Treatment of primary HIV infection
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chapter TWELVE

Summary & General discussion
The studies presented in this thesis focus on the treatment of primary HIV infection (PHI). The general discussion will provide a summary of the different studies, followed by clinical recommendations and suggestions for future research.

Part II Treatment during primary HIV infection

Combination antiretroviral therapy (cART) in chronically HIV infected persons has shown to be very effective in suppressing viral replication and preventing immunological deterioration and has remarkably altered the clinical course of HIV disease [1]. In current HIV research PHI has attracted tremendous attention, as studying transmission and events early in infection may aid the understanding of HIV pathogenesis and thereby contribute to future vaccine development [2, 3]. However, there is lack of consensus with regard to the clinical management of PHI. To date, it is the question whether or not temporary treatment during PHI offers unique long-term benefits, through preserving immune function otherwise lost, enhancing rapid viral control and limiting the viral reservoirs [1, 4]. Observational cohort studies have shown conflicting results with regard to the benefits of early treatment. Several research groups around the world have now published randomized studies that compared temporary early treatment during PHI with no treatment.

The first randomized controlled trial was published in 1995 and compared six months of zidovudine monotherapy with placebo in patients with PHI. The study reported a significant reduction of minor opportunistic infections after early treatment [5]. A second randomized trial with zidovudine monotherapy demonstrated similar immunological and virological benefits [6]. Subsequently, it lasted another seventeen years before the results of three randomized trials that were performed in the current cART era became available.

Between May 2003 and March 2010 we conducted the Primo-SHM trial, a multi-centre randomized trial comparing no treatment with 24 or 60 weeks of early cART (Chapter 3). The objective of the study was to assess the clinical benefit of temporary cART during PHI, 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 with laboratory evidence of PHI were recruited in 13 HIV treatment centres in the Netherlands and randomly assigned to receive no treatment or 24 or 60 wk of early cART. In case therapy was clinically indicated, subjects were randomized over the two treatment arms only. Primary end points were the viral set point, defined as the plasma viral load (pVL) 36 wk after randomization in the no treatment arm and 36 wk after treatment interruption in the treatment arms, and the total time that patients were off therapy, defined as the time between randomization and start of cART in the no treatment arm, and the time between treatment interruption and restart of cART in the treatment arms. cART was (re)started in case of a confirmed CD4 cell count below 350 cells/mm³ or symptomatic HIV disease. The modified intention-to-treat-analysis comprised 168 patients: 115 were randomized over the three study arms and 53 were randomized over the two treatment arms only. Most patients randomized over the three study arms were men who have sex with men (MSM), had a negative or indeterminate Western blot and were symptomatic during PHI. Mean viral setpoint at week 36 was significantly lower in the 24- and 60-week treatment arms as compared to the no treatment arm, with a mean...
difference of 0.5-0.8 log\(_{10}\) copies/ml. The median total time off therapy was significantly longer in the 24- and 60-week treatment arms as compared to the no treatment arm: restart of cART during chronic HIV infection was deferred with approximately two years. Combining all treated patients, including the patients randomized over the two treatment arms only, the median total time off therapy was not different between the 24- and 60-week treatment arms. In the adjusted Cox analyses, temporary early cART was associated with time to (re)start of cART. Summarizing, the key findings of the Primo-SHM study were that temporary cART initiated during PHI transiently lowered the viral setpoint and deferred the need for restart of cART during chronic HIV infection. The effects of temporary early cART were not different for the two treatment arms, suggesting that 24 weeks of early cART would be sufficient.

Our findings are supported by two other recent randomized studies, the Short Pulse Anti-Retroviral Therapy at HIV Seroconversion (SPARTAC) trial, which compared no therapy with 12 or 48 weeks of cART during PHI [7], and the SETPOINT study, which compared no therapy with 36 weeks of cART in early HIV infection [8]. The primary endpoint in the SPARTAC trial was time to CD4 cell count below 350 cells/mm\(^3\) or initiation of long-term cART. A total of 366 participants were randomized: 123 in the no therapy group, 120 in the 12-week and 123 in the 48-week treatment groups. Preliminary results showed that the 48-week treatment group had a 0.44 log\(_{10}\) copies/ml reduction in pVL 36 weeks after treatment interruption as compared to the no therapy group. 50% of the participants in the 48-week treatment group reached the primary endpoint, compared to 61% in both the no therapy and 12-week treatment groups. The median time to reach the primary endpoint was 65 weeks longer in the 48-week treatment group as compared to the no therapy group (average hazard ratio (HR) was 0.63 (95% CI: 0.45,0.90; p=0.01), whilst 12 weeks of treatment had no effect compared with no therapy. The SPARTAC trial demonstrated that 48 weeks of early cART modestly delayed disease progression, although not significantly longer than time already spent on treatment [7].

The aim of the SETPOINT study was to determine whether the viral setpoint could be altered after 36 weeks of early cART. However, the study was prematurely stopped by the Data Safety and Monitoring Board, because the untreated study arm experienced a higher rate of disease progression than expected compared to the treatment arm: the time to meeting eligibility criteria for initiating or reinitiating long-term cART was significantly shorter in the untreated arm than in the treated arm (log-rank, p=0.035) [8]. The viral setpoint endpoint could not be evaluated.

A major concern of temporary early cART during PHI is the potential negative impact on the health-related quality of life (HRQL), because of drug-related toxicity, pill burden and the need for strict adherence to cART, which may be more challenging during the acute stage of HIV, since patients are often physically and emotionally distressed. Another important concern is the risk of developing drug resistance mutations in non-adherent patients and/or after treatment interruption, which could compromise future treatment options [4]. To this end, we compared the HRQL and symptoms over 96 weeks in a cohort of untreated and early treated PHI-patients and found that early cART had a positive impact on patients’ HRQL as compared to no treatment, despite the initial, short-term occurrence of more physical symptoms that were related to drug toxicity (Chapter 4). Furthermore, we evaluated the effect of temporary early cART on the subsequent virologic response to long-term cART of the patients previously participating in the Primo-SHM
Twelve trial (Chapter 5). Temporary cART during PHI was not associated with a reduced virologic response after reinitiation of long-term cART during chronic HIV infection, when we compared early treated patients with untreated PHI-patients and when we compared the first and second treatment episodes in early treated patients. These results suggest that temporary early cART did not select for clinically relevant drug resistance mutations. Hence, potential disadvantages of early cART were not substantiated, which provides further support to initiate temporary cART during PHI.

A short course of cART during PHI deferred the need for subsequent restart of cART, which, according to findings of the Primo-SHM study, was most likely caused by the effects of the CD4 gain during treatment and the transient lowering of the viral setpoint (Chapter 3). After adding these two parameters to the Cox regression models, early cART was no longer significantly associated with time to restart of cART, suggesting that the increase of the CD4 cell count and the lowering of the viral setpoint during the early treatment period explained for the most part why early cART resulted in a clinical benefit. We examined whether the stage of PHI and the self-reported occurrence of an acute retroviral syndrome were possibly associated with time to (re)start of cART, but found no correlation.

It remains unclear how the lowering of the viral setpoint might be explained. Did early cART have a direct effect on the virus itself or did it affect the immunologic responses of the host? Therefore, in Chapter 6 we investigated whether the beneficial effect of early treatment was caused by the preservation of immunological responses. We compared 26 early treated with 13 untreated PHI-patients at viral setpoint (36 weeks after treatment interruption and randomization, respectively) and studied i) effector T-cell formation and function, ii) polyfunctionality of CD8+ T cells, by measuring the cytokines TNFα, IFNγ, and IL-2, and the chemokine Mip1β, and iii) regulation of the cellular immune response by measuring various inhibitory and regulatory markers on T, B and NK cells and dendritic cells. We also assessed, by measurement of the gut homing marker α4β7, whether early treatment may prevent severe CD4+ T cell depletion in the GALT and thereby prevent excessive immune activation. Surprisingly few of the immunological parameters that we studied were affected by early treatment, although the sample size of our study was small. Treatment during PHI led to the preservation of a more polyfunctional HIV-gag specific T cell response, suggesting that early treatment may preserve important cytotoxic T-lymphocyte (CTL) functions, which are crucial in control of the HIV viraemia.

Another mechanism that independently influenced the clinical course of untreated PHI-patients is described in Chapter 7. Here we analyzed the effect of dual HIV infections (co- or superinfection) on disease progression in a cohort of untreated MSM with primary infection with HIV-1 subtype B. Between 2000 and 2009, 37 PHI-MSM were characterized with regard to dual infection or single infection and coreceptor use. Patients were followed to estimate the effect of these two parameters on clinical disease progression, as defined by the rate of CD4+ T-cell decline and the time to initiation of long-term cART. Four patients presented with a coinfection and six patients acquired a superinfection, on average 8.5 months from their primary infection. The other 27 patients remained infected with a single strain. The slopes of longitudinal CD4+ T-cell counts and time-weighted changes from baseline were significantly steeper for the patients with a dual infection than for patients with a single infection. Multivariate analysis showed that the most important parameter associated with CD4+ T-cell decline over time was dual infection
(P = 0.001). Patients with a coinfection had a significantly earlier start of long-term cART (P < 0.0001). This study showed that HIV co- or superinfection was the main factor associated with CD4+ T cell count decline in a cohort of untreated PHI-MSM with subtype B virus. Thus, an additional benefit of temporary early cART may be the prevention of early HIV superinfection.

Several study groups suggested possible other viral or host factor(s) that might explain the lower viral setpoint after the initiation of temporary cART during PHI. Immunological events early in the acute stage are thought to fundamentally influence HIV outcome. Two crucial events in PHI are the massive destruction of CD4+ T cells in the gastrointestinal tract and the establishment of latent HIV reservoirs. Early treatment may result in viral suppression and immune restoration in gut-associated lymphoid tissue (GALT) [9]. A recent study revealed no viral evolution in the GALT during early cART, suggesting no or limited viral replication in this compartment during suppressive cART, which leads to less divergent viral populations over time, possibly contributing to the lower viral setpoint [10]. In addition, early cART may decrease the seeding of reservoirs of latent virus: on one hand by extinguishing viral production, and on the other hand by reducing the pool of latently infected CD4+ T cells, which will eventually lead to a smaller amount of virus production after treatment interruption. The prospective VISCONTI study (Virological and Immunological Studies in CONtrollers after Treatment Interruption) studied the distribution and magnitude of the HIV reservoir in 12 PHI-patients in whom treatment was initiated within 10 weeks post-infection during a period of 3 years and who controlled HIV for more than 6 years thereafter. Preliminary results suggest that early treatment lead to a limited HIV reservoir distributed mainly in short-lived memory CD4+ T cells which mimicked the distribution that is seen in elite controllers [11].

Another small study in early treated patients demonstrated that the fitness of viral strains present during PHI was higher than previously thought [12]. It is generally thought that the fitness of strains present during PHI is low relative to strains present during chronic HIV infection, due to the bottleneck imposed upon transmission. In patients with chronic HIV infection, rapidly replicating virus isolates have been associated with an increased disease progression [13]. The same study also observed that after early treatment the fitness of viral isolates reduced over time, whereas in the absence of treatment it increased over time, which could possibly affect the viral setpoint, even though the study did not find an association between viral fitness and the pVL [12]. Others have hypothesized that early treatment enables virus-specific CD8+ T cells to mature into fully differentiated effector cells, which might be important in viral control [14]. Another study observed a superior memory B-cell response to HIV and non-HIV antigens after one year of cART in early versus chronic HIV infected individuals, suggesting that temporary treatment during PHI is important for preserving overall immune competency [15].

The specific contribution of HIV specific CD4+ T cell responses in the control of viral replication in PHI is not clear. A recent cohort study observed that PHI-patients who were able to spontaneously control HIV replication in the absence of cART showed a significant expansion of HIV specific CD4+ T cell responses, which was characterized by robust cytolytic activity and expression of a distinct profile of perforin and granzymes, as compared to those who evolved to a higher viral setpoint [16]. The study revealed that the emergence of granzyme A(+) HIV specific CD4+ T cell responses at baseline was predictive of a slower disease progression.
Perhaps early cART supports the development of such HIV specific cytolytic CD4+ T cell responses and thereby causes a lower viral setpoint.

Part III Quadruple therapy in patients with primary and chronic HIV infection

In the Primo-SHM trial, patients initiated a triple-class quadruple regimen consisting of two nucleoside reverse transcriptase inhibitors (NRTIs), one non-nucleoside reverse transcriptase inhibitor (NNRTI) and one boosted protease inhibitor (PI). The reason we opted for this regimen is that we feared that standard-of-care triple therapy could possibly result in virological failure given the typically high pVL during PHI. In addition, at the time of treatment initiation genotypic resistance testing results are often not available, and since transmitted drug resistance is common [17], we favoured ‘overtreatment’.

Dual- or triple-class quadruple therapy has been suggested to augment the antiretroviral activity of cART compared to standard-of-care triple therapy. However, the randomized and non-randomized studies which support this contention are often out-dated, using quadruple or triple-class regimens containing an older generation unboosted PI as the supplementary drug or drug class, thereby questioning its relevance to current clinical practice [18-28]. As reported in many large HIV drug trials, a high baseline pVL is an independent predictor of virological failure. Therefore, adding an additional drug or drug-class to a standard-of-care regimen to increase its potency may in particular be of importance in patients with very high viraemia (≥500,000 c/ml).

Consequently, in Chapter 8 we investigated whether quadruple or triple-class therapy provides a more rapid pVL decline and an improved virologic response compared with standard dual-class triple therapy in treatment-naive chronic HIV infected patients with a pVL of 500,000 c/ml or more. Data were selected from the National observational HIV cohort in the Netherlands (ATHENA) [29]. 675 patients were included of whom 125 (19%) initiated quadruple and 550 (81%) triple therapy. The median pVL was similar in both groups (5.9 (IQR 5.8-6.1) log10 c/ml; P=0.49). The median time to viral suppression, defined as a pVL ≤ 50 c/ml, was 5.8 (IQR 4.6-7.9) and 6.0 (4.0-9.4) months in the patients on quadruple and triple therapy (log rank, P=0.42). In the adjusted Cox analysis, quadruple therapy was not associated with time to viral suppression (HR 1.07 (95% CI 0.86-1.33), P=0.53). Similar results were seen when comparing triple- versus dual-class therapy. The results of this study provide no evidence to add an extra drug or drug-class to standard triple therapy in patients with very high viraemia. Quadruple or triple-class therapy did not improve the antiretroviral activity of cART, but did expose patients to additional drug toxicity.

Similarly, studies comparing the virologic response to cART among individuals with primary versus chronic HIV infection have shown inconsistent results [30-34]. For PHI-patients a faster, similar and slower virologic response have all been reported, but most studies were small or did not adjust for differences between groups in baseline pVL. In Chapter 9 we compared the time to viral suppression between 70 PHI-patients and 80 naive chronic HIV infected patients, who were all treated with triple-class therapy and had an initial pVL above 100,000 copies/ml. The time to viral suppression after initiation of triple-class therapy was comparable for primary and chronic HIV infection, suggesting that the virologic response to therapy is not related to the stage of HIV infection.
Part IV Bone mineral density during primary HIV infection

Studies have shown an increased prevalence of low bone mineral density (BMD) among HIV infected individuals [35]. Low BMD in HIV infected individuals is caused by a multitude of factors, including traditional risk factors, which might be more prevalent among HIV infected individuals, HIV infection itself and cART [36]. In order to gain further insight into the contribution of HIV infection per se, we determined the BMD and the biochemical markers relevant for bone metabolism in a cohort of 33 untreated PHI-men, since they have limited exposure to HIV and no exposure to cART (Chapter 10). Osteopenia and osteoporosis were defined according to the WHO criteria as T-scores measured at lumbar spine, femoral neck and/or total hip between -1 and -2.5 SD and -2.5 SD or less, respectively. Mean lumbar spine T (P=0.001) and Z-scores (P=0.004) and femoral neck T-score (P=0.003) of the PHI-men were significantly lower than the average BMD of the NHANES IV reference population. Forty-five percent of the PHI-men had osteopenia and 6% had osteoporosis. The biochemical markers relevant for bone metabolism did not differ between patients with or without osteopenia/osteoporosis. In the multivariate linear regression analysis, age was negatively associated with femoral neck (β=-0.05, P=0.001) and total hip T-scores (β=-0.03, P=0.04). Body mass index (BMI) was associated with lumbar spine (β=0.3), femoral neck (β=0.2) and total hip (β=0.2) T-scores (P<0.001) and thyroid-stimulating hormone with lumbar spine (β=0.5, P=0.045) and femoral neck T-scores (β=0.4, P=0.005). Increased pVL was associated with lower total hip T-scores (β=-0.2, P=0.02). The current study presents the first data on the rate of osteopenia and osteoporosis in a cohort of untreated PHI-men, of whom more than half had osteopenia or osteoporosis. Given that these PHI-men were cART-naive, the results of Chapter 10 raised the question whether the low BMD was related to the recent acquisition of HIV, to other conventional risk factors affecting BMD, or alternatively, that the low BMD previously reported in HIV infected populations pre-dates HIV acquisition. For this reason, in Chapter 11 we compared the BMD and biochemical markers relevant for bone metabolism of 41 untreated primary and 106 untreated chronically HIV infected MSM with that of a control group of 30 HIV negative MSM. Low BMD, which in this study was defined as a Z-score ≤ -2.0 SD at the lumbar spine or hip according to novel guidelines by the International Society for Clinical Densitometry, was highly prevalent in all three groups. In the multivariate analyses, HIV infection was not associated with BMD. The results of this study suggest that the low BMD found in acute and chronically HIV infected MSM may pre-date HIV acquisition and that low BMD is not fully attributable to HIV infection itself or the use of cART.

Clinical implications and Future research

The results of the studies presented in this thesis demonstrate a virological, immunological and clinical benefit of temporary early cART during PHI. Although extended follow-up studies are needed to evaluate the long-term benefits of early treatment, initiating cART for a duration of 24 weeks seems at present the most reasonable advice for patients with PHI (Chapter 3 and 4). The clinician should pay attention to the variability in pharmacokinetics when interrupting cART, as
stopping with a pharmacologically unbalanced regimen (i.e., a drug regimen comprising three drugs with different half-lives) may lead to ‘functional monotherapy’ and may thereby possibly induce drug resistance [37]. To date, there is no clear clinical guidance how to stop cART, as this also depends on the regimen prescribed (balanced or unbalanced) and whether the patients has a detectable or undetectable pVL at the time of treatment interruption. In general, a staggered stop, in which the long half-life drug (e.g. the NNRTI) is interrupted prior to the short half-life drugs (e.g. the NRTIs), and a switched stop, in which the long half-life drug is temporarily replaced by a boosted PI with a short half-life, are preferred over a simultaneous stop [38, 39]. However, in our large Primo-SHM cohort concerns for developing drug resistance mutations after treatment interruption in PHI have not been substantiated (Chapter 5, [40]). Of note, patients should be well informed by health care workers of the viral rebound dynamics shortly after TI [41] and the potential increased risk of sexual transmission during this period [42].

Decisions regarding treatment initiation should always be made on a patient-by-patient basis. For example, for some patients it may be better to postpone cART, especially in those patients who have difficulty in accepting their seropositive status or have barriers to treatment (young age, social background, MSM-related stigma). For every patient, potential advantages and disadvantages should be carefully reviewed before starting early cART [43]. We do not know whether our results are generalizable to asymptomatic seroconverters, since most patients were symptomatic during PHI, which is a known predictor of disease progression [44]. The timing of treatment initiation in PHI (Fiebig stage I-II, III-IV or V-VI [45]) did not seem to have an influence on the total time that patients were off therapy (Chapter 3). This might be related to the actual delay between the diagnosis of PHI and the start of early cART, which in our study was approximately five weeks, partly caused by the delay between start of symptoms and HIV diagnosis, and partly as a result of a clinical trial setting. Perhaps the golden hour, in which the greatest benefits of early cART could have been achieved, was already missed. The greatest effect might be achieved when initiating early cART at the time of symptom presentation. A posthoc analysis from the SPARTAC trial showed a non-significant trend towards benefit in total time off therapy when early cART was initiated nearer to the estimated seroconversion date (HR 0.48, P=0.09, [7]). Inevitably, also in clinical practice, some time is necessary to prepare the patient for treatment initiation. Nevertheless, even with a reasonable delay we observed a clear clinical benefit of initiating cART during PHI.

The next important question is what drugs to prescribe during PHI. In an unblinded, non-randomized prospective cohort study 90 PHI-patients were allocated to either triple or quadruple dual-class NNRTI-containing cART or a PI-based dual-class regimen. The study showed that of the three treatment regimens, quadruple dual-class cART enhanced the rate of pVL decline but at the cost of drug toxicity [46]. We found that quadruple triple-class therapy had no advantage over standard triple therapy in chronic HIV infection, and indeed patients were exposed to more drug-related adverse events (Chapter 8). In addition, the time to viral suppression after initiation of triple-class therapy was comparable for primary and chronic HIV infection, suggesting that the virologic response to therapy is not related to the stage of HIV infection (Chapter 9). Therefore, the addition of a fourth drug is only of significance in case the results of baseline genotypic resistance testing are not yet available at the moment of initiation of early cART.
However, according to the Department of Health and Human Services (DHHS) guidelines, the recommended first-line therapy in chronic HIV infection (two NRTIs plus one NNRTI [47]) may not be suitable during PHI, because of the increased risk of drug-related toxicity and its low genetic barrier to resistance. Most studies on early cART propose a regimen containing a boosted PI, for reasons that the level of transmitted drug resistance to this drug class is low [48] and the risk of virological failure is small [43, 49]. A recent cohort study nonetheless endorsed the use of a once-daily, co-formulated NNRTI-based regimen (Atripla®) during PHI, and reported a rapid and sustained viral response in most patients [30]. Another study compared the number of drug modifications between NNRTI- and boosted PI-based regimens initiated during PHI and observed that it was equally frequent for both drug classes and mostly related to minor drug toxicities [50]. The long-term use of boosted PIs may potentially be more toxic than NNRTIs [51], though this is probably less applicable to temporary treatment during PHI.

Temporary cART during PHI may not only be beneficial for the individual patient, but may also have a public health benefit with the potential to significantly impact further spread of HIV. PHI is associated with an extremely high viral load in both plasma and genital tract secretions, which makes this period hyper-infectious [52]. Studies have shown that PHI accounts for almost half of the onward transmission events, thereby fueling the epidemic [53-56]. A study estimated that every 1 log₁₀ increase in genital HIV RNA was correlated with a 1.79-fold increased risk of heterosexual transmission [57]. A recent study in coastal Kenya reported a HIV incidence of 8.6 per 100 person years among a large cohort of 449 MSM, and many of these seroconverters maintained a pVL of > 4.0 log10 copies/ml for up to two years after infection [58]. Identifying individuals with PHI provides a crucial opportunity for the prevention of forward transmissions, either through behavioral prevention interventions to modify high-risk behaviors, frequent and targeted HIV testing, effective biomedical interventions such as pre-exposure prophylaxis (PrEP) and/or the initiation of early cART [30, 59, 60]. The downside of temporary early cART is however that patients will eventually be a longer period without therapy during chronic HIV infection, and will thus be a longer period at risk to transmit HIV to others.

Therefore, the final question is whether we should discontinue early cART at all. Given the concern that uncontrolled HIV replication and chronic immune activation carry an increased risk of morbidity and mortality [61], some clinicians will probably recommend their patients that once cART is initiated, it should be continued indefinitely. In addition, continuing cART might also favourably influence the epidemic (‘test and treat’) [62-64]. Recent studies showed that cART profoundly reduced the heterosexual transmission of HIV in discordant couples, presuming that the HIV positive patient is adherent to cART and has an undetectable pVL [65-67]. However, the costs and drug toxicity of such continuous long-term therapy have not been studied.

In conclusion, in this thesis we studied the treatment of PHI. Early cART transiently lowered the viral setpoint and deferred the need for restart of cART during chronic HIV infection, which was most likely caused by the effects of the CD4 gain during treatment and the transient lowering of the viral setpoint. Even though the exact mechanisms explaining the lowering of the viral setpoint after early cART remain unsolved, we observed a clear clinical benefit of temporary treatment during PHI. In case early cART is considered, it should be given for a duration of 24 weeks and contain a boosted PI, at least until resistance testing results are available.
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