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CVD risk in an aging HIV population – not just a question of biology

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Abstract

Purpose of review—The objective of this review is to 1) appraise recently published literature that describes the relationship between HIV, biologic and environmental risk factors, and CVD risk with particular emphasis on the aging HIV population and 2) to demonstrate that these biologic and environmental factors may interact to increase the risk of CVD in the HIV population.

Recent findings—The mechanisms linking HIV and CVD are multi-factorial and encompass biological and "environmental" modalities including multi-morbid conditions that co-occur with HIV, immunologic alterations associated with HIV, polypharmacy (which affects adherence and increases likelihood of adverse drug-drug interactions) and healthcare disparities in CVD risk reduction by HIV status.

Summary—Data regarding optimal treatment strategies that balance immunological restoration and CVD risk reduction are needed.

Keywords

Cardiovascular disease; HIV; multimorbidity; polypharmacy; clinical guidelines; healthcare disparities

Introduction

With the success of antiretroviral therapy (ART), HIV infection has transitioned from a rapid death sentence to a more complex chronic disease with increasing numbers of people worldwide living longer (Figure 1) without AIDS.(1) The price of this success is that people aging with HIV are at risk for similar diseases of aging as the general population.(2) HIV infection is associated with an increased risk of multiple cardiovascular diseases (CVDs) including acute myocardial infarction, coronary heart disease (CHD), ischemic stroke, and heart failure. While ART, Framingham risk factors and non-Framingham risk factors (e.g.,

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There are no conflicts of interest.

renal disease, anemia, and hepatitis C co infection) are all associated with CVD risk among HIV+ people, these risk factors do not explain the excess risk of CVD in this population compared to uninfected people. To explain this excess risk, investigators have turned their attention to deepening our understanding of biologic (e.g. immuno-virological, multimorbidity) and environmental (e.g. polypharmacy, healthcare disparities) risk factors (Figure 2). The objective of this review is to 1) appraise recently published literature that describes the relationship between HIV, biologic and environmental risk factors, and CVD risk with particular emphasis on the aging HIV population and 2) to demonstrate that these biologic and environmental factors may interact to increase the risk of CVD in the HIV population.

HIV is associated with CVD

CVD accounts for increasing proportions of HIV mortality as AIDS mortality declines and HIV populations age.(3–7) Multiple studies show that HIV is an independent risk factor for CVD.(8*, 9) Prior reviews have discussed findings from large prospective, longitudinal studies.(9, 10) Briefly, these earlier studies show increased MI and CHD incidence among HIV infected (HIV+) compared to uninfected comparators using large administrative and clinical databases(11, 12) or population-based comparators.(13) Similar studies have also demonstrated an increased risk of heart failure,(14) stroke(15) and sudden cardiac death(16) among HIV+ people. Results from the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study support a role for antiretroviral therapy in CVD risk(17, 18) although the Strategies for the Management of Antiretroviral Therapy (SMART) study(19) clearly shows the benefits of ART outweigh this potential risk. For this review we will focus on more recent data.

Is HIV an independent predictor of CVD and atherosclerosis?

Two recent large cohort studies with demographically and behaviorally similar HIV+ and uninfected groups found strong, consistent associations of HIV with acute myocardial infarction (AMI). Silverberg et al matched 230,069 uninfected Kaiser Permanente members to 22,081 HIV+ patients identified from HIV registries.(20**) They reported a 44% increased risk of AMI among HIV+ people compared to controls independently of age, race/ethnicity, calendar era, socioeconomic status, smoking, overweight, substance abuse, diabetes, hypertension and lipid lowering therapy. Similar results were reported from the Veterans Aging Cohort Study Virtual Cohort (VACS VC), a cohort of HIV+ Veterans matched on age, race-ethnicity, sex, and clinical site to two uninfected Veterans also in clinical care.(8, 21) Adjusting for Framingham risk factors, comorbid diseases, and substance use, HIV+ Veterans were 48% more likely to experience an AMI compared to their uninfected counterparts. This association persisted after adjusting for the competing risk of death and among Veterans maintaining viral suppression (HIV-1 RNA<500 cpm) over time.

Further evidence comes from subclinical CVD studies. Some but not all of these studies – often using coronary artery calcium (CAC) or carotid intima-media thickness (cIMT) as

surrogate measures of atherosclerosis – report an association between HIV and the occurrence and/or progression of subclinical CVD.

A 2009 meta-analysis from 13 studies reported similar CAC but increased cIMT (weighted mean difference was +0.04 mm 95% CI 0.02–0.06 mm, p<0.001) in HIV+ compared to uninfected participants.(22) There was significant heterogeneity among the studies and the authors concluded that HIV was not likely to be a strong independent risk factor for atherosclerosis. In more recent work, results are mixed with associations reported between HIV status and carotid lesions,(23) non-calcified plaque, (24) cIMT and cIMT progression(25) in some but not all (26–29) studies. Interestingly, Hsue et al showed increased cIMT and cIMT progression among HIV elite controllers (untreated with HIV-1 RNA <50cpm), suggesting that HIV factors separate from ART and HIV-1 RNA contribute to cIMT and its progression.(25) HIV+ children (97% vertically infected, mean age 15 years) had higher cIMT compared to a group of uninfected children of similar age, sex, ethnicity and BMI distribution.(30) Among non-smokers, Desvarieux et al reported higher cIMT among treated HIV+ compared to HIV- but similar levels among untreated HIV+ compared to the same HIV- referent group.(31) These latter two studies suggest a role of HIV infection in atherosclerosis over and above that of comorbid diseases (e.g. smoking) or pro-atherosclerotic conditions not yet present in children.

In summary, HIV infection is associated with an increased risk of CVD including AMI, CHD, heart failure, stroke and sudden cardiac death. The effect of HIV on subclinical CVD may be more dependent on, age, comorbid disease, gender, duration of infection, and modified by study design (biomarker of atherosclerosis, CAC/cIMT measurement site, subject characteristics).

Biologic Mechanisms of CVD in HIV

The studies we discuss in this section are recent studies that investigate potential mechanisms summarized in Figure 2.

Immuno-virology

Immune alteration is a shared feature of aging, CVD and HIV. Immune function declines with age and HIV infection,(32, 33) immune alterations are associated with atherosclerosis, (34, 35) and age and HIV infection are associated with CVD. Among healthy uninfected people, immune cell subsets (e.g. intermediate monocytes, CD4+ T-helper 1 cells), inflammation, T-cell activation and evidence of immunosenescence (e.g. low naïve to memory T-cell ratio) are associated with atherosclerosis.(36–38) HIV infection may alter the balance of immune cell subsets in a pro-inflammatory and pro-atherosclerotic manner. The association between HIV, immune function (including immune activation and immune cell depletion) and CVD risk was recently reviewed by Hsue et al(39**) and several important questions remain including:

1. Do specific immune cell subsets play a role in the pathogenesis of CVD in HIV?
2. Does activation of the innate and adaptive immune system mediate the effects of HIV, ART, and comorbid disease on incident CVD?

3. What is the role of T-cell senescence in aging related diseases like CVD? (see future directions)

More recent work addresses some of these knowledge gaps. Among HIV+ people, higher frequencies of $CD16^+$ monocytes (intermediate and nonclassic; pro-atherosclerotic(40)) were independently associated with CAC progression. Activated $CD4^+$ and $CD8^+$ T-cell phenotypes were not associated with CAC progression.(41*) Funderburg et al showed that uninfected participants with acute coronary syndrome (ACS) and HIV+ patients with elevated HIV-1 RNA levels (but without ACS) had similar proportions of $CD16^+$ monocytes. Both groups had higher proportions of $CD16^+$ monocytes compared to uninfected participants with stable coronary artery disease (CAD).(42**) T-cell activation markers ($HLA\text{-}DR^+$ and $CD38^+$ CD8 cells) were lower in uninfected ACS patients compared to HIV patients with elevated HIV-1 RNA levels suggesting different sources of activation despite the similar resultant monocyte phenotype. These studies suggest a role for immune cell subsets in CVD risk in the setting of HIV infection.

Similarly, others have reported increased arterial inflammation (measured by sCD163 (43)) in HIV+ versus controls with prior atherothrombotic events or atherosclerosis. (44**) Among HIV+ elite controllers (ART naïve, HIV-1 RNA<48cpm), Pereyra et al reported significantly increased coronary plaque (i.e. stenosis >50%), sCD163, high sensitivity interleukin 6 (biomarker of inflammation), soluble CD14 (biomarker of monocyte activation), CXCL10 (promotes monocyte migration) and $CD38^+HLA\text{-}DR^+$ CD4 cells (marker of lymphocyte activation) compared to uninfected controls.(45**) Differential associations by HIV status between markers of monocyte migration/activation and cIMT have been reported (with minimal covariate adjustment) though interactions were not tested. (29*, 46*) These studies suggest a relationship between HIV and atherosclerosis, independent of CVD risk factors and ART. Whether inflammation and immune activation are causes or effects of this association remains unclear. A limitation of these cross-sectional analyses is the inflammatory nature of ACS/CAD events such that having the event alters immune cell subset distribution making causal inference challenging.

Epidemiological associations between measures of adaptive immunity (e.g. low $CD4^+$ T-cell count) with CVD events are inconsistent.(8, 47**, 48, 49) Among HIV+ people, activated T cells (CD38+HLA-DR+) and senescent T cells (CD28-CD57+) are significantly associated with subclinical carotid atherosclerosis and carotid artery stiffness.(50–53)

In summary, recent data support at least a cross-sectional association of monocyte subset/activation and T-cell activation and CVD in HIV. Whether immune alterations mediate the relationship between HIV and CVD is still unclear.

Antiretroviral therapy (ART)

The SMART study makes it clear that the benefits of ART outweigh the cost of some regimens increasing the risk of CVD events. Additionally, ART treatment initiation studies show improvements in CVD risk factors(54–57) that may be regimen dependent.(58, 59) More cardio-protective or at least cardio-neutral ART regimens are available and clinicians should note regimens to avoid in patients at high risk for CVD.(59) Clinical management

should also anticipate excess weight gain in certain subgroups initiating ART.(60) Newer or non-protease inhibitor based ART regimens have improved metabolic side effect profiles(61, 62) though some debate about PI-regimens remains.(63) Lastly, ART clinical trials rarely include older patients – who often have significant co-morbidity and reduced immune response (64) – who nonetheless currently receive these drugs. Results from ongoing studies are keenly awaited (Table 1).

Treated and suppressed HIV+ people still have excess risk of CVD compared with uninfected controls.(8) This excess risk could be driven in part by high viremia exposure prior to ART initiation, ART, and/or residual low-level viral replication in ART suppressed patients. Current guidelines recommend ART initiation at HIV diagnosis regardless of CD4 count, which deals with the first source of excess risk.(59) Residual viremia is potentially important because in time updated analyses, HIV+ Veterans who maintained a viral load <500 copies per ml over time had a higher risk for acute myocardial infarction compared to uninfected Veterans after adjusting for multiple confounders.(8) HIV seroconversion and ART initiation studies suggest that some worsening in CVD risk factors that occurs after HIV infection (e.g. decreased HDL) do not improve to pre-HIV levels with ART initiation(65–67), potentially contributing to excess CVD risk. Likewise, cross-sectional studies suggest increased prevalence of coronary plaque, sCD163 and sCD14 among treated, controlled HIV+ people versus uninfected controls.(45)

A recent study described new cycles of HIV replication occurring with only modest ART non-adherence. Importantly, this residual replication is not detected as virological rebound on commercial HIV RNA assays.(68) As we improve our ability to measure residual viremia, (69) it would be useful to quantify the extent to which residual replication contributes to inflammation and how this relates to CVD in aging patients.

Comorbidity

Framingham CVD risk factors accumulate with age regardless of HIV status. These risk factors remain associated with CVD events in HIV+ populations. Whether the interaction of HIV status and CVD risk factors contributes to excess CVD risk is unclear partly because there are few studies that have large numbers of HIV+ and uninfected people with incident CVD events and detailed information on comorbid diseases. In a Veteran population, there was no significant interaction of elevated blood pressure with HIV status on the risk of acute myocardial infarction.(70*) Althoff et al reported no difference by HIV status in adjusted mean age at incident myocardial infarction (55.3 years for both groups) although HIV+ people had a greater risk of myocardial infarction.(71) In contrast, Fitch et al reported an interaction between age and HIV, and age, HIV and smoking on cIMT prevalence whereby cIMT increased more with age among HIV+ versus uninfected people.(24) Herrin et al described an interaction between HIV status and weight gain post-ART initiation on diabetes incidence. Although HIV+ people had lower risk of diabetes, the risk of diabetes associated with weight gain was 60% greater among infected versus uninfected people.(72)

Understanding whether comorbid CVD risk factors occur earlier and/or with increased severity in HIV+ compared to uninfected people will improve the effectiveness of CVD risk reduction in this group. HIV+ Veterans were more likely than uninfected controls to have

renal or liver disease, substance abuse disorders and multiple simultaneous comorbidities (multimorbidity) and less likely to have hypertension, diabetes, vascular disease or psychiatric disorders. (73) Older HIV+ Veterans were more likely than older uninfected Veterans to have, liver disease, substance abuse, and multimorbidity.(73)

Additional comorbidities that are less prevalent in the general population may also contribute excess CVD risk in HIV+ cohorts. Cardiovascular implications of comorbid infections have recently been investigated.(74) Earlier work suggested that HCV mono-infection is associated with increased risk of CVD(75, 76) though the data on HCV co-infection with HIV are somewhat conflicting.(77, 78) Data from a nested case-control study of the Multicenter AIDS Cohort Study found an association between increased coronary artery calcium herpes simplex virus 2 (HSV-2) co-infection with HIV, and number of herpesviruses among HIV+ men co-infected with compared to HIV mono-infected men.(79) Parrinello et al found no association between CMV antibody titres and cIMT or carotid artery lesions among HIV+ women, though they did find an independent association between CMV antibody titres and lower carotid artery distensibility/elasticity regardless of treatment/viremia status.(80*) CMV antibodies were not associated with any vascular parameters studied among the much smaller cohort of HIV uninfected controls though no statistical interaction was found between HIV status and CMV on any of the vascular outcomes studied. Earlier work found increased CMV specific T-cell responses to be associated with cIMT.(81)

In summary, there is limited evidence that comorbid conditions other than older age modify the association between HIV and CVD events or atherosclerosis. HIV specific CVD risk quantification tools have been investigated though external validation in diverse HIV populations is still needed.(82–87) Subsequent iterations should assess whether additional HIV specific comorbid CVD risk factors and interactions between HIV status and comorbid disease improve risk assessment.

Environmental Mechanisms of CVD in HIV

Understanding and addressing non-biological mechanisms of CVD in HIV may improve the success and sustainability of interventions focused on biological mechanisms, particularly in older, more complex patients (Figure 2).

Polypharmacy, multimorbidity, and medication adherence and interaction

HIV is now a chronic condition accompanied by multiple comorbidities, each adding additional treatment regimens that often become more complex with age. The linked issues of polypharmacy and multimorbidity in HIV have recently been reviewed.(88*, 89*, 90) Common themes emerging specific to CVD and aging in HIV are:

1. Increased prevalence of polypharmacy in older versus younger HIV patients
2. Increased multimorbidity in older HIV+ patients versus older uninfected patients(73)

3. Increased risk of drug-drug interactions and adverse drug events in older versus younger HIV adults with a high percentage of interactions involving CVD drugs(91**, 92, 93)
4. Poorer ART adherence with conditions that are either more prevalent in older HIV + versus older uninfected people or interact with older age or HIV status to reduce adherence e.g.:
    a. Increasing comorbidities(94)
    b. Drug interactions(92)
    c. Substance abuse(95, 96)
    d. Neurocognitive decline(97)
    e. Lack of social support (particularly among injection drug users)(98) and food insecurity(99)

Suggestions for clinical management have been proposed,(88, 100) ART/non-ART drug interactions have been described in detail,(101) and innovative solutions have been successfully piloted.(102**, 103) However, there is a need for development of comprehensive, effective evidence-based guidelines for managing older HIV+ patients with multiple comorbidities and multiple ART and non-ART drug regimens.

Clinical guidelines

HIV clinical guidelines are evolving to recognize the increasing impact of CVD in the aging HIV population. As mentioned earlier, CVD risk quantification tools are being investigated though external validation in diverse HIV populations is needed prior to widespread implementation.(82–87) Recommended CVD risk reduction strategies are similar to those for uninfected people because there is strong evidence linking these risk factors to CVD events. However, with a fuller understanding of the mechanisms of CVD in HIV, there exists a possibility for more effective and efficient CVD risk reduction. For example, if a unit increase in a CVD risk factor is associated with a greater increase in CVD risk in HIV+ versus uninfected persons, it may be appropriate to recommend stricter control of that comorbid condition among HIV+ people. However, lessons learned from stringent glucose and blood pressure control studies in older diabetic patients (104, 105) suggest that any alterations in CVD risk reduction guidelines for HIV+ people should be accompanied by evidence from randomized clinical trials involving HIV+ people. Alternatively, given the earlier discussion of the detrimental effects of polypharmacy, it may be more effective to control the major contributors to CVD risk instead of attempting to control all known risk factors. The inclusion of older people in ART and other HIV management trials is essential to the development of appropriate evidence-based guidelines (Table 1).

Healthcare disparities

Disparities in care by HIV status compound the differential CVD risk due to biological factors. In two recent studies, only 20% of HIV+ adults who met guidelines for receipt of aspirin therapy for primary prevention of CVD actually received this therapy. Moreover, in one academic medical center and, compared to uninfected adults, HIV+ adults were

significantly less likely to receive aspirin for CVD prevention.(106**, 107) Other data on medical management and outcomes following acute myocardial infarction show that HIV+ people received significantly fewer cardiovascular procedures and/or therapeutics (e.g., thrombolytic and anticoagulant agents, coronary arteriography, cardiac catheterization, CABG).(108**) In addition, the risk of in-hospital mortality following AMI was 38% higher among HIV+ adults. In spite of this, HIV+ people are likely to incur greater direct medical costs for non-infectious comorbidities (including CVD) compared to uninfected people.(109) Future studies reporting which processes of care for the prevention and management of AMI contribute to the increased risk of AMI and death after AMI among HIV+ people would likely be useful.(110–112)

Future directions and conclusion

Whether HIV+ individuals literally age faster and thus experience CVD events earlier is still unclear. Research is needed to understand whether they experience comorbidity (e.g. dyslipidemia, altered glucose metabolism, reduction in bone density, renal insufficiency, neurocognitive impairment) earlier; respond less well to comorbid disease burden than expected (e.g. decreased organ reserve); experience immune cell senescence (e.g. thymic involution, dramatic CMV specific T-cell response) at a (accelerated) rate more consistent with older age; or have “vascular ages” that are incongruent with chronological age.(113) Alternatively these may reflect HIV pathogenesis compounding the effects of aging in a more independent manner. The answers to these important question remain unclear though the latter explanation may be more likely and is probably organ specific.(114)

What is clear is that the mechanisms linking HIV and CVD are multi-factorial and encompass biological and “environmental” modalities. Controlling viremia with appropriate ART regimens, preventing and treating comorbid conditions, recognizing and avoiding healthcare disparities and the risks of polypharmacy associated with multimorbidity and aging will all likely be necessary to reduce the risk of CVD in this high risk population.

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Key points

- HIV infection is associated with cardiovascular disease across age groups
- The mechanisms linking HIV and CVD are multi-factorial and encompass biological and “environmental” modalities including immunologic alterations, multimorbidity, polypharmacy and healthcare disparities
- Data regarding optimal treatment strategies that balance immunological restoration and CVD risk reduction are needed

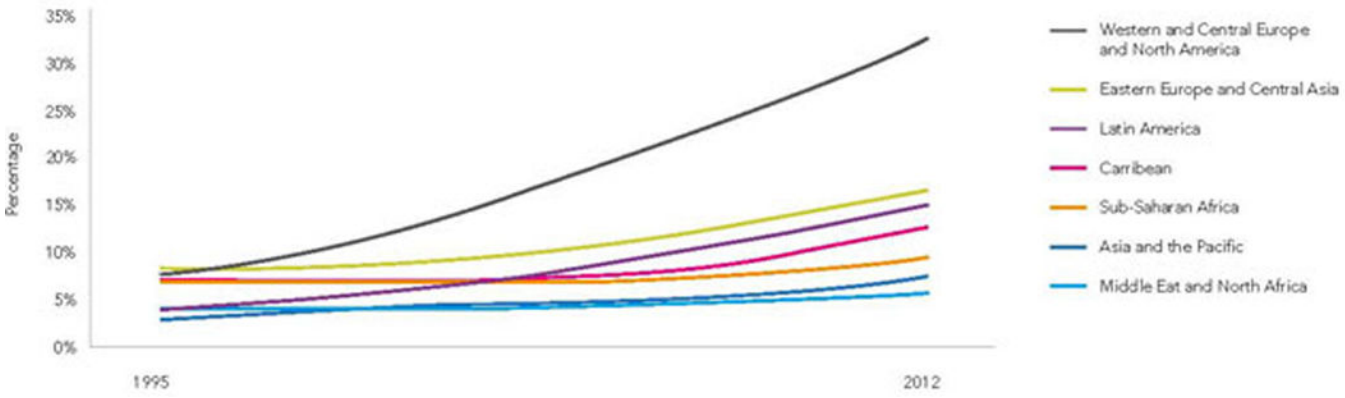

Figure 1.

People aged 50 years or older, as a percentage of all adults 15 years or older living with HIV, by region, 1995–2012 (Image from UNAIDS https://www.un.org/apps/news//story.asp?NewsID=46393&Cr=hiv&Cr1=aids#collapseTwo).

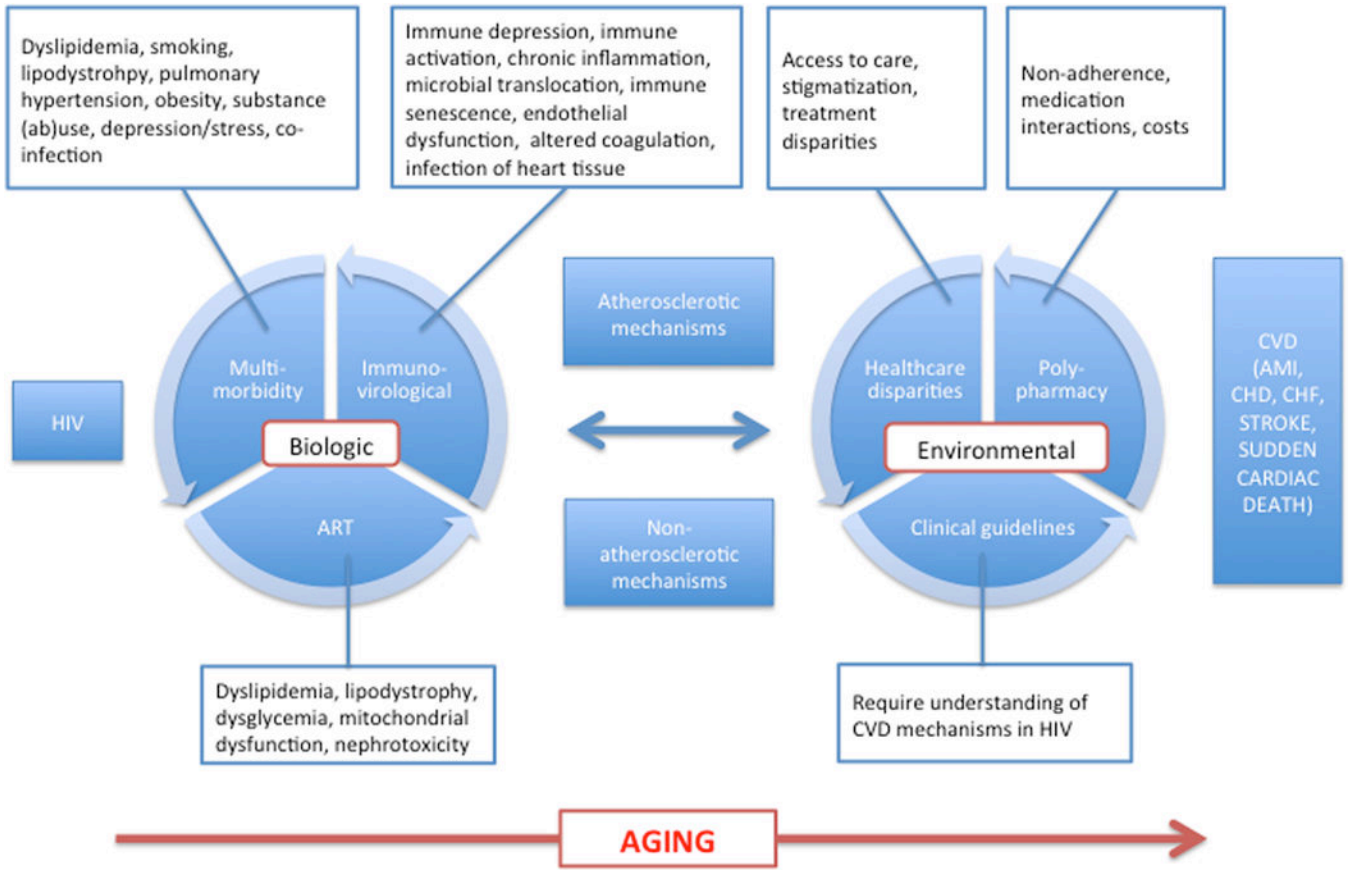

Figure 2.
Mechanisms of CVD in HIV

Table 1

Antiretroviral therapy trials focused on older people

ClinicalTrials.gov identifier	Title	Estimated completion date	Sponsor
NCT01737047	A Prospective, Observational Study to Examine the Effects of Ageing on the 'Pharmacokinetic and Clinical Observations in People Over Fifty' (POPPY)	2016	Gilead/Janssen/ViiV/Bristol Myers Squibb/Merck
NCT01213316	A Study to Assess the Efficacy of Raltegravir, Administered in Combination With Other Antiretroviral Drugs as Treatment for Adults and Older Adults Infected With the Human Immunodeficiency Virus 1 (HIV-1) (MK-0518-145) (Wirksamkeit Von Isentress® Unter Praxisbedingungen) (WIP)	2015	Merck
NCT01180075	Tenofovir, Emtricitabine, Efavirenz and Atazanavir Pharmacokinetics in the Aging HIV-Infected Population	2014	University of North Carolina, Chapel Hill, National Institute of Allergy and Infectious Diseases (NIAID) (collaborator)