Clinical implications of immune recovery during antiretroviral treatment for HIV infection
Kesselring, A.M.

Citation for published version (APA):

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Chapter 1

Introduction
Background
The life expectancy of HIV infected patients has increased from years to decades since the introduction of combination antiretroviral therapy (cART) [1-3]. The first available treatments were complex and associated with significant short-term and long-term toxicity, but current regimens are generally easier to administer, safer, and better tolerated. Co-formulation of antiretroviral drugs has greatly improved convenience by lowering the average pill burden for patients and thereby allowing to prescribe an effective antiretroviral regimen with minimal side effects consisting of a single daily tablet (e.g. tenofovir / emtricitabine / efavirenz). Also, second- and third-line options are available in case of emergence of viral drug resistance to the first-line regimen[4]. As a result of this development durable suppression of HIV replication has become a realistic scenario for the majority of patients. Of 18,380 patients currently registered and monitored in the national HIV registration and monitoring database in the Netherlands, the ATHENA cohort [5], 83 percent are currently on cART. The majority of the remaining 17 percent do not yet meet the current criteria for starting cART. Virological failure is observed in 5% of treated patients annually. Evidence of transmission of resistant virus is found in less than 5% of patients in the Netherlands, likely largely from persons who may not yet be aware of being HIV infected.

Determinants of immune reconstitution
Achievement of the best possible degree of immune restoration through sustained viral suppression in HIV type-1 (HIV-1)-infected patients treated with cART is an important measure of cART efficacy. There has been a growing recognition that short- and long-term adverse events [6,7], difficulties with maintaining high rates of adherence [8,9], the emergence of viral drug resistance [4], and cost may all affect the ability to sustain the positive effects of cART. In patients with sustained HIV suppression on cART, residual HIV replication [10,11], impaired thymic function [12,13], advanced age [14], enhanced T-cell activation [15,16], apoptosis [17,18], and, possibly viral coinfection [19,20] have all been associated with more limited immune restoration. In addition, patients starting with lower pre-cART CD4 counts experience less pronounced restoration of CD4 cell counts than patients starting with higher pre-cART CD4 cell counts [21,22]. In chapter 2 we provide more insight into the restoration of CD4 cell counts by use of cART in HIV-infected individuals to levels normally seen in uninfected individuals. Most HIV-1 infected patients in the Netherlands are still native Dutch, but the proportion of immigrants is increasing [23]. Most of the immigrants are from sub-Saharan Africa and the former Dutch colonies in the Americas (Surinam and the Netherlands Antilles). Immunological responses to cART of immigrants into Western countries have not been extensively investigated. In chapter 3, we sought to further investigate possible differences in long-term CD4+ T-cell responses among HIV-1-infected previously untreated patients achieving viral suppression on cART, from Western Europe/ North America, sub-Saharan Africa, Southeast Asia, Latin
America/the Caribbean and other regions now living in the Netherlands, and to determine whether a possible decreased immunological response in any of these groups translates into a poorer clinical outcome.

**Morbidity and mortality**

Since the introduction of cART survival of HIV-infected patients has improved dramatically, and accordingly the incidence of AIDS events has decreased. The degree of immune restoration while on cART is an important predictor for morbidity and mortality. For example, Lewden et al. found that restoration of CD4 counts to levels over 500 cells/mm³ was associated with improved survival rates, which were comparable to the general population [1,24].

Although the incidence of AIDS-defining infections and malignancies has decreased markedly [25], the incidence and proportion of deaths related to non-AIDS-related comorbidities are increasing among HIV-1-infected patients in the cART era [3,26-33]. Several studies strongly suggest that the risk of non-AIDS morbidity is higher among antiretroviral treated HIV infected individuals than among their age matched uninfected peers.

Although people living with HIV often have more traditional risk factors for heart disease (e.g. tobacco use [34], alcohol abuse and viral hepatitis co-infections [35]), these factors do not account for all of the increased non-AIDS morbidity risk [36-38]. Immunodeficiency on treatment is associated with a higher risk of cardiovascular, renal, and liver disease, as well as cancer [36,39] [40,41] [42,42-44]. Also other non-AIDS diseases, including pulmonary hypertension [45] and bone disease and non-traumatic bone fractures [46] [47] [48] are more common in HIV infected patients. There is also a concern that HIV-associated neurological disease persists or even progresses during otherwise effective long-term cART [49-51].

The advanced immunodeficiency associated with untreated HIV infection greatly increases the risk of Kaposi's sarcoma and non-Hodgkin's lymphoma. HIV infected patients also have an increased risk of other cancers, including lung cancer, skin cancer, colorectal cancer, and anal cancer [52]. Immunodeficiency is strongly associated with a higher cancer rate, even among patients on prolonged antiretroviral treatment [53]. Risk is particularly evident for those non-AIDS defining malignancies that are known or believed to be caused by infectious pathogens (e.g. anal cancer, Hodgkin's disease, liver cancer), while the risk of other cancers (e.g. lung, colorectal, melanoma) is less markedly increased. HIV-negative organ transplant recipients have comparable risks to those with HIV, which supports the idea that long term immunosuppression is causally related with cancer in HIV infected patients [35]. In chapter 4, using data from the ATHENA cohort we perform analyses into the role of cART, immunodeficiency, and HIV viremia in the cART-treated HIV infected population as contributors towards the risk of non-AIDS-defining malignancies, while adjusting to the best of our ability for traditional risk factors. As has been the case for non-AIDS malignancies, a strong independent association between HIV-associated immunodeficiency and risk of hepatocellular carcinoma [54] and liver-related death.
has also been reported [43]. Chronic liver disease has become one of the leading causes of death among HIV-infected individuals on cART [43,55-57] and is particularly associated with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) co-infection, as well as with chronic excessive alcohol consumption and drug-related toxicity [58-63]. As a possible reflection of the latter, non-alcoholic steato-hepatitis (NASH) is increasingly being recognized as an important cause of serious chronic liver disease in HIV-1 infected patients [64,65]. Restoration of immunodeficiency on cART may delay or even prevent progression to chronic liver disease [66] [67,68], but at the same time cART may also contribute to the development of chronic liver disease due to toxic effects of antiretrovirals on the liver [33,43,69]. Non-cirrhotic portal hypertension has recently been described in HIV-infected patients [70-74] and has been consistently linked to the (prior) use of didanosine [70,71]. Other studies have identified the use of didanosine and stavudine as risk factors for severe liver fibrosis in both HIV/HCV co-infected and HIV mono-infected patients [69]. In chapter 5, we describe the relationship of HIV-related factors (duration of HIV-infection, HIV-1 viraemia, immune deficiency) and antiretroviral treatment (duration of cART, use of specific antiretroviral agents) with the development of a severe chronic liver disease in the ATHENA cohort, while again adjusting to the best of our ability for traditional risk factors.

**HIV viraemia, immune deficiency and immune activation**

Despite effective suppression of HIV-replication on cART, chronic HIV-associated immune activation persists at levels high enough to cause significant persistent inflammation [75,76], which may be associated with more rapid progression to non-AIDS-related morbidity and mortality [77]. The extent of viral replication appears to be a strong determinant of kidney disease [78,79], bone disease [80] and possibly liver disease [81]. Additionally, HIV-infected persons who are able to durably control HIV infection in the absence of therapy (“elite controllers”) have more carotid disease than age-matched uninfected persons which possibly is related to the increased immune activation observed in such persons [82]. Also results from the SMART study suggest that a higher risk of opportunistic diseases and death in patients on treatment interruption is associated with spending more follow-up time with relative immunodeficiency and living longer with uncontrolled HIV replication even at higher CD4 counts [83]. In the SMART study, participants randomized to the cART interruption strategy where re-initiation of cART was deferred until the CD4 count decreased to less than 250 cells/μL, had a 2.6 fold increased risk of opportunistic disease and all cause mortality and an 84% significantly increased risk of all-cause mortality [26]. Likewise, two other randomized, controlled trials (Trivacan [84], and DART[85]) were prematurely halted on the recommendation of the data and safety monitoring boards because of a 2-fold excess risk of opportunistic diseases associated with chronic HIV infection in the group allocated to treatment interruption. Consistent with these results, in a fourth study (Staccato), an excess risk of opportunistic diseases in the CD4 count–guided interruption arm was also observed [86].
These findings argue for an effect of HIV-associated factors that is independent of direct drug toxicity, traditional risk factors and advanced immunodeficiency [82].

**Antiretroviral toxicity**

Although the goal of cART is achieving an optimal immune response in order to prevent HIV related morbidity and mortality, toxicity of cART is an important factor to take into account. The spectrum of drugs used in HIV-infected patients has changed dramatically since cART was introduced in the mid-1990's. Twenty-four antiretroviral drugs have been approved since 1986 and currently drug safety and tolerability are the most important issues that distinguish one drug from another. Several of the nucleoside-analogue reverse transcriptase inhibitors (NRTIs), in particular the thymidine analogues, have been associated with hyperlactataemia and a large spectrum of clinical and biological abnormalities that include peripheral and autonomic neuropathy, skeletal and cardio-myopathy, steatohepatitis, pancreatitis and peripheral lipoatrophy. Severe steatohepatitis can promote the onset of lactic acidosis, a life-threatening condition. Abacavir has been associated with cardiovascular events in some studies [87,88]. Additionally, prolonged exposure to some of the HIV protease inhibitors is associated with hyperlipidaemia, insulin resistance, and a higher rate of cardiovascular disease events [88]. Tenofovir and ritonavir-boosted protease inhibitors have been associated with reduced bone mineral density [47]. Many antiretroviral drugs are directly toxic to liver and kidney in HIV infected adults. Long term exposure to tenofovir and the protease inhibitors atazanavir, lopinavir and in the early cART-era indinavir has been associated with decline in renal function [89-92].

Hepatotoxicity is common and described with most antiretroviral drugs and is more frequent among patient with chronic viral hepatitis or increased baseline hepatic transaminases and in alcoholics [93]. Apart from direct antiretroviral toxicity, in those with chronic viral hepatitis and steatohepatitis secondary to NRTI-associated mitochondrial toxicity, immune status may also play a role in some antiretroviral-associated effects on the liver. An example of this mechanism is found in nevirapine-associated hypersensitivity reactions. Nevirapine is associated with a drug-induced hepatitis in 2.5-11% of patients, mainly during the first 12 weeks of treatment [94]. Approximately 50% of these reactions are associated with fever, rash or arthralgias, suggesting that hypersensitivity underlies many such cases. Severe, life-threatening and fatal cases of hepatotoxicity have also occurred. Because immuno-competence is a significant risk factor, guidelines recommend that nevirapine be initiated only in men and women with CD4 cell counts <400 and <250 cells/mm³, respectively, with a particular caution for those with chronic viral hepatitis [95]. Patients already receiving cART while switching to nevirapine might not have this greater risk of hepatitis [96], especially those patients who have an undetectable viral load at the time of switching to nevirapine. Stevens-Johnson syndrome and toxic epidermal necrolysis are severe forms of cutaneous hypersensitivity that are mainly associated with non-nucleoside reverse transcriptase inhibitors (NNRTI) (0.3-0.5% for nevirapine, 0.1% for efavirenz and 0.1%
for etravirine). Drug cessation is essential for any potentially life threatening adverse event. HLA immune response genes (HLA) screening has demonstrated the involvement of genetic factors in the abacavir [97] and nevirapine hypersensitivity reactions [98,99]. Several large cohort studies suggested that the risk of treatment-limiting toxicities for treatment-experienced patients who initiate nevirapine-based cART with high CD4 cell counts may be similar to the risk in treatment-naive patients with low CD4 cell counts [100] possibly due to low nadir CD4 counts and/or undetectable viral loads [101]. In chapter 6, we further investigated whether the risk of potentially fatal toxicities is increased similarly in treatment-experienced patients starting nevirapine-based cART, compared to treatment naïve patients[101]. In chapter 7, we aimed to extend the findings in chapter 6 by retrospectively evaluating the safety of nevirapine based cART in treatment experienced patients with high CD4 counts in an international collaboration of seven established cohorts [96].

Outline of this thesis

The main objective of this thesis was to investigate a range of clinical implications of immune status and immune recovery in HIV-1 infected patients during treatment with antiretroviral therapy. A background on this topic is provided in chapter 1. In chapter 2 we describe immunorestoration by use of cART in HIV-infected individuals to levels normally seen in uninfected individuals, defined as ≥800 CD4+ T-cells /mm³, according to CD4+ T-counts at the start of cART. Immunological responses to cART of immigrants into Western countries have not been extensively investigated. Chapter 3 compares long-term CD4+ T-cell responses among previously untreated HIV-1-infected patients achieving viral suppression on cART from Western Europe/North America, sub-Saharan Africa, Southeast Asia, Latin America/the Caribbean and other regions, currently living in the Netherlands. It also addresses whether differences in immunological response to cART between any of these groups translate into differences in clinical outcome. Chapter 4 analyses the contribution of cART, immunodeficiency, and HIV viraemia in the cART-treated HIV infected population towards the risk of non–AIDS-defining malignancies, while adjusting for traditional risk factors such as smoking, viral co-infections and excessive use of alcohol. In chapter 5, the association between HIV-related factors (estimated duration of HIV-infection, level of HIV-1 viraemia and immunodeficiency) as well as antiretroviral treatment-related factors (duration of cART, use of specific antiretroviral agents) and the development of a severe chronic liver disease is examined, while adjusting for risk factors known to be associated with chronic liver disease. In chapter 6, we investigate whether the risk of potentially fatal nevirapine-related toxicities is increased similarly in treatment-experienced compared to treatment naïve patients starting nevirapine-containing cART. In chapter 7, we extend the findings in chapter 6 by retrospectively evaluating the safety of nevirapine based cART in treatment experienced patients with high CD4 counts in an international collaboration of seven established cohorts. Implications of immune status and immune recovery in HIV-1 infected patients during treatment with antiretroviral therapy are discussed in chapter 8.

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