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CHAPTER 1

INTRODUCTION

INTRODUCTION

The etiologic agent of the acquired immunodeficiency syndrome (AIDS), the human immunodeficiency virus type 1(HIV-1) was identified in 1983.[1-4] Transmission of the virus by body fluids from an infected to an uninfected person can lead to the infection of predominantly CD4+ T-lymphocytes. After the reverse transcription of viral RNA into DNA, this viral DNA may be integrated into the genome of the host cell. When activated, the infected CD4+ T-lymphocyte produces new HIV-1 virions using the replication mechanism of the host cell. This process, from infection to the production of new virions is estimated to take at least 6 hours.[5]

Over time the immune system deteriorates as a consequence of the loss of CD4+ T-lymphocytes, which eventually leads to a variety of clinical events ranging from opportunistic infections, such as oesophageal candidiasis and *Pneumocystis carinii* pneumonia, to opportunistic malignancies as Kaposi's sarcoma, and cervical cancer. These HIV-related events have been well defined and categorised by the Centers for Disease Control and Prevention.[6] The relationship between the CD4+ T-lymphocyte count and the incidence of clinical events has been demonstrated in many studies.[7-9] From cohort studies on the natural history of HIV-1 infection it is known that AIDS-defining events occurred a median of 8 to 10 years after the primary infection,[10] and that the median survival time for HIV-1 infected patients after such a diagnosis of AIDS was 10-12 months.[11,12]

The introduction of antiretroviral therapy changed the natural course of the infection. Zidovudine (3'-azido-3'-deoxythymidine), a nucleoside analogue reverse transcriptase (RT-) inhibitor that inhibits HIV replication by terminating viral DNA-chain elongation,[13] was the first agent found to affect HIV-1 replication *in vivo*.[14] Subsequently, clinical trials evaluating antiretroviral therapy in HIV-1 infection were designed to demonstrate differences in clinical outcome. Death and disease progression were the primary outcome measures of these studies. Time to death and time to the first AIDS-defining event were used as outcome measures in analyses to demonstrate superiority of a treatment over placebo. In the first clinical trial demonstrating clinical benefit of zidovudine, in patients with AIDS or AIDS-related complex (ARC), a mortality risk reduction of 95% was found after a median follow-up of 130 days (15). This study also demonstrated that CD4+ T-lymphocyte counts increased in patients randomised to zidovudine, indicating that CD4+ T-lymphocyte counts could reflect the clinical benefit of antiretroviral therapy. However, the immunological improvement as assessed by the CD4+ T-lymphocyte count is at best only an indirect measure of the amount of suppression of viral replication. As a first attempt to directly obtain information on viral replication, HIV-1 p24 antigen, a quantifiable core antigen of HIV-1, was measured in serum.[15]

The utility of HIV-1 p24 antigen measurement was limited by the fact that only a minority of HIV-1 infected patients (30-50%) had demonstrable serum p24 antigen.[16,17] The p24 antigen level decreased in p24 antigen positive patients after the initiation of zidovudine treatment.[15,18-20] Immune complex dissociation could increase the proportion of patients with HIV-1 p24 antigenaemia, but whenever using this technique there were still a number of patients in whom no p24 antigen could be measured.[21,22] Obviously, clinical trials evaluating antiretroviral therapy will gain power if a virological parameter could be measured in every patient. By 1994, a technology for the measurement of HIV-1 RNA copies in serum or plasma became readily available for clinical use.[22] A direct virological parameter was now available. In Chapter 2 of this thesis a comparison of HIV-1 RNA versus that of p24 antigen in evaluating antiretroviral therapy is described.

The superiority of HIV-1 RNA over p24 antigen as a tool to monitor the effect of antiretroviral therapy was soon established.[23] By the availability of HIV-1 RNA quantification in serum or plasma, a measure of virus replication was introduced with major impact on both clinical practice and clinical trials. Quantitative measurement of HIV-1 RNA was and still is important for clinical staging,[24] initiation of therapy[25] and monitoring of therapy efficacy.[26,27] A good correlation has been found between HIV-1 RNA load in serum and infectious $CD4^+$ cellular load in peripheral blood mononuclear cells.[28] A comparison of available HIV-1 RNA assays in treated and untreated patients was warranted, because of the different techniques that were being used (Chapters 3 and 4). In Chapter 4 the reproducibility of HIV-1 RNA testing among different laboratories is presented as well.

Whether administered early or late in HIV disease, antiretroviral therapy by means of monotherapy was demonstrated to be of transient clinical benefit.[29-33] It was clear that only a transient rise in $CD4^+$ T-lymphocytes could be expected from monotherapy with only a short delay in clinical deterioration.[34] Results from several small studies investigating the efficacy of two nucleoside analogue RT-inhibitors in the treatment of antiretroviral naive patients with HIV-1 infection showed virological and immunological superiority over monotherapy.[35-37] More studies with a larger sample size were required to show clinical benefit and to investigate at what moment in HIV disease patients should initiate antiretroviral treatment. In two large studies with large numbers of antiretroviral naïve patients, one conducted by the AIDS Clinical Trials Group (ACTG protocol 175; 2467 participants)[38] and one conducted by a multinational research collaborative of national trial centres in Europe and Australia (the Delta trial; 3207 participants), the combination of either didanosine or zalcitabine with zidovudine was compared with zidovudine monotherapy. In Chapter 5 the clinical outcome of the Delta trial is described, as

well as a comparison of these results with findings of the other study. Results of double nucleoside therapies in studies conducted in zidovudine pretreated patients had a disappointing outcome.[39,40]

Several years after the introduction of zidovudine, the loss of antiretroviral treatment effect of this drug was found to be associated with the appearance of resistance to zidovudine,[41] caused by distinct mutations in the HIV-1 reverse transcriptase gene,[42] although the initial viral escape may be predominantly drug sensitive virus.[43,44] To determine whether the development of drug resistance in combination therapy was similar as compared to monotherapy, stored serum samples from a subgroup of Delta trial participants were used for retrospective measurements of HIV-1 RNA copies and genotypic and phenotypic drug resistance (Chapter 6).

In the mid-nineties a new class of antiretroviral agents was introduced that inhibited the cleavage of virus precursor proteins by blocking the viral-encoded protease enzyme, resulting in production of non-infectious virions.[45] These protease inhibitors were remarkably potent in inhibiting viral replication.[46,47] For the first time in the epidemic, clinical evaluation of antiretroviral therapy shifted from postponing time to AIDS-related events to improvement of clinical manifestations of the immune deterioration caused by HIV-1. In Chapter 7 the effect of the HIV-1 protease inhibitor indinavir in combination with nucleoside analogue RT-inhibitors on chronic HIV-related diarrhoea was investigated.

After the introduction of HIV-1 protease inhibitors, triple drug therapy, with a protease inhibitor and two nucleoside analogue RT-inhibitors, soon became the standard of care, leading to considerable and durable $CD4^+$ T-lymphocyte rises.[45,47] It was reported from cohort studies that incidences of AIDS-defining diseases dropped considerably after combination therapy including HIV-1 protease inhibitors (highly active antiretroviral therapy, HAART) became widely available.[48-50] According to the 1997 U.S. Public Health Service (USPHS) and the Infectious Diseases Society of America (IDSA) USPHS/IDSA guidelines for the prevention of opportunistic infections, it was advocated for patients with advanced disease, either with a $CD4^+$ T-lymphocyte count below 200 cells/mm^3 or with an AIDS-defining event, in particular *Pneumocystis carinii* pneumonia (PCP), to use prophylaxis to prevent a first or second PCP episode, respectively.[51] After the introduction of HAART, $CD4^+$ T-lymphocyte counts of patients with advanced HIV-1 infection often increase above the threshold of 200 cells/mm^3.[47] In Chapter 8 the results of a cohort study are described evaluating the safety of the discontinuation of PCP prophylaxis in HIV-1-infected patients who were using HAART.

The virologic and clinical superiority of triple drug therapy over treatment with two nucleoside analogue RT-inhibitors has been demonstrated convin-

cingly.[45,47] There are reasons to suspect, however, that current triple-drug regimens do not exert maximal antiviral pressure at the level of every infected cell. There is direct *in vitro*[52] and indirect *in vivo*[53] evidence that the necessary intracellular phosphorylation to the active triphosphate of available RT-inhibitors may not be equally efficient in different cell types. It is demonstrated in Chapter 9 that current triple-drug therapy does indeed not represent the zenith of anti-HIV activity.

Most of the results described above have been obtained from randomised clinical trials, the current (and future?) standard for the evaluation of therapeutic interventions. The purpose of randomisation is to eliminate physicians' treatment preferences, as well as to equally distribute unknown prognostic factors over the treatment allocations within a clinical trial. As disease-free survival of HIV-1 infected patients will further increase and exposure to different previous treatments will become more complex, balancing of prognostic factors over treatment allocations will become more difficult. However, controlling for allocation balance will be paid for by an increase of predictability of treatment allocation, which is not an issue in placebo-controlled studies. In most cases, randomised controlled trials in HIV-1 infection are open label studies and include a limited number of participants. Therefore, a minimisation procedure rather than a stratified allocation is indicated to optimise balancing and minimise predictability. In Chapter 10 computer simulations are described of randomised controlled trials investigating the predictability of allocations and the imbalance of different treatment allocation procedures, including the minimisation strategy.

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