Tangible effects of antiretroviral therapy in HIV-1 infected patients
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Chapter 7

"Discussion"
Discussion

Various antiretroviral combination regimens have been compared with regard to their potency to suppress plasma HIV-1 RNA levels. In addition, insights regarding the development of viral drug resistance, virus distribution among different body compartments and the immunologic effects of antiretroviral therapy have become important in trying to optimise the effects of treatment.

No single specific triple combination regimen is advised at this moment for the initiation of therapy in antiretroviral-naive patients. Current guidelines generally advocate to include a combination of two nucleoside analogue reverse transcriptase inhibitors (NRTI's) and at least one protease inhibitor (PI) or non-NRTI (NNRTI) (1). We and others have found that the NRTI combination of d4T plus 3TC over the long-term results in a significantly higher CD4⁺ cell count compared with the combination of AZT plus 3TC (2-4). As higher CD4⁺ cell counts are associated with a reduced risk of morbidity and mortality (5), the choice for the particular NRTI component of an antiretroviral regimen may be influenced by such a finding. One may expect that in the future the choice between specific drug combinations which are equally efficacious in virologic terms will be driven partially by differences in their immunologic profile as characterised by their effects on the CD4⁺ cell count, the CD8⁺ cell count, the CD4⁺/CD8⁺ cell ratio and the recovery of immune functions assessed in vitro. Beside the virologic and immunologic effects of antiretroviral regimens, the choice between specific regimens will increasingly be determined by their short- and longer term toxicities.

Increasing plasma HIV-1 RNA levels during antiretroviral therapy are considered as a sign of virologic treatment failure. Insufficient drug pressure, e.g. due to non-compliance and the subsequent development of resistance are the main causes for virologic treatment failure. According to international guidelines it is advised to replace, as much as possible, all drugs which compose a failing regimen (1). This concept may be challenged in the future, as certain mutations in the viral genome may actually confer a benefit in the context of treatment. We found an unexpected sustained degree of plasma HIV-1 RNA suppression in patients who had been treated with d4T plus 3TC or AZT plus 3TC with the addition of indinavir after 12 weeks,
Despite the presence of high level 3TC resistance in all patients tested prior to the addition of indinavir. This treatment strategy, which theoretically in view of the appearance of 3TC resistance had been reduced to a double combination regimen of d4T or AZT plus indinavir, after 72 weeks showed results in terms of HIV suppression which were comparable to those of standard concomitant triple drug regimens. Results of two other trials with sequential addition of a protease inhibitor to 3TC-containing regimens have shown similar results (6,7). These findings are in stark contrast to the loss of viral suppression which was observed after the withdrawal of 3TC therapy in patients in whom concomitant triple combination therapy with AZT plus 3TC plus indinavir had resulted in HIV suppression to an unquantifiable level (8). These intriguing results might be explained to some extent by a reduction in viral fitness which has been demonstrated to occur in the context of high level 3TC resistance (9). Potentially, these results may provide a rationale for maintaining the use of 3TC in future salvage regimens when virologic failure has occurred during the prior use of 3TC-containing regimens. Recently, similar results have been reported concerning genotypic indinavir associated resistance (10). Clinical trials are currently being designed to address the potential benefit of such a strategy.

Another major consideration in treating HIV infection is to target the virus in all body compartments, including possible sanctuary sites such as the central nervous system and the male and female genital tracts. Therapeutic regimens may be expected to fail if there is ongoing production and seeding of viral particles in such protected sites, despite adequate suppression of viral replication in the peripheral blood. Suppression of virus in these sanctuary sites supposedly largely depends on the concentration of antiretroviral drugs achieved in these compartments and the drug susceptibility of the virus within these sites. The central nervous system (CNS) is an important sanctuary site which is difficult to investigate directly. One way of trying to assess the penetration of antiretroviral drugs into the CNS is the measurement of drug levels in the cerebrospinal fluid (CSF). One should realise, however, that CSF-levels are likely to incompletely reflect levels within the brain. Drug levels in the CSF not only reflect passive diffusion between CNS and CSF, but are also influenced by active transport mechanisms present in the blood brain barrier (11). Nevertheless, at this moment, the best measure of antiviral drug efficacy in the CNS may be to assess the effect of treatment on CSF HIV-1 RNA levels.
Consistent with the hypothesis that viral replication within the CNS may occur independently from that in plasma, is the finding of the concomitant presence of drug-sensitive viral mutants in the brain/CSF and drug-resistant strains in the blood (12-14). Knowledge about such discordant drug resistance patterns between different body compartments may be important in designing treatment strategies for HIV infection. Discordant resistance patterns may be discovered by repeated sampling of CSF prior to the initiation of and during treatment. Currently CSF sampling is occasionally being performed as part of research protocols. In the future it may prove useful to assess CSF HIV-1 RNA and drug resistance patterns as part of routine clinical practice, as one of the tools to safeguard sustained virologic benefit of therapy.

In this thesis we have described the unmasking after the initiation of HAART of clinically silent mycobacterial infections which presented as unusual clinical syndromes in patients with late stage HIV infection. Similar unusual clinical syndromes shortly after starting HAART have been reported by others, not only involving patients with Mycobacterium avium infection, but also those with cytomegalovirus (CMV) infection, progressive multifocal leucoencephalopathy, cryptococcal infection, viral hepatitis, and Kaposi’s sarcoma. (15-25). Recognition of this syndrome might be of clinical importance as it should not be confused with toxicities resulting from the newly instituted antiretroviral drugs. In case there is no toxicity, if clinically acceptable, continuation of HAART would be the preferred option in order for protective immunity against the underlying infection to ultimately take precedence and help in controlling the infection. One may speculate that in case of severe immunopathologic reactions clinical control of such reactions may be achieved by the administration of steroids or non-steroidal anti-inflammatory agents. When considering such a strategy one should realise, however, that the use of indomethacin in mycobacterial infection has been associated with enhanced production of TNFα which at least partial contributes to pro-inflammatory responses and thus may in fact exaggerate the clinical syndrome (26,27).

We and other investigators have shown that an improved immunologic response after starting HAART may contribute to clearance of opportunistic infections without specific antimicrobial therapy (15,16). These observations strongly suggest that discontinuation of opportunistic infection-specific prophylactic or maintenance
therapies may likewise be possible in the wake of improved cellular immunity through the use of HAART. Several studies have meanwhile been reported showing this to be the case (21,25,28-31). For some opportunistic infections in particular, such as CMV, the potential for confidently discontinuing maintenance therapies, is expected to significantly improve patients' quality of life, and to have a major impact in reducing healthcare costs.

The discovery of new nucleoside analogue reverse transcriptase inhibitors (NRTI’s), protease inhibitors (PI’s), non-nucleoside reverse transcriptase inhibitors (NNRTI’s), and the possibility to reliably measure HIV-1 RNA levels have enormously expanded the armamentarium of physicians in trying to reach this goal. Nevertheless, although some qualitative and quantitative degree of reconstitution of immunity can be achieved leading to improved morbidity and mortality rates, persistent HIV infection remains the rule and eradication has so far never been demonstrated. Despite long-term viral suppression to below the lower limit of quantification of the most sensitive HIV-1 RNA PCR assays, continued HIV-messenger RNA expression and ongoing evolution within the HIV gp-120 envelope region have been shown, indicating persistent low level viral replication (32,33). Thus for the moment, chronic suppression of HIV-1 RNA replication by chronic use of potent antiretroviral combinations is the best achievable. From a virologic and immunologic point of view it is advised to start antiretroviral therapy as soon as possible, however, this strategy will be challenged by long-term toxicity of antiretroviral agents like lipodystrophy, increased risk of mitochondrial dysfunction and the difficulty of adherence to a high pill burden for an indefinite period of time (34-40).

We should also realise that future treatment options may be compromised by increasing circulation of resistant HIV-1 strains. Therefore, development of new antiretroviral agents and classes of agents that are non-cross resistant with currently available agents remains necessary.
References


