Clinical implications of immune recovery during antiretroviral treatment for HIV infection
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Chapter 8

General discussion
While successful suppression of HIV infection by cART is known to reduce the risk of well known AIDS-defining opportunistic infections such as for example Pneumocystis jirovecii pneumonia and cerebral toxoplasmosis, research conducted in recent years has demonstrated that treating HIV infection may also be key in preventing a number of non-AIDS complications, including cardiovascular disease, non-AIDS malignancies, liver disease, kidney disease, bone disease, and neurocognitive decline. Apart from traditional risk factors (e.g. substance abuse and other lifestyle-related factors), HIV-associated immune dysfunction may play an important role in the onset of these so-called non-AIDS co-morbidities [1-3]. As a result of these insights, in spite of a paucity of data from randomised trials regarding the optimal time to start cART, guidelines already are increasingly moving towards recommending earlier initiation of cART in all individuals who are infected and ready to adhere to lifelong therapy, regardless of CD4 count [4]. In order to extend our knowledge in this area, the studies presented in this thesis address both the factors associated with and a number of clinical consequences of (lack of) immune recovery on cART. Analyses were largely based on data collected as part of the Athena observational Cohort Study amongst individuals receiving care for their HIV infection in assigned treatment centers in the Netherlands.

Immunodeficiency, AIDS related morbidity and mortality

The degree of immunodeficiency at the start of treatment is an important determinant of the degree of immune restoration which can be achieved with cART, each of which may affect morbidity and mortality rates in HIV-1 infected patients on cART [5-12]. Cohort studies have consistently shown mortality benefits when cART is initiated at a CD4 count of 350 cells/mm³ or less [6,9,13-15]. For example, the Antiretroviral Therapy Cohort Collaboration [6], examining data from 24,444 patients from 15 mostly European cohorts who initiated antiretroviral therapy at CD4 counts less than 550 cells/mm³, found that deferring cART until a CD4 count of 251-350 cells/mm³ was associated with higher rates of AIDS and death than starting therapy in the range 351-450 cells/mm³. In a 2009 analysis of patients in NA-ACCORD, a large cohort collaboration that merged clinical data from 22 observational studies in the United States and Canada [5], two parallel analyses were conducted involving a total of 17,517 cART-naïve asymptomatic patients with HIV infection. The first analysis consistent with other studies concluded that deferral of therapy until a CD4 cell count below 350 cells/mm³ was associated with a 69% increase in the relative risk of mortality as compared to initiation of therapy between 350 and 500 cells/mm³. The second analysis showed that deferral of therapy until the CD4 count was below 500 cells/mm³, as compared to initiation at a CD4 count greater than 500 cells/mm³, also was associated with a 94% increase in the relative risk of death. Of note the number of events was small in this latter analysis. Another collaborative analysis of 18 HIV cohort studies (HIV CAUSAL Collaboration) showed that initiation of cART at or below a threshold of 500 cells/mm³ increased AIDS free survival, although mortality did not vary substantially with the use of CD4 thresholds between 300-500 cells/mm³[16].
CD4 cell recovery in patients on long-term cART was explored in chapter 2. Seven years after starting cART, patients with lower CD4 cell counts at the start of cART experienced less restoration of CD4 counts than patients starting with higher CD4 cell counts. These results suggested that restoration to CD4 cell counts >800 cells/mm³ is feasible within 7 years following start of cART in most HIV-infected patients who commence treatment at a CD4 count above 350 cells/mm³ and achieve suppression of viral replication. Older age at start of treatment and experiencing periods of detectable viremia (>500 cps/ml) were associated with lesser increases in CD4 cell count after 7 years and with a plateau (at a less than normal range) in CD4 cell restoration. These findings reinforce the recommendation expressed in most current guidelines for earlier initiation of treatment, including in older patients [17].

In the Netherlands, HIV-1-infected immigrants from sub-Saharan Africa, especially males, usually present with relatively low CD4⁺ T-cell counts and are therefore less likely to achieve optimal immune recovery (chapter 3). Unfortunately, a substantial number of immigrants from sub-Saharan Africa do not have health insurance and have limited access to care, which contributes to their late presentation for care. In contrast, women from sub-Saharan Africa who live in the Netherlands are frequently enrolled in HIV screening programmes during pregnancy, which might explain why women from sub-Saharan Africa tend to start cART with less delay and at higher CD4⁺ T-cell counts. The observation that patients from sub-Saharan Africa show slower immune reconstitution on cART than native Dutch patients may indicate geographic variation in normal CD4 ranges but also differences in adherence [18,19]. In our study population the latter seems less likely, given that only patients who had achieved HIV RNA suppression to below the level of detection were included in the analysis. Alternative explanations for our findings might include effect of differences in HIV subtypes [20-22] and host genetic factors [23], which might result in variation in normal values between patients from different regions of origin [24-29] [30,31].

In chapter 3 in which the incidence of AIDS events was investigated in immigrants in the Netherlands (who were at risk for incomplete immune reconstitution), no overall difference in AIDS events was found when comparing these immigrants to native Dutch HIV-infected cohort participants, with the exception of a higher incidence of tuberculosis in HIV infected patients from sub-Saharan Africa. This can partly be explained by a higher prevalence of latent infection resulting in higher rates of tuberculosis reactivation in the setting of profound immunodeficiency. In addition, compared with people from other regions immigrants may have been at a higher risk of re-exposure to tuberculosis through visits to their home country or through contact in the Netherlands with fellow immigrants newly arriving from sub-Saharan Africa. Although several studies have found a decrease in tuberculosis incidence rates in HIV-1-infected patients on cART [32-37], other studies, have reported that even individuals responding well to cART with relatively preserved CD4⁺ T-cell counts might still remain at increased risk for tuberculosis over a prolonged period of time [38-40]. Our findings therefore support the
existing recommendation to screen immigrants arrive from tuberculosis endemic areas for both latent and active tuberculosis, and to utilize isoniazid preventive therapy in case latent infection is documented [41].

**Immunodeficiency and non-AIDS related comorbidities.**

The extent to which incomplete immune recovery and chronic inflammation contribute to the pathogenesis of distinct non-AIDS related comorbidities remains to be clarified [42-48]. The question if, and to which extent, starting cART early will not only reduce residual inflammation but also the risk of non-AIDS outcomes such as renal disease, cardiovascular disease, liver disease, and non-AIDS malignancies, is being definitively addressed in the START trial (Strategic Timing of AntiRetroviral Therapy), in which participants are randomized to start treatment at a CD4+ T cell count above 500 cells/mm³ or defer until the CD4 count drops to 350 cells/mm³ or below [49].

At the time of HIV acquisition there is rapid early loss of CD4+ T-cells within gut-associated lymphoid tissue (GALT) [50-53]. There is evidence to suggest that this GALT CD4+ T-cell depletion leads to loss of immunological and epithelial integrity of the mucosal barrier, allowing bacterial products to translocate through the gut wall more readily and contribute to systemic activation of the immune system [54]. In addition, patients may experience variable degrees of ongoing immune activation as a consequence of continued low-level HIV replication, or the presence of other pathogens such as cytomegalovirus (CMV) and hepatitis C [55]. Generalized immune activation is thought to be associated with abnormal collagen deposition in lymph nodes, further impairing immune functioning [55]. Persistent inflammation is reflected by changes in a number of biomarkers, including measures of T-cell activation (e.g. expression of CD38 and HLA-DR on T-lymphocytes), proinflammatory cytokines (e.g. interleukin-6), and activation of the coagulation cascade (e.g. the fibrin degradation product D-dimer) [56,57]. In the SMART trial, treatment interruption resulting in uncontrolled HIV replication was strongly associated with many of these biomarkers [57] and an increase in all-cause mortality. Subsequent studies have demonstrated that the earlier mentioned biomarkers remain abnormally elevated despite durable ART-induced complete viral suppression when compared to HIV-negative control groups [58].

Ongoing immune activation which has been shown to be associated with reduced CD4 cell reconstitution on cART [56] may also contribute to reduced control of potentially oncogenic pathogens, such as hepatitis B / C virus, human papilloma virus (HPV), Epstein Barr virus (EBV) and human herpes virus 8 (HHV-8), as well as to a reduced ability of the immune system to identify and target malignantly transformed cells. Apart from their oncogenic potential, these co-pathogens may in themselves contribute to chronic ongoing inflammation. Not surprisingly therefore, immunodeficiency has been associated with a variety of malignancies in HIV infected
patients [44]. The findings described in chapter 4 complement previous studies [44,59,60], in showing a relationship between the degree of immunodeficiency and the risk of non-AIDS defining malignancies, particularly those malignancies which have been associated with an infectious etiology.

Similarly, a relationship between immunodeficiency and the risk of chronic liver disease is described in chapter 5. The Data collection on Adverse events of anti-HIV Drugs (D:A:D) study earlier reported immunodeficiency to be strongly associated with the risk of liver-related death [46]. Immunodeficiency has been linked to increased hepatocyte apoptosis and more rapid progression of liver fibrosis in hepatitis B and C virus (HBV/HCV)-infected individuals as CD4 and CD8 responses to HBV/HCV are altered. There has been limited assessment of the long-term consequences of cART on the liver in HIV mono-infected patients [61,62], although cART-induced suppression of HIV viraemia has been associated with less pronounced liver inflammation in HIV/HCV co-infected patients [63]. Apart from immunodeficiency, cART regimens containing didanosine, a combination of didanosine and stavudine, and zidovudine have also been associated with chronic liver injury in both HIV mono- and HBV/ HCV coinfected patients[64-66]. Finally, lifestyle factors such as intravenous drug use, viral coinfections, alcohol abuse and diabetes mellitus also remain important risk factors for developing chronic liver disease. In order to maintain liver-related health in HIV-infected patients, each of these factors needs to be addressed. This includes starting cART early before major loss of CD4-T+ cells has occurred, as well as prevention and treatment of viral hepatitis coinfections, including by testing for these coinfections, and vaccinating against hepatitis B and treating hepatitis B and C coinfection as appropriate.

**Immunodeficiency and toxicity of nevirapine**

The influence of the immune system also plays a role in certain antiretroviral drug-related toxicities. Nevirapine has been a commonly used antiretroviral drug in both Western as well as developing countries since its licensing in 1997. The package insert includes a toxicity warning against the initiation of nevirapine in adult women with CD4+ T cell counts greater than 250 cells/mm³ or in adult males with counts greater than 400 cells/mm³. Although the pathophysiology of nevirapine-associated hypersensitivity reactions remains unclear, the strong association with higher CD4 cell counts suggests the involvement of a CD4-dependent immune response directed to nevirapine-specific antigens. Several studies have described an association of certain HLA types with a higher incidence of hypersensitivity reactions to nevirapine [67-69]. Nevirapine-associated skin rash appears to be immune-mediated by CD4 cells in the female brown Norway rat model [18]. Evidence from the studies presented in chapter 6 and 7 and from several other studies [70-72] showed that this increased risk was not observed in ART-experienced patients who, after having achieved undetectable plasma HIV-1 RNA levels with another regimen, switched to nevirapine for the purpose of regimen simplification or to for
instance reduce dyslipidaemia by taking advantage of the more favourable lipid profile associated with nevirapine. This cumulative joint evidence has led to a revision in labelling information by the European Medicines Agency regarding the toxicity warning against the initiation of nevirapine in adult women with CD4+ T-cell counts greater than 250 cells/mm³ and in adult males with counts greater than 400 cells/mm³. A possible explanation for why the likelihood of nevirapine-associated hypersensitivity reactions at high CD4 counts may be reduced in the absence of viremia might be that in a setting in which HIV-1 replication is controlled, the lower antigenic HIV-1 load results in less immune system hyperactivation and dysregulation [73], which in turn might lessen the tendency of the immune system to react to nevirapine. Nevirapine is currently recommended on a large scale as part of initial treatment regimens in resource limited settings. Incidence of nevirapine-associated rash and hepatotoxicity is low and not associated with CD4 counts at initiation of nevirapine, according to several studies conducted in HIV infected patients (mostly women) in Uganda, Niger, Cote d'Ivoire and Kenya [74-77]. Of note however the median CD4 count at initiation of nevirapine in most of these studies was below 250 cells/mm³, which is the threshold currently used for initiation of nevirapine in women. In another study, severe rash, but not hepatotoxicity, was associated with higher NVP exposure in HIV-infected African women. Although observed in a small number of women, a baseline CD4 cell count of at least 250 cells/ml was significantly associated with NVP toxicity [78].

According to a large trial conducted in Uganda (DART), routine measurements of liver enzymes (ALT/AST) are currently not necessary for preventing hepatic toxicity associated with cART. However, with the scaling up of cART in this setting, and particularly as treatment is started at higher CD4 cell counts, nevirapine associated toxicity may become more prominent and monitoring of liver enzyme elevations may become more important [79].

**Management of aging HIV infected patients.**

The success of antiretroviral treatment will imply that HIV infected people will increasingly survive to older age and thus will increasingly experience aging-associated non-AIDS related comorbidities including cardiovascular, renal and liver-related disease, malignancies, osteoporosis, and declining mental acuity. Addressing lifestyle factors e.g. counselling and helping patients to stop substance abuse, as well as preventive care for cardiovascular disease (by early and aggressive treatment of metabolic abnormalities), earlier implementation of screening colonoscopy and screening for anal and cervical cancer will become more important in reducing the burden of such comorbidities in HIV infected patients using cART. The care of patients with HIV will probably become more complex as patients grow older. As polypharmacy is common in HIV infected patients, managing complex pharmacological interactions will become increasingly important. Cardiologists, oncologists, neurologists, gastroenterologists, endocrinologists, geriatricians, clinical pharmacologists, and other clinical specialists will be increasingly needed to help manage this complex disease.
In resource limited settings, the limited availability of cART is an important challenge for optimizing success of HIV care and treatment in these regions. As a consequence patients with advanced stages of HIV disease are prioritized to initiate ART [80,81] which, is associated with an increased risk of early mortality following treatment initiation [82-84]. Moreover, cART regimens used in sub-Saharan Africa, often continue to include thymidine analogs including stavudine, which are known to contribute towards serious comorbidities like lipoatrophy, peripheral neuropathy, insulin resistance and diabetes mellitus. This will hopefully change with an increasing move in these regions of the world towards better tolerated and less toxic initial ART regimens.

Nonetheless, as increasing numbers of patients in resource-limited settings will access ART, be treated earlier, and will survive to older age, treatment and prevention of non-infectious comorbidities will become increasingly important [85].

**Conclusions and implications for the future.**

Prevention and reduction of non-AIDS related comorbidity will become an increasingly important aspect of management of HIV in both resource rich and resource limited settings. Adapting a strategy of testing and treating HIV early will not only help in preserving and achieving optimal immune reconstitution and reducing the risk of opportunistic infections associated with HIV, but may also be expected to reduce the risk of these comorbidities. In treated HIV-1 infected patients, immunodeficiency and the effect of residual HIV replication and immune activation likely remain important factors associated with comorbidities, although this has not been conclusively proven. The question to what extent these factors are at play may be conclusively answered by clinical trials such as START, and particularly by pathogenesis-oriented substudies within the main trial. Nevirapine has been a commonly used antiretroviral drug in resource rich parts of the world, and remains an essential component of regimens in more resource constrained countries. The relatively low cost of nevirapine and its availability within generic fixed-dose ART combinations is a major reason for its widespread use in sub-Saharan Africa. With the scaling up of cART in resource limited settings and particularly as treatment is started at higher CD4 counts, nevirapine associated toxicity however may become a more prominent concern in these regions. For this reason, alternatives to nevirapine can be expected to become more preferred, with increased cost being an important concern in bringing such alternatives to scale. Based on some of our findings, an intermediate scenario which could be considered and could prove to be a safe and cost-effective strategy, would be switching to nevirapine once undetectable HIV viral load with a more expensive non-nevirapine containing first line regimen had been achieved.
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