Studies on the efficacy and toxicity of highly active antiretroviral therapy
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Summary

Chapter 1 provides the background to this thesis. It gives a general overview of HIV and the extent of the pandemic, and covers the developments in antiretroviral therapy up to the introduction of highly active antiretroviral therapy (HAART) into clinical practice in the mid-1990's, the period at which the studies for this thesis were initiated. The adverse effects of antiretroviral therapy are discussed in more detail.

Chapter 2 summarizes the first experiences with protease inhibitor-containing HAART in the HIV outpatient clinic of the Academic Medical Centre in Amsterdam. We followed 271 HIV-1-infected patients for 1 year after the start of HAART. New AIDS-defining events occurred in 6.3% of patients, and 3.0% died. Overall, virologic treatment failure occurred in 40% of patients. Virologic treatment failure occurred significantly more often in patients using HAART with saquinavir as the single protease inhibitor: saquinavir 59%, indinavir 27%, ritonavir 30%, and ritonavir plus saquinavir 32%. Risk factors for virologic treatment failure were a higher plasma HIV-1 RNA concentration at the start of HAART, a lower CD4+ T-lymphocyte count at the start of HAART, the use of saquinavir as a single protease inhibitor, and not adding new antiretroviral drugs to the regimen. During the first year of treatment, 53% of all patients changed (part of) their original HAART regimen at least once. This was significantly more frequent for regimens containing saquinavir (62%; 27% because of virologic failure) or ritonavir (64%; 55% because of intolerance) as single protease inhibitor. Even though the patients in the saquinavir group did worse virologically than the other groups, their immunological response was not significantly lower.

Chapter 3 summarizes the first experiences with nevirapine-containing HAART in the Netherlands. Before licensing nevirapine was available in the Netherlands through a compassionate use program. Patients failing therapy and who, in the opinion of their treating physicians, could only be adequately treated if they could obtain nevirapine, were eligible for the program. Within the program it was recommended to combine nevirapine whenever possible with at least two other antiretroviral agents that were expected to still be effective. We analyzed data from 187 patients who received nevirapine through this program in 13 HIV-outpatient clinics in the Netherlands. Even though after 1 year of treatment only 38% of patients had plasma HIV-1 RNA levels below 1000 copies/mL, the median CD4+ T-lymphocyte count remained stable. Sustained suppression of HIV-1 occurred more often in patients with less extensive pretreatment, and in patients with a higher
CD4+ T-lymphocyte counts at the start of nevirapine. Twenty (10.7%) patients experienced a new AIDS defining illness and/or died. The total incidence of rash (including rash not leading to discontinuation of nevirapine) was 13.9 and 6.4% of the patients discontinued nevirapine because of rash. Remarkably, none of the 28 patients with undetectable HIV-1 RNA levels at baseline developed a rash.

Chapter 4 In a large percentage of patients apparently successfully treated with HAART, more sensitive detection methods provide evidence of ongoing low-level replication. The question is whether more potent therapy can further suppress this residual replication. Thirty control patients who, using very strict criteria, had not experienced virological failure during 3 years of standard protease inhibitor-containing HAART, were compared with 10 patients treated with a five-drug regimen consisting of three different classes of antiretroviral drugs (alternative multidrug regimen). An ultrasensitive assay with a lower limit of quantification of 5 copies/mL was used to retest plasma obtained at week 48 and at three timepoints at and around week 144. At weeks 48 and 144 plasma HIV-1 RNA could be quantified significantly more frequently in control patients than in the patients using the alternative multidrug regimen (week 48: 42% vs 0% with quantifiable plasma HIV-1 RNA, p=0.017; week 144: 60% vs 14% with at least 1 quantifiable plasma HIV-1 RNA, p=0.036, respectively). A low CD4+ T-lymphocyte count at the start of HAART was predictive of having a quantifiable plasma HIV-1 RNA in the control patients, but not in the patients using the alternative multidrug regimen. This proof-of-principle-study demonstrates that the use of an alternative multidrug regimen results in stronger long-term suppression of plasma HIV-1 RNA compared to clinically successful treatment with standard therapy. This provides evidence that ongoing low-level viral replication during standard therapy is at least partially due to limited potency of the currently used drug regimens. It is evident that further long-term follow-up studies are required to answer the important question whether the advantages of improved viral suppression by this multidrug regimen outweigh the disadvantages of additional toxicity and costs of using more antiretroviral agents.

Chapter 5 In this study we investigated the risk of developing liver toxicity after initiation of protease inhibitor-containing HAART for HIV-1 infected patients with or without chronic hepatitis B virus or hepatitis C virus co-infection. We retrospectively studied 394 HIV-1-infected patients from the HIV-outpatient clinic of the Academic Medical Centre in Amsterdam. Liver toxicity was defined as liver enzyme concentrations in the blood of at least
five times the upper limit of normal. Of 394 patients 7% were chronically infected with hepatitis B virus and 14% with hepatitis C virus. Patients with chronic viral hepatitis had a higher risk for liver toxicity compared with patients without co-infection: 37% versus 12% respectively. After adjustment for higher liver enzymes at the start of HAART, the presence of chronic hepatitis B and C virus infections remained associated with an increased risk of liver toxicity. In the patients who developed liver toxicity the liver enzymes declined whether HAART was continued or modified. Of the patients with chronic hepatitis B virus infection 38% developed antibodies against hepatitis B virus after initiation of HAART. We conclude that HIV-1-infected patients co-infected with hepatitis B or C virus were at considerably higher risk of developing liver enzyme elevations when HAART was initiated compared with patients without these co-infections, but it is usually not necessary to modify antiretroviral therapy.

Chapter 6 builds on the results from chapter 5. We investigated whether the use of particular antiretroviral agents is associated with a higher risk of developing severe liver toxicity in a retrospective cohort study of HIV-1-infected patients starting HAART. Severe liver toxicity was defined as liver enzyme concentrations in the blood of more than 10 times the upper limit of normal. A multivariate Cox model was used to identify risk factors. The incidence of severe liver toxicity was 6.3%. The majority of these events occurred without symptoms. No patients died as a direct result of the severe liver toxicity. Risk factors for developing severe liver toxicity were: higher baseline liver enzyme concentrations, chronic hepatitis B or C virus infection, antiretroviral therapy-naïve patients using their first HAART regimen, recent start of nevirapine or high-dose ritonavir, and female gender. In patients coinfected with hepatitis B virus, discontinuing lamivudine was a risk factor. In 97% of cases 1 or more risk factors was present. In HBV-coinfected patients using lamivudine, continued use of lamivudine should be considered, even if lamivudine-resistant HIV-strains have developed.

Chapter 7 We determined the effect of adjuvant prednisolone use on the development of abacavir- and nevirapine-associated hypersensitivity reactions in a randomized open-label study in HIV-1 infected patients in which nevirapine and/or hydroxyurea and/or prednisolone were added to a regimen of abacavir, zidovudine and lamivudine. Prednisolone (40 mg once daily) was added for the first 2 weeks of treatment. As it was difficult to distinguish abacavir-associated hypersensitivity reactions from nevirapine-associated hypersensitivity reactions, these events were treated as a composite endpoint. Of the 229 patients 115 were randomized to
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prednisolone and 114 to no-prednisolone, 19 (17%) and 11 (10%) patients, respectively, developed a hypersensitivity reaction. The expected prevention of hypersensitivity reactions by prednisolone use was not observed. In fact use of prednisolone showed an increased risk for hypersensitivity reactions although this did not reach statistical significance. There was a higher incidence of hypersensitivity reactions in the nevirapine group than in the non-nevirapine group (20% versus 6%). An additional risk factor for developing hypersensitivity reactions was a high CD4+ T-lymphocyte count at the start of HAART. We conclude that the simultaneous start of abacavir and nevirapine in first-line HAART should be avoided because of a high (20%) incidence of hypersensitivity reactions. Short-term therapy with prednisolone did not prevent hypersensitivity reactions in patients using abacavir with or without nevirapine.

Chapter 8 provides a general overview of the developments in the treatment of HIV-1 infections. When HAART was first introduced into clinical practice in the mid-1990's there was tremendous enthusiasm about the possibilities to turn an invariably fatal disease into a treatable chronic disorder. There was even hope of being able to eradicate the virus completely from an infected person. The following years brought the sobering conclusion that, even though HAART greatly reduced the HIV-related morbidity and mortality, in a large proportion of treated patients viral resistance developed or successful therapy had to be discontinued because of drug-related toxicities. Eradication of HIV proved impossible using the currently available antiretroviral drugs. Current developments aim at bringing to the market more potent antiretroviral agents that are easy to administer, and have fewer side effects.