Clinical and pharmacological aspects of induction-maintenance therapy in HIV-1 positive patients: the ADAM study
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Summary
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Treatment with highly active antiretroviral therapy (HAART) has led to significant health benefits for HIV-1 infected patients. However, long-term use of multi-drug regimens is difficult to sustain. Simplifying antiretroviral treatment regimens would increase patient-adherence and minimise toxicity. In the Amsterdam Duration of Antiretroviral Medication (ADAM) study the feasibility of an induction-maintenance strategy in HAART was investigated.

In the introduction of this thesis, the background to the design of the study is outlined. HIV-1 infected patients with $\geq 200$ CD4$^+$ cells/mm$^3$, $\geq 1000$ HIV-1 RNA copies/ml in plasma and no previous exposure to antiretrovirals were enrolled in this multi-centre, randomised, open-label study. After 26 weeks of induction therapy (stavudine (d4T) + lamivudine (3TC) + saquinavir (SQV) + nelfinavir (NFV)), patients were randomised to maintenance therapy (either d4T + NFV or SQV + NFV) or prolonged induction therapy, if the plasma HIV-1 RNA level at weeks 24 and 25 had been < 50 copies/mL. The patients randomised to prolonged induction therapy were subsequently randomised at week 50 to continued quadruple drug therapy or one of the two maintenance therapies, if the plasma HIV-1 RNA level at weeks 48 and 49 had been the lower limit of quantification of the ultrasensitive assay.

In Chapter 2, the results of an interim analysis of the ADAM study are described. The quadruple induction regimen provided a rapid suppression of viral replication to below 50 copies/mL. Nevertheless, this level of suppression was not sustained in a considerable number of patients randomised to maintenance therapy at week 26. A sustained suppression of viral replication during maintenance therapy was associated with a relatively high initial viral clearance rate. In the light of these findings, and those reported by others, randomisation at week 26 was discontinued. Randomisation after 50 weeks of induction therapy was not discontinued.

The patients randomised at week 50 to induction or maintenance therapy were compared for the proportion of patients with a viral rebound (Chapter 3). Treatment failure was observed in 50% of the patients on maintenance therapy compared to only 20% of the patients on continued quadruple drug therapy (not statistically significant). Subsequently, the time to > 400 HIV-1 RNA copies/ml in plasma during maintenance therapy was compared between patients randomised at week 26 and at week 50. Time to >400 HIV-1 RNA copies/ml was comparable between patients randomised to maintenance therapy after 26 and 50 weeks of induction therapy. Apparently, a longer period of quadruple drug therapy does not postpone viral rebound during maintenance therapy.
Before discussing the association between the exposure to the protease inhibitors and toxicity and efficacy of the quadruple drug regimen in Chapter 5 and 6, the steady-state plasma pharmacokinetics of nelfinavir (Viracept®) and saquinavir (Invirase®) during a quadruple antiretroviral drug regimen are described in Chapter 4. In eighteen patients participating in the ADAM study, who used the quadruple antiretroviral drug regimen for at least 4 weeks, plasma concentrations of nelfinavir and saquinavir were quantified during a full (8-hour) dosing interval. Plasma pharmacokinetics of both protease inhibitors were calculated using noncompartmental methods. The positive pharmacokinetic interaction between nelfinavir and saquinavir was further explored by comparing saquinavir pharmacokinetics to those observed in historical controls treated with a saquinavir dosage of 1,200 mg tid (Invirase®), without the use of nelfinavir. Observed interindividual variation in pharmacokinetic parameters was approximately 4-fold for nelfinavir, and approximately 6-fold for saquinavir. Nelfinavir increased saquinavir plasma concentrations at least 2-fold, and reduced intrapatient fluctuation of saquinavir plasma concentrations. Interpatient variability in saquinavir pharmacokinetics was not reduced by concomitant administration of nelfinavir.

By means of these plasma drug concentrations during a full 8h-dosing interval, plasma drug concentration ratios were calculated as a measure for drug exposure. Using these ratios, plasma drug concentrations were adjusted for the time interval between drug ingestion and drawing of the sample. In addition, the elimination rate constant (k) for HIV-1 clearance was calculated during the first two weeks of treatment in 29 patients. It appeared that the variation in the rate of decline of HIV-1 RNA in plasma between patients after the initiation of therapy could be explained by differences in exposure to nelfinavir or saquinavir.

These results, described in Chapter 5, could be used to further optimise antiretroviral drug therapy and may be a first tool to assess antiretroviral activities of new or increasing doses of drugs administered in combination regimens. Furthermore, these data suggest that exposure to antiretroviral drugs should be incorporated in mathematical models to describe HIV-1 dynamics in more detail.

In Chapter 6, again the exposure to nelfinavir (NFV) and saquinavir (SQV) as part of the quadruple drug regimen are described, but now for the whole 26 weeks of induction therapy. The exposure to the protease inhibitors was relatively low, although the virological efficacy of the regimen used was satisfactory. In addition, the toxicity of the quadruple induction regimen was described. The quadruple drug regimen was rather well tolerated. Diarrhea was frequently reported but could be
relieved by the use of antidiarrheal agents. Lipid abnormalities in plasma were infrequent and mild. Subsequently, the association between toxicity and drug exposure was described. Except for diarrhea, all gastrointestinal complaints observed were found to be associated with the level of exposure to nelfinavir or saquinavir. Experiencing abdominal pain was associated with a relatively high exposure to nelfinavir, while the complaints nausea and abdominal distension were associated with a low exposure to the two protease inhibitors.

One of the sub-studies in which patients of the ADAM study could participate concerned Quality of Life (Chapter 7). The patients randomised at week 26 to prolonged induction therapy or maintenance therapy were compared for their quality of life (QoL). QoL declined more during maintenance therapy than during prolonged quadruple induction therapy. Most likely, inferior viral suppression associated with maintenance therapy added to this negative impact on QoL, that outweighed the burden of the quadruple regimen.

12 patients of the ADAM study were willing to participate in another sub-study, described in Chapter 8, in which cerebrospinal fluid (CSF) and semen were sampled after 26 or 50 weeks of continuous treatment with the quadruple drug regimen. The concentrations of stavudine, lamivudine, nelfinavir, and saquinavir, were assessed in plasma, CSF and semen. Of the protease inhibitors, only saquinavir was detected at a low concentration in seminal plasma. Neither nelfinavir nor saquinavir was detected in the CSF. The concentrations of stavudine and lamivudine in seminal plasma were higher than in CSF. For lamivudine, seminal plasma/blood plasma ratios were significantly higher than CSF/blood plasma ratios. These data support the hypothesis that poor penetration of the central nervous system and the male genital tract by antiretroviral drugs can contribute to differences in viral dynamics in these compartments.

The plasma- and CSF concentrations of stavudine were further investigated (Chapter 9). The metabolism of this nucleoside analogue reverse transcriptase inhibitor (NRTI), is partly unknown. In order to investigate the pharmacokinetics of stavudine, stavudine concentrations in paired samples of plasma and cerebrospinal fluid (CSF) of patients using four different treatment regimens were compared. Patients using stavudine without the addition of a protease inhibitor or in combination with nelfinavir and saquinavir were found to have significantly lower stavudine concentrations in plasma and CSF than patients using ritonavir and/or indinavir. CSF/plasma concentration ratios of stavudine were comparable. In a multivariate linear regression analysis, the use of ritonavir and/or indinavir and the baseline CD4+ T-cell count were significantly associated with the stavudine
concentrations in plasma and CSF. This unexpected finding suggested that stavudine metabolism may, at least in part, be inhibited by ritonavir and/or indinavir.

In conclusion, in Chapter 10, the results of three studies, the Trilège, ACTG 343, and ADAM study investigating induction-maintenance strategies are discussed. Probably, several factors such as insufficient potency of antiretroviral therapy, target cell availability, and the presence of cellular- and anatomical reservoirs, may contribute to viral rebound during maintenance therapy. Although simplified treatment regimens are still warranted, the Trilège, ACTG 343, and ADAM study have indicated that induction-maintenance therapy with the currently available agents is not advocated for antiretroviral therapy.