Treatment of primary HIV infection
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chapter ONE

General introduction
This general introduction will provide a brief overview of HIV/AIDS and will then narrow down to primary HIV infection, including a description of its pathogenesis, clinical manifestations, diagnosis and treatment. This will be followed by a summary of the outline of the thesis.

**HIV/AIDS**

Acquired Immunodeficiency Syndrome (AIDS) was first identified in San Francisco, USA, in the early 1980s [1], after which the discovery of a novel retrovirus, named human immunodeficiency virus (HIV), soon followed [2]. Of all problems in global health, not many have had such a devastating impact as HIV/AIDS, and are as unequally distributed across the world and certain subpopulations: men who have sex with men (MSM), sex workers, injecting-drug users. To date, some 60 million people have been infected with HIV since the beginning of the pandemic. HIV/AIDS has claimed the lives of more than 25 million people. Sub-Saharan Africa is the region most heavily affected and is home to more than half of all people living with HIV/AIDS worldwide [3]. The introduction of combination antiretroviral therapy (cART) has curbed the growth of the epidemic with a reduction in HIV/AIDS-related mortality and, as part of a public health strategy, has also reduced the spread of new infections [4-6].

HIV is an enveloped retrovirus that belongs to the genus of Lentiviruses. The virus is subdivided into two types: HIV-1, causing the majority of all HIV infections, and HIV-2, a less pathogenic variant concentrated in West Africa. HIV is transmitted through sexual intercourse, exposure to contaminated blood or from mother-to-child, including through breastfeeding. The transmission of HIV is inefficient: the probability ranges between 0.0001 to 0.004 per coital act [7]. This percentage is evidently influenced by factors which can either increase or decrease the transmission rate, i.e., the stage of HIV infection [8], the presence of sexually transmitted infections [9], or circumcision [10]. HIV is divided into four distinct stages, i.e. primary infection, asymptomatic chronic infection, symptomatic chronic infection, and AIDS. The silent asymptomatic period may last for many years. During this period the virus interferes with the immune system, causing a gradual decline of CD4+ T cells. If left untreated, the cell-mediated immunity will eventually be lost and the patient will become susceptible to opportunistic infections and neoplasms (AIDS), which will ultimately lead to death [11].

**Primary HIV infection**

**Pathogenesis**

Acute or primary HIV infection (PHI) is the earliest stage of HIV infection and refers to the first six months following HIV acquisition [12]. Transmission of HIV typically takes place at the genital mucosa. The first cellular targets of HIV are submucosal dendritic cells, macrophages and CD4+ T lymphocytes, followed by the spread of HIV to regional lymph nodes, and ultimately plasma [13]. Viral entry into these cells is mediated by the CD4 receptor and the CCR5 coreceptor. Once HIV infects a cell, the virus will integrate its HIV-DNA into the genetic material of the host and will either initiate viral replication or remain inactive, causing latent infection in resting T cells, lymphoid tissue and other sequestered sites throughout the body.
General introduction

[14]. The rapid viral replication in actively infected cells results in widespread dissemination of the virus to lymphoid tissues and organs [15-18]. This stage is characterized by an exponential rise of viral replication: virus populations may double every six to ten hours, causing a peak plasma vireamia of millions of RNA molecules per millilitre after approximately three to four weeks post-exposure [19]. During this stage several critical events occur, including the massive depletion of CD4+ T cells in the gastrointestinal tract [20-22], the irreversible destruction of T-helper cell reservoirs, the establishment of viral reservoirs [23, 24] and the development of host immune responses against the virus. A crucial immunologic response is the activation of virus-specific CD8+ cytotoxic T lymphocytes (CTLs), which coincides with a sharp decline in the plasma RNA levels until it reaches a steady state known as the viral setpoint approximately six months after infection [25-27]. This setpoint is a prognostic factor for disease progression [28-31]. Host polymorphisms in the human leukocyte antigens class I alleles (i.e. HLA-B27 en B57) are also key genetic determinants on the outcome of HIV disease progression and are associated with a more effective HIV control [32].

Symptoms

PHI involves a dynamic relationship between the host and the virus. Forty to ninety percent of patients with PHI develop an acute retroviral syndrome (ARS), which often coincides with the high-level viraemia and the initial immunologic response of the host [33, 34]. The acute illness typically occurs two to six weeks after initial exposure and usually lasts less than 14 days [35]. The most common signs and symptoms include fever, fatigue, skin rash, pharyngitis, weight loss, night sweats, lymphadenopathy, myalgias, headache, nausea, and diarrhoea [36, 37]. The majority of patients seek medical care during this acute phase, yet the nonspecific nature of the symptoms makes the ARS often not being recognized [38]. This makes the diagnosis of PHI challenging to health care providers and emphasizes the importance of an accurate history of previous sexual exposures and high-risk behaviour. The severity and the duration of an ARS is associated with a more rapid disease progression [39-42].

Diagnosis

The diagnosis of PHI may easily be missed, because at the time of clinical symptoms HIV antibodies have usually not been formed, and a standard serologic enzyme-linked immunosorbent assay (ELISA) used for chronic HIV infection will be negative [43, 44]. Diagnostic markers to establish a PHI are a p24 antigen assay or a detectable pVL, along with a negative or indeterminate Western blot [45, 46]. p24 antigen is a viral core protein that transiently emerges during the acute phase, approximately 17 days after transmission, and before the development of detectable HIV antibodies [47]. Recently, a novel ELISA, which can detect both p24 antigen and anti-viral antibodies, has been developed and approved for clinical use [48, 49]. Further, it is anticipated that a rapid point-of-care test will also be developed to detect an acute infection. The implementation of these two latter tests will increase the number of patients diagnosed with PHI who otherwise might have been missed [23].
Rationale for treatment of primary HIV infection

PHI is associated with intense viral replication and the development of an initial immune response against the virus, which makes this stage very different from chronic HIV infection and provides a unique opportunity for therapeutic and public health interventions [50]. Although thus far no consensus exists, evidence is accumulating that temporary early cART during PHI has a beneficial effect on early and late disease progression [51-53]. Observational studies have suggested that treatment during PHI may preserve HIV-specific immunity [54-61], limit viral evolution and restrict the establishment of viral reservoirs [62, 63]. An important immunological study observed that intermittent cART during PHI led to vigorous HIV-specific CD4 and CD8 T cell responses, which were similar to those seen in long-term nonprogressors. It was hypothesized that treatment interruptions enhanced the immune response by reexposure to HIV antigens [58]. Early cART may have a clinical benefit by lowering of the viral setpoint [64-66] and by reducing the rate of CD4 T cell decline [67, 68], and thereby delaying the need for long-term cART during chronic HIV infection. An additional rationale for early cART may be that current treatment guidelines recommend earlier therapy in chronic HIV infection (CD4 T cell count below 500 cells/mm³), to reduce the development of co-morbidities such as cardiovascular and metabolic diseases [69, 70], so a relevant point may be ‘why wait to treat?’ Especially since studies have shown that PHI-patients, who are often symptomatic, have a faster drop in CD4 T cell counts than expected and will rapidly meet the criteria for treatment initiation [71, 72]. The additional time spent on cART will then only be limited as compared to the total life-time spent on cART [73]. Finally, treatment of PHI may have significant public health implications by reducing the spread of HIV transmission, as patients are extremely infectious during this period, are often unaware of their HIV status, and if accompanied with high-risk behaviour, are prone to transmit the virus to others [74, 75].

In contrast, not all studies suggest a benefit on viral setpoint [76-79], and some cohort studies reported a similar or even faster CD4 T cell decline after interruption of early treatment [80, 81]. One could also argue that the early treatment is provided too late to have a major impact, since virus-induced immunopathogenesis has already taken hold [82].

In spite of the earlier mentioned benefits, there are also potential disadvantages of temporary early cART. An important concern is the drug-related (long-term) toxicity, although most cART regimens nowadays are better tolerated, have fewer side effects and are more convenient than older regimens, and its potential negative impact on the quality of life. Another reason not to intervene in PHI may be the risk of developing drug resistance mutations in non-adherent patients, which might be more common in PHI as patients are often physically and emotionally distressed and may have more difficulty with strict adherence to cART, which could compromise future treatment options. However, thus far, this fear has not been substantiated [83, 84]. Finally, the cost-effectiveness of temporary early cART has not been studied, although modelling studies have shown that earlier initiation of therapy is a cost-effective strategy because it prevents the person from more severe stages of HIV infection [85, 86]. Moreover, early cART may be cost-effective as it decreases the spread of new infections.

To date, clinical guidelines do not offer a definitive answer whether to intervene with (temporary) cART during PHI or not, and if so, for how long [87, 88]. The first randomized
controlled trial was performed in the early nineties and compared six months of zidovudine monotherapy with placebo in patients with PHI, and this study reported a significant reduction of minor opportunistic infections after early cART [89]. A second randomized trial with zidovudine monotherapy demonstrated similar immunological and virological benefits [90]. It lasted another fourteen years before results of randomized trials that were performed in the current cART era became available.

In 2003 we initiated the Primo-SHM trial, a multi-centre trial in which patients with laboratory evidence of PHI were randomized to receive no treatment, 24 or 60 weeks of early cART [91]. The aim of the study was to assess the clinical benefit of temporary early cART, measured by the time that patients could remain off therapy until subsequent (re)start of cART was indicated based on current treatment guidelines, and to assess the optimal duration of such early treatment. Patients were recruited in 13 HIV treatment centres in the Netherlands between May 2003 and March 2010. The large cohort of PHI-patients that was established during this time frame is the basis of most studies described in this thesis.

Scope of this thesis
The core of the thesis comprises three parts that include a randomized trial on the effect of temporary early cART during PHI (Part II), studies on quadruple or triple-class therapy in patients with primary and chronic HIV infection (Part III), and studies on bone mineral density during PHI (Part IV).

As an introduction to this thesis Chapter 2 reports an illustrative case study of a patient who presented with Kaposi’s sarcoma during PHI. Part II focuses on the clinical management of PHI. Chapter 3 describes the results of the Primo-SHM trial, an open-label randomized controlled trial comparing no treatment with 24- or 60-weeks of early cART during PHI. The aim of this study was to assess the clinical benefit of early cART, measured by the time that patients could remain off therapy until subsequent (re)start of cART was indicated based on current treatment guidelines, and to assess the optimal duration of such early treatment. In the Primo-SHM substudy, we compared the impact of temporary cART during PHI with no treatment on health-related quality of life, over a study period of 96 weeks (Chapter 4). In Chapter 5 we assess the effect of early cART on the subsequent virologic response to long-term cART, in patients who participated in the Primo-SHM trial. To this end, we compare the viral decay and the time to viral (re)suppression between the early treated patients who reinitiated cART and the patients in whom treatment was deferred until conventional criteria to start long-term cART had been reached. Finally, Chapter 6 addresses the pathogenic mechanisms of the lower viral setpoint that we observed after early cART and Chapter 7 investigates the effect of dual HIV infections (co- or superinfection) on disease progression in a well-defined cohort of 37 MSM with PHI and a subtype B virus.

Part III involves two clinical studies on the virologic response in primary and chronic HIV infected patients receiving triple-class quadruple antiretroviral therapy. When we started the Primo-SHM trial, we decided to initiate cART consisting of a quadruple, triple-class regimen, given the often very high pVL in PHI and the fear that standard triple therapy would easily result in virological failure, and that drug resistance test results were seldom available before
the initiation of cART. To examine whether indeed quadruple therapy has an advantage over standard-of-care triple therapy, Chapter 8 explores whether quadruple or triple-class therapy provides a more rapid pVL decline and an improved virologic response compared with standard-of-care dual-class triple therapy in treatment-naive patients with very high viraemia. An unanswered question so far is whether the virologic response to cART in PHI is comparable to that in CHI. The second study therefore compares the time to viral suppression in our relatively large cohort of PHI-patients treated with triple-class therapy with that of a cohort of naïve CHI-patients with comparable treatment and initial pVL (Chapter 9).

Low bone mineral density (BMD), including osteopenia and osteoporosis, and bone fractures appears to be common in HIV infected persons. Osteopenia is defined as the thinning of bone mass which may precede osteoporosis [92]. Osteoporosis is characterized by severe bone loss and structural deterioration of bone tissue and is associated with susceptibility for bone fractures [93]. A systematic review of cross-sectional studies revealed a 6.4-fold increased odds of osteopenia in HIV infected patients and a 3.7-fold increased odds of osteoporosis compared to the general population [94]. A recent study confirmed the higher prevalence of bone fractures in HIV infected adults compared to uninfected controls [95]. The causes of low BMD are multifactorial and represent a complex interaction between HIV infection itself, the use of cART, low vitamin D levels, and traditional risk factors, which might be more prevalent among HIV infected persons (smoking, alcohol and recreational drug use) or are exacerbated by the consequences of chronic HIV infection (e.g., low body weight, poor nutrition) [96]. HIV itself induces a direct effect on the cells of the bone and bone marrow microenvironment, activates T cells and produces an abnormal cytokine reaction, such as tumor necrosis factor-α and interleukin-1, which affect osteoblast and osteoclast function [97]. The subsequent bone demineralization results from a negative imbalance between osteolytic activities of osteoclasts and regenerative activities of osteoblasts. Every reduction of one standard deviation in vertebral BMD, results in a two-fold increased risk of vertebral fracture [98].

In order to gain further insight into the contribution of HIV infection per se on BMD, Part IV explores the BMD during PHI, which provides a unique opportunity to investigate BMD in HIV infected populations, because of the limited duration of HIV infection and the absence of exposure to cART. Chapter 10 studies the BMD and biochemical markers relevant for bone metabolism in a cohort of untreated PHI-men and Chapter 11 compares the BMD and biochemical markers relevant for bone metabolism of untreated primary and chronically HIV infected MSM with those of a control group of HIV negative MSM.

In the summary and general discussion, the main results of this thesis are summarized and discussed, followed by clinical recommendations and suggestions for future research.
References


