Studies on the efficacy and toxicity of highly active antiretroviral therapy
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CHAPTER 8

DISCUSSION

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Chapter 8

When HAART was first introduced in clinical practice in the mid-1990's, it was assumed that HAART completely blocks the ability of HIV to infected new cells, and based on mathematical models it was estimated that eradication of HIV from an infected individual would take about 2 to 4 years of therapy [1-4]. These insights resulted in the recommendation for early and aggressive treatment of HIV-infection [5-7]. Clinicians adapted guidelines to initiate antiretroviral therapy when i) the CD4+ T-lymphocyte count dropped below 500 cells/mm³, or ii) the plasma HIV-1 RNA concentration was higher than 30,000 copies/mL, or iii) there were clinical signs and symptoms of immune deficiency [5]. In the following years thinking about when to initiate antiretroviral therapy changed for several reasons.

First, several studies in patients using apparently fully suppressive HAART found evidence for ongoing low-level HIV replication and viral evolution [8-17], the existence of replication-competent proviral DNA in long-lived resting CD4+ T-lymphocytes [11,16,18-32], and anatomical [8,33,34] and cellular [35-40] sanctuary sites with poor penetration of antiretroviral drugs. Therefore it seems unrealistic to assume that HAART alone will eradicate HIV from an infected person within a reasonable period of time [41,42], so antiretroviral therapy must probably be continued indefinitely.

Second, the long-term use of HAART is associated with considerable toxicity. The pressing need for more antiretroviral drugs, led to the accelerated approval of new compounds by the regulatory authorities. Therefore, little was known about the mid- and long-term adverse effects of these drugs. Between 36 and 53% of patients change their initial HAART regimen within 48 weeks after initiating HAART, mostly because of drug related adverse effects [43-46].

Third, for HAART to be virologically successful almost perfect (> 95%) adherence is needed [47-53]. Antiretroviral drug related toxicities make it more difficult for patients to stay fully adherent [54-57]. If HAART is started early in HIV-infected patients without clinical signs and symptoms, the occurrence of side effects has a negative effect on the quality of life of these patients, which may make it more difficult for these patients to remain compliant with the prescribed antiretroviral regimen [58].

Fourth, in several cohort studies high rates of virological failure of HAART has been reported [43,59-62]. One of the reasons why the failure rates are higher in clinical practice than in the setting of randomized clinical trials might be a lower level of adherence. An interesting phenomenon is that in
many patients that fail virologically, the CD4+ T-lymphocyte counts remain stable or even increase [43,63-72]. A possible explanation for these discordant immunologic responses might be that protease inhibitors have a direct positive effect on T-cell survival [73-77], but these discordant immunologic responses have also been observed in patients not using protease inhibitors [63,78]. Another explanation might be that HIV strains harboring multiple resistance mutations have a reduced replicative fitness compared to wild-type HIV [79-83], but some studies found no difference in the number of HIV resistance mutations between virologically failing patients with and without discordant immunologic responses [69]. Furthermore, the discordant immunologic responses might just be the result of durable but partial suppression of viral replication to below the pretreatment plasma HIV-1 RNA concentrations [68,70,84].

And fifth, it has been demonstrated that the CD4+ T-lymphocyte count at the start of first-line HAART is a better predictor of virological treatment success, clinical progression and mortality than the baseline plasma HIV-1 RNA concentration [85-87]. These studies found that HIV-1 infected patients can safely defer antiretroviral therapy until their CD4+ T-cell counts are between 200 and 350 cells/mm³.

These issues have led most clinicians to follow a more conservative strategy of initiating first-line antiretroviral therapy when the CD4+ T-lymphocyte count has dropped to levels between 200 and 350 cells/mm³ [87-89]. It should be noted that initiation of antiretroviral treatment during the acute phase of HIV-1 infection might result in an improved cellular immune response against HIV [90-93].

Several strategies have been studied to improve upon the above listed shortcomings of standard HAART. Attempts to purge the latent HIV-1 reservoir of replication competent proviral HIV DNA in long-lived resting CD4+ T-lymphocytes have not been successful so far [94-97]. Treatment with an alternative multidrug regimen consisting of drugs from 3 different classes compared with standard of care HAART results in a stronger short- and long-term suppression of HIV-1 replication, but the complexity and toxicity of this regimen limits its application in clinical practice [98]. A few case reports of patients who after discontinuing antiretroviral therapy were able to (temporarily) contain HIV replication through vigorous CD8+ T-lymphocyte responses against HIV, sparked interest in so-called structured treatment interruption strategies [92,93]. The results of studies into the effects of structured treatment interruptions have been conflicting [99-107]. The concept of induction-maintenance was studied several times but failed to
keep HIV-1 replication suppressed in the majority of patients [108-110] but might still be feasible for some patients [111]. Simplification of antiretroviral regimens is safe, and is especially advantageous in patients currently experiencing side-effects on their initial regimen [112-118]. Daily-observed therapy using once daily antiretroviral regimens may be implemented for difficult-to-reach patient populations [119].

Because all possible antiretroviral combination regimens have advantages and disadvantages, current guidelines place much emphasis on tailoring the antiretroviral regime to the individual patient in order to maximize adherence [120]. Several drugs have become available in improved formulations. Combivir® contains zidovudine plus lamivudine, and Trizivir® contains zidovudine plus lamivudine plus abacavir thereby reducing the pill-burden. The chewing tablet formulation of didanosine has been replaced by capsules. Nelfinavir tablets are now coated, which makes them easier to swallow. Pharmacological boosting of protease inhibitors by the coadministration of low doses of ritonavir has several beneficial effects and is rapidly becoming the standard of care for most protease inhibitors. Pharmacological boosting i) enhances the antiretroviral activity by increasing the trough levels (it may even overcome reduced sensitivity of some HIV mutants), ii) diminishes food restrictions and requirements, iii) makes possible twice or even once daily dosing, and iv) reduces the pill burden [121,122]. The new protease inhibitor lopinavir is co-formulated with low-dose ritonavir under the brand name Kaletra® [123-125].

Several existing antiretroviral drugs will become available in new formulations. Stavudine and zidovudine will become available in a slow-release formulation making possible once daily dosing. The total daily dose of efavirenz will become available in a single 600mg capsule, thereby reducing the pill burden. FOS-amprenavir is a prodrug of amprenavir that requires a lower number of pills.

A large number of new antiretroviral agents are in various stages of development. These compounds improve upon the currently available drugs with respect to antiretroviral activity against both wild-type and resistant HIV strains, improved convenience of dosing, and fewer adverse effects. The currently most advanced new drug is tenofovir, the first nucleotide reverse transcriptase inhibitor. Tenofovir can be dosed once daily in single tablet, is active against multidrug resistance mutants of HIV, and has a favorable toxicity profile [126,127]. Tenofovir is also active against hepatitis B virus [128,129]. Emtricitabine is a new nucleoside analogue reverse transcriptase inhibitor with activity against both HIV-1 and hepatitis B virus, and can be dosed once daily [130-133]. Unfortunately, there is cross-resistance between
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Emtricitabine and lamivudine [134]. DAPD is a new nucleoside analogue reverse transcriptase inhibitor with activity against both HIV-1 and hepatitis B virus, and is active against multidrug resistant HIV mutants [135-139]. TMC-120 is a potent new non-nucleoside reverse transcriptase inhibitor, with activity against HIV mutants resistant for nevirapine and efavirenz [140,141]. DPC083 is a derivative from the non-nucleoside reverse transcriptase inhibitor efavirenz, with an extremely long half-life of more than 90 hours [142,143]. Tipranavir is a new protease inhibitor with activity against multidrug resistant HIV strains [144-149]. Atazanavir is a new protease inhibitor that can be dosed once daily, has activity against most resistant HIV strains, and its use is not associated with lipid abnormalities [150,151]. T-20 is the fusion inhibitor furthest in clinical development [152-155]. A major drawback of this compound is that it has to be administered by subcutaneous injection twice daily, so its main application will probably be in salvage regimens for highly treatment-experienced patients. Another new class of antiretroviral agents are the integrase inhibitors, but they are still in the early phases of development [156,157].

Because of the sharp decline in HIV-related morbidity and mortality, the morbidity and mortality caused by co-infections with hepatitis B and/or C virus became much more important [158-163]. In years to come much attention needs to be given to the combined treatment of HIV and hepatitis virus infections.
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