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

Reijers, M.H.E.

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General discussion.
With the introduction of potent antiretroviral therapy, the aim of the treatment of HIV-1 infection has focussed on preventing instead of delaying disease progression. The suppression of viral replication as strongly as possible for as long as possible, has resulted in prevention or (partial) restoration of the damage to the immune system.\textsuperscript{1-4} Subsequently, a significant decrease of the incidence of AIDS related morbidity and mortality has been observed in the Western world.\textsuperscript{5-8} However, since viral eradication was not expected to be feasible within years,\textsuperscript{9-11} the use of antiretroviral agents was anticipated to be necessary for a long period. Antiretroviral therapy often requires complicated dosing schedules, and dietary restrictions, and is causing toxicity, both on the short- and long-term. Especially for the considerable part of the HIV-1 infected patients coping with poverty, mental illness, or drug and/or alcohol use,\textsuperscript{12,13} these factors might interfere with the use of the drug combinations and foster the development of drug-resistance due to inadequate use of the antiretroviral agents.\textsuperscript{14-19}

Induction-maintenance therapy seemed a promising treatment strategy to reduce the complexity and long-term toxicity of antiretroviral drug regimens. Three different studies, were started to investigate the feasibility of such a strategy.\textsuperscript{20,21} In the ADAM study, described in this thesis, patients were treated with maintenance therapy consisting of two agents (stavudine plus nelfinavir or saquinavir plus nelfinavir) following a quadruple drug induction therapy of 26 or 50 weeks [Chapter 2 and 3]. The ACTG 343 and Trilège studies used an induction therapy consisting of zidovudine, lamivudine, and indinavir for 24 and 12 weeks, respectively. Subsequently, patients in the ACTG 343 study were randomised to maintenance therapy consisting of either indinavir mono-therapy, or zidovudine plus lamivudine or to continued triple drug therapy.\textsuperscript{20} The Trilège study randomised patients to either zidovudine plus lamivudine, or zidovudine plus indinavir or to continued triple drug therapy.\textsuperscript{21} Although all three studies were significantly different in design (see Table 1), each study concluded that with the currently available antiretroviral agents, induction-maintenance therapy was not resulting in a durable suppression of viral replication in HIV-1 infected patients. It did not matter whether the induction period consisted of a triple (ACTG 343, Trilège) or a quadruple drug regimen (ADAM) or whether the maintenance therapy consisted of two nucleoside analogue RT inhibitors (ACTG 343, Trilège ), a single protease inhibitor (ACTG 343), one nucleoside RT plus one protease inhibitor (Trilège, ADAM), or two protease inhibitors (ADAM) . One could argue that the induction period in the Trilège study was too short for attaining low HIV-1 RNA concentrations in plasma (27% had a
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HIV-1 RNA concentration >50 copies/mL at time of randomisation). But even in patients with an induction therapy for fifty weeks and an HIV-1 concentration <50 copies/mL (ADAM), viral rebound was found more frequently during maintenance therapy than during prolonged induction therapy. Patients participating the ACTG 343 study were mostly experienced with zidovudine. Pretreatment with zidovudine did predispose for virological failure during maintenance therapy compared to continued triple drug therapy. However this was not the only factor contributing to virological failure during maintenance therapy, since the antiretroviral therapy naïve patients in the Trilège and the ADAM study were having viral rebound during maintenance therapy as well.

<table>
<thead>
<tr>
<th>Table 1</th>
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<tr>
<td><strong>Inclusion criteria:</strong></td>
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<td><strong>HIV-1 RNA in plasma (copies/mL)</strong></td>
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<td>≥1000</td>
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<td><strong>CD4+ T-cell count (x10⁶ cells/mL)</strong></td>
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<td><strong>treatment experience</strong></td>
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**Induction regimen**

| **agents** | d4T+3TC+NFV+SQV | ZDV+3TC+IDV | ZDV+3TC+IDV |
| **duration** | 26 or 50 weeks | 24 weeks | 12 weeks |
| **criteria for randomisation** | <LLQ² at weeks | <200 copies/mL | <500 copies/mL |
| 24 and 25 or 48 and 49 | at weeks 16, 20 and 24 | at weeks 8 and 12 |

**Maintenance regimen**

| **agents** | d4T + NFV or NFV+SQV | IDV or IDV+3TC | ZDV+IDV or ZDV+3TC |
| **median duration of follow-up after randomisation** | 10 weeks | 8 weeks | 24 weeks |

**Virological failure definition**

| **% failure during maintenance** |
| **% failure during prolonged induction** |
| >LLQ² copies/mL at week 36 | >200 copies/mL (confirmed) | >500 copies/mL (confirmed) |
| 64% b | 23% | 27% |
| 9% b | 4% | 9% |

**Notes:**

- LLQ = the lower limit of quantification (<50 or variable quantification limit of an ultrasense HIV-1 RNA assay) 
- b after 26 weeks of induction therapy.
These three studies point out that in most patients, a simple maintenance regimen can not continue to suppress viral replication after an induction period in which a plasma HIV-1 RNA concentration below 50 copies/mL was achieved.

Why did induction-maintenance therapy fail? In the period these studies were conducted, evidence accumulated that even in patients with sustained viral suppression below a plasma HIV-1 RNA concentration of 50 copies/mL, viral replication was still present.\(^{22-26}\) In line with this evidence, Grossman et al. hypothesised that antiretroviral drug therapy only reduces ongoing virus production bursts and diminishes their frequency but fails to completely block them.\(^{27}\) Viral decay rates are therefore not a reflection of half lives of different cells infected before the initiation of therapy, but of cells infected after the initiation of therapy. The mathematical model describing the viral decay with these assumptions results in an equilibrium between infected cells with a certain reproduction ratio and a certain number of infected cells. This model fits to observations in earlier clinical studies, that triple drug combinations may not provide full suppression of viral replication in individual patients. The plasma HIV-1 RNA concentration was observed to decline below the quantification limit of an ultrasensitive assay more rapidly with a five-drug- than a three-drug-regimen.\(^{28}\) But even with five agents, suppression appears to be less than 100%: HIV-1 RNA could still be found in peripheral blood mononuclear cells.\(^{29}\)

The model also provides an explanation for the increase in plasma HIV-1 RNA concentration during maintenance therapy [Chapter 2 and 3]. With a reduction in the number of drugs during maintenance therapy, virus production bursts may increase in frequency and result in a new equilibrium at a detectable plasma HIV-1 RNA level. This is supported by observations in the ACTG 343 and Trilège studies.\(^{30,31}\) Both studies investigated whether viral rebound during maintenance therapy was associated with the selection of resistant mutant virus. The presence of resistant mutant virus with a decreased susceptibility to protease inhibitors was preceded by an increase in viral replication of wild-type virus or viral mutants resistant to other agents than the protease inhibitors, indicating that insufficient antiretroviral potency or poor compliance enabled the occurrence of viral replication and the subsequent development of resistant mutant virus.\(^{30,31}\)

In addition to incomplete inhibition of viral replication, the existence of a long-lived latent reservoir of infected cells may be another reason for virological failure during maintenance therapy.\(^{10,11,32}\) Using mathematical modelling, the time needed
to eradicate this reservoir was first estimated to be 2 to 3 years.\textsuperscript{9} Finzi et al. measured the decay rate of the latent infected resting CD4\(^+\) T-cells to result in a mean T\(\frac{1}{2}\) of 43.9 months. With a reservoir of 1 \(\times 10^5\) cells, the time required for eradication would be 60.8 years.\textsuperscript{25} Some trials already aimed at selectively activate the latently infected cells in this reservoir.\textsuperscript{26,33,34} OKT3 (a monoclonal antibody against CD3) and IL-2 (interleukine-2) indeed activated T-cells and viral replication, but the effect on the size of the pool of latently infected cells was not clear. Stimulation of these cells with incomplete suppression of viral replication by antiretroviral agents, is even suggested to result in newly infected cells.\textsuperscript{27} Moreover, the use of these agents was accompanied with considerable side effects.\textsuperscript{26}

So, with ongoing viral replication in the presence of potent antiretroviral therapy and the existence of long-lived latently infected cells, it is likely that a reduction of the antiretroviral pressure during maintenance therapy will result in viral rebound.

If viral replication during maintenance therapy can expand, replication might further benefit from the increased availability of target cells (e.g. proliferating CD4\(^+\)T-cells). For both resistant mutant viruses as wild type virus, an increase in the availability of activated CD4\(^+\) T-cells can contribute to the level of rebound of HIV-1 RNA in plasma.\textsuperscript{35-37} After induction therapy, at time of the randomisation to maintenance regimens, increased target cell availability was likely. Indeed, the ACTG 343 study found this 'predator-prey' mechanism to be of significance to the viral rebound during maintenance therapy.\textsuperscript{20} Fleury et al. recently showed that target cells were not expected to decline to normal levels before week 72,\textsuperscript{28} indicating that even after an induction therapy for 50 weeks as given in the ADAM study (Table 1), replication might have been facilitated by increased target cell availability [Chapter 3].

Another suggested threat to the efficacy of induction-maintenance therapy is the continued replication of viruses in the anatomical sanctuaries, such as the central nervous system (CNS) and the genital tract.\textsuperscript{39-42} Since it is difficult to obtain material from the CNS or the genital tract, cerebrospinal fluid (CSF) and semen are used as the accessible representatives of these respective compartments. Several studies have shown discrepancies between HIV-1 RNA concentrations in plasma and CSF or semen,\textsuperscript{43,44} both in treated as untreated patients. Moreover, the evolution of the viral gene differed in virus obtained from cells in the CSF or the semen and virus obtained form peripheral mononuclear cells in plasma.\textsuperscript{45-47} Most studies however show prompt decreases of HIV-1 RNA concentration in CSF and semen,\textsuperscript{42,48-50} suggesting that triple drug combinations do effect these sites. Still, as shown in
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Chapter 8 and by others, penetration of antiretroviral agents, is usually lower than in plasma. Especially the penetration of some of the protease inhibitors in these compartments is limited by high protein binding, high molecular weight, and the presence of transport molecules such as P-glycoprotein (PgP). This may have clinical consequences, as was shown by for example Gisolf et al. They observed less consistent decreases of HIV-1 RNA concentrations in CSF of patients treated with only saquinavir and ritonavir compared to patients treated with stavudine and the same protease inhibitor combination. In addition, a slower decay rate of virus was observed in CSF compared to plasma, and the development of drug resistant mutants in CSF and semen differed from that in plasma. Therefore, caution is warranted for insufficient efficacy of antiretroviral therapy in these sanctuary sites on the long-term. If necessary, the penetration of antiretroviral agents into the sanctuary sites might be improved upon, as is indicated by recent publications. Van Praag et al. found increased indinavir concentrations with the combined use of ritonavir and indinavir compared to indinavir alone. In addition, in Chapter 9, the concentrations of stavudine were described to be higher in patients using ritonavir and/or indinavir containing regimens than in regimens without these specific protease inhibitors. In vivo studies have demonstrated the possible use of PgP molecule blockers in order to increase drug concentrations in the CSF. At the annual meeting of the American Society for Clinical Pharmacology and Therapeutics, Dr. Choo et al. presented data from a mouse model, indicating that nelfinavir concentrations in the CSF and the testis could be increased by blocking the PgP molecules.

In the past few years the drawbacks of antiretroviral therapy only have become more pronounced. In addition to the toxicity on the short term, such as diarrhoea, nephrolithiasis, and hepatotoxicity, toxicity on the long-term, such as lipodystrophy and metabolic disorders, are limiting for the use of antiretroviral therapy. Although mitochondrial toxicity is suggested to be crucial in the majority of these side effects, the exact pathogenesis of most side effects is not yet unravelled, nor the impact of these side effects on morbidity on the long-term. With the awareness that eradication is not to be accomplished in several decades, more and more patients and doctors are inclined to delay treatment. Induction-maintenance regimens or other treatment strategies that minimise toxicity and improve tolerance and compliance are therefore more warranted than ever.
Induction-maintenance therapy with the currently available agents has not been successful. However, the concept may not be lost for antiretroviral therapy. The use of agents that decrease the availability of target cells, e.g. activated CD4+ T cells, such as mycophenolic acid or hydroxy urea might reduce the number of drugs required for suppression of viral replication during maintenance therapy.\textsuperscript{37,66,67} However, the side effects of these agents are considerable, and may therefore outweigh the benefit of this strategy.

The induction-maintenance strategy is not the only option to simplify therapy. A triple drug therapy may be simplified as well. Recently, equal virological efficacy of triple drug combinations containing protease inhibitors compared to triple drug combinations containing non-nucleoside RT inhibitors has been shown.\textsuperscript{68,69} So, patients may profit from the advantages of the non-nucleoside RT inhibitors over the protease inhibitors with respect to dosing and toxicity. Furthermore, the pharmacokinetic properties of agents may be used to improve drug intake schedules and pill burden.\textsuperscript{70-74} For example, the addition of a low dose ritonavir can facilitate the use of indinavir by changing the regular dosing schedule of two tablets thrice daily on an empty stomach, to two tablets twice daily without dietary restrictions.\textsuperscript{74}

As indicated in Chapter 5 and 6, both efficacy and toxicity may be associated with the level of drug exposure. Although there is a large inter- and intra individual variability in drug exposure (at least for the protease inhibitors [Chapter 6]) and plasma drug concentrations are only a rough representative of drug exposure, the monitoring of drug levels of antiretroviral agents, might help to identify the optimal drug level per patient with respect to efficacy and toxicity. Furthermore it can be used to gain further insight into the pharmacokinetic interactions which may be useful for establishing more convenient dosing and intake schedules, or for the selective improvement of drug exposure in certain cell or body compartments (see above).

Some case histories, like 'the Berlin patient',\textsuperscript{75,76} in which a vigorous mainly cellular, HIV-1 specific immune response was capable of controlling HIV-1 replication after discontinuation of antiretroviral therapy, has stimulated the use of immunological control of viral replication (with or without the stimulation of latently infected cells) in the treatment of HIV-1 infection. Although these case reports of recently infected patients were promising, in chronically infected patients this strategy usually led to HIV-1 RNA rebound.\textsuperscript{77} Nevertheless, strategies involving treatment interruptions are initiated to investigate the benefits of inducing an HIV-1 specific immune response by an increase in viral replication during treatment
Vaccination, with for example recombinant gp160, in combination with antiretroviral therapy was capable of inducing HIV-1 specific immune responses, however, no additional clinical benefit was observed so far.\textsuperscript{81,82}

For now, eradication of HIV-1 infection seems beyond the current treatment options. However, it should not be forgotten that major advances have already been made in the treatment of HIV-1 infection, and further progresses are expected to be made in the future. With long-term treatment assumed to be necessary, elucidating the pathogenesis of the metabolic disorders and lipodystrophy syndrome associated with the long-term use of antiretroviral agents is pivotal. In the meanwhile therapy in the Western world needs to become more individualised, carefully timing the initiation of therapy and balancing the pros en cons of long-term therapy for the HIV-1 infected patient.
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