammatory responses. In this era, the aim of treatment was to postpone blindness, and treatment was aimed at delaying replication of the infective agent. Immune compromised patients often suffered from multiple (opportunistic) infections, and treatment regimens were massive, and often complex and a heavy burden to the patient.

New perspectives arose with the introduction of cART in 1996. These drugs enabled achievement of effective control of HIV replication and partial restoration of the immune system. As a consequence, the incidence of opportunistic infections decreased dramatically. Resolution of certain (ocular) opportunistic infections could be achieved and it became possible to reach a level of immune restoration capable of controlling CMV retinitis, even without secondary prophylaxis. However, some patients receiving cART showed pathological inflammatory reactions and atypical presentations of opportunistic infections. This clinical entity is known as immune reconstitution inflammatory syndrome, or IRIS. Ocular forms of IRIS, often referred to as immune recovery uveitis (IRU), are usually associated with a history of CMV retinitis. In resource-limited settings, where the burden of other opportunistic infections is high, IRIS is of increasing importance.

Chapter 2 presents two clinical cases of severe late eye complications of recurrent cutaneous varicella zoster infection in advanced immune incompetent patients. One patient presented with a fulminant form of retinitis, leading to bilateral blindness in due time. The clinical course of this disease known as progressive outer retinal necrosis is markedly different from the classical VZV
associated acute retinal necrosis syndrome in the immune competent, and the disease reflects a total depletion of the immune system. The second patient presented with symptoms of bilateral optic neuritis, which was diagnosed as retrobulbar optic neuritis (RBON). This disease has been associated with VZV as well, and heralded imminent development of VZV retinitis in this patient. Early recognition of the latter and prompt intensification of intravenous antiviral treatment could prevent progression to blindness.

Chapter 3 is a monograph on fomivirsen, a phosphorothioate oligonucleotide intended for the treatment of CMV retinitis. Fomivirsen belongs to a new generation of drugs known as antisense compounds. These are potent drugs that act by hybridizing to complementary messenger RNA, thus inhibiting translation and subsequent production of specified proteins. Its action is complementary to DNA polymerase inhibitors like ganciclovir and foscarnet. Its in vitro capability of inhibiting CMV replication in human retinal pigment epithelium could also be demonstrated in in vivo studies. Fomivirsen is administered intravitreally, and is well tolerated. It was shown to be effective in treating “clinically resistant” as well. Side effects are usually limited to a transient elevation of intraocular pressure and in some cases intraocular inflammation, and appeared to be well manageable. We conclude that fomivirsen has a valuable place to combat CMV retinitis.

Chapter 4 was published soon after the advent of the new highly active antiretroviral drugs in 1996. It is the report of a prospective observational study of 15 consecutive patients on maintenance treatment for CMV retinitis, describing the effect of protease inhibitors on the course of in relation to the CD4 T-cell response. We distinguished 3 different patterns in the immune response during the first 6 months after PI treatment. Reactivation of CMV retinitis, necessitating re-induction therapy, was exclusively observed in patients who failed to respond to PI with a sustained increase of their CD4 T-cell count, whereas no recurrences of CMV retinitis were seen during a follow-up of 42-52 weeks in those who showed a sustained increase. These and similar observations of other investigators have encouraged some of our patients to discontinue their maintenance therapy for CMV retinitis after they had achieved a substantial rise of their CD4 T-cell count.

In the same paper, we report on the observation of enhanced ocular inflammation in the early phase after the initiation of PI. This inflammation presented in 6 patients as a mild and transient vitritis. Four of them showed a concomitant increase of their CD4 T-cell count to values above 100/µL. We postulate that this vitritis is the result of an enhanced ability to mount inflammatory reactions,
reflecting improved immune function. To date, we would designate this reaction as immune recovery vitritis (ocular IRIS or IRU).

Chapter 5 illustrates the diagnostic dilemma that may arise in patients with poor immune restoration on treatment with cART. A patient with a history of proven Leishmania Major, responding well to antibiotic treatment, developed severe bilateral ocular inflammation with extensive granulomas six months after initiation of cART. This was regarded as ocular IRIS, and treated with topical, later systemical corticosteriods. The patient was referred because the process deteriorated further. Adherence to cART appeared to have been poor in this patient. Although the process initially responded well to intravenous antibiotic treatment, one eye, already blind, became painful and was enucleated. Histopathologic examination and PCR analysis of eye specimens were suggestive for the diagnosis of active ocular recurrence of Leishmania. This case proves the need of a multidisciplinary approach in complex cases. Repeated eye examinations with short intervals are indicated in immunocompromized patients during treatment with corticosteroids, and if no rapid response is observed, the diagnosis should be reconsidered.

Chapter 6 is a review of the literature on Immune Recovery Uveitis (IRU), which can be regarded as the ocular equivalent of the so called Immune Reconstitution Inflammatory Syndrome (IRIS). This name is used to describe a spectrum of disorders that may result from at least partial restoration of the immune response following successful treatment with combined antiretroviral therapy (cART). These disorders are characterized by enhanced inflammatory reactions, that may result in worsening of the clinical manifestations of opportunistic infections (“paradoxical reaction”), or to the appearance of new manifestations, usually depicted as “unmasking syndromes”. Unfortunately, the terminology with respect to IRIS and IRU is not always consistent and there exists no uniformly applied definition of IRU. In this chapter, we attempt to bring the most frequently reported clinical features of IRU under one common denominator and propose a case definition.

Chapter 7 is a review paper that was originally published in the Dutch language. Immune reconstitution inflammatory syndromes affecting the eye have been documented in association with CMV retinitis in a large number of patients. These reports are usually based on retrospective analysis of data from cohorts of patients treated for CMV retinitis. Such reports may therefore suffer from selection bias. Many studies mention the risk of permanent visual loss due to developing long-term complications. However, in our experience, such complications are rare, and
the course of IRU is usually mild and self-limiting. In addition, there is increasing evidence that there exist less severe forms of IRU which seem unrelated to CMV retinitis, and may become manifest in previously apparently unaffected eyes. Clinicians may over-estimate the potential risk of developing (severe) IRIS in eyes with newly diagnosed CMV retinitis. Although primary treatment of opportunistic infections for a short period preceding initiation of cART has been proven useful to reduce the risk of IRIS in systemic diseases, CMV retinitis is associated with a very high risk of mortality. Delaying initiation of cART is therefore seldomly justified. In this chapter, we also address the potential danger of misclassification of diseases; especially differentiating the “unmasking” forms of IRU from manifestations of infectious origin, that occur due to a yet incompetent immune system, may be extremely complicated and requires a multidisciplinary approach and ophthalmological expertise.

Chapter 8 is the first of two chapters presenting the results of our study in Maun, Botswana. In this country, a national ARV program started in 2002, providing free access to cART for HIV infected patients with advanced immune deficiency. The cross-sectional study presented in this chapter was performed to investigate whether research of ocular immune restoration phenomena would be feasible in this country. This was not a priori obvious, because – unlike in high income countries – the prevalence of CMV infection is very low in sub-Saharan Africa. This chapter describes the ophthalmological findings of 357 consecutive HIV infected individuals, who visited the outpatient clinic of the IDCC unit for follow-up in the context of their retroviral (cART) treatment. Special attention was paid to the presence or absence of signs of intraocular inflammation in these people. We investigated whether intraocular inflammation was related to the time of initiation of their cART. While the observed prevalence in the whole population was found to be 10 percent, nearly one third of the patients who had recently (i.e., less than 16 weeks before) initiated cART showed signs of intraocular inflammation. These results suggest that this phenomenon is related to recent use of cART, and may reflect an ocular form of IRIS.

We conclude that conducting a prospective study in Botswana was justified in order to investigate the incidence and associated risk factors of IRU, and to gain more insight into the clinical course of ocular forms of IRIS.

Chapter 9 describes the results of the prospective study which was performed between 2006-2007. The study design of several observational episodes of 5 weeks each with regular 3 monthly intervals allowed for follow-up data up to one
year. cART–naive adult HIV positive individuals who were about to initiate cART were included on a voluntary basis. Potential participants were invited for baseline eye examination and 3 monthly follow-up examinations, synchronously with their cART monitoring visits to the IDCC unit. None of the investigated participants had signs of actual or previous CMV retinitis. Out of 168 patients, 83 were available for statistic analysis. 23% Developed signs of intraocular inflammation during the first 3 months of cART. The observed inflammation was mild and transient in the majority of cases. At 6 months, in only 2 out of 25 patients the inflammation was persistent. Advanced statistical analysis for longitudinal data, and additional multivariable logistic regression analysis were used to investigate potential risk factors for the development of IRU. A low CD4 T-cell count at baseline was found to be the main associated risk factor. A history of TB was associated with IRU as well. The burden of TB and CMV retinitis in this population is quite different from that in the western world, and this association may indicate that IRU in these patients is related to mycobacterial antigens rather than to CMV, and this may also account for a milder course.