Comorbidity and ageing in HIV infection
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Chapter 8

General discussion
The use of combination antiretroviral therapy (cART) has led to increasing longevity of the HIV-infected population. Consequently, the burden of age-related noncommunicable comorbidity (AANCC) in the ageing HIV-infected population is growing. This thesis presents the findings of several comparative studies, performed within the context of the AGEhIV Cohort Study. We compared prevalence, disease progression, and potential underlying pathophysiological mechanisms of several age-related conditions in HIV-positive and HIV-negative study participants.

The study of AANCC in the HIV-infected patient constitutes a complex multifactorial problem. The current understanding of contributing factors and pathophysiological mechanisms researched within this thesis are presented against the background of existing research both in- and outside of the HIV context. We draw specific attention to the scientific value of a carefully selected HIV-uninfected control group, discuss the consequences of an ageing HIV-infected population, and give recommendations for further research.

**HETEROGENEITY WITHIN THE HIV-INFECTED POPULATION**

Studies consistently report a higher burden of AANCC in HIV-infected individuals compared with HIV-uninfected controls and the general population. These include cardiovascular disease (CVD), cancer, renal disease and osteoporosis [1,2]. Comorbidity in the context of HIV infection is multifactorial; the extent of the respective contributions of HIV infection, ART exposure, coinfections, behavioural, socio-demographic, and genetic factors remains to be further clarified [3–5]. Pathophysiologic mechanisms through which HIV infection may contribute to comorbidity are not completely understood, nor is the mechanism by which HIV may directly affect the ageing process itself [6]. Due to the multifactorial aetiology of AANCC, the risk for particular comorbidities may be unevenly distributed within HIV-infected populations.

The AGEhIV Cohort provides an optimal context for the study of the relative contribution of HIV infection and its treatment to the increased risk of AANCC and to provide insight in the underlying pathophysiologic mechanisms, because of the inclusion of a behaviourally and demographically comparable HIV-uninfected control group and the meticulous collection of a wide range of traditional and (possible) HIV-related risk factors for comorbidities and organ dysfunction. Through frequency matching we were able to recruit a control group highly similar regarding age distribution, gender and HIV transmission risk group. Despite our best efforts to recruit comparable controls, HIV-infected individuals differed in some important aspects from the controls. Importantly,
HIV-infected individuals were more likely to be cigarette smokers and of African descent. By performing multivariable analyses we were able to adjust for these potentially confounding factors.

The vast majority of HIV-infected individuals included (more than 95%) receive cART. The cohort should thus be regarded as a treated HIV-infected cohort; we were therefore seldom able to distinguish the effects of treatment from those of HIV per se on the individual outcomes with certainty. Regarding disease history, the HIV-infected study group was more heterogeneous. Due to late diagnoses and changing guidelines regarding timing of cART initiation, participants had been exposed to varying levels of immunodeficiency. A considerable proportion had been infected for a long time; approximately 20% of the included HIV-infected individuals had been infected prior to 1996, before effective cART was available. Many of these individuals were exposed to advanced immunodeficiency and severe AIDS-related disease for a longer period, as well as to ineffective and more toxic mono- or dual antiretroviral therapy. This heterogeneity regarding disease history and exposure to cART in the HIV-infected cohort enabled us to investigate HIV-disease and ART-related factors as potential determinants of age-related comorbidity. The composition of the HIV-infected cohort reflects the population of people living with HIV in care in the Netherlands [7] and in other Western countries [8], allowing us to generalize our results to these HIV-infected populations.

Similar to previous studies, our group has found a greater burden of comorbidity in HIV-infected cohort participants as compared to controls; after adjusting for traditional risk factors, treated HIV remains independently associated with a greater number of AANCC [9]. Likewise, when studying these individual comorbidities in detail, we found a significantly higher prevalence of both osteoporosis and osteopenia, renal tubular and glomerular dysfunction, and chronic kidney disease in HIV-infected individuals (chapters two and three). In addition, HIV-infected individuals exhibited a significantly greater aortic stiffness and, in the absence of chronic viral hepatitis coinfection, more liver fibrosis compared to HIV-uninfected individuals (chapters four and five). HIV-infected individuals also more commonly exhibited a frailty phenotype (chapter six).

After adjustment for traditional risk factors, however, treated HIV infection was not independently associated with several of these conditions. In analyses adjusted for behavioural and demographic factors, HIV-infected status was no longer independently associated with a lower bone mineral density (BMD) or a higher pulse wave velocity (PWV) indicating greater aortic stiffness (chapters two and four). Although HIV infection (in the absence of chronic viral hepatitis coinfection) was independently associated with a higher Fibrosis 4 (FIB-4) score, indicative of more liver fibrosis, the difference in FIB-4
score with HIV-uninfected individuals was small and of uncertain clinical relevance. Furthermore, a FIB-4 score indicative of advanced liver fibrosis was uncommon in both the HIV-infected and uninfected study groups (1.4% and 1.0% respectively) (chapter five). Cigarette smoking, in particular, appeared to be an important confounder of the association between HIV infection, comorbidity, and organ dysfunction. The higher lifetime exposure to cigarette smoking in the HIV-infected study group explained a large part of the lower BMD in HIV-infected individuals (chapter two). Similarly, the difference in aortic stiffness was largely explained by a higher lifetime exposure to cigarette smoking in those with HIV (chapter four). A higher prevalence of chronic hepatitis C virus (HCV) infection in HIV-infected individuals contributed to the observed higher prevalence of several conditions, although to a lower extent than cigarette smoking. We found chronic HCV infection to be independently associated with lower BMD in the total hip and the femoral neck and with a higher likelihood for frailty (chapter six).

A potential explanation for the absence of an independent association between HIV infection and several conditions lies in the fact that the majority of the HIV-infected group had suppressed HIV viraemia and CD4 count restoration for a prolonged period of time. Attaining a substantial level of immune restoration and the initiation of cART before the occurrence of significant immunodeficiency appear to be beneficial in lowering the risk of AANCCs and consequently increasing life expectancy of HIV-infected individuals.

Studies have shown reductions in the life expectancy gap between HIV-infected and uninfected individuals in recent years [10–12]. Increasing CD4 counts in treated HIV-infected individuals may contribute to declining mortality rates. Current CD4 counts strongly predict the incidence of non-AIDS events and mortality in treated HIV infection [13]. Results from a European cohort collaboration demonstrated similar mortality rates between HIV-infected individuals with treatment-induced restoration of the immune system (CD4 counts above 500 cells/mm$^3$) and the general population. Mortality in individuals with a prior AIDS diagnosis remained higher, even after attaining a CD4 count above 500 cells/mm$^3$ [14]. The duration and severity of immunodeficiency before cART initiation may also affect long term mortality risk; a North-American study reported a large difference in estimated life expectancy between patients initiating cART at CD4 counts above compared to below 350 cells/mm$^3$. The same study showed that the life expectancy of men who have sex with men (MSM) newly initiating cART at CD4 counts above 350 cells/mm$^3$ approached that of the general population [11].

The Strategic Timing of Antiretroviral Treatment (START) trial demonstrated that even relatively mild immunodeficiency may increase all-cause mortality and risk for serious non-lethal clinical events. Participants initiating cART with CD4 counts above 500 cells/
mm\(^3\) showed decreased risk for AIDS, all-cause mortality, and serious non-AIDS events during the 3 year follow-up [15]. Continued follow-up of START-trial participants [15] and observational cohort studies are necessary to demonstrate long-term beneficial effects of early cART initiation on various non-AIDS comorbidities.

Behavioural and demographic factors may largely explain the remaining gap in life expectancy between HIV-infected individuals and the general population, particularly in patients who have been diagnosed and treated early [10,16]. Mortality rates in injecting drug users (IDU) remain elevated compared to the general population, both in European and North-American cohorts independent of current CD4 counts [11,14]. This may be attributed to non-natural causes of death, behavioural and socio-demographic factors, and HCV coinfection [11,12,17].

Within the AGE\(_i\)IV Cohort, those individuals with historic and current immunodeficiency exhibited increased risk for AANCC and organ dysfunction. Patients with longer exposure to more advanced immunodeficiency were at increased risk for low BMD in the total hip (chapter two), prefrailty and frailty (chapter six), faster progression of renal function decline (chapter three), and greater aortic stiffness (chapter four). Furthermore, individuals with prior as well as current immunodeficiency demonstrated increased liver fibrosis (chapter five).

Policies implemented following the publication of the 90-90-90 treatment target by the Joint United Nations Programme on HIV/AIDS (UNAIDS) in 2014 aim to reduce the number of infections and decrease the incidence of AIDS [18]. Such policies may also lead to a significant decrease in age-related comorbidity and mortality in the HIV-infected population as a whole due to an increase in the average CD4 count at cART initiation. However, despite these efforts late diagnosis continues to be a global problem; even in the Netherlands, where in 2015 52% of newly diagnosed HIV-infected individuals presented with a CD4 count below 350 or AIDS and 29% with a CD4 count below 200 or AIDS [7].

CAUSAL FACTORS AND PATHOPHYSIOLOGICAL MECHANISMS

The pathophysiology of age-related comorbidity in HIV-infected individuals is multifactorial; immune activation, chronic-low level inflammation, insulin resistance, dyslipidaemia, body composition changes, weight loss, sarcopenia, and (visceral) obesity may all be involved. In addition, behavioural factors may have either a direct or indirect effect on the onset of comorbidity.
Inflammation and immune activation

Persistent low-level HIV replication, chronic coinfections, and microbial translocation are all thought to contribute to the observed chronic low-level inflammatory state in treated HIV infection [19]. Within the AGE_{n}IV Cohort Study, information on markers of inflammation [high-sensitivity C-reactive protein (hsCRP)], coagulation (D-dimer), and monocyte/macrophage activation [soluble (s)CD14 and sCD163] was available. This panel of biomarkers was selected to cover a reasonable range of inflammatory and immune activation processes. The Strategies for Management of Antiretroviral Therapy (SMART) study showed that hsCRP and D-dimer remain elevated in treated HIV infection [20], and are associated with CVD and all-cause mortality [21,22]. Soluble CD14 is a soluble lipopolysaccharide (LPS) receptor, shed from activated monocytes [23]. Higher levels of sCD14 in treated HIV infection were shown to be associated with all-cause mortality [24], and subclinical vascular disease [25]. CD163 is exclusively expressed by circulating and tissue residing monocytes and macrophages [26]. Plasma sCD163 levels are increased in conditions with increased monocyte/macrophage activation or proliferation [26]; higher levels are associated with the presence of atherosclerotic plaques [27] and all-cause mortality [28] in HIV-infected individuals. Higher sCD163 levels in patients (co)infected with chronic viral hepatitis possibly originate from liver residing macrophages or Kupffer cells and are associated with liver fibrosis [29,30]. Plasma levels of various markers of inflammation and immune activation have been associated with low BMD [31], renal disease [32], cancer [33], functional impairment, frailty [34–36], and neurocognitive dysfunction [37] in HIV-infected individuals.

Findings from the AGE_{n}IV Cohort corroborate results published in previous studies showing higher levels of hsCRP, sCD14 and sCD163 in HIV-infected compared to uninfected study participants. An interesting exception was D-dimer, which in the AGE_{n}IV Cohort Study was not higher in HIV-infected individuals. Previous studies reported higher D-dimer levels in treated HIV infection [20], but levels have been shown to decrease after cART initiation [38] and may potentially return to normal levels during long-term treatment. The Veterans Aging Cohort Study has reported similar D-dimer levels in treated HIV-infected individuals with a suppressed HIV viral load when compared to uninfected controls [39].

To examine the potential contribution of inflammatory processes, we explored associations between these markers and several clinical conditions. The results of our aortic stiffness analysis suggested that ongoing inflammatory processes may contribute to aortic stiffening in both HIV-infected and uninfected individuals as indicated by elevated hsCRP levels. Adjusting for hsCRP levels attenuated the association between prior immunodeficiency and greater aortic stiffness in multivariable regression analysis,
suggesting a mediating effect of higher hsCRP levels (chapter four). Both sCD14 and sCD163 have previously been associated with atherosclerotic disease in HIV-infected individuals, suggesting a role for monocyte activation in the pathophysiology thereof [25,27]. However, these markers were not associated with greater aortic stiffness in our cohort. Aortic stiffness may be increased by atherosclerotic plaque formation through deposition of collagen and calcification of the vessel wall, but may also develop independently from atherosclerotic disease [40,41]. As such, biomarkers indicative of aortic stiffness may not necessarily be related to atherosclerosis.

Higher sCD163 levels were associated with higher FIB-4 scores, indicative of more liver fibrosis in HIV-infected individuals without concurrent HBV or HCV infection. Immune phenotyping was performed in a subset of the cohort including HIV-uninfected individuals and HIV-infected individuals with suppressed HIV viraemia. Higher levels of activated T-cells and regulatory T-cells were associated with higher FIB-4 scores in HIV-infected individuals only (chapter five). These markers of innate and adaptive immune activation may be elevated as a result of enhanced microbial translocation [23,42]. Previous studies have suggested that microbial translocation may contribute to an increased burden of liver fibrosis in patients coinfected with HIV and chronic viral hepatitis [29,43,44]. We hypothesized that the observed associations between markers of immune activation and higher FIB-4 scores may indicate a role for microbial translocation in the pathophysiology of liver fibrosis in HIV-infected individuals without concurrent HBV or HCV infection (chapter five).

The panel of inflammatory markers was measured once, at the time of study enrolment. As such, inflammatory processes which occurred in the past and may have contributed to the pathophysiology of AANCCs, would not be captured. We did not observe associations between markers of currently ongoing inflammation or immune activation and lower BMD or frailty (chapters two and six). Other pathophysiological mechanisms may have been more important contributors to these conditions.

**Wasting and obesity**

Body composition changes are frequently observed in HIV-infected individuals for various reasons. A low body mass index (BMI) or body weight may be a sign of a lean build, but may also be a persisting effect of historic weight loss, wasting, or sarcopenia. Unsuppressed HIV viral replication as well as exposure to certain antiretroviral drugs may influence lipid metabolism and fat distribution, including peripheral lipoatrophy and central lipohypertrophy [45]. Changes in diet and physical activity, among other behavioural factors, affect body composition in HIV-infected and uninfected individuals alike [46].
Weight loss during HIV infection, as a marker of wasting syndrome [47], is associated with increased risk for HIV-related mortality [48], but also likely leads to long-term adverse outcomes. Erlandson et al. studied the long-term consequences of HIV-associated wasting in the Multicenter AIDS Cohort Study (MACS). Individuals who survived for at least two years following wasting syndrome were at increased risk for lower physical health-related quality of life (HRQL) and lower grip strength [49]. Similarly, in the general population a low body weight at age 21 or weight loss any time after the age of 21 years is associated with increased risk for mortality at older age [50]. Having a low body weight is associated with increased risk for frailty in the general population as well [51].

In our cohort, HIV-infected individuals had a lower average body weight and BMI than HIV-uninfected individuals. We found a historic BMI below 20 kg/m², which may be an indication of HIV-related weight loss or wasting, to be associated with increased likelihood for prefrailty and frailty (chapter six). A BMI below 20 kg/m² at the time of study entry, potentially a persisting effect of historic weight loss, was also associated with a greater likelihood of prefrailty and frailty in HIV-infected individuals. This was not the case in HIV-uninfected individuals where the same BMI is otherwise explained and may more often be a sign of a healthy lean build (chapter six). Weight loss in the context of advanced HIV disease involves loss of both fat and lean mass, importantly including loss of muscle mass [48]. Loss of muscle mass, or sarcopenia, may contribute to the frailty phenotype [52].

A low body weight is also associated with lower BMD in HIV-infected patients and is thought to be a mediating factor in the relationship between HIV and low BMD [53]. We found that a lower nadir body weight in HIV-infected individuals was strongly associated with a lower BMD, even more so than historic immunodeficiency (chapter two). In the general population a lower body weight and body weight loss are risk factors for fractures. A possible explanation is that total body weight is thought to physiologically increase BMD through mechanical strain [54]. Whether lean or fat mass is more important is debated; a recent meta-analysis showed stronger associations between lean mass and BMD in the general population [55]. One study including HIV-infected, predominantly African-American women showed that both a greater lean and trunk fat mass were associated with higher BMD [56]. Another study, including HIV-infected individuals initiating cART, showed a positive association between increases in lean, but not fat mass, and increases in BMD [57].

Both very low and very high BMI have been associated with an increased risk of frailty in the general elderly population [51]. In our cohort obesity was relatively uncommon in both HIV-infected and HIV-uninfected individuals. High waist-to-hip ratio and high
waist circumference, as markers of abdominal obesity, however were observed more frequently, especially in HIV-infected individuals. In HIV-infected individuals a lower hip circumference, which may be an expression of lipoatrophy also contributed to the higher average waist-to-hip ratio. In the general population, abdominal obesity is a stronger risk factor for mortality than obesity defined by BMI, even for those with normal BMI [58]. Similarly, abdominal obesity is a risk factor for frailty [59] regardless of body weight and even in underweight individuals [51]. A higher BMI, waist circumference and increased total and trunk fat mass were all associated with frailty in a small study of predominantly overweight and obese HIV-infected individuals [60]. In our larger cohort, a higher waist-to-hip ratio was associated with a higher likelihood of (pre)frailty in both HIV-infected and uninfected individuals (chapter six).

Recent studies have reported increases in the prevalence of obesity in HIV-infected populations [46,61,62], particularly in North America [46]. The increasing prevalence of obesity in HIV-infected individuals likely reflects similar trends in the general population. Average BMI values at cART initiation are increasing, which may partly be the result of earlier initiation of cART during less advanced disease stages [46]. Exposure to modern antiretroviral drugs, in particular protease inhibitors (PI), may also contribute to adverse changes in body composition. Initiation of a PI-containing regimen was associated with larger gains in body weight and visceral adipose tissue when compared to a regimen containing the non-nucleoside reverse transcriptase inhibitor efavirenz [61,63]. Conversely, a recent study found no differences in lean or fat mass gain between regimens containing the PI ritonavir-boosted atazanavir or darunavir vs. the integrase inhibitor raltegravir [64]. We found PI exposure to be associated with (pre)frailty. This association was attenuated by adjusting for waist-to-hip ratio and BMI (chapter six), suggesting that PI exposure may contribute to the onset of frailty mediated by changes in body composition.

Cigarette smoking

Cigarette smoking is more common in HIV-infected populations than in the general population [65,66]. As such, cigarette smoking is a particularly important risk factor for many AANCCs observed in HIV-infected populations. For patients on long-term cART, cigarette smoking may have a greater impact on comorbidity and mortality than HIV-related factors [67,68].

HIV-infected individuals in the AGEhIV cohort were more often cigarette smokers compared with uninfected controls. Cigarette smoking was independently associated with lower BMD (chapter two), higher prevalence and progression of albuminuria (chapter
three), higher aortic stiffness (chapter four), and greater likelihood of (pre)frailty (chapter six).

The detrimental effects of cigarette smoking may be more severe in HIV-infected individuals than in HIV-uninfected smokers. Several studies found stronger relations between smoking and adverse outcomes in HIV-infected compared to uninfected individuals [69,70]. Both smoking and HIV infection may have proinflammatory effects. Synergistic effects of cigarette smoking and HIV infection on T-cell activation were observed in a recent study of 40 HIV-infected participants and 40 HIV-uninfected controls [71]. A comparable interaction between smoking and HIV infection was not observed in the larger AGEhIV Cohort when assessing soluble markers of inflammation, immune activation, and coagulation. Cigarette smoking was significantly associated with all four studied markers in our study, but the magnitude of the association was not significantly different in HIV-infected individuals compared with uninfected controls (chapter seven). Likewise, cigarette smoking has been associated with markers of inflammation in HIV-infected individuals in other studies [72,73], suggesting an additive but not synergistic contribution of cigarette smoking to the inflammatory state in HIV-infected individuals.

Potential synergistic effects of HIV infection and cigarette smoking may also be due to socio-demographic and behavioural factors associated with cigarette smoking. Cigarette smokers in the general population are more likely to be of a lower socio-economic status [74], and HIV-infected cigarette smokers are more likely to abuse other substances, including alcohol, and to suffer from depression compared to individuals who have never smoked [75]. Several studies reported that cigarette smoking was associated with an increased risk for nonadherence or imperfect adherence to cART [76–78], as well as an increased likelihood of having a detectable HIV viral load [75,79].

In light of the numerous independent adverse effects of cigarette smoking, interventions directed at smoking cessation are extremely important in HIV-infected individuals. Few studies have specifically addressed such interventions in this population [80,81]. HIV-infected individuals may be less likely to successfully quit smoking cigarettes [79,82]. This may in part be due to emotional problems such as depression, common in HIV-infected populations, which may limit the success of efforts to quit smoking [81]. Findings from a small pilot study suggest that smoking cessation efforts might be more successful when simultaneously targeting depression [83]. Some HIV-infected individuals may believe that they will not live long enough to experience the negative effects of cigarette smoking, which may negatively affect the motivation to quit smoking [81]. A small study investigating beliefs and behaviours in HIV-infected cigarette smokers however did not find such beliefs to be prevalent [84].
THE IMPORTANCE OF A COMPARABLE CONTROL GROUP

The AGEₙIV Cohort is one of the largest and most well defined cohort studies investigating ageing of in HIV-infected individuals. The inclusion of a comparable HIV-uninfected control group is an invaluable asset of the cohort.

Throughout the enrolment period of the AGEₙIV Cohort Study, every effort was taken to ensure a high degree of comparability in terms of socio-demographic and behavioural factors. The HIV-epidemic in the Netherlands is predominantly MSM driven; a large majority of both HIV-infected and uninfected participants are MSM. Both groups were likely to have exhibited sexual risk behaviour leading to the acquisition of HIV or motivating them to attend a sexual health clinic (in the case of uninfected controls). Similarities in lifestyle and sexual risk behaviour between the HIV-infected and uninfected cohorts have likely diminished the degree of unmeasured confounding in our studies. These same behavioural factors, inherent to the population under study, may have increased the risk of AANCCs in both HIV-infected and uninfected study participants relative to the general population.

For example, we observed a low BMD in younger HIV-infected as well as uninfected MSM participants compared to older MSM and heterosexual males and females (chapter two). Other studies similarly showed a strikingly low BMD among HIV-uninfected young MSM and young MSM with primary HIV infection [85–87]. BMD results are reported as z-scores, allowing direct comparison with a reference population of the same age and sex.

Along similar lines, an analysis of T-cell activation markers, measured by immune phenotyping, was carried out within a subset of the AGEₙIV Cohort’s HIV-infected participants, all with a suppressed HIV viral load, and uninfected participants. Although HIV-infected individuals showed higher levels of T-cell activation, differences in markers of immunological ageing between the groups were remarkably small. A second comparison was performed between participants of the AGEₙIV Cohort and healthy blood bank donors. Markers of T-cell activation, exhaustion, and senescence in both HIV-infected and HIV-uninfected participants were significantly higher compared with those in the blood bank donors [88]. In some aspects, the uninfected controls included in our study, predominantly MSM, may have a similarly affected immune system compared with the HIV-infected patients.

Factors underlying the observed differences between AGEₙIV participants and blood bank donors may also increase the risk for comorbidities in both our HIV-infected and HIV-uninfected cohort participants alike. Infections other than HIV may contribute to
immune activation and an inflammatory state in our predominantly MSM study population. The prevalence of CMV coinfection is very high in HIV-infected individuals [89] but also in the HIV-uninfected MSM population as has been shown in the AGE_HIV Cohort [90]. Rates of sexually transmitted infections (STIs) among MSM have been increasing in recent years [91–93] and the availability of pre-exposure prophylaxis may potentially lead to further increases in the incidence of STIs among MSM due to risk compensation behaviours [94].

Behavioural factors more prevalent in MSM, in particular cigarette smoking, may also contribute to comorbidity and adversely affect the immune system. Smoking is more prevalent in gay- and bisexual women as well as MSM compared with the general population [95–97]. A recent study performed in the United States found that although the prevalence of cigarette smoking in MSM participating in the MACS cohort study was declining, it remained high. No difference in cigarette smoking prevalence was observed between HIV-infected and uninfected MSM enrolling in this cohort since the early 2000s [98].

Sexual orientation and related behaviours may also have an effect on the composition of the gut microbiome and thereby the immune system and overall health [99]. Several comparative studies have shown differences in the richness and composition of the gut microbiome in HIV-infected compared to uninfected individuals [100], while other studies reported an association between the gut microbiome composition and higher levels of inflammation [101]. Recently, findings were published demonstrating significantly richer and more diverse faecal microbiota in MSM compared to non-MSM, regardless of HIV-status, in two geographically unrelated European cohorts [102].

**AGEING OF THE HIV-INFECTED POPULATION**

Relatively small differences between HIV-infected and uninfected individuals observed in our cohort suggest that well suppressed HIV infection may have a less significant effect on the prevalence of certain age-related conditions than previously appreciated. Nonetheless, the burden of both comorbidity and frailty in HIV-infected AGE_HIV Cohort participants is higher than in uninfected participants (this thesis and [9,103]). Likewise, HIV-infected participants are characterized by a higher burden of comorbidities than the general population [1]. The higher prevalence of traditional risk factors in HIV-infected populations likely contributes to the observed excess comorbidity.
It is still uncertain whether HIV infection in addition may directly affect the ageing process [104]. Although a borderline significant interaction was observed between age and HIV infection when examining the burden of comorbidity within the AGE$_{n}$IV Cohort [9], we did not find such an interaction when investigating any of the conditions individually (this thesis). Furthermore, two recently published studies found no difference in the mean age at which several AANCC occurred in HIV-infected individuals compared to uninfected controls or the general population. Such findings do not support the hypothesis that HIV infection may lead to accelerated ageing [1,2]. Whether or not HIV itself directly affects the ageing process, and regardless of what the most important determinants of comorbidity in HIV-infected individuals are, the HIV-infected population as a whole nonetheless will continue to age, and thereby exhibit an increased burden of comorbidity [105].

Concurrent with the growing rate of multimorbidity, HIV-infected individuals will be at increased risk for polypharmacy and thus for experiencing suboptimal therapy or side-effects because of drug-drug interactions [106]. Furthermore, several studies have shown that HIV-infected individuals are at increased risk for a lower HRQL compared to HIV-uninfected individuals [107,108]. Within the AGE$_{n}$IV Cohort study we found a lower HRQL and more depression in HIV-infected compared to uninfected individuals. These differences however could not be completely explained by the higher burden of comorbidity in HIV-infected cohort participants [109].

Managing the burden of chronic disease, as well as safeguarding the quality of life in an ageing HIV-infected population will pose substantial challenges to individual caregivers and place considerable demands on the health care system [4,110]. Reduced physical function is associated with lower HRQL, both within the AGE$_{n}$IV Cohort and another study among HIV-infected individuals [109,111]. One way to potentially improve quality of life may be through interventions directed at improving physical function [111].

The frailty phenotype has been proposed as a tool to identify the most vulnerable ageing individuals [112]. However, an ongoing discussion casts doubt onto whether the frailty phenotype is the most appropriate marker of vulnerability in HIV-infected individuals. Hand grip strength, included in the frailty phenotype, has been proposed as a method for risk stratifying. Although not a marker of frailty per se, hand grip strength has been associated with all-cause mortality in the general population [113]. Another operationalization of the frailty concept is the frailty index, consisting of a list of deficits encompassing illnesses, symptoms, signs, laboratory variables, and disabilities [114]. The frailty index may be more sensitive to changes in frailty severity [115]. In the context of the AGE$_{n}$IV Cohort, we demonstrated that the frailty phenotype was predictive of
mortality, falls, and hospital admissions during a 2 year follow-up period in HIV-infected and uninfected participants [116].

FUTURE DIRECTIONS

At the time of publication of this thesis we have completed extensive cross-sectional analyses making use of baseline data collected within the AGEhIV Cohort Study. Future prospects include longitudinal analyses following the clinical outcomes of our cohort participants. These will be important to overcome some noted limitations inherent to cross-sectional analyses. They may be less affected by reverse causality and will provide more certainty in assessing pathophysiological mechanisms underlying observed associations.

Markers of past HIV-related disease, including experienced immunodeficiency and low body weight suggestive of historic weight loss, were associated with age-related conditions studied throughout this thesis. Due to the cross-sectional character of the performed analyses, we were unable to assess whether these associations were the result of historical processes, or may represent ongoing accelerated disease progression. Through longitudinal analyses, we will be able to distinguish this.

Several of the studies performed in the context of this thesis used markers of pre-clinical or clinical disease as outcome measures. For example, reduced BMD as a predictor for future fracture risk, aortic stiffness measured by PWV as a marker for preclinical CVD, and the frailty phenotype as a marker indicating vulnerability for future adverse events. Prospective longitudinal clinical-endpoint studies will be better able than cross-sectional studies to establish a causative link between these various bio-markers and clinical outcome and whether this relationship differs according to HIV status. Follow-up of the HIV-infected and uninfected younger MSM may elucidate as to whether the observed low BMD will translate into an increased risk for fragility fractures as these individuals age. Likewise, the AGEhIV Cohort will be able to address the question of whether the frailty phenotype is a superior indicator of vulnerability for future adverse events compared to the frailty index or hand grip strength alone.

The population of the AGEhIV Cohort Study is predominantly middle-aged; only a small proportion of patients are currently aged over 70. This reflects the general HIV-infected population in Western countries, which is only starting to become older. With advancing age, the differences in expression of comorbidity may become more pronounced allow-
ing for a more in-depth investigation of the pathogenesis of AANCC in the HIV-infected population and testing of the hypotheses about accentuated or accelerated ageing.

Changing guidelines and ongoing efforts to diagnose and treat HIV infection early [18,117] will hopefully lead to HIV-infected individuals initiating cART at increasingly early disease stages, with increasingly preserved immunological function. Such individuals will be different from the AGEhIV participants in that they have not been exposed to severe immune deficiency and will not be treated with the older more toxic cART regimens. Newer antiretroviral drugs may have much better short- and medium-term tolerability than first and second generation antiretroviral agents, nonetheless we need to continue monitoring for potential side-effects resulting from extended exposure to these newer agents.

CONCLUSIONS

Through the inclusion of an appropriate and comparable control group we demonstrated that the association between treated HIV and age-related conditions may not be as strong as was previously thought. Instead, the observed high rates of comorbidities in the HIV-infected population compared to the general population appears to be driven to a large extent by traditional and other HIV-unrelated factors. The risk appears to be unevenly distributed within the HIV-infected population. Those who previously experienced advanced HIV disease, and were exposed to more toxic old-fashioned antiretroviral drugs may particularly be at risk. HIV-uninfected individuals attending a sexual health clinic, specifically MSM, may also be at increased risk for some inflammation- and immune-activation associated disorders. Ongoing longitudinal studies will provide further insight into the pathophysiology of AANCC in the ageing HIV-infected population.

REFERENCES


