Studies on the efficacy and toxicity of highly active antiretroviral therapy

Wit, F.W.N.M.

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INTRODUCTION

Ferdinand WNM Wit
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HIV / AIDS

The first cases of what later became known as the acquired immunodeficiency syndrome (AIDS) were recognized in 1981 in young, previously healthy homosexual males who developed rare malignancies and opportunistic infections [1-6]. These patients all had a profound depletion of their CD4+ T-lymphocytes. It quickly became apparent that the disease was infectious and could be transmitted via homo- [3,5,6] and heterosexual contacts [7], blood products [8-10], and from mother to child [11]. A T-cell tropic retrovirus, later named human immunodeficiency virus (HIV), was identified as the putative cause [12-14]. HIV infects cells expressing the CD4 receptor on their surface, primarily T-helper lymphocytes, monocytes and macrophages [15-17]. HIV belongs to the subfamily of lentiviruses [18,19] and consists of two major subtypes, the global dominant type HIV-1, and HIV-2. HIV-2 is primarily found in West Africa [20-22] and appears to be less pathogenic than HIV-1, but still leads to AIDS eventually [23,24]. HIV-1 has many genetic subtypes of which type B is the most prevalent in the developed world [25]. HIV-1 and -2 probably originated from related lentiviruses, simian immunodeficiency virus (SIV), found in African chimpanzees and sooty mangabees, respectively [26]. The oldest documented cases of HIV-1 infection date back from 1959 [27-30], but HIV-1 probably originated prior to 1940 [26,31].

HIV-disease has a broad clinical spectrum ranging from acute symptomatic primary infection, followed by a usually prolonged asymptomatic phase, to symptomatic disease characterized by profound immunodeficiency, ultimately leading to death from opportunistic infections and malignancies. Acute or primary HIV-infection can be accompanied by flu-like symptoms [32-35]. During primary HIV-infection high levels of plasma viraemia are detected [36-38]. The asymptomatic phase is characterized by ongoing rapid viral replication and a slow decline in CD4+ T-lymphocyte counts [39-41]. The diagnosis of AIDS is made when certain opportunistic infections or malignancies occur in HIV-infected individuals [42]. Most untreated patients develop AIDS within 8 to 10 years after infection [43-46]. Most patients die within two years after AIDS is diagnosed [47,48]. More than 60 million people are estimated to have been infected with HIV worldwide, of which about 20 million have already died from the disease [49]. Currently, most people living with HIV are in sub-Saharan Africa (28.1 million) and South East Asia (7.1 million) [49]. In the US and western Europe about 940,000 and 560,000 persons, respectively, are currently living with HIV-1-infection [49].
**Antiretroviral therapy**

Currently, three classes of drugs are licensed in the Netherlands for the treatment of HIV-1 infected individuals: the nucleoside analogue reverse transcriptase inhibitors (NRTI), the non-nucleoside reverse transcriptase inhibitors (NNRTI), and the protease inhibitors (PI).

**NRTI**
The NRTI are synthetic analogs of the nucleosides thymidine (zidovudine [50], stavudine [51]), adenosine (didanosine [52]), guanosine (abacavir [53]), and cytidine (zalcitabine [54], lamivudine [55]). After being phosphorylated intracellularly into their respective active triphosphate metabolites, the NRTI are incorporated into newly synthesized viral DNA strands by the HIV reverse transcriptase where they act as chain terminators because NRTI lack a 3' hydroxy group [56]. The intracellular phosphorylation of NRTI by different cellular enzymes results in anti-HIV activity that may vary across cell types [57-63]. NRTI that are analogs of the same nucleoside may be antagonistic with respect to inhibition of HIV replication because they may compete for the same cellular enzymes. Examples are zidovudine plus stavudine [64,65], and zalcitabine plus lamivudine [66]. NRTI are predominantly cleared by the kidney [67-71]. Cross-resistance between different NRTI is considerable because of overlapping patterns of resistance mutations.

**NNRTI**
The NNRTI inhibit HIV replication by direct binding of the HIV reverse transcriptase, inactivating the enzyme by inducing a conformational change [72,73]. NNRTI do not need to be phosphorylated to become active. Currently, three NNRTI are licensed for the treatment of HIV-1 infection: delavirdine (licensed in the USA, not in Europe) [74], efavirenz [75], and nevirapine [76]. All NNRTI are metabolized in the liver by the cytochrome p450 enzyme system, giving rise to potential drug-drug interactions [77,78]. Cross-resistance between NNRTI is extensive [79]. There is no cross-resistance between NRTI and NNRTI, albeit that NNRTI resistance mutations may negate the effect of some NRTI resistance mutations. NNRTI have no activity against HIV-2 infection.

**PI**
The HIV-1 protease is an aspartic protease that is needed for the formation of mature infectious virions [80,81]. The protease inhibitors bind to the active site of the HIV-1 protease, thereby interfering with the cleavage of the Gag-
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Pol polyprotein precursor. This results in the formation of noninfectious HIV particles with abnormal structure. The currently available PI are amprenavir \[82\], indinavir \[83\], lopinavir \[84\], nelfinavir \[85\], ritonavir \[86\], and saquinavir \[87\]. There is considerable cross-resistance between the PI \[88,89\]. Because all PI are metabolized in the liver by the cytochrome p450 enzyme system there is a large potential for drug-drug interactions \[90,91\]. PI do not need to be metabolized intracellularly to become active.

A brief history: from monotherapy to HAART

Zidovudine was the first antiretroviral drug to be used for treatment of HIV-1-infected individuals \[92\]. Although monotherapy with zidovudine only resulted in a short-term suppression of HIV-1 replication, it nevertheless temporarily delayed disease-progression and prolonged survival in HIV-1-infected individuals with symptomatic HIV disease \[93,94\]. The use of zidovudine monotherapy in asymptomatic HIV-1-infected individuals with CD4+ T-lymphocyte counts below 500 cells/mm\(^3\) remained controversial \[95,96\]. Didanosine and zalcitabine became licensed in 1991 and 1992 respectively. Until 1995 didanosine and zalcitabine were mainly used in patients failing or intolerant to zidovudine \[97-101\]. In 1995 lamivudine and stavudine became available. Dual NRTI therapy became the standard of care \[102\] after it was shown to be superior to NRTI monotherapy in suppressing viral replication, increasing CD4 cell counts, decreasing disease progression and increasing survival \[103-108\]. The duration of these beneficial effects however remained limited because of the emergence of drug-resistant HIV strains \[107,109-113\]. Because of the high replication rate of HIV \[114-117\] and the low fidelity of the HIV reverse transcriptase \[118,119\], therapy for HIV needs to suppress HIV-replication to very low levels and needs to have a high genetic barrier for the development of HIV drug resistance. In 1996 the PI became available for use in routine clinical practice. Studies comparing dual NRTI therapy with triple therapy (2 NRTI plus 1 PI) demonstrated for the first time that long-term suppression of HIV-replication was possible \[120-123\]. This was subsequently also demonstrated for triple therapy with 2 NRTI plus 1 NNRTI and triple therapy with 3 NRTI \[124-128\]. These insights were translated into the current guidelines for the treatment of HIV-infection \[129-134\] with what was named “highly active antiretroviral therapy” or HAART. Initially, HAART was assumed to completely block the ability of the virus to infect new cells, and it was estimated that eradication of HIV might be achieved after 2 to 4 years of HAART \[115,117\]. However, it was demonstrated that HIV continues to replicate at low levels during apparently successful antiretroviral therapy \[135-145\]. Replication-
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competent proviral HIV DNA remains present in long-lived resting CD4+ T-lymphocytes [138,143,146-160]. Furthermore, certain antiretroviral drugs penetrate poorly in tissues with blood-tissue barriers, like the central nervous system, retina, and testes [135,161,162]. Certain cell types actively transport antiretroviral drugs out of the cell using molecular efflux pumps like the transmembrane P-glycoprotein, thereby preventing these drugs from reaching therapeutic intracellular concentrations [163-168]. Together these factors represent a major barrier for the eradication of HIV from an infected individual using currently available therapeutic options [169,170].

HAART in clinical practice

In 1996 it became possible for the first time to treat HIV-infected individuals with HAART outside the setting of clinical trials. As of 1996 the incidence of AIDS and HIV-related mortality has declined sharply in the US and Western Europe [171-179]. The use of HAART not only prevented HIV-related morbidity and mortality, but also resulted in the improvement of several HIV-related conditions like Kaposi's sarcoma [180-184], progressive multifocal leukoencephalopathy [185-188], cytomegalovirus disease [189], mycobacterial infections [190,191], microsporidiosis and cryptosporidiosis [192-195], oropharyngeal candidiasis [196-198], and AIDS-related lymphoma [199-203]. It was also shown that in the setting of HAART-associated improvements in CD4+ T-lymphocyte counts, prophylaxis (both primary and secondary) could be discontinued for several opportunistic infections: Pneumocystis carinii pneumonia [204-211], cytomegalovirus disease [212-216], cerebral toxoplasmosis [217-219], cryptococcal menigitis [220], and Mycobacterium avium complex disease [221-223]. Unfortunately, HAART was found to result in less durable suppression of HIV-1 replication in clinical practice than in the well controlled setting of clinical trials [224-227]. Within the first year of treatment between 36 and 53% of patients were found to have to modify / discontinue their initial HAART regimen, mostly because of drug related adverse effects [224,228-230].

Adverse effects of antiretroviral therapy

Immune reconstitution syndromes
Immune reconstitution syndromes are the result of preexisting subclinical (asymptomatic or mildly symptomatic) infections becoming clinically manifest or worsening shortly after the start of HAART in the face of recovering pathogen-specific cellular immunity [231]. Immune reconstitution syndromes have been described for cytomegalovirus disease [232-234],
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chronic hepatitis B virus infections [235], chronic hepatitis C virus infections [236], tuberculosis [237,238], atypical mycobacterial infections [239,240], and cryptococcal infections [241,242]. Strictly speaking, immune reconstitution syndromes are not side effects of antiretroviral therapy, since improving the function of the immune system is a primary goal of antiretroviral therapy. Therefore antiretroviral therapy should be continued whenever deemed clinically possible, with or without concomitant therapies for the opportunistic infections.

Mitochondrial toxicity
The NRTI act as chain terminators of DNA strands synthesized by the HIV reverse transcriptase [56]. NRTI also have affinity for the human DNA polymerases β and γ, but far less so for α, δ, and ε [243-247]. Human DNA polymerase β is involved in the repair of damaged DNA, and has so far not been linked with NRTI related toxicity [248]. Human DNA polymerase γ is solely responsible for of mitochondrial DNA synthesis, and its inhibition by NRTI results in mitochondrial DNA depletion and impaired mitochondrial function [249]. Mitochondria provide energy (ATP) to the cell by oxidative phosphorylation. An alternative albeit much less efficient route for ATP production is anaerobic glycolysis in the process of which glucose is converted into lactate. The most serious and often fatal NRTI-associated mitochondrial toxicity is lactic acidosis [250-252]. Other examples of mitochondrial toxicity are pancreatitis, myopathy, cardiomyopathy, anemia, hepatic steatosis, and polyneuropathy [253]. Mitochondrial dysfunction may also be involved in the pathogenesis of peripheral lipatrophy, although there is still no formal proof for this being the case [254,255]. Mitochondrial toxicities usually develop fairly slowly and are progressive if therapy is continued. The capacity to recover after discontinuation of the offending NRTI varies depending on the affected tissues, the duration of treatment with the NRTI, and the severity of the symptoms. Mitochondrial toxicities are relatively tissue- and drug-specific, possibly because the NRTI are phosphorylated intracellularly by different cytoplasmic and intramitochondrial enzymes the activity of which may vary across cell types [57-63]. The management of mitochondrial toxicities consists of the withdrawal of the assumed causative NRTI.

Hypersensitivity reactions
Hypersensitivity reactions occur much more frequently in HIV-infected patients than in the general population [256]. The pathogenesis of these hypersensitivity reactions is unknown. Hypersensitivity reactions are early side effects of several antiretroviral drugs including all currently licensed NNRTI, the NRTI abacavir, and the PI amprenavir [257]. Most
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Hypersensitivity reactions occur within the first 6 weeks of treatment, and may be life threatening [258-263]. The clinical presentation of hypersensitivity reactions usually includes a maculopapular, erythematous, pruritic rash with or without constitutional symptoms. Life threatening complications, like Steven's Johnson syndrome, toxic epidermal necrolysis and anaphylactic reactions, can occur when patients who develop a hypersensitivity reaction continue treatment or are rechallenged with the same drug following a temporary interruption of treatment. Most mild hypersensitivity reactions resolve spontaneously without specific treatment. Clinical management guidelines with detailed instructions when to discontinue therapy have been issued for abacavir and nevirapine [264]. Antipyretics and antipruritics are widely used for the symptomatic treatment of mild rashes, but their effectiveness has not been studied. More serious cases are managed by permanently discontinuing the causative drug. Prevention of hypersensitivity reaction by the use of corticosteroids has been studied for nevirapine, but with conflicting results [265-269].

Hepatotoxicity

Liver enzyme elevations are a frequently occurring side effect of antiretroviral therapy [270-274]. Liver enzyme elevations associated with the use of NRTI might be the result of hepatic mitochondrial toxicity [253]. NNRTI associated liver enzyme elevations are sometimes part of a hypersensitivity reaction [275,276]. The mechanisms by which PI contribute to the etiology of liver enzyme elevations are unknown. In addition, it has been postulated that antiretroviral combination therapy associated liver enzyme elevations in the setting of chronic viral hepatitis may be part of an immune-restoration disease [235,236]. The most well established risk factors for liver enzyme elevations are chronic hepatitis B and C co-infections [270-274]. Virtually every licensed antiretroviral drug has been associated with liver enzyme elevations [85,105,106,123,127,275-281]. Most cases of liver enzyme elevations resolve whether antiretroviral therapy is continued or not [270].

Elevated unconjugated bilirubin without histological evidence of liver damage develops in 6% to 25% of patients using indinavir [83,121,122]. The investigational PI atazanavir is associated with the same phenomenon. This unconjugated hyperbilirubinaemia is strongly linked with the presence of the Gilbert’s syndrome polymorphism in the bilirubin UDP-glucuronosyltransferase gene [282].
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Lipodystrophy syndrome and metabolic abnormalities
Although a formal case definition is still lacking, physicians generally agree that the main clinical features of this syndrome are fat redistribution presenting as central fat accumulation (visceral abdominal fat accumulation, breast enlargement, dorsocervical fatpad enlargement) and peripheral fat atrophy of the face, limbs and buttocks [283,284]. The reported incidence of lipodystrophy varies widely from less than 20% to over 80% after one year of HAART [283,285-287]. Several metabolic abnormalities like insulin resistance, hyperglycemia, hypercholesterolemia, and hypertriglyceridemia that are frequently found in HIV-infected individuals using HAART, are associated with the lipodystrophy syndrome [285,286,288,289]. The pathogenesis of lipodystrophy is unclear. Although PI were initially most consistently associated with the development of lipodystrophy, several papers have argued for a role of NRTI (stavudine in particular) in its pathogenesis [254,290]. The clinical significance of fat redistribution is primarily cosmetic, but together with the associated metabolic abnormalities the risk of premature atherosclerotic cardiovascular disease [291-295]. Treatment of lipodystrophy has generally been disappointing thus far [266,296-304]. Hypercholesterolemia and hypertriglyceridemia are managed with dietary instructions, exercise, and lipid lowering drugs [305,306].

Miscellaneous side effects
Gastrointestinal side effects: Gastrointestinal side effects like nausea, vomiting and diarrhea are early and often transient side effects of most antiretroviral drugs. However, for the PI diarrhea can be more severe and prolonged.

Nervous system symptoms: The most common side effects of the NNRTI efavirenz are headache, dizziness, impaired concentration, insomnia, and fatigue, occurring in up to 58% of patients [78,124]. Most of these side effects are mild to moderate and disappear after a few weeks to months of therapy with efavirenz.

Nephrolithiasis: Because the PI indinavir is poorly soluble in water, it can crystallize in the urine. This can result in nephrolithiasis with obstruction of the urinary tract. Patients with high plasma concentrations of indinavir, insufficient fluid intake, fever, or those living in a hot climate have a higher chance of developing nephrolithiasis [307,308].

Drug-drug interactions: The PI and NNRTI are metabolized by the cytochrome P450 system in the liver and gut wall. These agents (and any other concomitantly used drug that is likewise metabolized through the cytochrome P450 system) can either inhibit or induce the cytochrome P450 system, leading to increased or decreased plasma concentrations of other
drugs. Plasma concentrations of antiretroviral agents can either become too low (possibly leading to incomplete virological suppression and emergence of resistant HIV variants) or too high (with increased risk of developing toxicities). Plasma concentrations of concomitantly used medications can also either become too low (subtherapeutic) or too high (toxic). These interactions are also exploited for the pharmacological boosting of certain PI by the concomitant use of low doses of the PI ritonavir. Ritonavir is a powerful inhibitor of the metabolism of other PI via the cytochrome P450 system, thereby enhancing the antiretroviral effect, eliminating food-restrictions or making it possible to dose these PI twice or even once daily [309-312].

Outline of this thesis

In July 1996 the PI indinavir, ritonavir, and saquinavir became available for routine treatment of HIV-1-infected individuals in the Netherlands. In chapter 2 we describe the virologic, immunologic, and clinical outcome of the first group of patients treated with PI containing HAART in the Academic Medical Centre in Amsterdam.

The NNRTI nevirapine became available in the Netherlands prior to licensing through a so-called Named Patient Program that ran from May 1997 to April 1998. Patients failing previous antiretroviral therapy and who in the opinion of their treating physicians could only be adequately treated if they could obtain nevirapine were eligible for the program. Based on our previous experiences with the introduction of the PI it was recommended that nevirapine whenever possible should be combined with at least two other antiretroviral drugs expected still to be effective. In chapter 3 we evaluate the efficacy and safety of the use of nevirapine within this program.

Since HIV-1 cannot be eradicated form the body with currently available antiretroviral drugs, antiretroviral treatment must be sustained indefinitely. Prevention of viral resistance is therefore of utmost importance. Ongoing low-level HIV-1 replication during standard of care HAART has been linked with the selection of HIV-1 resistant mutants. In chapter 4 we investigate whether treatment with an alternative multidrug regimen consisting of five drugs from three different classes, results in a stronger suppression of HIV-1 replication than standard of care triple drug HAART.

One of the major obstacles to lifelong sustained antiretroviral therapy are drug related toxicities. Liver failure has become an important cause of death in HIV-1-infected individuals. In chapters 5 and 6 we investigate the incidence of and risk factors for hepatic toxicity associated with the use of HAART.
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Hypersensitivity reactions are a frequent side effect of several antiretroviral drugs, they can be life threatening, and may preclude the patient from ever again using a antiretroviral drug. In chapter 7 we investigate whether the adjuvant use of corticosteroids can prevent the occurrence of abacavir and nevirapine associated hypersensitivity reactions.
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