Clinical implications of immune recovery during antiretroviral treatment for HIV infection
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Summary
The life expectancy of HIV infected patients has increased from years to decades since the introduction of combination antiretroviral therapy (cART). As a result, clinical manifestations of HIV have altered significantly in the cART era. This thesis describes a range of clinical implications of immune status and immune recovery in HIV-1 infected patients during treatment with antiretroviral therapy. An outline is provided in chapter 1. The studies described in chapters 2-6 have been conducted in the setting of the ATHENA (AIDS Therapy Evaluation in the Netherlands project) cohort study, which includes registred HIV-infected patients in the Netherlands.

Achievement of the best possible degree of immune restoration through sustained viral suppression in HIV type-1 (HIV-1)-infected patients treated with combination antiretroviral therapy (cART) is an important measure of cART efficacy and leads to reduction of HIV related morbidity and mortality. In chapter 2, we aimed to explore the capacity of patients on long-term cART to improve CD4 cell counts. We assess how these improvements, 7 years after starting cART, compare with CD4 cell levels in the non–HIV-infected population. In addition, we describe the determinants of reaching a plateau in CD4 cell restoration between 5 and 7 years of uninterrupted cART. Three endpoints were studied: (1) time to 800 CD4 cells/mm³ in 5299 therapy-naive patients starting cART, (2) CD4 cell count changes during 7 years of uninterrupted cART in a subset of 544 patients, and (3) reaching a plateau in CD4 cell restoration after 5 years of cART in 366 virologically suppressed patients. 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 results suggested that restoration to CD4 cell counts >800 cells/mm³ is feasible within 7 years of cART in most HIV-infected patients starting with >350 cells/mm³ and achieving suppression of viral replication.

Most HIV-1 infected patients in the Netherlands originate from the Netherlands, but the proportion of patients from other regions of origin is increasing. Most of the new non-native patients are immigrants 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 potential differences in long-term CD4+ T-cell response to cART among HIV-1-infected previously untreated virologically suppressed patients from Western Europe/ North America, sub-Saharan Africa, Southeast Asia, Latin America/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 poorer clinical outcome. CD4$^+$ T-cell response on cART was determined over 7 years using mixed models. Among 6057 patients participating in the Netherlands observational ATHENA cohort and adherent to treatment, immunological response in the first 6 months of cART in immigrants from sub-Saharan Africa was decreased compared with patients from Western Europe and in males compared to females. Because men from sub-Saharan Africa started with lower CD4$^+$ T-cell counts than Western patients, they continued to lag behind and had lower absolute CD4$^+$ T-cell counts after 7 years of cART. Furthermore, cumulative tuberculosis incidence after 7 years of cART was higher in patients from sub-Saharan Africa. Results suggested that HIV-1-infected immigrants from sub-Saharan Africa have blunted immune restoration on fully suppressive cART and should be identified at an earlier disease stage. Our results call for more intensive screening for both latent and active tuberculosis in these immigrants.

Limited data are available about the relationship between immunodeficiency, viremia, and exposure to (specific) antiretroviral agents and the risk of non–AIDS-related malignancies. In chapter 4, we describe the role of cART, immunodeficiency, and HIV viremia in the treated HIV infected population as risk factors for non–AIDS-defining malignancies, while as much as possible adjusting for traditional risk factors. Patients starting combination antiretroviral therapy as of 1 January 1996 were selected from the AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort. In Cox regression models, risk factors for non-AIDS defining malignancies were investigated. In a cohort of 11,459 patients, 236 non-AIDS defining malignancies were diagnosed; 102 with a possible infectious etiology, and 134 attributable to other causes. In Cox regression models, cumulative exposure to CD4 cell counts <200 cells/mm$^3$ during cART was associated with an increased risk of infection-related non–AIDS defining malignancies. No significant effect of viremia or cART regimens was seen in either type of cancer.

Chronic liver disease is associated with chronic hepatitis B virus (HBV) infection, chronic hepatitis C virus (HCV) infection, alcohol consumption and drug-related toxicity. In addition, non-alcoholic steato-hepatitis (NASH) is increasingly being recognized as an important cause of serious chronic liver disease in HIV-1 infected patients without chronic viral hepatitis. Also, non-cirrhotic portal hypertension has been described in HIV-infected patients.

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 setting of a cohort of treated HIV-infected adults, while adjusting for traditional risk factors. Patients starting cART as of 1 January 1996 were selected from the Netherlands ATHENA cohort. Patients with portal hypertension and/or Metavir stage F3-F4 were classified as chronic...
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Liver disease. Cases of chronic liver disease without traditional risk factors (intravenous drug use, chronic viral hepatitis, alcohol abuse, diabetes mellitus) were classified as cryptogenic chronic liver disease. In Cox models risk factors for chronic liver disease were investigated. Of a total of 14,247 included patients starting cART, 169 new cases of chronic liver disease were diagnosed. 107 (63%) cases were chronically co-infected with hepatitis B or C virus. Events included cirrhosis (n=138), hepatorenal syndrome (n=2), liver transplantation (2), bleeding esophageal varices (12), hepatocellular carcinoma (n=10) and non-cirrhotic portal hypertension (n=4). Forty-eight patients died due to chronic liver disease. Immunodeficiency and exposure to didanosine/stavudine and didanosine were independently associated with chronic liver disease, in patients with and without traditional risk factors.

Recommendations that nevirapine should be avoided in female individuals with CD4 cell counts >250 cells/mm³ and in male individuals with CD4 cell counts >400 cells/mm³ are based on findings in treatment naïve patients. It is unclear whether these guidelines also apply to treatment-experienced patients switching to nevirapine-based combination therapy.

In chapter 6, we investigated whether the risk of potentially fatal toxicities is increased similarly in treatment-experienced patients starting nevirapine-based cART who may have experienced substantial CD4 cell count increases during prior treatment. We included patients in the ATHENA cohort study who had used nevirapine-based combination therapy. Patients who discontinued nevirapine-based combination therapy because of hypersensitivity reactions (rash and/or hepatotoxicity) within 18 weeks after starting such therapy were identified. Patients were stratified according to their C4 counts at initiation of NVP-based cART, either having a high CD4 cell count (for female patients, >250 cells/mm³; for male patients, >400 cells/mm³) or a low CD4 cell count. Treatment experienced patients were further subdivided according to the last available CD4 cell count before first receipt of antiretroviral therapy using the same criteria. Risk factors for hypersensitivity reactions were assessed using multivariate logistic regression. Of patients receiving nevirapine-based combination therapy (n=3752), 231 patients (6.2%) discontinued nevirapine based therapy because of hypersensitivity reactions. Independent risk factors included female sex and Asian ethnicity. Having an undetectable viral load (VL) at the start of nevirapine based therapy and having low nadir CD4 counts were associated with reduced risk of developing an hypersensitivity reaction. Results suggested that nevirapine based cART may be safely initiated in patients with high current CD4 counts but undetectable viral loads and low nadir CD4 counts, but that in similar patients with a detectable viral load it is prudent to continue to adhere to current CD4 cell count thresholds.
In chapter 7, we aimed to retrospectively evaluate the safety of nevirapine based cART in treatment experienced patients with high CD4 counts in a collaboration of seven established cohorts. Patients starting nevirapine-based cART VPc after 1 January 1998 were included. CD4 cell count at starting nevirapine-based cART was classified as high (>400/ml/>250/ml for men/women, respectively) or low. Cox regression models were used to investigate risk factors for discontinuations due to hypersensitivity reactions (n=6547) and discontinuation of nevirapine-based cART due to treatment-limiting toxicities and/or patient/physician choice (n=10 186). Patients were classified according to prior antiretroviral treatment experience and CD4 cell count/viral load at the start of nevirapine-based cART. Models were stratified by cohort and adjusted for age, sex, nadir CD4 cell count, calendar year of starting nevirapine-based cART and mode of transmission.

The median time to discontinuation of cART due to treatment-limiting toxicities and/or patient/physician choice was 162 days, due to hypersensitivity reactions was 30 days.

In adjusted Cox regression analysis, treatment-experienced patients with high CD4 cell count and detectable viral loads over 400 cps/ml had a significantly increased risk for hypersensitivity reactions and treatment-limiting toxicities within 18 weeks of starting nevirapine-based cART. In contrast, treatment-experienced patients with high CD4 cell count and undetectable viral loads had no increased risk for hypersensitivity reactions or treatment-limiting toxicities within 18 weeks of starting nevirapine-based cART. Our results suggest it may be relatively safe to initiate nevirapine-based cART in antiretroviral-experienced patients, even in those with high CD4 cell counts provided there is no detectable viremia.

Implications of immune status and immune recovery in HIV-1 infected patients during treatment with antiretroviral therapy are discussed in chapter 8. Prevention and reduction of non-AIDS related morbidity 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, which will decrease the adverse effects of immunodeficiency and immune activation, can be expected to help in preserving and achieving optimal immune reconstitution and reducing the risk of these comorbidities. In patients starting cART with high CD4 counts, switching to nevirapine after achieving undetectable HIV viral load is a potential cost-effective strategy for prevention of nevirapine associated toxicity.