Clinical and pharmacological aspects of induction-maintenance therapy in HIV-1 positive patients: the ADAM study
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Chapter 1

Introduction.
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The lentiviruses, or human immunodeficiency viruses types 1 and 2 (HIV-1 and HIV-2, respectively), are the causative agents of the acquired immunodeficiency syndrome (AIDS). Of these two, HIV-1 is the more predominant and the more aggressive. The development of antiretroviral drugs has been focussed exclusively on HIV-1, yet a number of drugs that are active against HIV-1 are also active against HIV-2.

The first antiretroviral agent available to treat HIV-1 infection was zidovudine (3'-azido-3'-deoxythymidine), a nucleoside analogue reverse transcriptase (RT) inhibitor. This class of agents needs to be intracellularly metabolised to an active triphosphate, before it can exert its antiretroviral activity. The active triphosphate competes with the natural nucleotide, for incorporation into the growing viral DNA chain by HIV-1 reverse transcriptase, resulting in termination of DNA-chain elongation. In 1987, the use of zidovudine in persons with advanced HIV-1 infection was found to result in a decline of HIV-1 related morbidity and mortality. By 1990, the indication for treatment with zidovudine was extended to patients with less advanced disease. In the following years, more nucleoside analogue RT-inhibitors such as didanosine and zalcitabine, became available for the use in HIV-1 infected patients. However, the increase in CD4+ T-cells and the clinical benefit of monotherapy was only transient, both in early and late HIV-1 disease. In addition to smaller clinical trials indicating virological and immunological benefit of dual therapy over monotherapy, two large studies reported in 1995 superior clinical outcome in patients treated with dual therapy.

Already from 1990 on, the use of another class of agents, the non-nucleoside RT inhibitors (such as the TIBO-derivates, nevirapine, pyridinones and delavirdine), was explored for the treatment of HIV-1 infection. These highly potent agents, directly inhibit the viral reverse transcriptase by binding to it non-competitively. However, a rapid emergence of mutant virus was observed in both in vitro- and phase I/II studies, which was associated with a loss of antiretroviral activity. This rapid appearance of drug resistance delayed further development of these agents for the use in clinical practice.

A few years later, another class of agents was introduced: the protease inhibitors. These agents inhibit viral replication by targeting a different viral protein than the nucleoside analogue and non-nucleoside RT inhibitors. The protease inhibitors, for example saquinavir, indinavir, ritonavir and nelfinavir, bind to a specific site of the HIV-1 protease enzyme, thus inhibiting the production of essential structural and enzymatic components of HIV-1, rendering the virus non-
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infectious. Just as the non-nucleoside RT inhibitors, these agents proved to be potent inhibitors of viral replication. However, with the use of these agents in monotherapy or in addition to a failing combination, the development of drug resistance was again reducing antiviral efficacy. Here, the protease inhibitors are however in advantage compared to the non-nucleoside RT inhibitors since a sequential appearance of multiple mutations is required for a decreased drug susceptibility of the virus. The use of protease inhibitors in antiretroviral therapy was approved from 1995 on. It lasted till 1996, when both the protease inhibitors and the non-nucleoside RT inhibitors proved their value in triple drug combination therapies, before the non-nucleosides were approved for the use in antiretroviral treatment of HIV-1 infected patients as well.

In the same period that these drugs were evaluated, the assessment of HIV-1 RNA in plasma in addition to the CD4+ T-cell count proved to be an important parameter for the progression of HIV-1 disease and treatment response. With the availability of this parameter, the efficacy of antiretroviral drug regimens could be evaluated more directly than before.

The limited efficacy of mono- and dual therapies was associated with the appearance of drug resistant viral mutants. The rapid replication rate of HIV-1 is resulting in large amounts of virus produced on a daily basis \(10^{10}\) virus particles per day. In addition, the mutation rate of HIV-1 per replication cycle is estimated to be \(3.4 \times 10^5\) mutations per nucleotide. So, with incomplete suppression of viral replication, the occurrence of a point mutation in the HIV-1 genome is quite probable. If, in the presence of an antiretroviral drug, the wild-type virus is less fit than the mutant virus, the latter will eventually predominate.

Since the high replication rate and not the rate of mutation appeared the predominant factor in the development of the variety of mutant virus, a significant reduction of the replication rate by the concomitant use of at least three antiretroviral drugs was suggested to be profitable. Moreover, in the presence of non-cross-resistant agents, the virus would have to mutate simultaneously at several positions in the viral genome to become resistant to the antiretroviral drugs used. A rough approximation of the probability of three simultaneous, random mutations in a viral genome per replication cycle would be \(3.9 \times 10^{10}\), with a viral genome consisting of \(10^4\) nucleotides. This is a very low probability in comparison to a probability of 0.34 if only one mutated nucleotide would suffice for decreased drug-susceptibility of the virus.
Indeed, the virological and immunological efficacy of a three-drug regimen consisting of two nucleoside analogue RT inhibitors with one protease inhibitor or one non-nucleoside RT inhibitor appeared to be superior to mono- or dual therapy regimens. Subsequently, it was confirmed that the substantial and durable suppression of viral replication and a lasting rise in CD4+ T cell count observed with the use of triple drug combination therapies, resulted in a greater decrease in morbidity and mortality than during mono- and dual therapy regimens. In the late nineties, when triple drug combination therapy became standard of care in the Western world, the decrease of HIV-1 related morbidity and mortality has been impressive.

There are however limitations to the triple drug combination therapies for HIV-1 infection. These multi-drug regimens are more effective but are also more complex and less well tolerated than monotherapy. The daily pill burden of triple combination regimens may be large, and require rigid time schedules and in some cases dietary restrictions. In addition, toxicity frequently occurs and is a reason for discontinuation of the medication in many patients. Considering that adherence to medication is a prerequisite for a durable suppression of viral replication, these features of multi-drug regimens in HIV-1 infection are a major drawback to the efficacy of triple drug combinations. Poor compliance and toxicity are not the only factors leading to treatment failure. In cohort studies evaluating the efficacy of triple drug combination regimens, treatment failure appears to be multifactorial. The initial plasma HIV-1 RNA concentration and the CD4+ T-cell count appeared to be predictive for treatment failure in observational cohorts. Patients with a low HIV-1 RNA concentration or a high CD4+ T-cell count at the start of therapy are more likely to have a virological response in which the plasma HIV-1 RNA concentration declines below the quantification limit of the available assays and is maintained at that level during therapy. In addition, the nadir of the plasma HIV-1 RNA concentration achieved, is a predictor for long-term virological outcome. Another factor of importance to drug failure, is the prevalence of drug resistant mutant viruses in pre-treated patients, reducing the chances of virological success of subsequent regimens. Furthermore, the pharmacokinetic characteristics of a drug, such as low bio-availability or unfavourable drug interactions, may contribute to treatment failure. For example, in observational cohort studies, the use of saquinavir in the hard gelatin capsule formulation, known for its relatively poor bio-availability, was a predictor for treatment failure. Considering the several risk factors for treatment failure, it is not surprising, that a considerable proportion of the
patients using a triple drug combination regimen are found to have virological treatment failure.\textsuperscript{59} To at least improve compliance and minimise intolerance, more simplified, tolerable treatment regimens are a necessity; however, not at the cost of virological efficacy.

In other chronic infectious diseases, like tuberculosis, the concept of induction-maintenance regimens has proven to be useful in reducing long-term toxicity and improving adherence to therapy.\textsuperscript{72} This concept implicates a vigorous treatment of the infection in the first phase, quickly reducing the total load of the infectious agent in the body, and reducing the risk of the emergence of drug resistant mutants. Afterwards, a simpler regimen may suffice for the suppression of the residual microbial load, in which the risk of resistance development is low. The analogy between HIV-1 infection and tuberculosis is only limited. Nevertheless, some observations in antiretroviral therapy trials have supported the idea that induction-maintenance should be feasible for HIV-1 infection. In the Incas study, for example, five antiretroviral-naive patients who had undetectable plasma HIV-1 RNA concentrations using a combination of zidovudine, didanosine and nevirapine, discontinued didanosine, violating the study protocol. In some of these patients sustained suppression of viral replication for more than one year was described during the period of didanosine interruption.\textsuperscript{73} In addition, triple drug regimens had shown to rapidly reduce HIV-1 RNA concentrations in blood, lymphoid tissues and cerebrospinal fluid to levels below the detection limit of the available assays in antiretroviral naive patients.\textsuperscript{74-77} Together with the observation, that prolonged suppression of viral replication by two agents is more likely in case of a lower rather than a higher baseline viral load,\textsuperscript{69,78,79} it seemed worthwhile to investigate the induction-maintenance concept. For this purpose the Amsterdam Duration of Antiretroviral Medication (ADAM) study was designed.

The induction-maintenance concept was tested in antiretroviral naive HIV-1 positive patients, to avoid the possibility of the presence of drug resistant viral mutants, which are less susceptible for the maintenance regimens used.\textsuperscript{67,69,80} In the induction phase, a quadruple drug regimen consisting of two nucleoside analogue RT inhibitors (stavudine and lamivudine) and two protease inhibitors (nelfinavir and saquinavir) was used for 26 or 50 weeks. The randomisation to one of the two maintenance regimens or prolongation of the quadruple drug regimen at both week 26 and 50 was restricted to patients with a plasma HIV-1 RNA concentration below the detection limit of an ultrasensitive assay. Maintenance therapy consisted of
stavudine plus nelfinavir or nelfinavir plus saquinavir. A dual nucleoside analogue RT-inhibitor regimen was not used, since generally the intracellular phosphorylation required for intracellular activity of the nucleoside analogue RT inhibitors, is not equally efficient in all infected cells.\(^8\) Van 't Wout et al. found differences in suppression of replication of viruses with different cellular tropism, which is in line with the observed differences in phosphorylation in activated and non-activated cells.\(^9\) The contents of Chapter 2 and 3 address the actual feasibility of the induction-maintenance therapy used in the ADAM study.

Although a favourable pharmacokinetic interaction between nelfinavir and saquinavir was anticipated, the exact pharmacokinetic interaction in the quadruple drug regimen was not known at the time of the study design. Therefore, a full (8-hour) concentration curve of the protease inhibitor combination was assessed in a subset of the patients. The steady state pharmacokinetics of the combination of saquinavir and nelfinavir in the quadruple drug induction regimen are described in Chapter 4. In the Chapters 5 and 6, the efficacy of the induction regimen within the first four weeks of induction therapy and the toxicity of the induction therapy within the first 26 weeks are discussed in relation to the exposure to the used protease inhibitors.

Chapter 7 and 8 are focussing on the sub-studies within the ADAM study. Patients could participate in a quality of life and compliance study. In case of equal virological and immunological efficacy, it is of interest to find out whether the induction-maintenance strategy adds to the quality of life or facilitates compliance compared to standard treatment strategies. The impact of induction-maintenance therapy on quality of life is highlighted in Chapter 7. Chapter 8 describes the presence of drugs in the cerebrospinal fluid and semen of a subset of the patients participating in the ADAM study. The limited penetration of antiretroviral agents in the central nervous system and the genital tract might contribute to the presence of an anatomical reservoir of HIV-1 in these tissues,\(^8\)\(^3\)\(^4\) which could facilitate virological failure during the maintenance phase. As a measure for the drug penetration into these compartments, drug concentrations in the cerebrospinal fluid and semen were assessed in a proportion of the patients. In Chapter 9 the concentrations of stavudine in the plasma and cerebrospinal fluid of patients on quadruple induction therapy are compared with those found in patients using other drug combination regimens.

In the general discussion, Chapter 10, a perspective of induction-maintenance strategies in the current treatment of HIV-1 infected patients is outlined.
References


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