Comorbidity and ageing in HIV infection
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Introduction
HIStoryCAL CONTEXT

The human immunodeficiency virus pandemic

The first cases of the disease that became known as acquired immune deficiency syndrome (AIDS) were reported in 1981 [1]. In 1983 the causative agent, the human immunodeficiency virus (HIV), was identified [2]. The main transmission routes for HIV are sexual intercourse, mother-to-child transmission, injection drug use, and exposure to contaminated blood. Upon entering the body, HIV preferentially infects CD4+ macrophages and T-lymphocytes leading to the hallmark immunological effect of a gradual depletion of CD4+ T-cell compartment. The depletion of the CD4+ T-cell compartment results in an increasing degree of immunodeficiency and susceptibility to opportunistic infections and malignancies; their occurrence defines the clinical syndrome of the acquired immune deficiency syndrome or AIDS [3,4].

Worldwide, the African continent is most severely affected by HIV/AIDS, with many countries suffering from a generalized epidemic [5]. In Western Europe, and more specifically in the Netherlands, the epidemic is largely concentrated in certain risk groups. In the Netherlands, these are particularly men who have sex with men and migrants from countries with a high HIV prevalence and their sexual partners [5–7].

Antiretroviral therapy and side effects

Development of antiretroviral drugs started in the mid-1980s and, following almost a decade of use of single and dual antiretroviral regimens, finally led to the availability of the first effective triple combination antiretroviral treatment (cART) regimens in 1996 [8], which for the first time achieved long-term suppression of HIV replication in the majority of treated patients [9].

Initial cART regimens were associated with significant toxicities and adverse effects. In particular, concerns were raised regarding the potential of certain antiretroviral drugs to increase the risk of cardiovascular disease (CVD) [10,11].

The recognition of the serious side-effects of cART, together with the risk of selecting for viral resistance because of reduced treatment adherence, and the cost of lifelong treatment, motivated researchers to perform studies of cyclical antiretroviral treatment (ART) interruption once patients had achieved adequate viral suppression and immune recovery in an effort to balance the benefits and risks of ART [12]. The largest of these studies was the Strategies for Management of Antiretroviral Therapy (SMART) trial. It was designed to compare a strategy of CD4+ T-lymphocyte count (CD4 count) guided treatment interruption with a strategy of continuous cART in terms of the risk for both AIDS and non-AIDS
associated morbidity and mortality [13]. However, completely contrary to expectations, the study showed an increased risk of morbidity and mortality in the group randomly assigned to CD4 count-guided treatment interruption. This risk was largely driven by severe non-AIDS events (including major cardiovascular, renal, and liver events), which up to that point were nearly universally thought of as a side effect of ART [13].

The findings from SMART not only lead to a paradigm shift in thinking about the contribution of HIV replication and immune deficiency to the pathogenesis of comorbidity, but also strongly influenced the prevailing opinions about the benefits of early HIV diagnosis and treatment. Whilst guidelines early on in the era of cART had recommended cART initiation only when CD4 counts dropped below 200 cells/mm³ or in symptomatic HIV-disease [14], guidelines gradually shifted to promoting cART initiation at increasingly higher CD4 count thresholds. This was not only a result of trials like SMART, but also of the development of antiretroviral drugs with reduced toxicity, further shifting the benefit-risk balance in favour of early initiation of cART. As of September 2015, guidelines globally, including those issued by the World Health Organization (WHO), recommend cART initiation for all HIV-infected patients regardless of CD4 count [15].

**An ageing HIV-infected population**

The widespread use of effective antiretroviral drugs has led to a markedly increased life expectancy, and thereby to a growing population of middle-aged and elderly HIV-infected individuals (Figure 1) [7,16,17].

Along with increasing life expectancy of the population of long-term treated HIV-infected individuals, incidence rates of several age-associated non-communicable comorbidities (AANCC) have understandably increased as well [18]. And as mortality due to AIDS dramatically decreased, AANCC, including CVD, non-AIDS cancer, and liver disease, have become more frequent causes of death than AIDS-related conditions [19].

Studies suggested that AANCC were more common in HIV-infected compared to uninfected individuals, even in adequately treated HIV infection [20–22], and occurred at a younger age [20]. Furthermore, compared to the general population, the mortality rate in HIV-infected populations remained higher and life expectancy lower compared to the general population [23–25].

In view of these observations the question arose which (traditional and HIV-related) risk factors in the context of treated HIV infection might be driving the increased rate of (potentially prematurely developing) AANCC, including if and to what extent the increased incidence of AANCC might be the result of an acceleration of the ageing process itself [26].
THE MULTIFACTORIAL NATURE OF AGE-ASSOCIATED COMORBIDITY IN HIV

Several factors likely contribute to the pathophysiology of AANCC observed in ageing HIV-infected individuals, including some that potentially affect the process of ageing (Figure 2) [27,28]. Exposure to unsuppressed viraemia is likely to be involved [13]. Chronic untreated HIV infection leads to a state of chronic immune activation and inflammation, in part resulting from increased gut microbial translocation, a state which persists at a reduced level after start of cART [29]. Moreover, toxic effects of certain antiretroviral drugs might constitute an important factor as well [27]. Coinfections with cytomegalovirus (CMV), hepatitis B and C virus (HBV and HCV), and life-style related factors each are likely to contribute to the risk of AANCC [28].
HIV, immune activation, and inflammation

As definitively demonstrated by the SMART study, untreated HIV is a strong risk factor for major cardiovascular, renal, and hepatic disease [13]. Chronic inflammation is thought to be one of the mechanisms contributing to this increased risk [31,32].

Untreated HIV infection likely causes inflammation both through direct and indirect mechanisms. Direct effects include T-cell activation, induced by HIV antigens [29]. Important indirect effects of HIV include the damaging effect HIV infection has on gut epithelial cells, and on preferentially depleting CD4+ T-lymphocytes in the intestinal mucosa starting very early during infection. This leads to impaired defence against gastrointestinal microbes, increased gut wall permeability, and increased microbial translocation – translocation of microbial products into the systemic circulation [33]. The increased systemic exposure to microbial products in turn can cause monocyte and macrophage activation, thereby driving innate immune and coagulation activation [29,33]. In addition, microbial products may also directly activate the coagulation cascade or contribute to a hypercoagulable state by affecting liver function [29].
Levels of markers of inflammation, immune activation, and coagulation generally decline upon initiation of cART [34,35], but remain higher compared to in individuals without HIV infection [29,35,36].

In the general population, chronic inflammatory states contribute to the pathophysiology of several AANCC. Markers of chronic inflammation have been associated with increased rates of CVD [37,38], chronic kidney disease (CKD) [39], cancer [40], and bone disease [41]. Activation of the innate immune system, particularly monocytes and macrophages, is involved in the pathophysiology of atherosclerosis [42], thereby contributing to increased cardiovascular risk. Microbial translocation contributes to progression of liver fibrosis in HCV and alcohol related liver disease through the involvement of Kupffer cells, which are specialized macrophages residing in the liver [43,44]. Chronic inflammation may also contribute to a state of increased vulnerability, referred to as frailty [45]. Frailty develops as a result of age-related decline across multiple physiological systems and is associated with a higher risk for adverse outcomes including falls, hospitalization, and mortality [45].

Likewise, the chronic inflammatory state likely contributes to comorbidity in both untreated and treated HIV infection. The SMART study and subsequent studies have demonstrated associations between higher levels of markers of inflammation, immune activation, and coagulation and the development of incident severe non-AIDS events [35,46] as well as all-cause mortality [32,46–48]. HIV-associated chronic inflammation is particularly thought to contribute to bone mineral density (BMD) loss [49], and to the pathophysiology of CVD [31,36,50].

**Side effects of antiretroviral drugs**

As mentioned previously, toxicity of antiretroviral drugs may contribute to organ dysfunction and disease [10,51]. Some toxicities are related to a whole drug class, while others are drug-specific. Several of the most toxic first-generation antiretroviral drugs are no longer used in Western countries [52]. However, since ageing HIV-infected individuals may historically have been exposed to these drugs, their mention is noteworthy. An important toxic effect of thymidine analogue nucleoside reverse transcriptase inhibitors (NRTI), which were frequently used in the past, is mitochondrial toxicity. One of the mechanisms leading to mitochondrial toxicity is nucleoside analogue induced inhibition of mitochondrial DNA polymerase gamma; mitochondrial DNA polymerase is able to use these analogues as substrates which results in the termination of the replicating mitochondrial DNA [53]. Mitochondrial toxicity may cause peripheral subcutaneous fat atrophy [10,51,53]. Hepatotoxicity associated with mitochondrial toxicity may lead to liver steatosis and fibrosis [54]. Stavudine, zidovudine and didanosine are NRTIs strongly
associated with mitochondrial toxicity, but no longer recommended as preferred components of antiretroviral regimens [55].

Although many antiretroviral drugs potentially have adverse effects on blood lipids [56], these effects are especially strong for several of the protease inhibitors (PI). PI containing regimens are associated with pro-atherogenic dyslipidaemia including increases in low-density lipoprotein (LDL) cholesterol and triglycerides [57]. These changes in lipid metabolism may affect cardiovascular risk [58,59]. PIs may also exhibit bone toxicity; studies have linked PI exposure to loss of BMD [60] and exposure to ritonavir-boosted lopinavir to an increased risk of fragility fractures [61]. In addition, several PI may have nephrotoxic effects. Ritonavir-boosted atazanavir and indinavir may both cause crystalluria and nephrolithiasis; ritonavir-boosted atazanavir, lopinavir, and indinavir are associated with an increased risk of CKD [62,63].

Drug-specific toxic effects also include the increased cardiovascular risk associated with the NRTI abacavir, though this is still subject to debate [64,65]. Tenofovir disoproxil fumarate (TDF) is associated with renal tubular dysfunction, manifested by decreased phosphate reabsorption, increase in urine low-molecular weight proteins and normoglycaemic glycosuria. Fanconi syndrome (overt proximal renal tubular dysfunction) is a rare complication of TDF use [62]. TDF also is associated with a greater BMD decline after cART initiation compared to other antiretroviral regimens [66] and with increased fragility fracture risk [61], it is as yet unclear whether renal phosphate loss contributes to this risk [67].

**Behavioural, demographic factors and coinfections**

Behavioural factors, genetics, and coinfections may each further influence the likelihood of developing AANCC. The distribution of these factors in HIV-infected populations in Western countries likely differs from the general population, partly because HIV is predominantly spread in certain high-risk groups with particular behavioural and demographic characteristics [6,7].

Behavioural factors such as cigarette smoking, excessive alcohol intake, and substance abuse are well-known risk factors for the development of many AANCC in the general population [68,69] and in HIV-infected individuals [70]. HIV-infected individuals however may be more likely to smoke cigarettes, and less likely to quit smoking [71]. Excessive alcohol intake and both injection and non-injection drug use are also more common in HIV-infected populations [72].
Individuals of African descent exhibit a high prevalence of hypertension and diabetes compared to those with different ethnic backgrounds; this is probably in part a result of a genetic predisposition [73]. A considerable proportion of the HIV-infected population in the Netherlands originates from sub-Saharan African countries (in 2015 this was 14%) [7].

HBV and HCV infection are more common in HIV-infected individuals due to shared modes of transmission [74]. Coinfection with viral hepatitis increases the risk of liver fibrosis, cirrhosis, and hepatocellular carcinoma [74].

**Potential interactions between involved mechanisms and the ageing process**

Several of the factors potentially contributing to the increased risk of AANCC may share common pathogenic mechanisms, potentially with synergistic effects. This may complicate attempts to unravel the mechanisms behind AANCC in the HIV-infected individual.

The immune system is closely related to cholesterol metabolism and to metabolically active adipose tissue [75,76]. As part of the inflammatory response the immune system affects cholesterol metabolism, which in turn amplifies the inflammatory response [76]. In acute inflammatory states this feedforward mechanism may benefit the resolution of infection, but in chronic inflammatory diseases such as chronic HIV infection it contributes to dyslipidaemia [76,77]. On the other hand, ART-related dyslipidaemia may in turn contribute to the inflammatory state in HIV infection through similar mechanisms [77]. And obesity, particular visceral obesity, is associated with increased levels of systemic inflammatory markers [75].

Coinfection with HCV and CMV infection likely contribute to a chronic inflammatory state [27,29]. CMV infection is common in HIV infection and HIV-infected individuals may experience reactivation more often than uninfected individuals [78]. Several behavioural factors may also adversely affect the inflammatory state. Cigarette smoking has been associated with a higher level of inflammation in the general population [79], and both smoking and alcohol intake with higher levels of inflammation in HIV-infected individuals [80,81]. Potentially, the effects of smoking on the immune system may be stronger in HIV-infected compared with HIV-uninfected individuals [82]. Some studies have observed a stronger relation between smoking and adverse health outcomes in HIV-infected individuals compared to the general population [83], which may part be due to a synergistic pro-inflammatory effect of smoking and HIV infection.
It has been hypothesized that HIV-associated inflammation and/or exposure to antiretroviral drugs may directly affect the ageing process itself. The idea that HIV-infected individuals may experience accelerated ageing was proposed in reaction to the observation of high rates of AANCC in HIV-individuals of relatively young ages [20,26,28]. Further support for this hypothesis came from changes in body fat distribution, a consequence of atrophy of peripheral subcutaneous tissue due to NRTI exposure, which resembled age-related changes in body composition [20,84]. Another factor that was hypothesized to contribute to accelerated ageing was accumulation of pre-lamin A, associated with ritonavir-boosted PI use [85]. This farnesylated precursor of lamin A induces cell senescence, thereby directly affecting the ageing process [28,85]. Furthermore, chronic inflammation may contribute to age-related deterioration of the immune system, a state referred to as immunosenescence [86,87]. Metabolic dysregulation is also hypothesized to contribute to accelerated ageing [88].

However, the hypothesis of accelerated ageing remains controversial [89,90]. An alternative explanation for the relatively young age at which AANCC are observed in the HIV-infected population, may be related to a difference in age-distribution between the HIV-infected populations which are being studied and the general population controls to which they are being compared: HIV-infected populations on average often are younger than the general population controls and thus AANCC in those with HIV are more likely to be observed at a younger age [91]. Without appropriate adjustment for any such difference in age distribution, the conclusion could be drawn that AANCC appear in an accelerated fashion (i.e. occurring at a younger age) in the HIV-infected population, while in fact they may merely be accentuated (i.e. at similar age but more frequent) [89,90,92,93]. A large study compared the age at non-AIDS cancer diagnosis between individuals previously diagnosed with AIDS and the general population. Although the average age at cancer diagnosis was lower in individuals with AIDS, for most cancers this difference could be explained by differences in the underlying age distribution of both populations [92].

**STUDY POPULATION**

The research presented in this thesis took place in the context of the AGEdIV Cohort Study. This prospective comparative cohort study was designed to investigate the prevalence, incidence, and underlying pathophysiology of AANCC and organ dysfunction in ageing HIV-infected patients. Almost 600 HIV type 1 (HIV-1-)infected patients aged 45 years old and older, attending the HIV outpatient clinic of the Academic Medical Center (AMC), participate in the study. In order to best take into account the effects of age,
sex, ethnicity, and other demographic as well as behavioural factors as determinants of comorbidity, 550 HIV-uninfected controls aged 45 years and older and from a similar background were recruited at the sexual health clinic of the Public Health Service in Amsterdam. Characteristics of the recruited population were monitored regularly during the recruitment period, and recruitment of the HIV-uninfected cohort was adjusted to match the HIV-infected cohort if necessary. The HIV-infected and HIV-uninfected participants undergo biennial study visits. Most research discussed in this thesis relates to baseline measurements, conducted between 2010 and 2012.

**AIMS AND OUTLINE OF THIS THESIS**

This thesis aimed to contribute to the body of knowledge on the prevalence and progression of, as well as factors contributing to AANCC in HIV-1-infected patients. Previous studies reported on a high burden of comorbidity in HIV-infected patients, but many included no or suboptimal control groups or lacked information on important potential confounding factors. The detailed information on clinical events, biomarkers of organ dysfunction, demographic and behavioural risk factors, markers of body composition and inflammation enabled us to in depth discuss the potential pathophysiological pathways leading to a variety of clinically significant age-associated conditions in HIV-infected individuals. The contribution of HIV-associated factors and ART exposure was explored by making use of the data collection of the Netherlands Stichting HIV Monitoring (HIV Monitoring Foundation) [7]. The inclusion of a highly comparable HIV-uninfected control cohort allowed us to better control for factors related to the demographic risk group that may contribute to AANCC in the HIV-infected population.

In **chapter two** we performed a cross-sectional comparison of lumbar spine, femoral neck, and total hip BMD, as assessed by dual-energy X-ray absorptiometry (DXA), between the HIV-infected and uninfected study participants. Low BMD, as measured by DXA, is an important risk factor for fractures [94]. We hypothesized that HIV-infected individuals would be at increased risk for low BMD and that both exposure to certain antiretroviral drugs, ongoing inflammation, and behavioural risk factors would be involved in its pathogenesis. In **chapter three** we cross-sectionally compared the prevalence of renal disease, investigating markers of renal proximal tubular function and of glomerular function and damage, between HIV-infected and uninfected participants. In addition, we compared progression of renal function decline and progression of albuminuria over a 4 year follow-up period. We investigated whether HIV was independently associated with each of the assessed markers and explored the extent to which this may be due to exposure to nephrotoxic antiretroviral drugs. **Chapter four** contains the results of a
comparative analysis of aortic stiffness, assessed by aortic pulse wave velocity. Aortic stiffness is a marker of arteriosclerosis and a preclinical marker of CVD [95]. We investigated whether HIV was independently associated with a greater aortic stiffness, and explored whether this was mediated by increased levels of inflammation and immune activation. In chapter five we cross-sectionally investigated the Fibrosis 4 (FIB-4) score as a noninvasive marker of liver fibrosis [96], focusing on study participants who had no evidence of historic or current chronic HBV or HCV infection. HIV infection has been shown to accelerate liver fibrosis in individuals coinfected with HCV [74]; we investigated whether HIV infection without chronic viral hepatitis coinfection would also be associated with more advanced liver fibrosis, and also explored possible contributions of historic exposure to hepatotoxic antiretroviral drugs and markers of inflammation and immune activation. In chapter six we compared the prevalence of frailty between the HIV-infected and uninfected study participants, and investigated whether historic or current HIV-disease and exposure to antiretroviral drugs may be determinants of this clinical condition. In chapter seven we performed an exploratory analysis into the potential synergy between cigarette smoking and HIV-status at the level of the immune system. Chapter eight provides a general discussion of the results, overall conclusions, and a discussion of implications for future research.

REFERENCES


