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CARDIOVASCULAR-KIDNEY-HEPATIC-METABOLIC SYNDROME IN PEOPLE WITH HIV

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ABSTRACT

Background

The cardiovascular–kidney–hepatic–metabolic (CKHM) framework links cardiovascular risk, kidney disease, liver health, and metabolic dysfunction in a patient-centered model. The aim of this study was to determine the prevalence of CKHM stages, to characterize stage-to-stage transitions over the period 2005–2025, and to identify clinical and metabolic factors associated with progression and reversion across CKHM stages among people with HIV (PWH).

Methods

This was a longitudinal observational study including PWH attending Modena HIV Metabolic Clinic from 2005 to 2025 divided into three time periods: 2005-2015, 2016-2020 and 2021-2025.

CKHM stages were defined as follows: Stage 0 represented the absence of metabolic risk factors with preserved renal function and favorable cardiometabolic parameters; Stage 1 encompassed early metabolic or anthropometric abnormalities in the presence of preserved renal function; Stage 2 indicated the coexistence of metabolic or cardiovascular risk factors with established cardiometabolic disease, including ectopic fat deposition, chronic kidney disease (CKD), diabetes, or hypertension; Stage 3 was characterized by the additional presence of subclinical or high-risk cardiovascular disease (CVD), significant liver fibrosis, or very high estimated CV risk, while Stage 4 represented the most advanced stage, defined by overt CVD events, end-stage CKD, CAC score exceeding 400, or solid organ transplantation.

Transitions across CKHM stages and death were modelled using Markov models, accounting for patient age at the time of each transition. Stage 4 CKHM and death were considered as irreversible states. Sex, age, duration of HIV infection, physical activity, INSTI, PI and statin use were included as covariates to weight relative risks of progression and reversion across CKHM stages.

Results

Among 31,232 observations, 3,838 PWH had at least two CKHM assessments during the study period. The median follow-up was 6.36 years (Q1–Q3: 2.03–12.2), during which 171 deaths occurred.

Across the three study periods, the prevalence of advanced CKHM stages (stages 3 and 4) increased significantly, rising from 36% in 2005–2015 to 63% in 2021–2025. In contrast, the prevalence of CKHM stages 0, 1, and 2 progressively declined over the same periods.

At the last available observation, participants in more advanced CKHM stages (0–4) were older, with median age increasing from 42 to 56 years ($p<0.001$), and were more likely to be male (53% to 84%, $p<0.001$). Sedentary lifestyle and smoking status also differed significantly across CKHM stages ($p<0.05$). HIV duration increased with advancing CKHM stage ($p<0.001$), whereas nadir CD4 count progressively declined ($p<0.001$).

In the Markov models of CKHM stage transitions, physical activity was associated with regression from stage 1 to stage 0 (HR 1.48, 95% CI 1.06–2.06). Among individuals in stage 1, male sex and longer HIV duration were consistently associated with progression to stages 2 and 3, whereas higher levels of physical activity were protective against progression to stage 2 (HR 0.76, 95% CI 0.66–0.88). Older age and longer HIV duration were strong predictors of progression from stage 2 to stage 3. Mortality risk increased with advancing age. INSTI use was associated with a lower likelihood of regression from stage 2 to stage 1 (HR 0.61, 95% CI 0.49–0.76), while PI use was associated with a lower likelihood of regression from stage 3 to stage 2 (HR 0.77, 95% CI 0.63–0.94).

Conclusions

In a large and well-characterized cohort, PWH show a rising prevalence of advanced CKHM stages over time. Both HIV-related and traditional modifiable risk factors were associated with progression and regression across CKHM stages. The CKHM framework offers a patient-centered model to characterize cardiometabolic, renal, and hepatic disease progression in PWH, enabling longitudinal risk stratification and supporting the development of targeted, integrated strategies to preserve cardiometabolic health.

INTRODUCTION

1 THE HIV EPIDEMIC

1.1 History of HIV

HIV was identified in the early 1980s as the causative agent of AIDS and rapidly emerged as a global epidemic. Before effective treatment became available, HIV infection led to progressive immune deterioration and was associated with high morbidity and mortality (1–4).

1.1.1 Introduction of Antiretroviral Therapy

The introduction of combination antiretroviral therapy in 1996 marked a turning point in the history of HIV infection. The development of protease inhibitors (PI) enabled the implementation of highly active antiretroviral therapy (HAART), which transformed HIV from a uniformly lethal disease into a manageable chronic condition (5).

The impact of HAART was immediate and profound. In high-income countries, both the incidence of AIDS and AIDS-related mortality declined sharply after the mid-1990s (6). At the same time, the number of people with HIV (PWH) increased significantly as survival improved (7). Early studies demonstrated that combination therapy reduced the risk of progression to AIDS by approximately 65% compared to monotherapy and significantly prolonged AIDS-free survival (8).

This therapeutic revolution also led to substantial gains in life expectancy. For individuals initiating treatment, life expectancy at age 20 increased markedly, rising from approximately 63 years in the early 2000s to over 70 years by the end of that decade (9,10).

Despite these advances, early antiretroviral regimens were complex, associated with significant toxicity, and initially available primarily in resource-rich settings (11). Nevertheless, the progressive global expansion of access to therapy has dramatically

altered the epidemiology of HIV infection, contributing to a steady decline in AIDS-related mortality worldwide (12).

1.1.2 Modern Antiretroviral Therapy

Modern antiretroviral therapy (ART) has achieved remarkable levels of efficacy, safety, and tolerability. Current first-line regimens are typically based on integrase strand transfer inhibitors (INSTI), combined with two nucleoside reverse transcriptase inhibitors (NRTI), often co-formulated into single-tablet regimens taken once daily. These therapies achieve sustained virologic suppression in more than 90% of patients in clinical trials (13).

The therapeutic landscape has continued to evolve. Two-drug regimens, such as dolutegravir/lamivudine (14), are now viable options for selected patients, while long-acting injectable therapies, such as cabotegravir plus rilpivirine administered every two months, offer alternatives to daily oral treatment (15).

The goals of modern ART are well established: durable suppression of plasma HIV RNA, restoration and preservation of immune function, reduction of HIV-related morbidity, prolongation of survival, and prevention of transmission (16). The concept of "treatment as prevention" has been strongly supported by clinical evidence, demonstrating that individuals with sustained undetectable viral loads do not transmit the virus sexually (17,18).

Globally, the widespread use of ART has had a profound epidemiological impact. The annual number of new HIV infections has declined substantially - from a peak of approximately 3.4 million in the mid-1990s to around 1.3 million in recent years - while AIDS-related mortality has decreased by more than half since its peak in 2004. Nevertheless, HIV remains a major global health issue, with over 40 million people currently living with the infection, the majority in resource-limited settings, particularly in sub-Saharan Africa (5,12).

1.2 HIV Nowadays

1.2.1 Life Expectancy Approaching the General Population

The widespread availability and effectiveness of ART have dramatically improved the prognosis of PWH. Today, individuals receiving long-term treatment can achieve life expectancy approaching that of the general population, particularly when therapy is initiated early and at higher CD4+ cell counts.

For example, individuals aged 40 years who started ART after 2015 with CD4 counts ≥500 cells/μL have life expectancy gaps of only a few years compared to the general population. Overall, the difference in life expectancy has narrowed to five years or less for well-treated individuals (19).

This remarkable improvement has led to a significant demographic shift. The number of older adults living with HIV is increasing rapidly, with a growing proportion of patients aged 50 years and older. This change reflects both improved survival and ongoing, albeit reduced, rates of new infections (20).

Globally, the number of PWH has steadily increased due to improved survival, reaching tens of millions worldwide. At the same time, AIDS-related deaths have declined substantially, highlighting the success of modern treatment strategies (12).

1.2.2 The Burden of Comorbidity-Free Years

Despite near-normal life expectancy, PWH experience a disproportionate burden of comorbidities, which significantly reduces the number of years lived in good health. Studies have shown that PWH may spend up to 10–15 more years with chronic conditions compared to individuals without HIV, even when treatment is initiated early (21) (Figure 1).

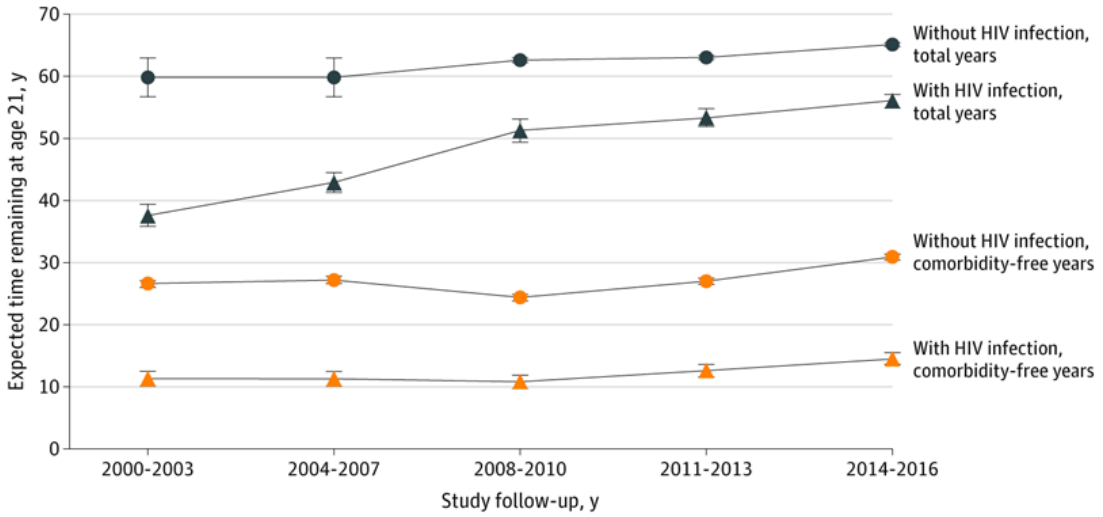


Figure 1. Overall and comorbidity-free life expectancy at age 21 years for individuals with and without HIV infection. *Adapted from Marcus et al., JAMA Netw Open, 2020.*

In the modern ART era, non-AIDS-related conditions have become the leading causes of morbidity and mortality (16). Cardiovascular disease (CVD), non-AIDS-defining cancers, chronic kidney and liver disease, diabetes, osteoporosis, neurocognitive disorders, and frailty are all highly prevalent in this population (5). In high-income countries, the majority of deaths among treated individuals are now unrelated to AIDS (19).

This increased burden of comorbidity is driven by multiple interconnected factors. First, traditional risk factors such as smoking, metabolic disorders, and aging are more prevalent among PWH. Second, chronic immune activation and inflammation persist despite effective viral suppression, contributing to long-term organ damage. Third, some antiretroviral drugs may have cardiometabolic side effects (5).

The concept of accelerated or accentuated aging has been proposed to describe this phenomenon (22), as multimorbidity tends to occur approximately a decade earlier in PWH compared to the general population (5,23). Projections suggest that, in the coming years, a substantial proportion of individuals on ART will develop multiple chronic conditions, including both physical and mental health disorders (24).

Frailty, characterized by reduced physiological reserve and increased vulnerability to adverse outcomes (25), is also more common and occurs earlier in PWH . It is associated with an increased risk of CVD, falls, cognitive decline, and mortality (16).

Consequently, the management of HIV infection has evolved into a comprehensive, multidisciplinary approach. In addition to maintaining viral suppression, care now focuses on the prevention and treatment of comorbidities, including lifestyle interventions such as smoking cessation, healthy diet, physical activity, and the management of cardiovascular risk factors. Emerging strategies, such as the use of statins for primary prevention, show promise in reducing the long-term burden of disease (26,27).

2 CARDIOMETABOLIC CHANGES IN PWH OVER TIME

People with HIV (PWH) experience progressive cardiometabolic alterations characterized by weight gain, increased visceral adiposity, insulin resistance, dyslipidemia, and metabolic syndrome (28). These changes result from a complex interplay between HIV infection itself, chronic inflammation, antiretroviral therapy (ART), aging, and lifestyle factors (29).

The introduction of ART marked a turning point in HIV care, transforming HIV infection from a fatal disease into a manageable chronic condition and allowing life expectancy among PWH with access to treatment to approach that of the general population. However, this remarkable improvement in survival has also revealed new challenges. Long-term exposure to both HIV and ART contributes to the development of non-AIDS comorbidities, including cardiovascular disease (CVD), diabetes, liver disease, osteoporosis, and neurocognitive disorders (16,30).

As a consequence, cardiometabolic health has become a central concern in the long-term management of HIV. Chronic inflammation, persistent immune activation, and cumulative ART exposure are major drivers of metabolic dysfunction and cardiovascular risk, contributing to the earlier onset of age-related diseases (28,31). As PWH grow older, the prevalence of multimorbidity - defined as the coexistence of multiple chronic conditions - becomes substantially higher than in HIV-negative populations and often resembles that observed in individuals 10–15 years older (5,16,23). These observations have led to the concept of premature or accelerated aging in HIV, whereby cardiometabolic diseases emerge earlier and with greater severity than in the general population (22).

2.1 Changes in Main Cardiometabolic Domains

2.1.1 Changes in BMI and Body Composition

Weight and BMI changes in PWH have evolved dramatically across the ART era (28). In untreated HIV infection, patients commonly experience progressive weight loss (HIV wasting), driven by reduced caloric intake, malabsorption resulting from depletion of gut

mucosal T cells and impaired epithelial barrier integrity, and elevated metabolic requirements fueled by persistent systemic inflammation (32). Loss of body cell mass - particularly lean tissue - rather than fat mass is the hallmark of HIV wasting and has been independently associated with accelerated disease progression, impaired functional status, and increased mortality (33).

With the initiation of ART, however, weight gain has become the predominant pattern. This gain occurs across all drug classes but is most pronounced with integrase strand transfer inhibitors (INSTI) and tenofovir alafenamide (TAF) based regimens, is more likely in women and Black individuals, and appears to occur mostly within the first year of treatment, with BMI trajectories subsequently converging with those of the general population (34–36). Long-term data from the ADVANCE trial support this pattern, showing that while weight gain continued through 192 weeks - with the greatest increases in the TAF/FTC + DTG arm - the trajectory slowed considerably after the first year (37) (Figure 2). Notably, whether INSTIs directly promote weight gain or whether comparator agents (e.g., tenofovir disoproxil fumarate, efavirenz) suppress it remains an area of active investigation (38).

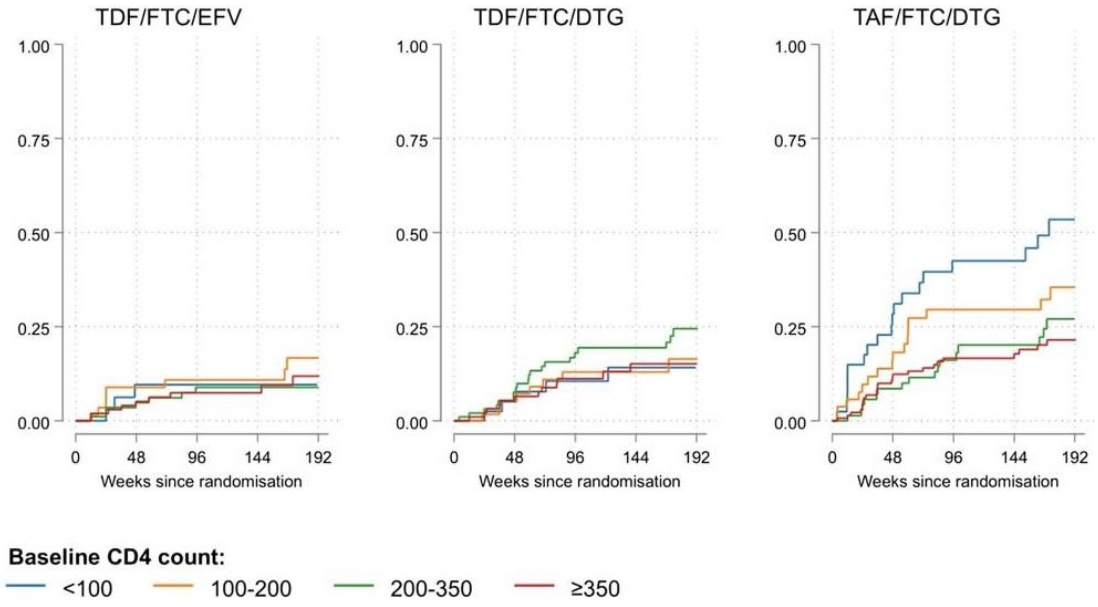


Figure 2. Time to clinical obesity by treatment arm and baseline CD4 count. *DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate. Adapted from Sokhela et al., Open Forum Infect Dis, 2024.*

Body composition has also shifted over time. In the early ART era, lipodystrophy - characterized by peripheral subcutaneous fat loss (lipoatrophy) and accumulation of visceral adipose tissue (VAT) - was common, with prevalence estimates of 20–50% within two years of initiating therapy (39). Lipoatrophy was causally linked to thymidine analogue nucleoside reverse transcriptase inhibitors (NRTIs) through mitochondrial toxicity and impaired adipocyte differentiation, while early protease inhibitor therapy contributed to abdominal fat gain (40,41).

In the modern ART era, this phenotype has changed: with the discontinuation of thymidine analogues and the use of newer agents, gains in both subcutaneous and visceral fat are observed with ART initiation regardless of regimen, and rates of generalized obesity are rising among PWH (28). Central fat accumulation, particularly excess VAT, is strongly linked to insulin resistance, ectopic lipid deposition in the liver and muscle, increased coronary plaque burden, and overall mortality (28,42).

2.1.2 Insulin Resistance and Metabolic Syndrome

Insulin resistance and diabetes are increasingly prevalent in PWH, with prevalence estimates of diabetes ranging up to 10% in those on ART and up to 25% for any disorder of insulin–glucose homeostasis (43). Mechanistically, these conditions arise from a combination of adipose tissue dysfunction, chronic systemic inflammation, and ART-related metabolic effects (30,42). HIV infection itself promotes adipokine dysregulation and a proinflammatory state within adipose tissue that exacerbates insulin resistance (32,43). Specific ART classes contribute through distinct pathways: protease inhibitors (PI) impair glucose transporter expression and may induce pancreatic β-cell apoptosis, while NRTI promote mitochondrial dysfunction and lipodystrophy (44). More recently, INSTI have been associated with weight gain and adipocyte hypertrophy, adding a further layer of metabolic risk (45,46). Early pancreatic β-cell dysfunction has also been observed, with certain antiretrovirals shown to reduce insulin secretion through oxidative stress, suggesting that glucose metabolism abnormalities may develop early in the disease course (29).

Metabolic syndrome - defined by central obesity, insulin resistance, dyslipidemia, and hypertension - has a pooled global prevalence of approximately 25% in PWH (47). Excess

visceral adipose tissue plays a central role, being associated not only with metabolic abnormalities but also with increased coronary plaque burden and cardiovascular mortality (30,48). As PWH age, the coexistence of metabolic syndrome with other chronic conditions such as cerebrovascular disease and renal impairment substantially increases the odds of frailty and functional decline, with central obesity and hypertension identified as independent risk factors for incident physical frailty (28,49).

2.1.3 Cardiovascular Risk

PWH carry a markedly elevated CVD burden. Relative risks of myocardial infarction, stroke, heart failure, and other CVD manifestations are generally 1.5- to 2-fold greater than in uninfected individuals, and these excess risks persist even after adjustment for traditional demographic and clinical risk factors (28,50) (Figure 3). Meta-analytic data confirm a risk ratio for myocardial infarction of 1.79 (95% CI, 1.54–2.08) and for stroke of 2.56 (95% CI, 1.43–4.61) (51).

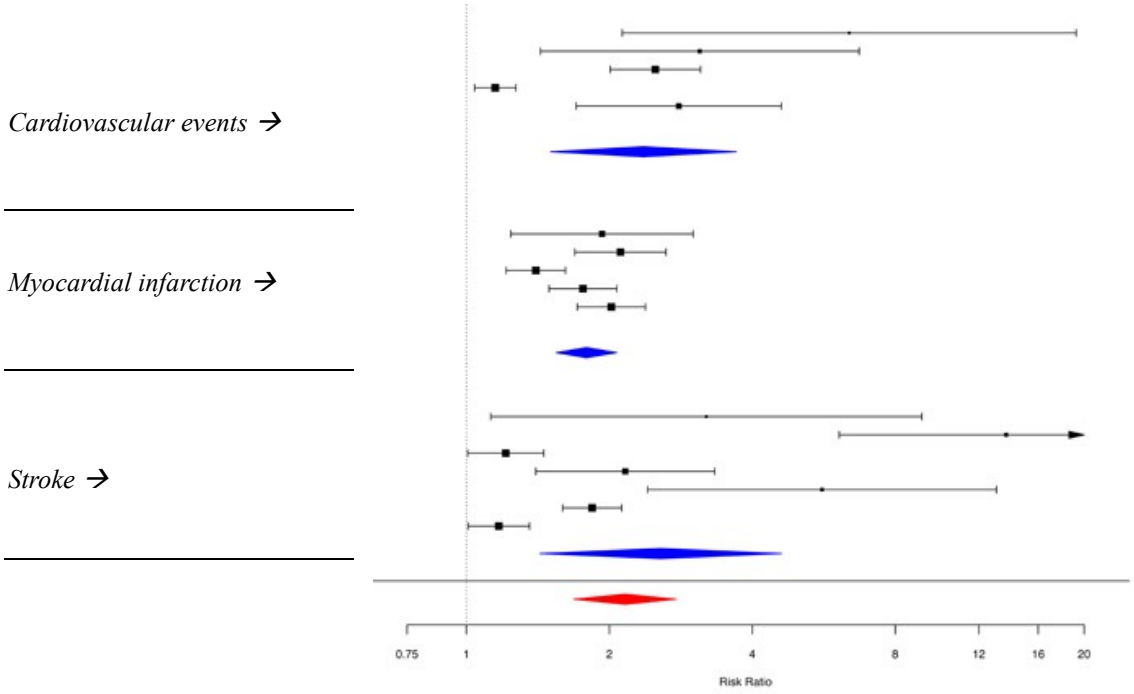


Figure 3. Forest plot. Pooled risk ratio for risk of cardiovascular disease in people living with HIV compared to those without stratified by type of event. *Adapted from Shah et al., Circulation, 2018.*

Importantly, the landscape of HIV-associated CVD has shifted dramatically over time. In the pre-ART era, the predominant cardiac manifestations were dilated cardiomyopathy, pericardial disease, and pulmonary hypertension; with the advent of effective ART, atherosclerotic complications - including myocardial infarction, ischemic stroke, and heart failure - have become the dominant cardiovascular phenotype (52).

Although ART has reduced the relative risk of CVD events, the absolute burden has paradoxically risen as PWH live longer: the global burden of HIV-associated CVD tripled between 1990 and 2015, reaching 2.6 million disability-adjusted life-years per year, with the greatest impact in sub-Saharan Africa and the Asia-Pacific region (50) (Figure 4). Proportionate CVD mortality among PWH increased from 1.95% to 4.62% between 1999 and 2013, and in some urban cohorts, one in five deaths among PWH is now attributable to CVD (49,53).

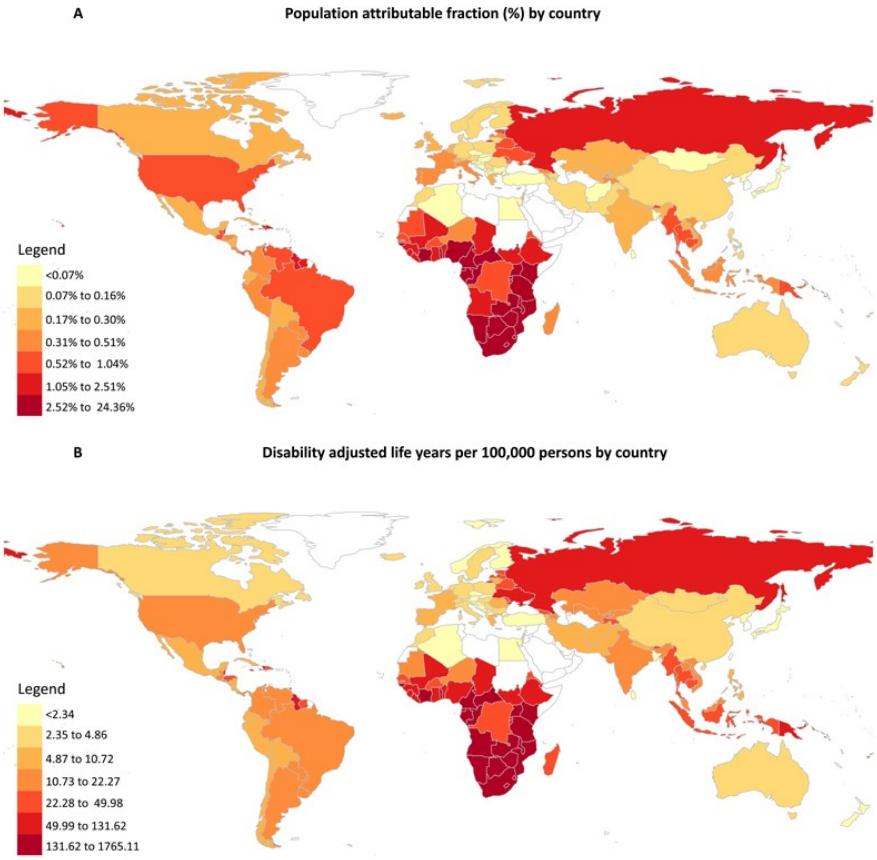


Figure 4. Cartograms. *Cartograms showing population attributable risk* ***(Figure 4A)*** *and HIV attributable disability-adjusted life years per 100,000 persons* ***(Figure 4B)*** *for HIV associated cardiovascular disease. Each colour category represents a septile. Adapted from Shah et al., Circulation, 2018.*

Longitudinal data from Europe and North America do show a decline in cardiovascular mortality rates over calendar time (adjusted mortality rate ratio per period: 0.83; 95% CI, 0.79–0.87), likely reflecting improvements in post-CVD care and the reduced toxicity of contemporary ART regimens (54). Nevertheless, the underlying drivers of excess risk - chronic immune activation, residual inflammation, ART-related metabolic complications, and a high prevalence of traditional risk factors such as smoking, hypertension, diabetes, and dyslipidemia - continue to fuel a disproportionate CVD burden in this population (28,55) (Figure 5).

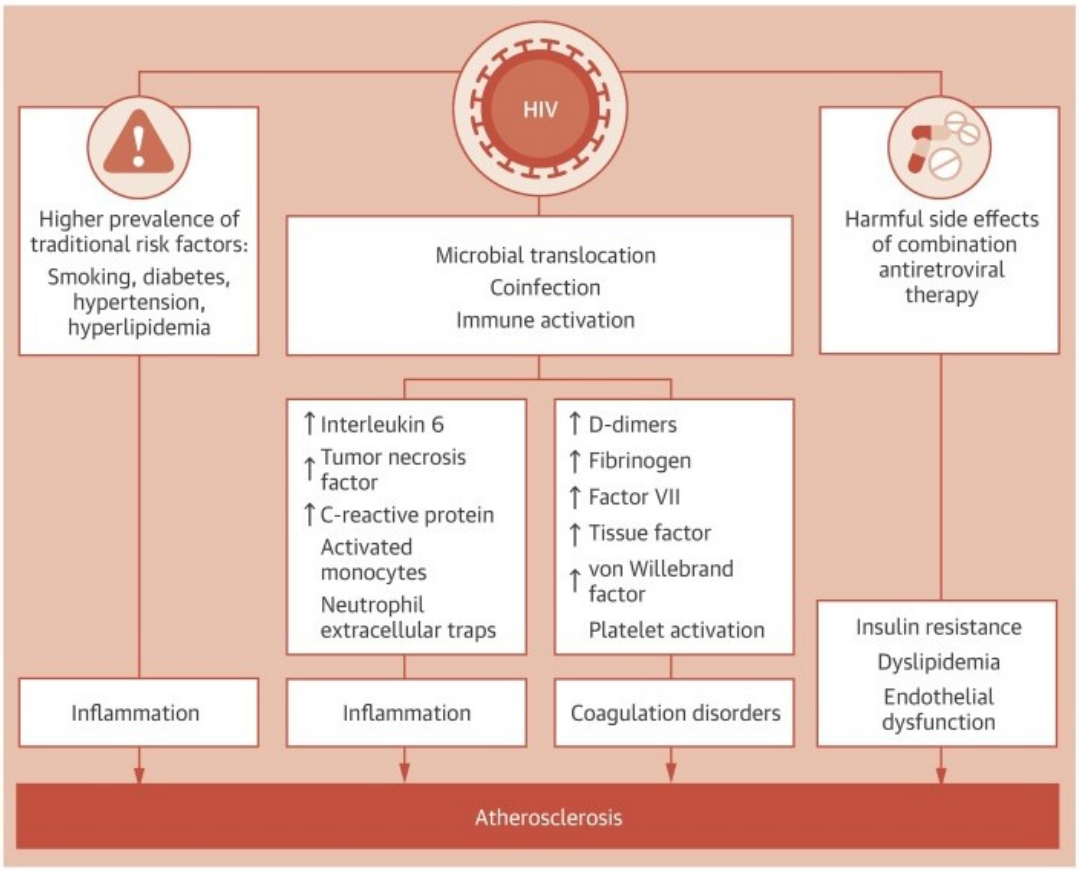


Figure 5. Central Illustration. HIV and Ischemic Heart Disease: Etiopathogenesis of HIV-Associated Coronary Artery Disease. *The figure schematically represent the multifactorial etiopathogenesis of HIV-associated coronary artery disease, showing the interaction between direct viral effects, chronic inflammation, traditional risk factors, and ART side effects. Adapted from Vachiat et al., J Am Coll Cardiol, 2017.*

2.1.4 Chronic Kidney Disease

Chronic kidney disease (CKD) remains a significant comorbidity among PWH, with a reported prevalence of reduced glomerular filtration rate (eGFR <60 mL/min/1.73 m²) ranging from 4.7% to 9.7% in North America and Europe, and a 2- to 5-fold higher prevalence of albuminuria compared with HIV-negative individuals (56). The incidence of CKD in PWH has been estimated at 3.9 to 12.4 per 1,000 person-years, driven by both HIV-specific factors - including viremia, low CD4 cell count, and nephrotoxic antiretroviral agents - and conventional risk factors such as hypertension, diabetes, and dyslipidemia (56,57).

The epidemiology of kidney disease in PWH has undergone a profound transformation since the introduction of ART. In the pre-ART era, HIV-associated nephropathy (HIVAN) was the predominant renal manifestation, with a prevalence of 3.5% to 10% among HIV-infected persons and a rapid progression to end-stage kidney disease (58). The widespread use of combination ART reduced HIVAN risk by approximately 60%, and the condition has largely disappeared in regions with broad ART availability (59). However, this decline in HIVAN has been offset by a shift toward kidney pathology driven by the comorbidities of an aging HIV population - particularly hypertension- and diabetes-related nephrosclerosis - as well as by the cumulative nephrotoxic effects of long-term ART exposure (59,60).

Longitudinal studies demonstrate that PWH on ART experience faster eGFR decline (−0.56 mL/min/1.73 m²/year excess) and a 2.3-fold higher odds of worsening albuminuria compared with HIV-uninfected controls (61) (Figure 6). Once CKD develops, PWH face a twofold higher mortality risk than individuals without HIV, underscoring the clinical urgency of early detection and management (62). CKD also acts as a powerful amplifier of cardiovascular risk, creating a vicious cycle in which kidney dysfunction and vascular disease reinforce each other - a dynamic that is particularly pronounced in PWH, where overlapping drivers such as chronic inflammation, metabolic dysfunction, and immune dysregulation accelerate both conditions simultaneously (57,63).

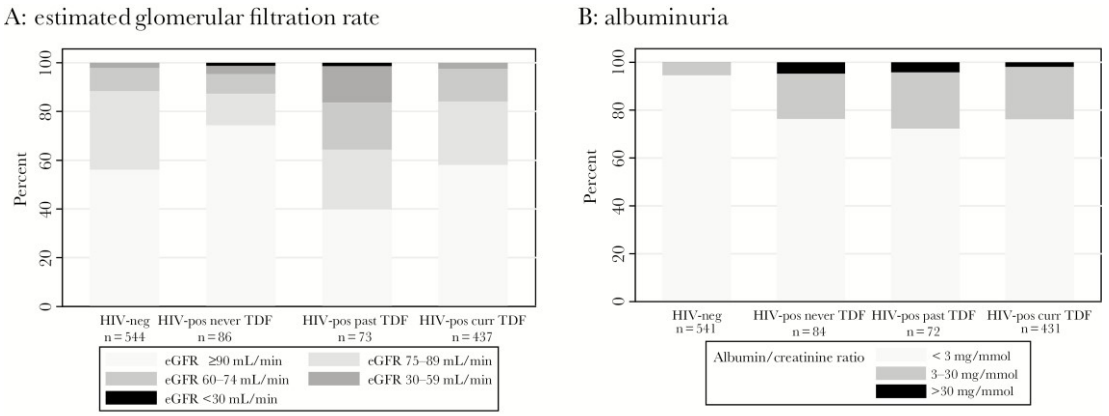


Figure 6. Distribution at baseline of categories of estimated glomerular filtration rate (A) and albumin/creatinine ratio (B), between HIV–uninfected individuals and HIV-infected individuals who have never been exposed to tenofovir disoproxil fumarate (TDF), were previously exposed to TDF, and are currently being exposed to TDF. *Abbreviations: HIV-neg, individuals uninfected with HIV; HIV-pos curr TDF, HIV-positive individuals currently exposed to tenofovir disopoxil fumarate; HIV-pos never TDF, HIV-positive individuals never exposed to tenofovir disopoxil fumarate; HIV-pos past TDF, HIV-positive individuals previously exposed to tenofovir disopoxil fumarate; TDF, tenofovir disoproxil fumarate. Adapted from Kooij et al., J Infect Dis, 2017.*

2.1.5 Metabolic Dysfunction-Associated Steatotic Liver Disease

Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as the most common cause of chronic liver disease in PWH, with its burden growing substantially in the era of effective ART (64).

Meta-analyses estimate the pooled prevalence of MASLD (previously termed NAFLD) at approximately 33–35% based on imaging studies in PWH with HIV monoinfection, with individual studies reporting prevalence ranging widely from 20% to 63% depending on the population studied and diagnostic modality used (27,64,65).

The prevalence of MASLD in PWH appears to be increasing over time, driven by several converging factors: the improved life expectancy afforded by modern ART (making liver disease now the second leading cause of non-AIDS-related deaths), ART-associated weight gain - particularly with INSTI - and the rising prevalence of traditional metabolic risk factors such as obesity and type 2 diabetes in this aging population (64,66,67) (Figure 7).

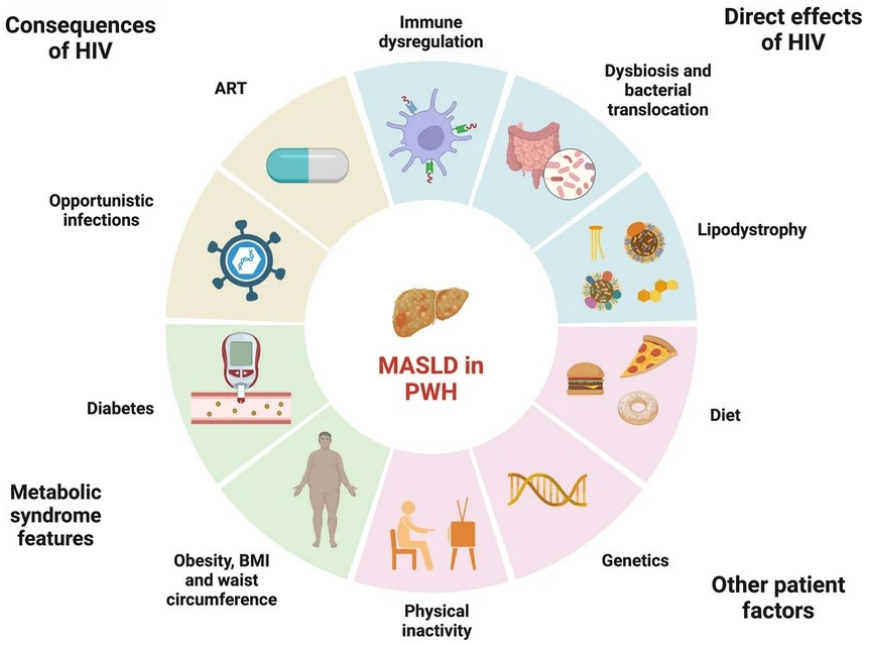


Figure 7. Pathogenesis of metabolic dysfunction-associated steatotic liver disease (MASLD) in people with HIV (PWH). *Adapted from Wegermann et al., Current HIV/AIDS Reports, 2023.*

Longitudinal data from a cohort of 740 PWH initiating ART demonstrated that MASLD detection rates increased steadily with longer ART duration, with patients experiencing >10% weight gain showing a rise in MASLD prevalence from 48.8% at baseline to 87% after 3 years of therapy (68).

Notably, MASLD in PWH occurs at lower BMI thresholds than in the general population and carries a higher risk of progression to fibrosis - with 21% of PWH with MASLD having advanced fibrosis in one biopsy study, representing a 42% higher fibrosis risk compared to matched HIV-negative controls (27,69).

While earlier-generation ART agents such as didanosine and stavudine were directly associated with hepatic steatosis, the relationship with newer regimens is less clear, and the current rise in MASLD prevalence is thought to be more closely linked to metabolic consequences of weight gain and chronic inflammation rather than direct drug hepatotoxicity (27,70).

2.2 Role of HIV Infection

HIV infection itself directly contributes to metabolic dysfunction through several viral mechanisms independent of ART. Viral proteins such as Nef, Tat, gp120, and Vpr interfere with lipid metabolism, adipocyte differentiation, and insulin signaling. These effects promote dyslipidemia, adipose tissue dysfunction, and insulin resistance (49).

Additionally, HIV alters lipid profiles even before treatment. Untreated infection is typically associated with elevated triglycerides, low HDL cholesterol, and increased oxidized LDL, reflecting an atherogenic profile. HIV also promotes hepatic steatosis and disrupts glucose metabolism through increased gluconeogenesis and pancreatic β-cell dysfunction (28,32,49).

Adipose tissue can act as a viral reservoir, with infected immune cells contributing to local inflammation and metabolic dysregulation (32,71,72). These mechanisms highlight that HIV itself - not only its treatment - plays a central role in cardiometabolic disease (49).

2.3 Role of Chronic Inflammation

Chronic inflammation is a defining feature of HIV infection and a major driver of cardiometabolic complications. Even with effective ART and viral suppression, PWH exhibit persistent immune activation and elevated inflammatory markers compared to uninfected individuals (16,28).

This ongoing inflammation is multifactorial. Key contributors include microbial translocation due to gut barrier dysfunction, low-level viral replication in tissue reservoirs, and co-infections such as cytomegalovirus (CMV) and hepatitis C virus (HCV). These factors sustain activation of the innate immune system and promote the release of pro-inflammatory cytokines such as TNF-α and IL-6 (73).

Chronic immune activation contributes to atherosclerosis through impaired HDL function, increased oxidized LDL, and enhanced foam cell formation. It also promotes insulin resistance, endothelial dysfunction, and arterial inflammation (49).

Recent insights from immunometabolism further deepen this understanding. HIV induces metabolic reprogramming of immune cells, shifting them toward glycolysis and a pro-inflammatory phenotype (74). This process fuels chronic inflammation and contributes to "inflammaging," a state of accelerated biological aging associated with increased risk of cardiovascular, metabolic, and neurocognitive diseases (75).

Importantly, older PWH show poorer immune recovery despite effective viral suppression, reinforcing the importance of early ART initiation to limit long-term inflammatory damage (16).

2.4 Role of Antiretroviral Therapy

2.4.1 Metabolic Consequences

ART plays a dual role in cardiometabolic health. On one hand, it suppresses viral replication and reduces systemic inflammation, thereby lowering the risk of many complications. On the other hand, certain antiretroviral agents contribute directly to metabolic disturbances (28).

PIs, particularly older-generation agents (indinavir, ritonavir, nelfinavir), have been strongly associated with insulin resistance, dyslipidemia, and lipodystrophy, with metabolic complications developing in up to 60% of treated patients (76). Their mechanisms include interference with lipid metabolism, adipocyte function, and mitochondrial activity. Newer PIs such as atazanavir and darunavir have more favorable metabolic profiles, but long-term effects of earlier therapies persist in many patients (49).

NRTIs, especially thymidine analogues (stavudine, zidovudine), have been linked to subcutaneous fat loss, ectopic fat deposition, and mitochondrial toxicity (39,49).

INSTIs, now widely used as first-line therapy, are associated with significant weight gain, particularly when combined with TAF. A large NA-ACCORD cohort analysis (n = 32,514) found that at 2 years, INSTI-treated patients gained a mean of 4.9 kg versus 2.7 kg with NNRTIs, with bictegravir showing the highest numerical gain (6.9 kg); Black females on bictegravir or dolutegravir with TAF experienced the greatest weight increase (~10 kg at 2 years) (77). In the ADVANCE trial, most weight gain in dolutegravir groups

was fat accumulation in trunk and limbs, and was amplified with concomitant TAF use (34). This weight gain may increase the risk of metabolic syndrome, diabetes, and hypertension, with RESPOND consortium data showing that BMI changes mediate the association between INSTIs and incident hypertension (78). Additionally, efavirenz has well-documented neuropsychiatric effects including sleep disturbances, dizziness, and depression, while INSTIs have been associated with insomnia and depressive symptoms primarily in patients with pre-existing psychiatric conditions, with discontinuation rates due to neuropsychiatric side effects of up to 6% for dolutegravir (79,80).

2.4.2 Cardiovascular Consequences

Despite the metabolic effects described above, continuous ART use has a net cardiovascular benefit. The SMART trial demonstrated that continuous ART significantly reduced cardiovascular events compared with episodic, CD4-guided therapy (HR 1.57 for the interruption arm; 95% CI 1.00–2.46), and early ART initiation has been shown to achieve a lower inflammatory setpoint during viral suppression (81–83).

Among specific drug classes, older-generation PIs increase CVD risk approximately 2-fold (95% CI 1.7–2.37), with a clear dose-response relationship between cumulative PI exposure and myocardial infarction incidence demonstrated in the D:A:D cohort (49).

Abacavir use has also been associated with increased MI risk in several large observational cohorts, although meta-analyses of clinical trials have yielded conflicting results (28).

Whether INSTI-associated weight gain translates into increased cardiovascular events remains uncertain: a large target trial emulation found no association between INSTI initiation and ASCVD events in treatment-naïve individuals, while the RESPOND cohort reported a transient increase in the first two years of INSTI use (38,84).

Current guidelines recommend that people with or at high risk for CVD receiving abacavir should switch to a non-abacavir regimen if an active alternative is available (38).

Despite these concerns, modern ART regimens are substantially safer than earlier therapies, and their benefits in reducing HIV-related morbidity and mortality clearly outweigh their risks. The challenge lies in individualizing treatment to minimize long-

term metabolic and cardiovascular complications, with particular attention to sex- and race-based differences in drug-related adverse effects (16,34).

2.5 Role of Lifestyle Factors

Lifestyle factors significantly influence cardiometabolic risk in PWH and often have a disproportionate impact compared to the general population (28).

Smoking is highly prevalent among PWH and represents one of the most important modifiable cardiovascular risk factors. It is strongly associated with coronary artery disease and myocardial infarction, and cessation significantly reduces cardiovascular risk (16,28).

Physical inactivity contributes to poor metabolic health, whereas regular exercise improves inflammation, insulin sensitivity, and overall cardiometabolic outcomes (28). However, maintaining long-term behavioral changes remains challenging (85).

Diet also plays a crucial role. Diets rich in fruits, vegetables, whole grains, and healthy fats are associated with improved metabolic profiles, while high intake of sugar-sweetened beverages and red meat contributes to increased cardiovascular risk (28).

Alcohol consumption may further exacerbate cardiometabolic risk, particularly at high levels. Comprehensive lifestyle interventions - including smoking cessation, increased physical activity, dietary optimization, and reduced alcohol intake - are essential components of HIV care (28).

3 COMORBIDITIES AND MULTIMORBIDITY IN PWH

The advent of ART has transformed HIV into a chronic disease, shifting the clinical burden from opportunistic infections to long-term non-infectious comorbidities (NICM) / non-AIDS comorbidities (NACM). As a result, understanding multimorbidity in PWH has become central to both clinical care and public health planning.

3.1 Prevalence and Incidence of Comorbidities in PWH Versus the General Population

PWH experience a substantially higher burden of comorbidities and multimorbidity compared to the general population. Large cohort studies consistently demonstrate higher prevalence, earlier onset, and greater severity of chronic conditions (86). Multimorbidity, commonly defined as the presence of two or more comorbidities, is significantly more frequent in PWH, with higher mean numbers of coexisting diseases and greater overall disease burden. In the NA-ACCORD cohort, multimorbidity prevalence among ART-treated PWH nearly tripled between 2000 and 2009, even after adjusting for age (87). Modeling projections estimate that multimorbidity will affect approximately 70% of PWH receiving ART by 2030 (5,24) (Figure 8).

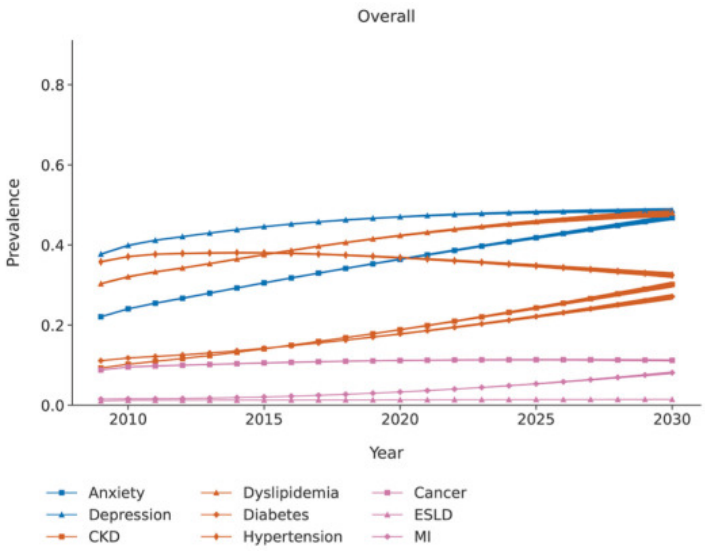


Figure 8. Forecasted prevalence (and shaded 95% uncertainty ranges) of individual comorbidities among people with HIV using antiretroviral therapy to the year 2030. *Adapted from Althoff et al., PLoS Med, 2024.*

The most prevalent comorbidities include hypertension, hyperlipidemia, and type 2 diabetes, all of which occur at higher rates than in the general population, reflecting the growing importance of cardiometabolic disease in HIV care (86). In addition, PWH exhibit increased rates of chronic kidney disease (CKD), liver disease (particularly related to hepatitis B and C coinfections), cardiovascular disease (CVD), non-AIDS-defining malignancies, osteoporosis, neurocognitive impairment, and psychiatric conditions such as depression and anxiety (5). Substance use disorders and alcohol abuse are also more common, further compounding health risks (27).

A defining feature of multimorbidity in HIV is its earlier onset. Comorbidities tend to appear approximately 10 years earlier in PWH compared to HIV-negative individuals. This observation supports the concept of premature or accelerated aging, whereby HIV infection, chronic immune activation, and long-term ART exposure collectively shift disease trajectories toward earlier morbidity. Indeed, epidemiological data show that PWH aged 41–50 years may exhibit comorbidity profiles similar to HIV-negative individuals aged 51–60 years (5,23,88) (Figure 9).

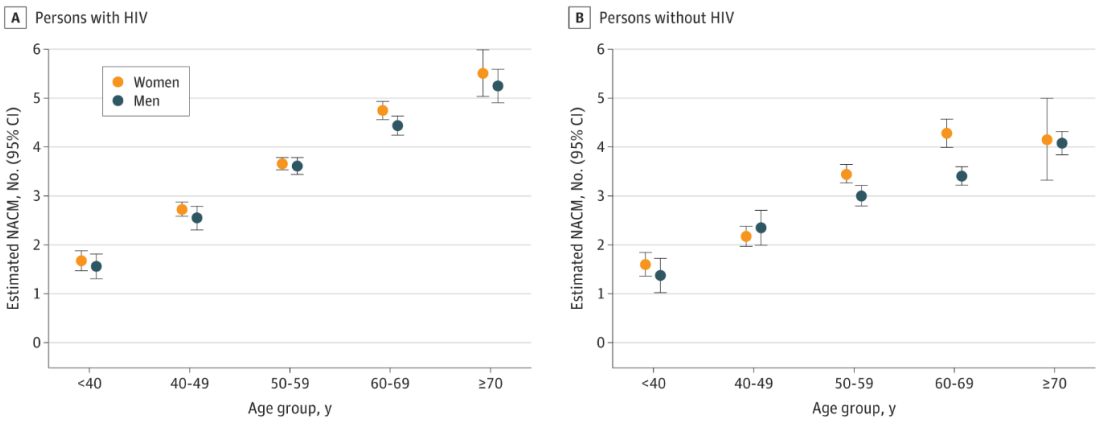


Figure 9. Estimated Mean Number of Non-AIDS Comorbidities (NACM) Among Persons With and Without HIV Stratified by Sex and Age Group. *Participants were enrolled in the Women's Interagency HIV Study (for women) or the Multicenter AIDS Cohort Study (men), stratified by sex and age group. Adjusted linear regression (model 2) was performed with the following covariates included: race and ethnicity, body mass index, socioeconomic status, cigarette use, alcohol use, crack or cocaine use, in addition to HIV serostatus, age, sex, and all interaction terms (HIV × age × sex, P for interaction = .04). Adapted from Collins et al., JAMA Netw Open, 2023.*

This increased burden is driven by multiple interacting mechanisms. First, traditional risk factors such as smoking, alcohol use, and substance abuse are overrepresented in PWH. Second, persistent immune activation and chronic inflammation (despite effective viral suppression) contribute to vascular, metabolic, and end-organ damage. Third, cumulative exposure to ART, particularly older regimens, has been associated with metabolic disturbances, renal dysfunction, and bone disease (16,28).

Importantly, HIV-specific factors also influence risk. Lower nadir CD4 cell counts, uncontrolled viremia and prolonged ART exposure are independent predictors of multimorbidity across multiple cohorts, highlighting the importance of early diagnosis and timely treatment initiation (16,23).

The clinical and economic consequences are substantial. PWH experience higher rates of polypharmacy, increased hospitalization, and markedly higher healthcare costs compared to the general population (89). These burdens are further amplified by aging, as non-AIDS comorbidities - particularly CVD and cancer - have become leading causes of mortality in this population (16,19).

3.2 Future Predictions of Comorbidities and Multimorbidity in PWH

Projections indicate that the burden of comorbidities and multimorbidity in PWH will continue to rise in the coming decades. Modeling studies, such as PEARL, suggest that the prevalence of multimorbidity among PWH receiving ART will increase from 63% in 2020 to 70% by 2030, driven by both population aging and improved survival (16,24,90) (Figure 10).

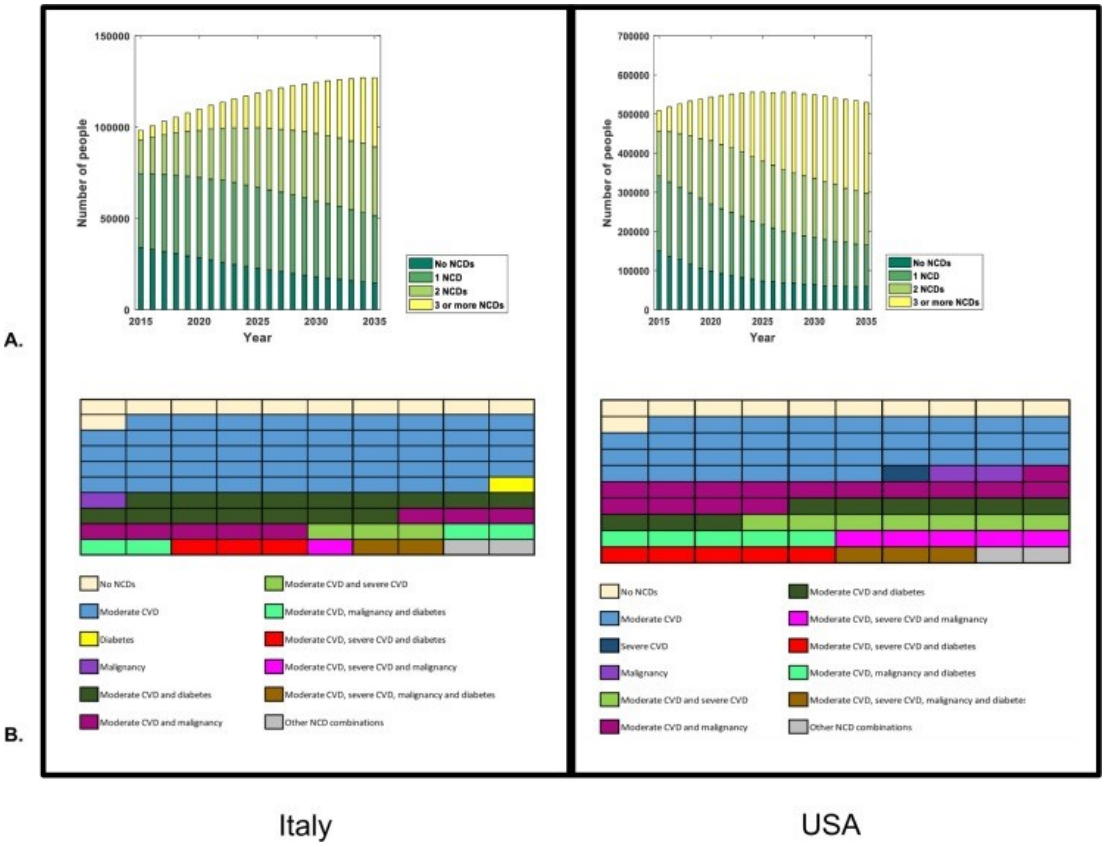


Figure 10. The predicted change in non-communicable disease burden. *A. The number of HIV-positive patients on antiretroviral therapy with 0,1, 2 or 3 and more non-communicable diseases between 2015 and 2035 in Italy and USA. Note: the two graphs are not on the same axis. B. The predicted co-morbidities profiles amongst HIV-positive patients on antiretroviral therapy in 2035 based on a cross-section of 100 patients (each square represents one patient) for Italy and the USA. Abbreviations: Cardiovascular disease (CVD), Chronic kidney disease (CKD), Moderate CVD (dyslipidemia and/or hypertension) and Severe CVD (MI or stroke); United States of America (USA). Adapted from Smit et al., PLoS One, 2017.*

The demographic shift is striking: approximately half of the global population of PWH is already over the age of 50, and this proportion is expected to grow steadily (5,91). As HIV has become a chronic condition, patients are living long enough to develop age-related diseases, often at earlier ages and with greater complexity. Encouragingly, recent longitudinal data from the Spanish CoRIS cohort (n = 18,659) show that the incidence of serious non-AIDS events (SNAEs) has declined over successive calendar periods (aHR 0.68 for 2018–2023 vs. 2006–2011), with the predicted age at first SNAE rising from 42.2 to 48.6 years, consistent with improvements in HIV management (92). However, the

overall comorbidity burden and polypharmacy continue to rise, particularly among women (92).

Specific comorbidities are projected to follow heterogeneous trends. Mental health disorders, particularly depression and anxiety - which affect up to 55% of PWH in large cohort studies (93) - are expected to increase further, reflecting both biological and psychosocial vulnerabilities. Cardiometabolic conditions - including dyslipidemia, diabetes, CKD, and myocardial infarction - are also projected to rise, while hypertension trends may stabilize or decline. Cancer and advanced liver disease are expected to remain relatively stable but still contribute significantly to morbidity (24). Notably, the proportion of deaths due to non-AIDS malignancies has increased from 5% in 1996–1999 to 19% in 2016–2020, while AIDS-related mortality has declined from 49% to 16% over the same period (54).

Marked disparities exist across demographic groups. Older individuals, women, and those with a history of injection drug use are expected to experience the highest burden of multimorbidity. In the PEARL model, Black women with a history of injection drug use - the oldest demographic subgroup (median age 66 years by 2030) - are projected to have a 92% prevalence of multimorbidity (24). Women with HIV also carry a nearly 2-fold higher risk of cardiovascular events compared to men, and exhibit a higher overall NACM burden across racial and ethnic groups (88). These disparities underscore the importance of considering social determinants of health, access to care, and structural inequalities in HIV management (94).

Importantly, the rising burden of multimorbidity is not limited to high-income settings. A systematic review and meta-analysis of studies from sub-Saharan Africa documented high prevalence of hypertension (21%), dyslipidemia (22–52%), and depression (24%) among PWH in LMICs, with NCDs frequently undiagnosed or poorly managed (95). This global dimension highlights the need for health systems worldwide to adapt to the dual challenge of infectious and noncommunicable diseases (95–97).

The implications for healthcare systems are profound. HIV care must increasingly integrate management of chronic diseases, requiring coordination across specialties, expansion of clinical capacity, and continuous updating of clinical guidelines (27). Even in virally suppressed individuals, the risk of cardiovascular mortality remains

significantly elevated compared to uninfected populations, emphasizing the need for proactive prevention and monitoring strategies (16,28) - as underscored by the REPRIEVE trial, which demonstrated a 35% reduction in major adverse cardiovascular events with pitavastatin in PWH at low-to-moderate baseline risk (HR 0.65; 95% CI 0.48–0.90), a benefit that extended across demographics, CD4 ranges, and viral load levels (26).

3.3 Limitations of the Comorbidity and Multimorbidity Construct

Despite its widespread use, the construct of multimorbidity in HIV has important limitations that constrain its clinical and research utility.

From a methodological perspective, definitions of multimorbidity vary widely across studies. Some rely on simple counts of conditions, while others use weighted indices or disease-specific combinations. This heterogeneity limits comparability and may obscure clinically meaningful differences in disease burden (98,99). Furthermore, many studies rely on administrative data or self-reported diagnoses, which are subject to misclassification and detection bias (100).

Another limitation is the inability of current frameworks to capture the dynamic and systemic nature of disease in PWH. Traditional constructs such as single comorbidities or even metabolic syndrome provide only a partial and relatively static view. More recently, the concept of cardiovascular-kidney-metabolic (CKM) syndrome has been proposed as a more integrated and dynamic framework, recognizing the interconnected progression of cardiovascular, metabolic, and renal disorders. Compared with metabolic syndrome, CKM offers a broader scope by integrating multiple organ systems rather than focusing solely on metabolic risk factors. It is also more outcome-oriented, as it emphasizes the prediction of hard clinical endpoints such as CVD, CKD, and mortality, rather than representing a simple cluster of risk factors (63,101–103).

Importantly, CKM provides a dynamic framework that captures disease progression across stages, in contrast to the static definition of metabolic syndrome. This makes it more actionable in clinical practice, as it supports earlier intervention and improved risk stratification (103,104). In addition, it is more inclusive, accounting for heterogeneity across patient populations and the complex interactions between comorbidities, beyond

obesity and insulin resistance alone (63). Overall, CKM may better align with modern multimorbidity management by supporting a more integrated and clinically useful approach to care in PWH (102).

Risk prediction tools further illustrate these limitations. Commonly used cardiovascular risk scores, developed for the general population, systematically underestimate risk in PWH (105). Even HIV-specific models show variable performance, highlighting the need for improved tools that incorporate HIV-related factors such as immune status, inflammation, and ART exposure (106).

The concept of accelerated aging, while widely invoked, also lacks standardized definition and measurement (107). Biological markers such as telomere length, epigenetic clocks, and inflammatory biomarkers do not always correlate consistently with clinical outcomes, making it difficult to operationalize aging in HIV (108,109).

Moreover, standard multimorbidity constructs fail to account for key HIV-specific contributors to disease burden. These include chronic viral coinfections, long-term ART toxicities, mental health disorders, substance use, and social determinants such as stigma and healthcare access. Sex and gender differences, which influence immune responses and disease trajectories, are also inadequately captured (94).

Clinically, guidelines for managing multimorbidity in PWH remain underdeveloped. Most recommendations focus on individual conditions rather than integrated care, despite the reality that patients often present with complex, interacting diseases (110). Additionally, the number of comorbidities alone does not fully capture disease burden; measures such as disability-adjusted life years (DALYs) may provide a more comprehensive assessment by incorporating both morbidity and mortality (111).

Finally, the aging of the HIV population introduces additional complexity through the emergence of geriatric syndromes and frailty. These multidimensional conditions - encompassing functional decline, vulnerability to stressors, and increased risk of adverse outcomes - extend beyond traditional disease-based models. Polypharmacy, drug–drug interactions, and inappropriate prescribing further complicate management, necessitating a multidisciplinary and geriatric-informed approach to care (16).

In this context, the CKM framework may serve as a conceptual bridge between multimorbidity management and the promotion of healthy aging in PWH. Its bidirectional staging system - from stage 0 (no CKM risk factors) through stage 4 (clinical CVD with CKM risk factors) - allows not only risk stratification but also the possibility of regression to earlier stages through targeted preventive interventions, aligning with the goals of prolonging health span rather than merely extending lifespan (63). This is particularly relevant in PWH, where HIV-associated chronic inflammation and immune dysregulation accelerate the biological mechanisms underlying CKM progression, including dysfunctional adiposity, endothelial dysfunction, and cellular senescence (94,102). From a geroscience perspective, the shared pathophysiological pathways between CKM syndrome and accelerated aging in HIV - such as inflammaging, mitochondrial dysfunction, and epigenetic alterations - suggest that stage-specific CKM interventions may simultaneously address both cardiometabolic-renal risk and aging-related vulnerability (94,112). Furthermore, the CKM construct supports a patient-centered, multidisciplinary model of care by integrating screening for social determinants of health, sex- and gender-specific risk factors, and geriatric syndromes into a unified clinical pathway (63,94). This holistic approach moves beyond disease-focused silos toward a care model that prioritizes what matters most to the individual patient - functional independence, quality of life, and the prevention of disability - consistent with the Age-Friendly 4Ms framework (Mentation, Medication, Mobility, What Matters Most) increasingly advocated for aging PWH (113). Adopting such an integrated perspective may help overcome many of the limitations outlined above, by embedding multimorbidity management within a broader strategy of healthy aging that is both clinically actionable and responsive to the unique needs of PWH.

4 CKM SYNDROME IN THE GENERAL POPULATION

Cardiovascular-kidney-metabolic (CKM) syndrome represents a paradigm shift in understanding the interconnected pathophysiology of metabolic dysfunction, chronic kidney disease (CKD), and cardiovascular disease (CVD). Rather than viewing these conditions as separate entities, CKM syndrome conceptualizes them as components of a unified, self-reinforcing system of multiorgan damage driven primarily by metabolic dysfunction, insulin resistance, and chronic inflammation (63,106).

The American Heart Association (AHA) formalized this framework in 2023 (101), emphasizing the need for integrated prevention and management strategies across the disease continuum. This shift reflects growing recognition that upstream metabolic abnormalities - such as obesity, dysglycemia, and ectopic fat deposition - precede and drive both cardiovascular and renal disease. Earlier conceptual models, such as cardiovascular-renal disease (CVRD), failed to fully capture this central metabolic origin, leading to the emergence of more comprehensive frameworks like CKM and even expanded models incorporating hepatic involvement (114).

4.1 The AHA 2023 CKM Framework: Definition and Staging

The AHA defines CKM syndrome as a systemic disorder characterized by interactions among metabolic risk factors, CKD, and the cardiovascular system, resulting in multiorgan dysfunction and a high rate of adverse cardiovascular outcomes. This definition includes both individuals at risk for CVD and those with established disease complicated by metabolic and renal dysfunction (63).

The framework introduces a five-stage classification system designed to guide early identification and intervention:

- Stage 0: absence of CKM risk factors, with normal body composition, metabolic parameters, kidney function, and no evidence of CVD;
- Stage 1: presence of excess or dysfunctional adiposity. This stage highlights adipose tissue as the initiating driver, including both simple excess weight and early metabolic dysfunction such as impaired glucose tolerance;

- Stage 2: development of metabolic risk factors (e.g., hypertension, dyslipidemia, prediabetes, diabetes, metabolic syndrome) and/or moderate-to-high-risk CKD;
- Stage 3: subclinical CVD or high predicted cardiovascular risk, including imaging or biomarker evidence of early organ damage;
- Stage 4: established clinical CVD (e.g., coronary artery disease, heart failure, stroke), often with persistent metabolic and renal abnormalities (63,101) (Figure 11).

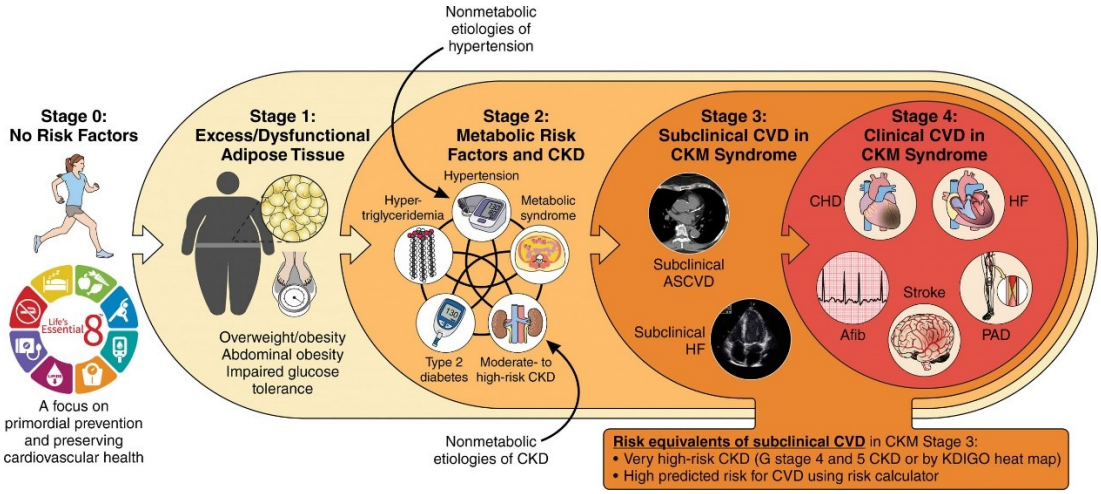


Figure 11. Stages of cardiovascular-kidney-metabolic (CKM) syndrome. *Adapted from Ndumele et al., Circulation, 2023.*

A key feature of this staging system is its bidirectional nature, allowing for both progression and regression. This emphasizes that CKM syndrome is not a linear, irreversible process but a dynamic continuum amenable to early and sustained intervention (103).

Importantly, the framework also incorporates risk-enhancing factors such as chronic inflammatory conditions, adverse social determinants of health, mental health disorders, sleep disturbances, and sex-specific factors (e.g., pregnancy complications, premature menopause), reflecting the multifactorial nature of CKM progression (63).

4.2 Pathophysiological Mechanisms

CKM syndrome is fundamentally driven by metabolic dysfunction, particularly excess and dysfunctional adipose tissue. Visceral adiposity plays a central role, acting as an active endocrine organ that secretes proinflammatory cytokines, adipokines, and reactive oxygen species, thereby promoting systemic inflammation and insulin resistance.

The pathophysiology involves complex bidirectional crosstalk between organs through several key mechanisms:

- Hemodynamic injury: hyperglycemia and hypertension induce glomerular hyperfiltration and endothelial stress, promoting both kidney damage and atherosclerosis;
- Metabolic toxicity: dysregulated glucose and lipid metabolism lead to accumulation of advanced glycation end products and oxidative stress;
- Inflammatory amplification: chronic low-grade inflammation, often originating from adipose tissue and metabolic dysfunction-associated steatotic liver disease (MASLD), amplifies systemic injury;
- Fibrotic progression: persistent inflammation leads to fibrosis in cardiovascular and renal tissues, which can become self-sustaining.

Ectopic fat deposition further exacerbates these processes. Accumulation of fat in the liver, heart (epicardial and pericardial fat), and kidneys contributes directly to organ dysfunction. For example, epicardial fat promotes arrhythmias and myocardial dysfunction, while hepatic steatosis (MASLD) is increasingly recognized as both a driver and consequence of CKM syndrome (63) (Figure 12).

This has led to proposals to expand the CKM framework into a cardiovascular-kidney-hepatic-metabolic (CKHM) model, acknowledging the liver as a central organ in metabolic regulation and disease propagation (114,115).

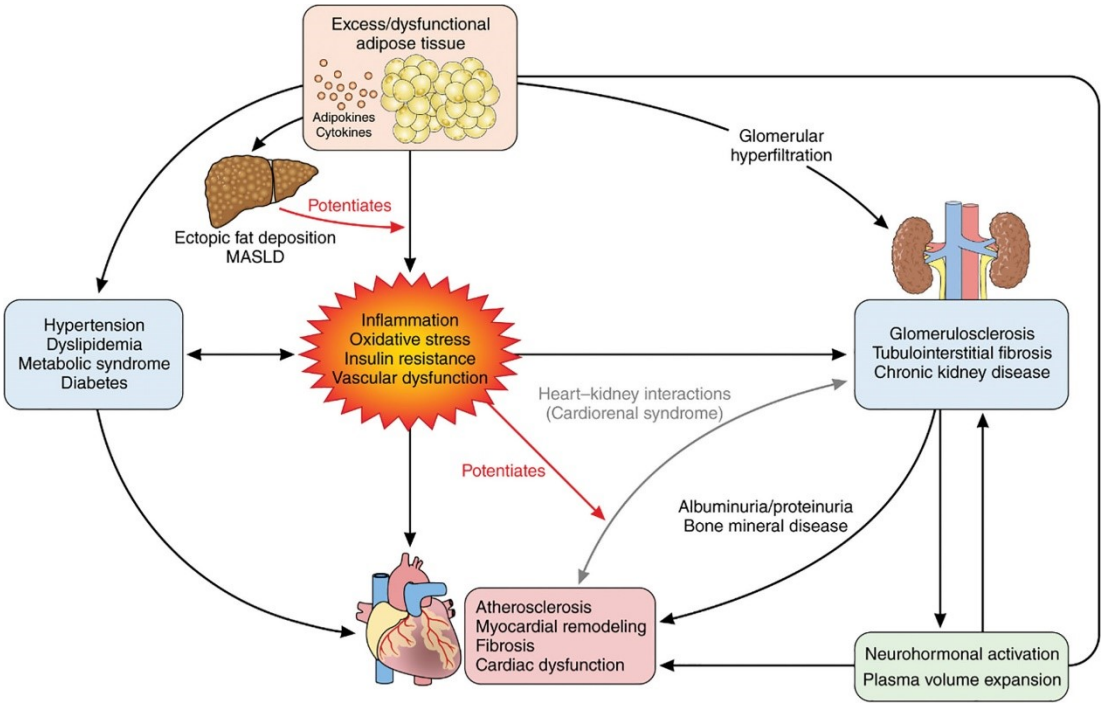


Figure 12. Conceptual diagram for CKM syndrome. *The image displays the pathophysiology underlying cardiovascular-kidney-metabolic (CKM) syndrome. Adapted from Ndumele et al., Circulation, 2023.*

4.3 An Expanded Framework: CKHM Syndrome

In 2025, Theodorakis and Nikolaou argued that the 2023 CKM syndrome framework has a critical omission: the liver (114). MASLD, which can progress to metabolic dysfunction-associated steatohepatitis (MASH), is tightly linked to insulin resistance and obesity and contributes directly to both cardiovascular and renal impairment (114,116). Importantly, MASLD is bidirectionally associated with the development and progression of CKM syndrome: hepatic dysfunction accelerates cardiorenal deterioration, while cardiovascular and renal disease worsen hepatic outcomes (114,117).

To address this gap, Theodorakis and Nikolaou proposed the cardiovascular-kidney-hepatic-metabolic (CKHM) syndrome (or cardiovascular-renal-hepatic-metabolic syndrome - CRHM), an expanded framework that incorporates the liver's pivotal role in inter-organ metabolic crosstalk (114). The CKHM model advocates for an integrated diagnostic and therapeutic approach - rather than organ-specific management - leveraging agents such as SGLT2 inhibitors, GLP-1 receptor agonists, and dual GIP/GLP-1 receptor agonists that target shared pathophysiological pathways and confer benefits across

multiple organ systems simultaneously (116). This concept has since gained traction, with subsequent multidisciplinary consensus statements similarly calling for the inclusion of the liver in cardiometabolic syndrome frameworks (115,118).

4.4 Epidemiology in the General Population

CKM syndrome is highly prevalent and represents a major public health challenge. Population-based studies indicate that the majority of adults fall within the CKM spectrum, with stage 2 (metabolic risk factors or early CKD) being the most common.

Large epidemiological analyses show that:

- Stage 2 affects the largest proportion of the population, reflecting widespread metabolic dysfunction. In recent surveys, 43–56% of adults were classified as stage 2, making it the predominant CKM stage (119,120);
- Stage 1 affects approximately 25-35% of adults, reflecting the high prevalence of excess adiposity and early metabolic risk before the development of established metabolic abnormalities or CKD (120);
- Advanced stages (3–4) account for approximately 10–15% of adults, a smaller but steadily increasing proportion associated with markedly higher cardiovascular and all-cause mortality (121,122);
- Stage 0 represents only 8–12% of the adult population and has shown a declining trend over the last two decades, indicating progressive deterioration in cardiometabolic health at the population level (119–121,123–125).

Overall, nearly 90% of adults meet the criteria for CKM syndrome (stage 1 or higher), underscoring the enormous public health burden of this condition and the need for early preventive interventions (123,126).

CKD is often the most prevalent individual component, followed by diabetes and CVD. Importantly, these conditions frequently overlap, reinforcing the concept of a shared pathophysiological continuum (127).

Disparities are evident across geographic, socioeconomic, and demographic groups. Higher CKM burden is observed among older individuals, those with obesity, smokers,

individuals with lower education and income, and residents of rural areas. These patterns highlight the critical role of social determinants of health in shaping CKM risk (124,125,128).

4.5 Mortality and Clinical Outcomes

CKM syndrome is associated with markedly increased mortality and adverse clinical outcomes. Multiple large prospective cohort studies have consistently demonstrated that the risk of all-cause mortality, cardiovascular death, and progression to end-stage kidney disease rises progressively with each advancing CKM stage (129). In the UK Biobank (n = 110,933; median follow-up 14.7 years), all-cause mortality rates increased from 6.3% at Stage 0 to 30.1% at Stage 4, with adjusted HRs of 1.14 for Stage 2, 1.25 for Stage 3, and 2.13 for Stage 4 (130) (Figure 13). The association was even more pronounced for CVD-specific mortality, with adjusted HRs reaching 3.46 (95% CI 2.50–4.77) at Stage 4 (130) (Figure 14). Similarly, Wang et al. (eClinicalMedicine, 2025; n = 413,547 UK Biobank participants) reported a stepwise increase in CVD-specific mortality across CKM stages, with an adjusted HR of 10.40 (95% CI 7.61–14.21) for Stage 4 vs. Stage 0, and notably stronger associations among younger individuals (<60 years) and younger females (131).

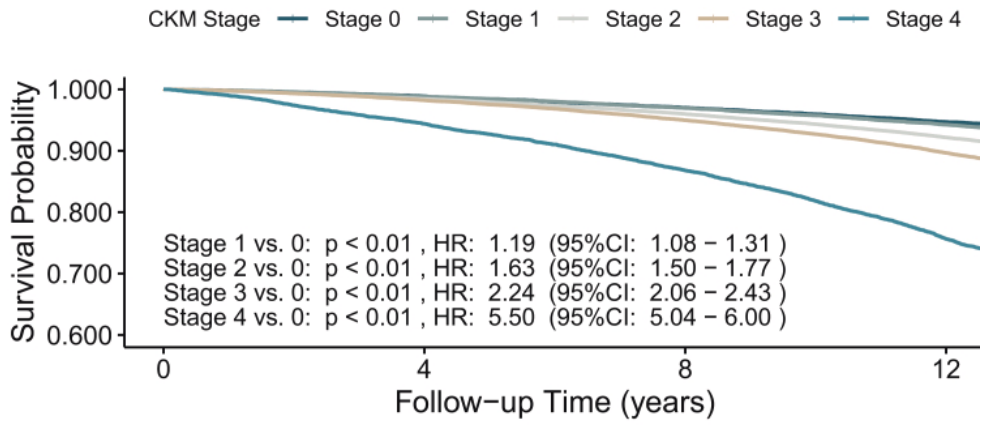


Figure 13. K-M Curves by Stage (All-Cause Death Endpoint). *The curves represent the survival probabilities for patients categorized into 5 CKM stages (Stage 0-4). Adapted from Chen et al., JACC Adv, 2025.*

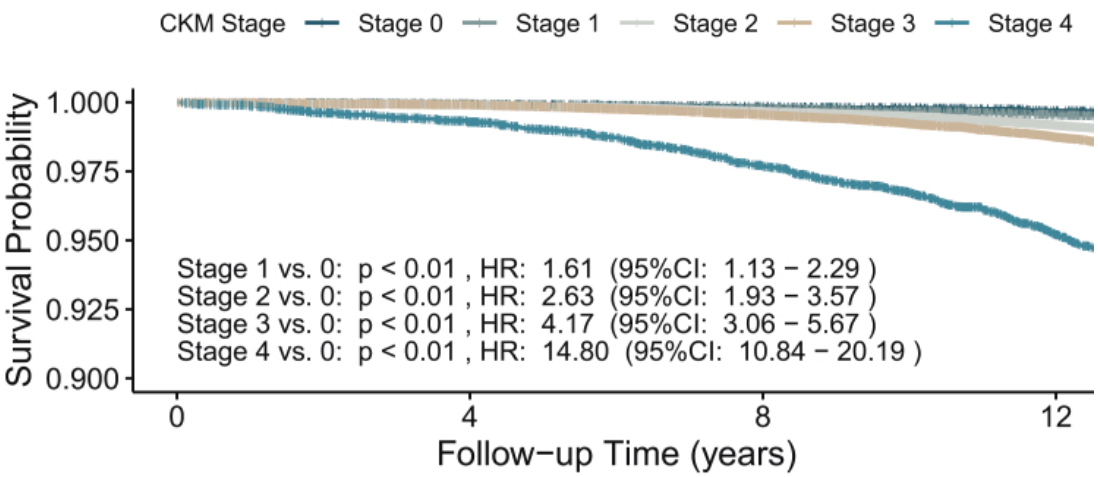


Figure 14. K-M Curves by Stage (CVD Death Endpoint). *The K-M curves illustrate survival probabilities for individuals classified into 5 CKM stages (Stage 0-4). Adapted from Chen et al., JACC Adv, 2025.*

Each component contributes cumulatively to risk, with additive effects on mortality and reductions in life expectancy. In a large Taiwanese cohort (n = 515,602; median follow-up 16.5 years), each additional CKM component was associated with a 22% increase in all-cause mortality risk (HR 1.22; 95% CI 1.21–1.23), a 37% increase in CVD mortality (HR 1.37; 95% CI 1.35–1.40), and a reduction in average life expectancy of approximately 3 years per component (129). The population-attributable fraction of CKM syndrome was 55% for CVD mortality, underscoring its dominant contribution to cardiovascular death at the population level (129). Notably, CKD plays a critical role in amplifying cardiovascular risk: the AHA Scientific Statement on CKM syndrome emphasizes that CKD is a "major amplifier of cardiovascular risk", and that the most common causes of death for people with diabetes and CKD are heart failure and atherosclerotic CVD, with only ~10% of CKD patients surviving to reach kidney failure (63). Failure to account for renal disease leads to underestimation of cardiovascular mortality - Tsai et al. estimated that excluding CKD from CKM syndrome would result in the missed attribution of 11% of CVD deaths (129).

Advanced CKM stages are associated with particularly high death rates. In the UK Biobank (n = 413,547), Wang et al. reported adjusted HRs for all-cause mortality rising from 1.21 (Stage 2) to 2.30 (Stage 4), with CVD-specific mortality reaching an HR of 10.40 at Stage 4 - associations notably stronger in younger adults (<60 years) (131). Zhou

et al. (CHERRY study; n = 764,856) confirmed this gradient in an Asian population (CVD mortality HR 5.64 at Stage 4), identifying CKD as the most potent risk amplifier at every stage (132). Gunnarsson et al. (2026) further highlighted that 34% of Stage 1 individuals progress to higher stages, driven by self-reinforcing cycles of metabolic, renal, and cardiac damage (126). These consistent findings across diverse populations reinforce the value of the CKM staging system in risk stratification and support early, stage-specific intervention.

4.6 Risk Prediction and Screening

To address limitations in traditional cardiovascular risk assessment, the AHA introduced the PREVENT equations, which incorporate kidney function and provide both short- and long-term risk estimates. These tools complement the CKM staging system and support more precise risk stratification (101,103).

Screening strategies are increasingly risk-based and span the life course:

- Early life: focus on identifying obesity, hypertension, and early metabolic abnormalities, with attention to family history and social determinants;
- Adulthood: regular monitoring of BMI, waist circumference, blood pressure, lipid profile, glucose metabolism, and kidney function;
- Higher-risk individuals: more frequent screening, including assessment of albuminuria, imaging for subclinical CVD, and evaluation of liver fibrosis in those with suspected MASLD (63,101).

Emerging approaches also emphasize the importance of detecting subclinical disease, such as coronary artery calcium and early cardiac dysfunction, to guide preventive interventions (63,133).

4.7 Management Strategies Across CKM Stages

Management of CKM syndrome is stage-specific and emphasizes both lifestyle and pharmacological interventions.

- Stage 0 (no CKM risk factors): primordial prevention through healthy lifestyle behaviors aligned with the Life's Essential 8 framework, including heart-healthy diet, regular physical activity, smoking cessation, adequate sleep, and avoidance of excess weight gain across the life course (134) (Figure 15);

Figure 15. Life's Essential 8. *Adapted from Lloyd-Jones et al., Circulation, 2022.*

- Stage 1 (excess or dysfunctional adiposity): focus on preventing metabolic risk factor development through comprehensive lifestyle modification, targeting ≥ 5% weight loss for clinically meaningful cardiometabolic benefit. Obesity pharmacotherapy (e.g., GLP-1 RAs) and bariatric surgery should be considered in selected cases. Metformin or lifestyle intervention may be used in those with impaired glucose tolerance to prevent progression to diabetes;

- Stage 2 (metabolic risk factors and/or CKD): addition of pharmacological therapies targeting hypertension (goal <130/80 mmHg), dyslipidemia (moderate- to high-intensity statins), and diabetes. A comorbidity-driven approach guides selection of cardioprotective glucose-lowering agents: SGLT2 inhibitors are preferred for those with CKD or heart failure risk, while GLP-1 receptor agonists are favored for those with obesity or high ASCVD risk, providing cardiovascular and renal protection beyond glycemic control;
- Stage 3 (subclinical CVD with CKM risk factors): intensified preventive strategies guided by subclinical disease detection. Coronary artery calcium (CAC) scoring is endorsed to refine risk stratification and statin therapy decisions in borderline-to-intermediate risk patients. BNP-based screening for subclinical heart failure is supported, particularly in older adults with diabetes;
- Stage 4 (clinical CVD with CKM risk factors): comprehensive guideline-directed medical therapy for established CVD - including the four pillars of HFrEF management (β-blockers, ARNI, MRA, and SGLT2 inhibitors) and high-intensity statins with antiplatelet therapy for ASCVD - combined with aggressive management of metabolic and renal risk factors. SGLT2 inhibitors benefit both HFrEF and HFpEF regardless of diabetes status (63,101,135) (Figures 16, 17).

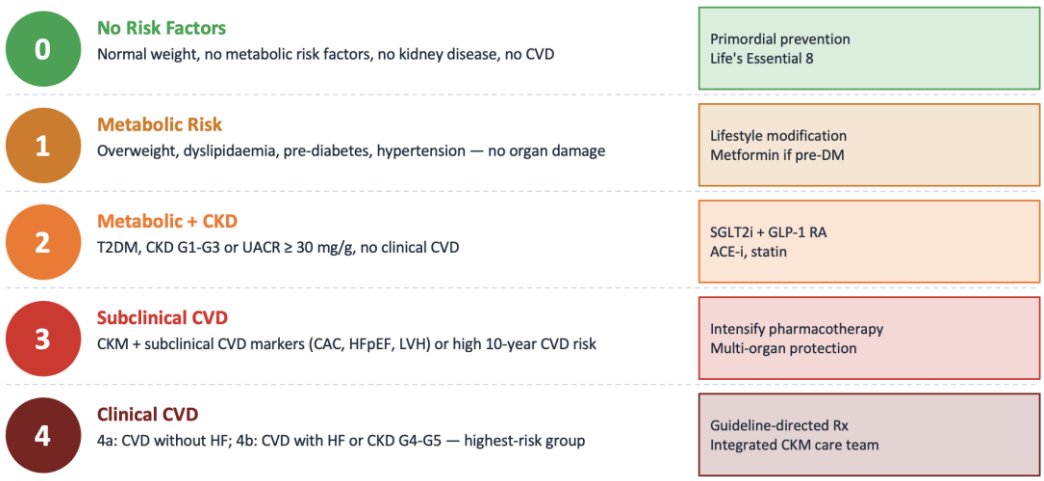


Figure 16. CKM syndrome stages and intervention strategies. *Adapted from Ndumele et al., Circulation, 2023.*

Intervention	Hallmarks Modulated	Clinical Impact
Physical activity	Inflammation, senescence, mitochondrial function	↑ Biological age · ↑ vascular function
Caloric restriction / diet	mTOR/AMPK, autophagy, oxidative stress	↓ Cardiometabolic risk (CALERIE trial)
Statins	Inflammation, endothelial senescence	↓ MACE 35% in PLWH (REPRIEVE)
Metformin	AMPK/mTOR, inflammaging, proteostasis, NFκB	↓ CV mortality · TAME trial ongoing
GLP-1 agonists	Nutrient sensing, oxidative stress, mitochondria	↓ CV events · weight loss · renal protection
SGLT2 inhibitors	Inflammation, autophagy, nutrient sensing	Cardio-renal protection · ↑ metabolic resilience
Optimized ART	Inflammation, epigenetics, telomere length	Epigenetic age acceleration: ~14 → ~6 years

CKM prevention and healthy aging may represent the same therapeutic target.

Figure 17. Targeting Hallmarks of Aging to Prevent CKM Progression. *Several interventions used in HIV and cardiometabolic care act as gerotherapeutics, modulating hallmarks of aging – extending benefit beyond disease control toward biological resilience.*

Across all stages, the AHA emphasizes interdisciplinary care and systematic screening for social determinants of health (SDOH), recognizing that adverse social conditions are intrinsically linked to access to CKM therapies. Care teams should include care navigators, social workers, or community health workers to connect patients to resources, and prevention efforts must extend beyond clinical settings to address the social context in which individuals live (63,101,135).

4.7.1 Statins

Statins represent a cornerstone pharmacological intervention across CKM stages, with benefits extending beyond lipid lowering. Their pleiotropic effects - including anti-inflammatory, antioxidant, and endothelial-protective properties - may attenuate the interconnected pathophysiology linking metabolic, renal, and cardiovascular damage (131,136).

In patients with CKD (a key driver of CKM progression), a Cochrane meta-analysis (43 RCTs; 41,273 participants) confirmed that statins reduce all-cause mortality and major adverse cardiovascular events (MACE) with high-certainty evidence, though benefits diminish in those on dialysis (137).

A meta-analysis by Lin et al. (2025) specifically evaluating statin therapy in CKM Stage 2 demonstrated significant reductions in LDL-C and total cholesterol, with favorable trends toward improved eGFR and reduced proteinuria - effects more pronounced with high-intensity regimens (138).

The AHA Scientific Statement on CKM syndrome supports statin use for cardiovascular risk reduction across CKM stages, particularly in patients with established CKD or elevated ASCVD risk, as part of a comprehensive, stage-specific management strategy (63).

4.7.2 Metformin

Metformin remains a foundational glucose-lowering agent with potential relevance across CKM stages, particularly in early disease. Beyond glycemic control, metformin exerts pleiotropic effects - including AMPK activation, anti-inflammatory signaling, improved endothelial function, and reduced oxidative stress - that may attenuate the interconnected metabolic, renal, and cardiovascular pathways central to CKM pathophysiology (63,139,140).

The UK Prospective Diabetes Study demonstrated reductions in myocardial infarction (39%) and all-cause mortality (36%) in overweight patients with type 2 diabetes (139), and a subsequent meta-analysis (>1 million patients) confirmed reduced cardiovascular and all-cause mortality with metformin use (141).

In patients with CKD, metformin is recommended at eGFR ≥30 mL/min/1.73 m², with dose reduction below 45 mL/min/1.73 m², though direct cardiorenal benefits in this subgroup remain less established (141,142).

The AHA Scientific Statement on CKM syndrome positions metformin as a cost-effective adjunct to newer cardioprotective agents (SGLT2 inhibitors, GLP-1 RAs), particularly for achieving glycemic targets in patients with uncontrolled hyperglycemia (63).

4.7.3 SGLT2i

SGLT2 inhibitors have emerged as a cornerstone therapy across CKM stages, with benefits extending well beyond glycemic control. Their primary actions - glycosuria and natriuresis - trigger a cascade of pleiotropic effects including hemodynamic optimization, enhanced myocardial energetics via ketone utilization, reduced inflammation and oxidative stress, and attenuation of sympathetic overactivity (143,144).

A meta-analysis of 13 trials (n = 90,413) demonstrated that SGLT2 inhibitors reduced the composite of heart failure hospitalization or cardiovascular death by ~24% in heart failure, ~23% in type 2 diabetes, and ~23% in CKD, with consistent benefits across varying combinations of these conditions (145).

Crucially, cardiorenal protection is independent of diabetes status: the DAPA-CKD and EMPA-KIDNEY trials confirmed reductions in kidney disease progression and cardiovascular death in patients with CKD regardless of the presence of diabetes (146,147). A Cochrane review (2024) estimated that SGLT2 inhibitors prevent death in 19 per 1,000 patients with CKD stages 1–2 and 3 per 1,000 with CKD stages 3–5 treated over one year (147).

Current guidelines provide Class I recommendations for SGLT2 inhibitors across heart failure phenotypes and in CKD, positioning them - alongside RAAS inhibitors, beta-blockers, and mineralocorticoid receptor antagonists - as foundational therapy within the CKM framework (144,148).

4.7.4 GLP1/GLP1Ra

GLP-1 receptor agonists and the dual GIP/GLP-1 receptor agonist tirzepatide have emerged as key therapeutic tools across CKM stages, offering integrated benefits on weight, glycemia, cardiovascular risk, and kidney protection. Their mechanisms extend beyond metabolic control to include anti-inflammatory effects, improved endothelial function, and RAAS modulation (63,149,150).

A meta-analysis of 10 cardiovascular outcome trials (n = 71,351) demonstrated that GLP-1 RAs reduce MACE by 14%, heart failure hospitalization by 14%, a composite kidney outcome by 17%, and all-cause mortality by 12% (151). The FLOW trial further

confirmed a 24% reduction in kidney disease progression with semaglutide in patients with type 2 diabetes and CKD (152).

Tirzepatide, through dual incretin receptor agonism, appears to extend these benefits: in the SURPASS-CVOT trial (n = 13,165), it reduced the primary composite kidney outcome by 23% compared with dulaglutide, with greater effects in high-risk CKD subgroups, and retrospective data suggest superior reductions in mortality and MACE versus GLP-1 RAs alone (153,154).

Current ADA guidelines position incretin-based therapies alongside SGLT2 inhibitors as foundational agents for cardiovascular and renal protection in CKM management (63,155).

4.7.5 Finerenone

Finerenone is the mineralocorticoid receptor antagonist (MRA) with the strongest evidence across CKM syndrome stages. In the FIDELITY pooled analysis (n = 13,026), finerenone reduced cardiovascular events by 14% and kidney events by 23% on top of maximally tolerated ACEi/ARB (156).

The INFINITY individual participant data meta-analysis (n = 14,574) confirmed reductions in HF hospitalization (22%), CV death (18%), and kidney composites (24%), with benefits consistent regardless of CKD etiology, glycemic status, or SGLT2 inhibitor use (157).

A post hoc FIDELITY analysis mapped these effects across AHA-defined CKM stages 2–4, showing consistent cardiorenal protection at every stage, with the greatest absolute benefit in stage 4 (established CVD) (158).

Finerenone is now FDA-approved for both CKD associated with type 2 diabetes and HF with LVEF ≥40%, and current KDIGO/ADA guidelines position it as a key pillar - alongside SGLT2 inhibitors and GLP-1 Ras - in the multi-drug management of CKM syndrome (155).

4.8 CKM Syndrome in Special Populations

Significant disparities exist in CKM syndrome across different populations. Racial and ethnic minorities, particularly Black and Indigenous populations, experience higher rates of advanced disease and mortality, largely driven by social determinants of health (124,159).

Sex-specific differences are also evident. Women, particularly after menopause, may have higher prevalence of advanced CKM stages. Pregnancy-related conditions such as gestational diabetes and preeclampsia further increase long-term risk (63,160).

Age is a major determinant, with advanced stages more common in older adults. However, early metabolic dysfunction often begins decades earlier, highlighting the importance of early-life prevention (63,130).

Socioeconomic and geographic disparities further shape CKM risk. Lower income, limited education, rural residence, and reduced access to healthcare are all associated with worse outcomes, emphasizing the need for health system-level interventions (63,128,161).

4.9 Heterogeneity Within CKM Syndrome

CKM syndrome is highly heterogeneous. Individuals with similar body mass index may have vastly different metabolic profiles, reflecting differences in fat distribution, particularly visceral and ectopic fat (63,162).

Some individuals with obesity remain metabolically healthy, while others develop severe metabolic dysfunction at lower levels of adiposity. This variability underscores the importance of assessing metabolic health beyond simple anthropometric measures (63).

Progression through CKM stages also varies widely, influenced by genetic factors, lifestyle behaviors, environmental exposures, chronic inflammation, and social determinants (63,125). Understanding this heterogeneity remains a major challenge and area of active research.

4.10 CKM Syndrome Versus Metabolic Syndrome: a Conceptual Advance

The CKM syndrome framework, introduced by the AHA in 2023, represents a substantial conceptual advance over the traditional metabolic syndrome (MetS) construct (63,101). While MetS has been valuable in highlighting the clustering of cardiometabolic risk factors - abdominal obesity, dysglycemia, atherogenic dyslipidemia, and hypertension - it has well-recognized limitations (163). MetS operates as a binary classification (present or absent), which neglects both the risk gradient associated with an increasing number of components and the continuous risk gradient observable for individual risk factors (163). Moreover, MetS focuses narrowly on metabolic risk factor aggregation without directly linking to hard clinical outcomes such as MACE, heart failure, CKD progression, or mortality, and it excludes kidney involvement entirely from its diagnostic framework (63).

The CKM construct addresses these limitations across several dimensions. First, it expands the organ scope beyond metabolism alone to explicitly integrate the kidney and the cardiovascular system as central, interacting components of a unified pathophysiological process (63,101). CKD is incorporated from Stage 1 onward, reflecting the growing recognition that kidney dysfunction is both a consequence and an amplifier of metabolic and CVD (164). Second, CKM syndrome replaces the binary MetS classification with a 5-stage dynamic continuum (Stages 0–4), in which each stage transition confers an incrementally higher absolute CVD and mortality risk (126,130). Critically, this staging path is bidirectional: stage regression is explicitly targeted, with evidence supporting that individuals can regress even back to Stage 0 through targeted preventive interventions such as lifestyle modification, weight-loss pharmacotherapy, or remission of metabolic risk factors (63,103). Third, the CKM framework is outcome-oriented, anchored to hard endpoints including MACE, heart failure hospitalization, kidney failure, and all-cause mortality, rather than serving merely as a risk cluster (63,130).

From a therapeutic perspective, the CKM construct provides stage-specific, mechanism-guided management recommendations - ranging from lifestyle interventions and weight-loss pharmacotherapy (GLP-1 receptor agonists) in early stages to multi-drug cardio-renal

protection (SGLT2 inhibitors, RAAS blockade, finerenone) in advanced disease - rather than the generic lifestyle and statin approach traditionally associated with MetS (63,126). Furthermore, the CKM framework accommodates lean metabolic dysfunction, recognizing that individuals with dysfunctional adiposity or metabolic risk factors may develop CKM syndrome even in the absence of overt obesity, a phenotype that MetS - with its obesity-centric diagnostic criteria - tends to miss (63,165). Finally, the CKM construct aligns with emerging geroscience principles: the pathways driving CKM progression - including AMPK dysregulation, mTOR hyperactivation, and cellular senescence - overlap substantially with the hallmarks of biological aging, providing a mechanistic bridge between metabolic disease and accelerated organ damage that MetS does not address (140,166) (Figure 18).

Feature	Metabolic Syndrome	CKM Syndrome
Organ scope	Metabolic only	Metabolic + Kidney + Heart
Clinical outcome focus	Risk cluster (no outcome)	Hard outcomes: MACE, CKD, mortality
Disease staging	Binary (yes/no)	5-stage dynamic continuum (0–4)
Reversal possible?	Rarely addressed	Stage regression explicitly targeted
Therapeutic guidance	Generic lifestyle + statins	Stage-specific, mechanism-guided Rx
Kidney involvement	Excluded	Central component from Stage 1
Geroscience integration	None	AMPK, mTOR, senescence pathways
Population applicability	Obesity-centric	Includes lean metabolic dysfunction

Figure 18. Comparison between Metabolic Syndrome and CKM Syndrome.

In summary, while MetS remains a useful screening tool for identifying clusters of metabolic risk, the CKM syndrome framework offers a more comprehensive, dynamic, and clinically actionable model that better reflects the multiorgan pathophysiology, progressive nature, and therapeutic opportunities of cardiometabolic disease (63).

5 CKM SYNDROME IN PWH

As ART has transformed HIV into a chronic condition, PWH face a growing burden of non-infectious comorbidities, among which CKM syndrome - the convergence of metabolic dysfunction, CVD, and CKD - is particularly concerning. With nearly 41 million people living with HIV globally and the majority in high-income settings now over 50, chronic comorbidities occur two to four times more frequently than in the general population and rarely in isolation, instead clustering within the interconnected CKM framework. Visceral adiposity further amplifies these interactions, accelerating disease progression across metabolic, cardiovascular, and renal domains (5,27,28,63,102).

Despite the growing clinical importance of CKM syndrome in PWH, this area remains poorly characterized. Presentations at the 2026 Conference on Retroviruses and Opportunistic Infections (CROI) described CKM in PWH as "an emerging frontier for clinical pharmacology", emphasizing that inflammation, pharmacokinetic complexity, ART-associated metabolic effects, and gut dysbiosis collectively amplify risk. Yet, fundamental questions about prevalence, natural history, and optimal management remain unanswered (102).

5.1 Mechanistic Pathways: a Converging Network

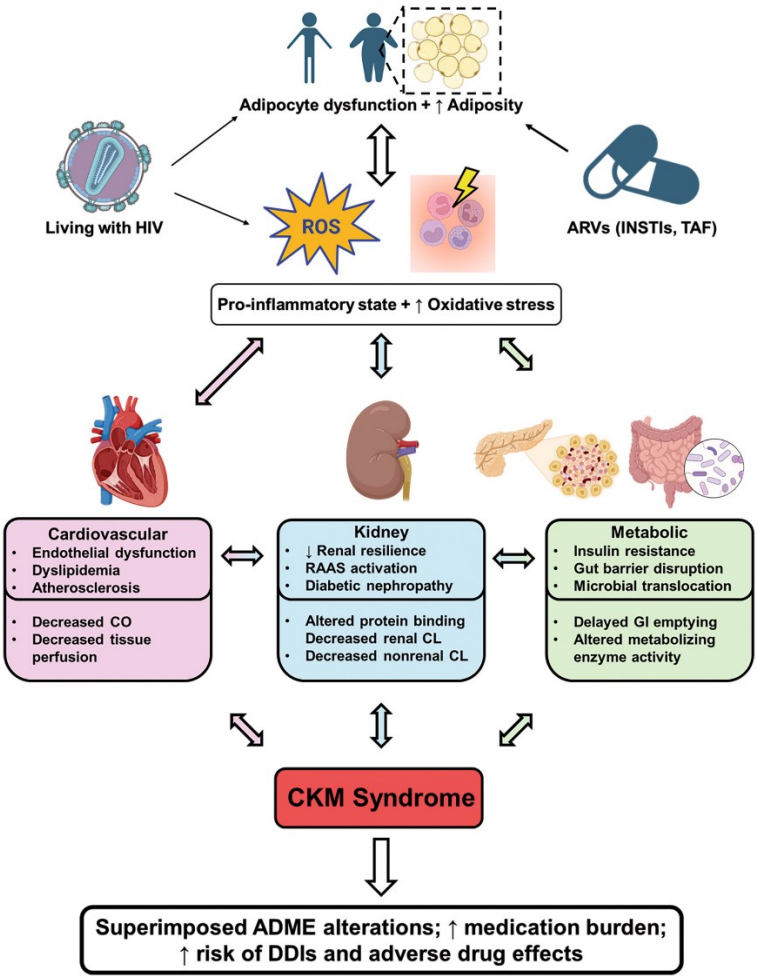
Multiple interconnected mechanisms drive CKM syndrome in PWH, creating a distinct and multifaceted phenotype:

- Chronic inflammation and immune activation: persistent immune activation remains a hallmark of treated HIV infection. Elevated cytokines, monocyte activation markers, and endothelial dysfunction contribute to atherosclerosis, insulin resistance, and renal injury (16,28);
- HIV viral effects: viral proteins directly disrupt lipid metabolism, promote insulin resistance, and impair adipocyte function, contributing to metabolic dysregulation (49);
- ART-associated metabolic effects: while modern ART regimens are safer, they are not metabolically neutral. Weight gain, visceral adiposity, and altered glucose and lipid metabolism are increasingly recognized, particularly with newer agents (29,34);

- Gut dysbiosis and microbial translocation: disruption of the gut barrier allows microbial products such as lipopolysaccharide to enter circulation, fueling systemic inflammation. Microbiota-derived metabolites such as trimethylamine N-oxide (TMAO) are implicated in atherosclerosis, thrombosis, and renal fibrosis. Other metabolites, including myristic acid, may further link lipid metabolism to kidney injury (167–169);
- Pharmacokinetic complexity: HIV infection and its treatment can alter drug absorption, distribution, metabolism, and excretion. Obesity further modifies these parameters, affecting drug efficacy and safety in CKM therapies (170);
- Renin-angiotensin-aldosterone system (RAAS) activation: RAAS dysregulation contributes to hypertension and metabolic dysfunction, interacting with inflammatory pathways (171);
- Accelerated aging and sarcopenic obesity: PWH experience premature biological aging characterized by mitochondrial stress, cellular senescence, and muscle loss. When combined with obesity, this leads to sarcopenic obesity, a phenotype strongly associated with functional decline and CKM progression (94,172).

Together, these mechanisms create a CKM phenotype in PWH that is earlier in onset, more complex, and often more aggressive than in the general population (102) (Figures 19, 20).

Figure 19. Intertwined relationships and HIV-specific mechanisms that promote obesity and accelerate CKM trajectories. *The pathophysiology and pharmacokinetic alterations are displayed. Adapted from Devanathan et al., Clin Pharmacol Ther, 2025.*



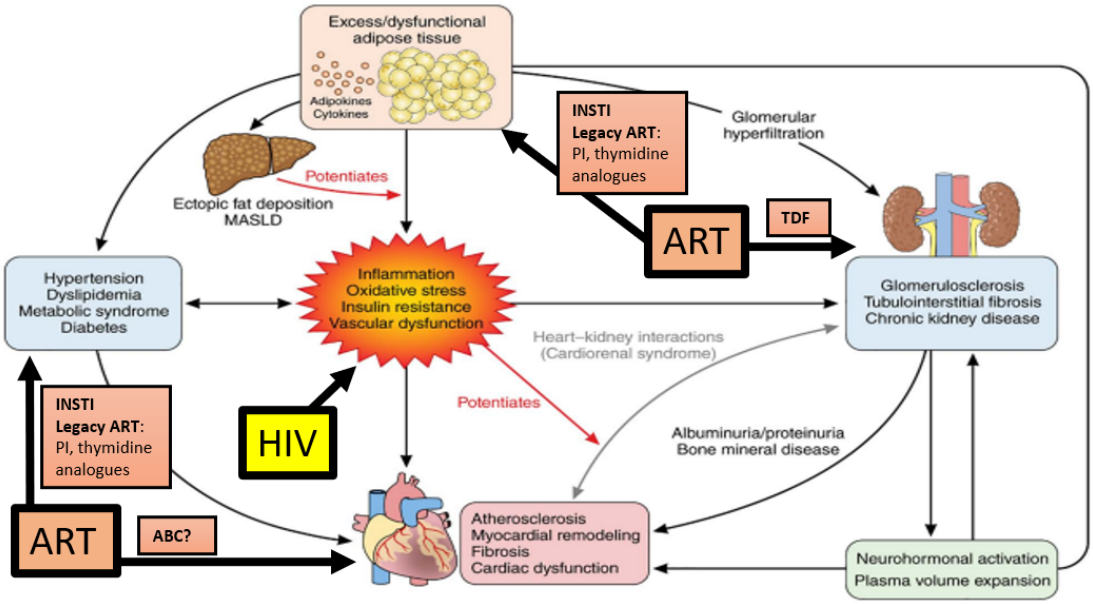


Figure 20. Proposed pathophysiology of CKM syndrome in PWH.

Recognizing this mechanistic convergence has direct implications for clinical care. The geroscience hypothesis proposes that therapeutically targeting fundamental aging processes - rather than addressing each comorbidity individually - could have a greater impact on delaying CKM progression and preserving functional capacity in PWH (112). This principle aligns with the shift from disease-centered to patient-centered care models, in which the goal extends beyond lifespan to the preservation of health span - the period of life free from significant disability and multimorbidity (94). Translating this vision into practice requires integrated care platforms that embed CKM risk assessment within broader multidomain screening for aging-related vulnerabilities, including cognitive decline, frailty, polypharmacy, and psychosocial needs. Early real-world experiences with such programs - incorporating multidisciplinary teams of HIV specialists, geriatricians, cardiologists, pharmacists, and social workers - have demonstrated high rates of identification of previously unrecognized aging-related conditions and improved engagement with cardiometabolic preventive care, even among virologically suppressed individuals (113,173,174). These models illustrate how a mechanistic understanding of CKM in PWH can be operationalized into holistic, patient-centered care pathways that address not only what drives disease, but what matters most to the individual patient.

5.2 The Knowledge Gap: What Remains Unknown

Despite advances in understanding individual components of CKM, the integrated syndrome remains insufficiently studied in PWH. Most research has focused on single-organ outcomes, leaving a gap in multidomain approaches that capture the full syndemic.

Key unanswered questions include:

- How prevalent is CKM syndrome across its stages in PWH?
- Does HIV accelerate progression through CKM stages?
- How do ART and CKM therapies interact pharmacologically?
- Can HIV-specific biomarkers improve risk prediction?
- Do standard CKM treatments provide equivalent benefits in PWH?

Additionally, there is growing recognition of the need for multidomain biomarker panels that capture overlapping pathways. For example, distinct phenotype "signatures" may emerge:

- A vascular–renal–inflammatory profile suggesting benefit from early statins and SGLT2 inhibitors;
- A gut–inflammation profile pointing toward microbiome-targeted interventions;
- A metabolic–adiposity profile favoring GLP-1 receptor agonists and lifestyle modification.

Such stratification could enable more precise and personalized CKM care in PWH.

5.3 Study Hypotheses: Advancing CKM Research in PWH

Building on current knowledge, several key hypotheses emerge:

- Accelerated CKM progression: PWH likely transition through CKM stages more rapidly due to persistent inflammation, metabolic disruption, and HIV-specific factors;
- Inflammation-driven phenotype: inflammatory biomarkers may independently predict CKM risk and improve stratification beyond traditional models;
- Differential therapeutic response: SGLT2 inhibitors and GLP-1 receptor agonists may remain beneficial but could exhibit altered efficacy or safety due to pharmacokinetic changes and ART interactions;
- Gut microbiome as a therapeutic target: interventions restoring gut integrity may reduce inflammation and slow CKM progression;
- ART regimen effects: integrase inhibitor–based therapies may reduce some metabolic risks compared to older regimens, though their association with weight gain complicates this relationship;
- Impact of early ART initiation: early treatment may mitigate long-term CKM risk by limiting cumulative inflammation and preserving immune function.

STUDY OBJECTIVE

The aim of this study was to determine the prevalence of CKHM stages, to characterize stage-to-stage transitions over the period 2005–2025, and to identify clinical, metabolic, and HIV-related factors associated with progression and reversion across CKHM stages among people with HIV (PWH).

METHODS

Study Design, Setting and Inclusion Criteria

This was a longitudinal observational study including ART-experienced PWH attending the Modena HIV Metabolic Clinic (MHMC), Italy, between 2005 and 2025.

MHMC is a tertiary-level referral center established in 2004, where each patient is routinely followed for the screening and management of comorbidities, including subclinical cardiovascular disease, immuno-metabolic disorders, geriatric syndromes, and frailty, as previously described (175). At each annual visit, every patient undergo a standardized one-day comprehensive evaluation. This includes blood sampling for HIV-related parameters as well as endocrinological and immuno-metabolic biomarkers, assessment of liver fibrosis by transient elastography, and body composition analysis by Dual-energy X-ray absorptiometry (DEXA). DEXA provides detailed measures of total and regional lean mass, fat mass - including visceral adipose tissue (VAT) - and bone mineral density (176).

For the estimation of CKHM prevalence, all PWH with at least one CKHM assessment during the study period were eligible for inclusion. Analyses of transitions across CKHM stages were restricted to PWH with at least two assessments over time.

To better characterize temporal trends in CKHM burden and stage transitions, the observation period was divided into three predefined intervals: 2005–2015 (Period 1), 2016–2020 (Period 2), and 2021–2025 (Period 3). These intervals were defined according to major changes in antiretroviral therapy (ART) practices:

- Period 1 (2005–2015) corresponds to the pre-INSTI and first-generation INSTI era, preceding the widespread adoption of integrase strand transfer inhibitors (INSTIs), and to a period in which protease inhibitors (PIs) were still commonly used as part of standard regimens;
- Period 2 (2016–2020) is characterized by the introduction and progressive widespread use of second-generation INSTIs, alongside a gradual decline in PI-based regimens, which were progressively replaced in clinical practice;

- Period 3 (2021–2025) represents the post-COVID-19 era, during which second-generation INSTIs had been in use long enough to allow evaluation of their potential long-term impact on CKHM progression and reversion. In this period, PIs were no longer used as first-line therapy in ART-naïve patients in routine clinical practice.

CKHM Criteria

CKHM status was evaluated at each visit at the MHMC. The classification system was derived from the American Heart Association/American College of Cardiology (AHA/ACC) CKM framework and adapted to the study population by integrating hepatic involvement. The primary aim of this adaptation was to ensure complete patient classification at all time points, following a "no one left behind" principle. To ensure longitudinal consistency, CKHM Stage 4 was considered irreversible. Accordingly, once a patient fulfilled criteria for Stage 4, subsequent visits were no longer used for stage reclassification, as further transitions were not considered clinically plausible within the study framework. In line with this assumption, certain chronic conditions - namely diabetes, hypertension, and chronic kidney disease (CKD) - were also treated as non-reversible for staging purposes, despite their potential partial reversibility in real-world clinical practice.

CKHM stages were defined as follows:

- CKHM Stage 0 was defined as the absence of metabolic risk factors, including all of the following: age <40 years or low-to-moderate cardiovascular (CV) risk, preserved renal function (eGFR ≥60 mL/min/1.73 m^2), absence of hypertension and diabetes, and at least two favorable metabolic or anthropometric parameters, including optimal glucose metabolism, LDL cholesterol, triglycerides, and body composition indices;
- CKHM Stage 1 was defined by preserved renal function (eGFR ≥60 mL/min/1.73 m^2) in the presence of at least one of the following: moderate-to-high CV risk or at least one metabolic, anthropometric, or lipid abnormality, consistent with early cardiometabolic risk without evidence of target organ damage;
- CKHM Stage 2 was characterized by the coexistence of metabolic and cardiovascular risk factors, including high CV risk and/or lipid, metabolic, or anthropometric

abnormalities, together with established cardiometabolic disease, defined as ectopic fat accumulation, CKD, diabetes, or hypertension, indicating early organ involvement;

- CKHM Stage 3 was defined by the presence of at least one cardiometabolic condition (ectopic fat, CKD, diabetes, hypertension, or lipid/anthropometric abnormalities) together with evidence of subclinical or high-risk cardiovascular disease (CVD), including elevated coronary artery calcium (CAC) score, increased carotid intima-media thickness (IMT), very high estimated CV risk, or significant liver fibrosis;
- CKHM Stage 4 represented the most advanced stage and was defined by the presence of at least one of the following: clinical CVD, coronary artery calcium (CAC) score >400, solid organ transplantation (liver or kidney), or end-stage CKD, defined as eGFR <30 mL/min/1.73 m² confirmed on at least two measurements separated by at least three months.

The specific cut-off values applied for each criterion across all CKHM stages are detailed in Figure 21.

Stage	Criteria
Stage 4	**At least one of the following criteria (1-4):** 1. CVD event (CVD yes) **OR** 2. CAC score > 400 **OR** 3. Any solid organ transplant (liver or kidney or both) **OR** 4. End-stage chronic kidney disease defined as eGFR <30 mL/min on at least two visits ≥3 months apart
Stage 3	**Both criteria (1 and 2)** 1. At least one of the following a. Presence of the ectopic fat* **OR** b. CKD (eGFR 30-60 ml/min on at least two visits ≥3 months apart or albuminuria) **OR** c. Diabetes **OR** d. Hypertension **OR** e. 1 criteria from the metabolic cluster* **OR** f. 1 criteria from the anthropometric cluster* **OR** g. LDL >100 mg/dl 2. At least one of the following: a. Subclinical CVD defined as: i. CAC score 100-399 **OR** ii. IMT >= 1 mm b. Very high CV risk (SCORE-2 or SCORE-2 OP) c. Significant liver fibrosis defined as E_med >=8 kPa (preferable) or FIB-4>=1.45
Stage 2	**Both criteria (1 and 2)** 1. High CV risk (SCORE-2 or SCORE-2 OP depending on age) **OR** At least one of the following: a. 1 criteria from the metabolic cluster* **OR** b. 1 criteria from the anthropometric cluster* **OR** c. LDL >100 mg/dl 2. At least one of the following: a. Presence of the ectopic fat* **OR** b. CKD (eGFR 30-60 ml/min on at least two visits ≥3 months apart or albuminuria) **OR** c. Diabetes **OR** d. Hypertension
Stage 1	**Both criteria (1-2)** 1. Moderate-to-high CV risk (SCORE-2 or SCORE-2 OP depending on age) **OR** At least one of the following: a. At least 1 criteria from the metabolic cluster* **OR** b. At least 1 criteria from the anthropometric cluster* **OR** c. LDL >100 mg/dl 2. eGFR >= 60 ml/min
Stage 0	**All 5 criteria** 1. Age <40 years **OR** low-to-moderate CV risk (SCORE-2 or SCORE-2 OP) **AND** 2. eGFR >= 60 ml/min **AND** 3. Absence of hypertension **AND** 4. Absence of diabetes **AND** 5. At least 2 of the following: a. (Glucose <100 mg/dl **OR** HOMA-IR <2.5 **OR** HbA1c <38 mmol/mol) b. LDL cholesterol <100 mg/dl c. Triglycerides <135 mg/dl d. (BMI <25 kg/m2 **OR** Waist-to-height ratio <0.49 **OR** Waist circumference <88/102 cm in women/men)

Figure 21. Cardiovascular-kidney-hepatic-metabolic (CKHM) syndrome stages criteria.

Further definitions of the anthropometric, ectopic fat, and metabolic cluster cut-offs are provided below.

Anthropometric cluster:

- BMI ≥ 25 kg/m²;
- Waist-to-height ratio ≥ 0.5;
- Waist circumference ≥ 88 cm (women) / ≥ 102 cm (men).

Ectopic fat cluster:

- Visceral adipose tissue (VAT) ≥ 150 cm²;
- Hepatic steatosis defined as CAP ≥ 248 dB/m or FEG/MIL < 1.1.

Metabolic cluster:

- Fasting plasma glucose ≥ 100 mg/dL;
- HOMA-IR ≥ 2.5;
- HbA1c 39–47 mmol/mol.

Covariates and Data Collection

All clinical and laboratory data were extracted from electronic medical records and systematically collected at each visit performed at the MHMC.

Collected variables included demographic characteristics (age, sex, ethnicity, and education), anthropometric measures (weight, height, BMI, waist circumference, visceral adipose tissue, and waist-to-height ratio), and lifestyle factors (physical activity, smoking status including pack-years, and alcohol consumption). Physical activity was assessed with International Physical Activity Questionnaire (IPAQ) as metabolic equivalent of task (MET). A MET is the ratio of the rate of energy expended during an activity to the rate of energy expended at rest (1 MET is the rate of energy expenditure while at rest). Level of physical activity was further categorized as low (MET score <600), moderate (601<MET score>1500) and intense (MET score >1500) (177).

HIV-related parameters included current CD4 cell count, nadir CD4 count, CD4/CD8 ratio, HIV RNA viral load, time since HIV diagnosis, and cumulative exposure to the four

main ART classes: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INSTIs), and protease inhibitors (PIs).

Biochemical variables included fasting glucose, HbA1c, insulin, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, C-reactive protein (CRP), and D-dimer.

Cardiovascular risk was estimated using the SCORE2 or SCORE2-OP algorithms, as recommended by the European Society of Cardiology, which incorporate age, sex, smoking status, systolic blood pressure, and lipid levels. Italy was classified as a moderate cardiovascular risk region according to SCORE2 regional calibration (178).

Visceral adipose tissue (VAT) was assessed using either computed tomography (CT) or dual-energy X-ray absorptiometry (DEXA), depending on availability.

Subclinical CVD was assessed using coronary artery calcium (CAC) score and carotid intima–media thickness (IMT). In a subset of PWH at high cardiometabolic risk, chest CT scans were performed between 2005 and 2020 to evaluate the presence and extent of coronary artery calcium. CAC scores were calculated using the Agatston method (179). CAC scores ranging from 100 to 400 were considered indicative of subclinical CVD, whereas a CAC score >400 was considered equivalent to established coronary artery disease and indicative of the need for secondary prevention strategies. Carotid IMT was assessed using high-resolution B-mode ultrasonography, and an IMT >1 mm was considered clinically significant.

Comorbidities were defined according to European AIDS Clinical Society (EACS) guidelines (180). Diabetes mellitus was defined as fasting plasma glucose >126 mg/dL and/or HbA1c >48 mmol/mol, or the current use of antidiabetic medication. Hypertension was defined as two consecutive blood pressure measurements ≥140/90 mmHg or the use of antihypertensive medication. CKD was defined according to the 2024 Kidney Disease: Improving Global Outcomes (KDIGO) classification (181), as adopted by the EACS guidelines, as abnormalities of kidney structure or function persisting for at least 3 months. For the purposes of this study, CKD was defined by an eGFR <60 mL/min/1.73 m^2 and/or persistent albuminuria lasting for more than 3 months.

CVD was defined as the presence of major cardiovascular events, including acute coronary syndrome, myocardial infarction, unstable angina, coronary or other arterial revascularization, stroke or transient ischemic attack, and peripheral arterial disease of atherosclerotic origin. These diagnoses were retrieved from patients' electronic medical records and were considered regardless of calculated cardiovascular risk score.

Study Outcomes

Primary outcome: the prevalence of CKHM syndrome stages (0–4) among people with HIV over the study period (2005–2025).

Secondary outcomes:

1. Stage-to-stage transition rates (progression and reversion) across CKHM stages over the study period;
2. Clinical, metabolic, and HIV-related factors associated with progression to a higher CKHM stage;
3. Clinical, metabolic, and HIV-related factors associated with reversion to a lower CKHM stage.

Statistical Analysis

Continuous variables were summarized using median, lower (Q1), and upper (Q3) quartile, while categorical variables were reported as counts and percentages. Between-group comparisons at T0 and T1 were performed using the t-test or its non-parametric equivalent for continuous variables, and the χ^2 test for categorical variables.

Prevalence was estimated across three study periods. When a patient had more than one CKHM assessment within the same period, the highest stage recorded during that interval was used, in order to avoid underestimating disease burden.

Transitions across CKHM stages and death were modelled using continuous-time multi-state Markov models, a framework that extends conventional survival analysis by allowing individuals to move between multiple health states simultaneously over a period

of follow-up. Unlike approaches that consider only a single event, multi-state models accommodate both disease progression and reversion, enabling the joint estimation of transition rates across all clinically plausible directions.

The state space comprised six mutually exclusive health states: CKHM stages 0, 1, 2, and 3, which were defined as transient states, and CKHM stage 4 and death, which were treated as absorbing states. An absorbing state is one from which no backward transition is modelled. Individuals reaching CKHM stage 4 could not regress to a lower CKHM stage, and death represented the terminal event from which no further transitions were possible. All transient states permitted both forward transitions to higher CKHM stages and backward transitions to lower stages, as well as direct transitions to death, reflecting the potentially reversible yet ultimately progressive nature of CKHM syndrome. Non-adjacent transitions (for example, from stage 0 directly to stage 2, or from stage 2 directly to stage 4) were also permitted where clinically plausible and supported by the observed data, allowing the model to capture accelerated progression without requiring passage through all intermediate stages.

Under the Markov assumption, the probability of transitioning to any future state depends solely on the state currently occupied and not on the sequence of states previously visited. Transition intensities, representing the instantaneous rates of moving between states, were modelled as functions of the current state, individual patient characteristics, and age at the time of each observed transition. Patient age at the time of transition was incorporated as a time-varying component to allow transition rates to change as individuals age, which was considered clinically necessary to adequately capture the age-dependent trajectory of cardiometabolic risk.

Each covariate was assumed to act multiplicatively on the baseline transition intensity through a proportional hazards parameterisation, yielding hazard ratios that quantify the relative change in transition rate per unit change in the covariate, conditional on all other variables in the model. The following covariates were included to estimate the relative risks of progression and reversion across CKHM stages: biological sex, age at transition, duration of HIV infection categorised into tertiles (medium and long duration relative to short), level of physical activity, use of integrase strand transfer inhibitors (INSTIs), use of protease inhibitors (PIs), and use of statins. The subset of covariates included for each

specific transition was determined through model selection, as not all predictors were retained for all transitions.

Model selection was based on Akaike's Information Criterion (AIC), a standard statistical measure that rewards better fit to the observed data while penalising unnecessary model complexity. In practical terms, a lower AIC indicates a model that more accurately describes the data without being overly complicated. Three models were compared: a null model containing no covariates, a simpler covariate model, and the final selected model. The selected model provided the best balance between accuracy and parsimony, and its superiority over the null model confirmed that including patient characteristics and age-dependent transition rates was necessary to adequately capture disease trajectories in this population.

RESULTS

Among 31,232 observations, 3,838 PWH had at least two CKHM assessments during the study period. The median follow-up was 6.36 years (Q1–Q3: 2.03–12.2), during which 171 deaths occurred. Across the three study periods, the prevalence of advanced CKHM stages (stages 3 and 4) increased significantly, rising from 36% in 2005–2015 to 63% in 2021–2025. In contrast, the prevalence of CKHM stages 0, 1, and 2 progressively declined over the same periods (Figure 22).

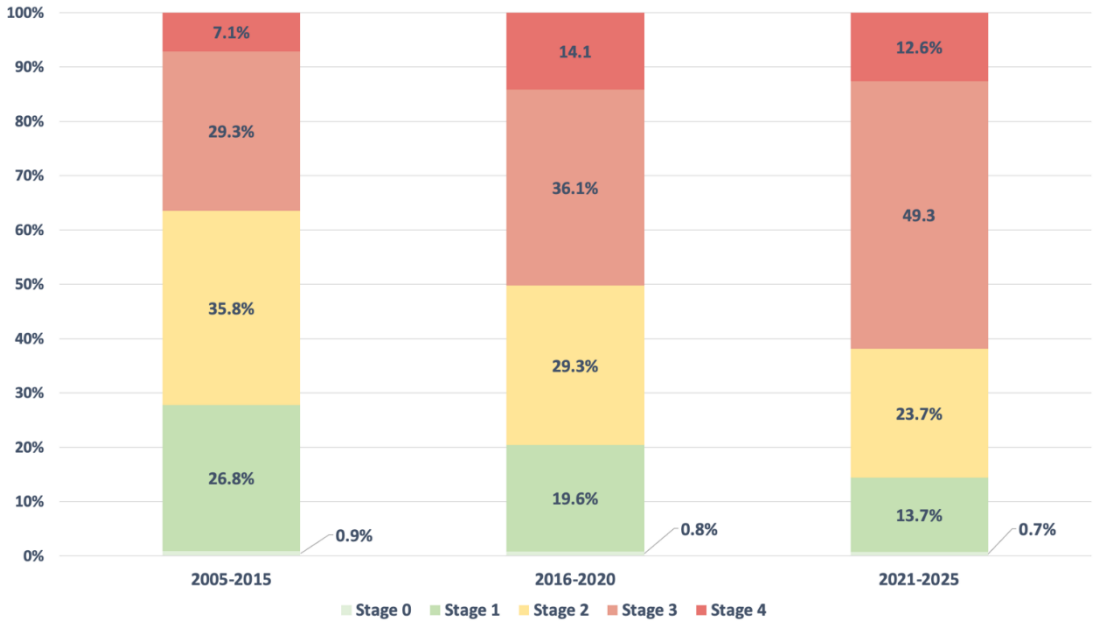


Figure 22. Prevalence of cardiovascular-kidney-hepatic-metabolic (CKHM) stages across 3 time periods. *Total number of people with HIV (PWH) included in each period: (i) 2005-2015: 3717; (ii) 2016-2020: 2285; (iii) 2021-2025: 2067.*

At the last available observation, among the 3,838 participants, the distribution across CKHM syndrome stages was as follows: stage 0 (2.1%), stage 1 (33.6%), stage 2 (33.3%), stage 3 (23.1%), and stage 4 (7.9%). Increasing CKHM stages were associated with older age (median 42 years in stage 0 vs. 56 years in stage 4, $p<0.001$), a higher proportion of men (53% vs. 84%, $p<0.001$), and a progressive increase in BMI and waist-to-height ratio (both $p<0.001$). More advanced CKHM stages were also characterized by longer HIV duration (13 vs. 23 years, $p<0.001$), lower nadir CD4 cell counts ($p<0.001$), and a higher prevalence of current INSTI exposure (31% vs. 53%, $p<0.001$), whereas current CD4

count and CD4/CD8 ratio did not differ across groups. Cardiometabolic abnormalities progressively worsened with increasing CKHM severity, including declining eGFR and increasing insulin resistance. HbA1c levels increased and lipid profiles became less favorable, with a progressive increase in triglycerides, a reduction in HDL cholesterol, and a higher prevalence of dyslipidemia (52% in stage 0 vs. 91% in stage 4, all p<0.001). Similarly, markers of ectopic fat accumulation and liver involvement increased across CKHM stages, with VAT measured by DEXA rising from a median of 61 to 166 cm² and liver stiffness increasing from 4.9 to 6.0 kPa (both p<0.001), indicating a progressive burden of metabolic dysfunction and liver fibrosis in patients with more advanced CKHM syndrome (Table 1).

Table 1. Demographic, anthropometric, lifestyles, HIV-related, and cardiometabolic characteristics of people with HIV (PWH) at the last available observation.

Median (Q1, Q3) or N (%)		**Stage 0 N= 81 (2.1%)**	**Stage 1 N = 1,288 (33.6%)**	**Stage 2 N = 1,277 (33.3%)**	**Stage 3 N = 887 (23.1%)**	**Stage 4 N = 305 (7.9%)**	**p**
Demographics, anthropometrics and lifestyles							
Age (years)		42 (37, 50)	45 (40, 50)	47 (43, 53)	55 (50, 61)	56 (50, 62)	<0.001
Male sex		43 (53%)	807 (63%)	912 (71%)	697 (79%)	256 (84%)	<0.001
BMI (kg/m²)		21.2 (19.2, 22.6)	22.6 (20.8, 24.5)	24.6 (22.3, 27.4)	24.7 (22.3, 27.5)	24.9 (22.1, 27.3)	<0.001
Waist-to-Height Ratio (WHtR)		0.45 (0.43, 0.48)	0.49 (0.46, 0.53)	0.53 (0.49, 0.57)	0.54 (0.50, 0.59)	0.55 (0.50, 0.60)	<0.001
Physical activity	**Vigorous**	11 (14%)	127 (9.9%)	116 (9.1%)	84 (9.5%)	14 (4.6%)	0.009
	Moderate	33 (41%)	474 (37%)	445 (35%)	367 (41%)	111 (36%)	
Smoking		32 (39%)	612 (48%)	430 (34%)	339 (38%)	129 (42%)	<0.001

Alcohol consumption	**Moderate**	31 (38%)	488 (38%)	496 (39%)	320 (36%)	110 (36%)	0.021
	Intense	0 (0%)	18 (1.4%)	20 (1.6%)	29 (3.3%)	5 (1.6%)	
HIV-related variables							
HIV duration (years)		13 (7, 24)	17 (10, 22)	17 (11, 22)	23 (16, 29)	23 (17, 29)	<0.001
Nadir CD4 cell count (c/µL)		272 (169, 392)	200 (96, 313)	200 (70, 300)	175 (60, 291)	161 (65, 261)	<0.001
Current CD4 cell count (c/µL)		650 (476, 887)	636 (460, 846)	625 (450, 835)	619 (443, 824)	639 (446, 870)	0.500
CD4/CD8 ratio		0.90 (0.72, 1.18)	0.84 (0.62, 1.14)	0.83 (0.61, 1.19)	0.83 (0.55, 1.20)	0.82 (0.59, 1.19)	0.3
Current exposure to INSTI		25 (31%)	271 (21%)	362 (28%)	424 (48%)	163 (53%)	<0.001
Current exposure to PI		33 (41%)	583 (45%)	506 (40%)	317 (36%)	115 (38%)	<0.001
Cardiometabolic variables							
eGFR (mL/min/1,73 m²)		98 (84, 104)	99 (86, 105)	94 (80, 103)	92 (78, 103)	92 (70, 104)	<0.001
HOMA-IR		1.20 (0.85, 1.53)	1.83 (1.15, 2.95)	2.69 (1.69, 4.37)	2.73 (1.65, 4.52)	3.10 (1.90, 5.73)	<0.001
HbA1c (mmol/mol)		32 (31, 35)	33 (31, 37)	34 (31, 38)	36 (32, 40)	37 (33, 42)	<0.001
LDLc (mg/dL)		83 (70, 91)	119 (98, 139)	120 (98, 143)	110 (84, 137)	99 (77, 126)	<0.001
Triglycerides (mg/dL)		86 (62, 112)	115 (82, 173)	136 (95, 198)	127 (87, 190)	142 (101, 206)	<0.001
HDLc (mg/dL)		56 (43, 66)	50 (40, 60)	46 (38, 57)	47 (38, 57)	43 (36, 52)	<0.001
Total cholesterol (mg/dL)		151 (134, 165)	191 (167, 218)	191 (167, 221)	180 (151, 212)	168 (136, 204)	<0.001

Dyslipidemia	42 (52%)	997 (77%)	1,027 (80%)	749 (84%)	277 (91%)	<0.001
Current exposure to atorvastatin	6 (7.4%)	25 (1.9%)	69 (5.4%)	108 (12%)	80 (26%)	<0.001
Current exposure to rosuvastatin	5 (6.2%)	42 (3.3%)	81 (6.3%)	137 (15%)	78 (26%)	<0.001
Ectopic fat and liver fibrosis						
VAT (DEXA) (cm²)	61 (44, 87)	82 (58, 111)	149 (100, 196)	158 (105, 212)	166 (108, 230)	<0.001
CAP score (dB/m)	200 (178, 224)	209 (186, 226)	248 (221, 280)	245 (211, 292)	239 (200, 276)	<0.001
Liver fibrosis (kPa)	4.90 (4.20, 5.40)	4.70 (4.00, 5.70)	5.20 (4.10, 6.10)	5.90 (4.70, 8.20)	6.00 (4.70, 7.90)	<0.001

Baseline characteristics differed significantly across the three calendar periods (3,880 observations in Period 1, 2,344 in Period 2, and 2,101 in Period 3). Patients assessed more recently were older (median age 44 to 57 years) and showed greater adiposity (BMI 23.2 to 24.9 kg/m², VAT 110 to 142 cm²). ART shifted markedly, with current INSTI use rising from 6.4 to 71.9% and PI use falling from 50.7 to 14.6%, while immunological status improved (current CD4 530 to 709 cells/μL). Lipid lowering therapy became more frequent, and the CKHM stage distribution shifted toward more advanced disease, with stage 3 increasing from 10.8 to 40.2% and stage 4 from 3.6 to 12.1% (Table 2).

Table 2. Baseline characteristics of the study population across three calendar periods. *Baseline was defined as a patient's first visit within each period at which a CKHM stage could be calculated, so that a patient seen in more than one period contributes one observation to each.*

Median (Q1, Q3) or N (%)		**Period 1 (2005-2015), N = 3,880**	**Period 2 (2016-2020), N = 2,344**	**Period 3 (2021-2025), N = 2,101**	**p**
Demographics, anthropometrics and lifestyles					
Age (years)		44.0 (40.0, 48.0)	52.0 (47.0, 56.0)	57.0 (51.0, 62.0)	<0.001
Male sex		2,649 (68.3%)	1,729 (73.8%)	1,507 (71.7%)	<0.001
BMI (kg/m²)		23.2 (21.0, 25.6)	24.0 (21.8, 26.3)	24.9 (22.4, 27.8)	<0.001
Waist-to-Height Ratio (WHtR)		0.5 (0.5, 0.5)	0.5 (0.5, 0.6)	0.5 (0.5, 0.6)	<0.001
Physical activity	**Vigorous**	0 (0.0%)	27 (1.2%)	198 (9.4%)	<0.001
	Moderate	0 (0.0%)	213 (9.1%)	925 (44.0%)	
Smoking status	**Non-smoker**	1,987 (51.2%)	1,480 (63.1%)	1,353 (64.4%)	<0.001
	Moderate (≤10/day)	653 (16.8%)	350 (14.9%)	350 (16.7%)	
	Intense (>10/day)	1,074 (27.7%)	425 (18.1%)	354 (16.8%)	
	Other	166 (4.3%)	89 (3.8%)	44 (2.1%)	
Alcohol consumption	**Moderate**	1,675 (43.2%)	725 (30.9%)	827 (39.4%)	<0.001
	Intense	52 (1.3%)	33 (1.4%)	99 (4.7%)	
HIV-related variables					
HIV duration (years)		15.0 (9.3, 20.1)	21.4 (12.9, 27.3)	25.5 (15.7, 32.5)	<0.001
Nadir CD4 cell count (c/µL)		190.0 (80.0, 292.0)	205.0 (98.0, 318.0)	200.0 (70.0, 316.0)	<0.001
Current CD4 cell count (c/µL)		530.0 (378.0, 712.5)	707.0 (532.0, 900.0)	709.0 (533.0, 928.0)	<0.001
CD4/CD8 ratio		0.7 (0.5, 1.0)	0.9 (0.6, 1.2)	1.0 (0.7, 1.3)	<0.001

Current exposure to INSTI	249 (6.4%)	996 (42.5%)	1,511 (71.9%)	<0.001
Current exposure to PI	1,967 (50.7%)	875 (37.3%)	307 (14.6%)	<0.001
Cardiometabolic variables				
eGFR (mL/min/1,73 m²)	98.0 (82.6, 105.0)	92.8 (79.9, 103.1)	92.8 (76.5, 102.1)	<0.001
HOMA-IR	2.6 (1.6, 4.5)	2.1 (1.3, 3.2)	2.3 (1.5, 3.9)	<0.001
HbA1C (mmol/mol)	34.0 (31.2, 36.6)	34.0 (31.0, 38.0)	35.0 (32.0, 38.0)	<0.001
LDLc (mg/dL)	113.0 (90.0, 140.0)	112.0 (91.0, 134.0)	120.0 (97.0, 142.0)	<0.001
Triglycerides (mg/dL)	142.0 (97.0, 212.5)	118.0 (83.0, 169.0)	102.5 (76.0, 144.0)	<0.001
HDLc (mg/dL)	44.0 (36.0, 55.0)	48.0 (39.0, 60.0)	51.0 (43.0, 61.0)	<0.001
Total cholesterol (mg/dL)	188.0 (158.0, 221.0)	186.0 (161.0, 212.0)	190.0 (160.0, 218.0)	0.041
Dyslipidemia	3,121 (80.4%)	1,779 (75.9%)	1,685 (80.2%)	<0.001
Current exposure to atorvastatin	68 (1.8%)	253 (10.8%)	366 (17.4%)	<0.001
Current exposure to rosuvastatin	78 (2.0%)	201 (8.6%)	307 (14.6%)	<0.001
Ectopic fat				
VAT (DEXA) (cm²)	110.0 (70.0, 164.0)	121.0 (77.0, 174.0)	142.0 (98.8, 204.3)	<0.001
CKHM stage prevalence				
Stage 0	60 (1.7%)	47 (2.1%)	20 (1.0%)	<0.001
Stage 1	1,412 (40.4%)	671 (30.3%)	371 (18.3%)	
Stage 2	1,518 (43.5%)	650 (29.3%)	576 (28.4%)	
Stage 3	376 (10.8%)	603 (27.2%)	816 (40.2%)	
Stage 4	125 (3.6%)	245 (11.1%)	246 (12.1%)	

Among the 981 patients with CKHM assessments across all three study periods, the prevalence of advanced CKHM stages (stages 3 and 4) was even more pronounced, reaching nearly 80% in Period 3. Longitudinal transitions demonstrated a progressive increase in the burden of CKHM stages 3 and 4 over time, characterized by frequent progression to more advanced stages and only limited regression to lower stages (Figure 23).

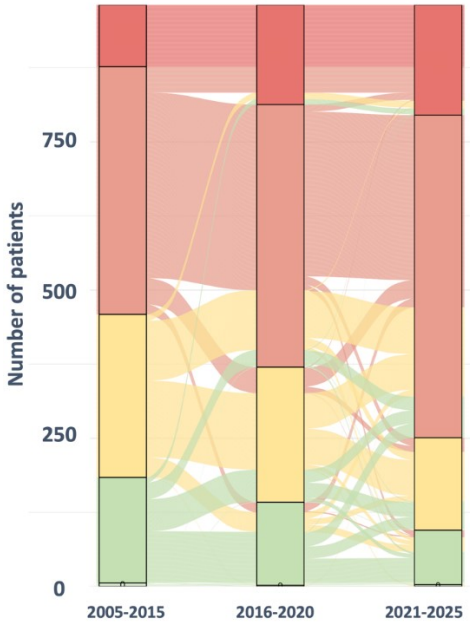


Figure 23. Alluvial plot showing transitions in 981 people with HIV (PWH) with available data in all three time periods. *Within each period, the highest cardiovascular-kidney-hepatic-metabolic (CKHM) stage ever reached by the patient was considered.*

Regarding disease progression, male sex was independently associated with increased rates of transition from CKHM stage 1 to stage 2 (HR 1.44, 95% CI 1.23 to 1.68), from stage 1 to stage 3 (HR 1.53, 95% CI 1.22 to 1.91), and from stage 2 to stage 3 (HR 1.39, 95% CI 1.17 to 1.65), while no significant sex effect was identified for transitions originating from stage 0 or for direct transitions to death. Higher physical activity was associated with a reduced rate of progression from stage 1 to stage 2 (HR 0.76, 95% CI 0.66 to 0.88) but did not significantly influence other progressive transitions. Older age was associated with a marginally lower rate of progression from stage 1 to stage 2 (HR

0.98, 95% CI 0.97 to 1.00), yet consistently increased the rate of transition to stage 3 from both stage 1 and stage 2 (HR 1.09, 95% CI 1.07 to 1.10 for both) and the rate of transition to death across all stages in which it was included (HR 1.04, 95% CI 1.01 to 1.07). Longer duration of HIV infection was associated with accelerated progression to stage 3 in a dose dependent fashion: compared with short duration, medium duration (11 to 18 years) was associated with a 36% higher rate from stage 1 to stage 3 (HR 1.36, 95% CI 1.04 to 1.78) and a 27% higher rate from stage 2 to stage 3 (HR 1.27, 95% CI 1.07 to 1.50), while long duration (19 to 40 years) conferred substantially greater increases of 96% (HR 1.96, 95% CI 1.51 to 2.53) and 62% (HR 1.62, 95% CI 1.37 to 1.92) for the same transitions, respectively. HIV duration did not significantly influence transitions from stage 0 or direct transitions to death. Use of INSTIs, PIs, and statins was not significantly associated with any progressive transition (Table 3).

Table 3. Hazard ratios (95% confidence intervals) for progressive transitions across cardiovascular-kidney-hepatic-metabolic (CKHM) stages, estimated from a multivariable continuous-time multi-state Markov model. *Reference categories are female sex and short HIV duration (up to 10 years). Age is expressed in years at the time of each transition. A slash (/) indicates that the covariate was not retained for that transition following model selection. INSTI: integrase strand transfer inhibitor. PI: protease inhibitor.*

Transitions from	**Stage 0**		**Stage 1**			**Stage 2**			**Stage 3**		**Stage 4**
Progression	**0-1 transition**	**0-2 transition**	**1-2 transition**	**1-3 transition**	**1-death transition**	**2-3 transition**	**2-4 transition**	**2-death transition**	**3-4 transition**	**3-death transition**	**4-death transition**
Sex	1.21 (0.83–1.77)	1.09 (0.26–4.49)	**1.44 (1.23–1.68)**	**1.53 (1.22–1.91)**	1.03 (0.63–1.69)	**1.39 (1.17–1.65)**	1.55 (0.58–4.10)	1.03 (0.63–1.69)	/	1.03 (0.63–1.69)	1.03 (0.63–1.69)
Physical activity	0.97 (0.67–1.40)	/	**0.76 (0.66–0.88)**	1.06 (0.86–1.31)	/	0.92 (0.80–1.06)	/	/	/	/	/
Age	/	/	**0.98 (0.97–1.00)**	**1.09 (1.07–1.10)**	**1.04 (1.01–1.07)**	**1.09 (1.08–1.10)**	/	**1.04 (1.01–1.07)**	/	**1.04 (1.01–1.07)**	**1.04 (1.01–1.07)**
HIV duration (11-18 years)	/	/	1.10 (0.93–1.30)	**1.36 (1.04–1.78)**	/	**1.27 (1.07–1.50)**	/	/	/	/	/
HIV duration (19-40 years)	/	/	1.08 (0.89–1.30)	**1.96 (1.51–2.53)**	/	**1.62 (1.37–1.92)**	/	/	/	/	/
INSTI use	/	/	0.97 (0.80–1.17)	1.09 (0.86–1.37)	/	0.96 (0.82–1.13)	/	/	0.96 (0.69–1.35)	/	/
PI use	/	/	0.87 (0.76–1.00)	0.90 (0.73–1.11)	/	1.14 (0.99–1.32)	/	/	1.20 (0.87–1.67)	/	/
Statin use	/	/	/	/	/	1.06 (0.88–1.27)	/	/	/	/	/

Regarding disease regression, male sex was associated with significantly lower rates of reversion from stage 2 to stage 1 (HR 0.69, 95% CI 0.58 to 0.81) and from stage 3 to stage 1 (HR 0.48, 95% CI 0.38 to 0.63), indicating that males were less likely to regress to lower CKHM stages than females. Higher physical activity was associated with increased regression rates from stage 1 to stage 0 (HR 1.48, 95% CI 1.06 to 2.06) and from stage 3 to stage 1 (HR 1.37, 95% CI 1.08 to 1.75), suggesting a beneficial role of physical activity in facilitating disease reversion. Older age consistently and significantly reduced regression rates across all transitions in which it was included, with hazard ratios ranging from 0.93 to 0.97 per year of age. Use of INSTIs was associated with a lower rate of regression from stage 2 to stage 1 (HR 0.61, 95% CI 0.49 to 0.76), while PI use was associated with reduced regression from stage 3 to stage 2 (HR 0.77, 95% CI 0.63 to 0.94). HIV duration and statin use were not significantly associated with any regressive transition (Table 4).

Table 4. Hazard ratios (95% confidence intervals) for regressive transitions across cardiovascular-kidney-hepatic-metabolic (CKHM) stages, estimated from a multivariable continuous-time multi-state Markov model. *Reference categories are female sex and short HIV duration (up to 10 years). Age is expressed in years at the time of each transition. A slash (/) indicates that the covariate was not retained for that transition following model selection. INSTI: integrase strand transfer inhibitor. PI: protease inhibitor.*

Transitions from	**Stage 1**	**Stage 2**	**Stage 3**	
Regression	**1-0 transition**	**2-1 transition**	**3-1 transition**	**3-2 transition**
Sex	1.00 (0.72–1.39)	**0.69 (0.58–0.81)**	**0.48 (0.38–0.63)**	0.95 (0.75–1.21)
Physical activity	**1.48 (1.06–2.06)**	1.08 (0.93–1.25)	**1.37 (1.08–1.75)**	1.00 (0.82–1.21)
Age	/	**0.93 (0.92–0.94)**	**0.94 (0.93–0.96)**	**0.97 (0.96–0.99)**
HIV duration (11-18 years)	/	1.11 (0.93–1.33)	0.92 (0.68–1.26)	/
HIV duration (19-40 years)	/	1.17 (0.96–1.41)	0.76 (0.56–1.04)	/
INSTI use	/	**0.61 (0.49–0.76)**	0.97 (0.75–1.26)	0.87 (0.71–1.08)
PI use	/	1.00 (0.86–1.16)	1.18 (0.92–1.51)	**0.77 (0.63–0.94)**
Statin use	/	/	/	0.87 (0.68–1.11)

DISCUSSION

In this large longitudinal cohort of people with HIV (PWH) followed for two decades, we observed a progressive shift toward more advanced stages of cardiovascular-kidney-hepatic-metabolic (CKHM) syndrome, with stage 3 becoming the predominant disease state over time. Importantly, CKHM emerged as a dynamic rather than static condition, characterized by both progression and regression across stages. Older age, male sex, and longer HIV duration were independently associated with progression toward more advanced stages, whereas physical activity was associated with more favorable transitions. Taken together, these findings suggest that metabolic health in PWH evolves along measurable trajectories that may benefit from prevention strategies and lifestyle changes.

The progressive increase in advanced CKHM stages likely reflects the ageing of the HIV population, as antiretroviral therapy (ART) successfully transformed HIV into a chronic condition (94,111,182). In the general population, recent large cohort studies indicate that advanced CKHM disease (stages 3–4) is relatively uncommon, with prevalence estimates typically around ~10-15% (130). In contrast, PWH show substantially higher burden and earlier progression: in our cohort, CKHM stage 3–4 prevalence was already 36% in Period 1 and increased to 63% in Period 3, likely reflecting longer duration of HIV infection, chronic inflammation, and cumulative cardiometabolic and renal risk exposure. Conversely, CKHM stage 0 remained exceedingly uncommon throughout the study (<1%), underscoring how complete cardiometabolic health is rarely observed among PWH referred to MHMC. This finding may also be partially explained by our methodological approach, which classified individuals according to the highest CKHM stage reached during the observation period. Low prevalence of CKHM stage 0 is also observed in the general population; however, it is consistently higher than in our cohort, with population-based studies reporting approximately 8-12% of individuals classified as stage 0 (130).

In order to better characterize CKHM, we expanded the original American Heart Association (AHA) CKM framework by incorporating liver involvement as a relevant

component of disease staging. This adaptation reflects the growing recognition that MASLD and liver fibrosis are central manifestations of systemic metabolic dysfunction and contribute to cardiovascular and kidney risk through shared mechanisms including insulin resistance, chronic inflammation, and ectopic fat accumulation (63,114). In PWH, where hepatic steatosis and fibrosis frequently coexist with visceral adiposity and metabolic dysfunction, inclusion of the hepatic domain may provide a more comprehensive representation of multiorgan risk. Additionally, the CKHM construct is inherently flexible and can be adapted according to the diagnostic resources available across different clinical settings and time periods. For example, stage 3 was defined using either direct assessment of subclinical cardiovascular disease, when available, or validated clinical algorithms when advanced diagnostic testing was not available. Therefore, the goal is not strict uniformity of criteria across centers, but preservation of the CKHM conceptual framework while tailoring its operationalization to local resources and practice (63).

Our findings further support the value of the CKHM framework as an integrated approach to cardiometabolic risk assessment that extends beyond the evaluation of individual comorbidities. Rather than relying on a dichotomous “yes/no” classification of single diseases, CKHM captures the natural history of disease, including dynamic transitions and longitudinal trajectories of cardiometabolic health (63,101). This multidimensional perspective is particularly relevant in the context of HIV care, where cardiometabolic disorders frequently coexist and interact through shared pathophysiological mechanisms. In this setting, the CKHM framework may therefore provide a more comprehensive and clinically meaningful tool for risk stratification and longitudinal patient management in PWH (102), while also supporting a shift from disease-centered approaches toward a more integrated, person-centered assessment of multiorgan health trajectories.

Male sex was associated with progression toward more advanced stages and with a lower probability of favorable transitions. Although the mechanisms underlying this association remain uncertain, sex-related differences in visceral adiposity, insulin sensitivity, cardiovascular risk, and hormonal regulation may contribute to distinct CKHM trajectories (183).

Among potentially modifiable factors, physical activity demonstrated the most consistent association with favorable CKHM trajectories. Individuals reporting regular physical activity were less likely to progress and more likely to experience favorable transitions. Although causal inference is not possible in an observational study, these findings are biologically plausible given the well-established effects of exercise on body composition, insulin sensitivity, blood pressure, inflammation, and cardiovascular risk (184). Importantly, they suggest that at least part of CKHM progression may be modifiable and support the incorporation of lifestyle interventions within long-term HIV care.

Longer HIV duration was independently associated with progression across multiple transitions, suggesting that cumulative exposure to HIV-related biological processes contributes to the evolution of multiorgan dysfunction. Previous studies have shown that prolonged HIV infection is associated with greater multimorbidity, frailty, metabolic dysfunction, and cardiovascular disease despite virological suppression (87,185). Our findings extend these observations by indicating that HIV duration may influence the trajectory through which CKHM evolves over time.

The role of ART deserves careful interpretation. After adjustment for demographic, behavioral, and other HIV-related factors, we found limited evidence that antiretroviral classes independently drove CKHM progression. These findings suggest that the evolution of CKHM syndrome is largely determined by the interaction of ageing, lifestyle, HIV duration, and baseline metabolic risk rather than antiretroviral exposure alone. However, in the Markov models, exposure to INSTI and PI was associated with lower probability of regression, probably reflecting the fact that INSTI regimens have often been used as a switch strategy to address cardiometabolic adverse effects associated with PI. As a result, a more cardiometabolically vulnerable population with a longer time since HIV diagnosis has been switched to INSTI-based regimens over the past decade. Moreover, future research should move beyond the traditional paradigm of antiretroviral toxicity. Effective treatment may modify biological ageing trajectories through sustained viral suppression, reduction of immune activation, and attenuation of chronic inflammation (94,186). Integrating biomarkers of immune recovery, inflammation, metabolomics, and epigenetic ageing within the CKHM framework may provide new insights into how HIV treatment influences long-term cardiometabolic health.

More broadly, CKHM progression can be interpreted within a geroscience framework, as it reflects the cumulative impact of biological aging processes; in PWH, chronic immune activation and inflammaging may accelerate these mechanisms, leading to earlier onset of multimorbidity and frailty (94,112). Within this perspective, proactive interventions aimed at identifying and addressing cardiometabolic risk early in the disease course may play a key role in modifying these trajectories. Accordingly, strategies designed to prevent CKHM progression may not only reduce cardiometabolic risk but also contribute to slowing biological aging and delaying the development of future frailty (140).

This study has several strengths, including a large and well-characterized HIV cohort, nearly two decades of follow-up, repeated clinical assessments, and the application of multistate modelling to characterize disease trajectories over time. In addition, it provides specific insights into CKHM progression in PWH, a population that remains relatively underrepresented and insufficiently characterized within the current CKHM literature (102).

However, the present work has also several limitations that should be acknowledged. First, its single-center observational design precludes causal inference and may limit the generalizability of the findings to other settings and populations. Second, the adaptation of the original CKM framework to a CKHM model may influence transition estimates. Moreover, the different ART classes do not capture cumulative exposure, treatment sequencing, or causal effects, thereby limiting the ability to infer pharmacological impacts on CKHM progression. Similarly, physical activity should be interpreted cautiously, as it may reflect overall better health status, lower frailty, or greater engagement in care rather than an isolated protective intervention (187). The inclusion of patients observed across all three study periods may also introduce survivor and follow-up bias, as these individuals likely represent a selected subgroup with better longitudinal retention and survival. Finally, the operational definition of irreversibility for conditions such as diabetes, hypertension, and CKD within the CKHM framework is primarily methodological and reflects modeling choices rather than true biological irreversibility, since in clinical practice these conditions may improve or remit with appropriate interventions and disease course variability.

Future research should focus on defining pragmatic and scalable criteria for the broader clinical implementation of the CKHM framework, particularly in resource-limited settings where access to advanced diagnostic tools may be restricted. Further studies are needed also to explore the potential for CKHM improvement or partial regression within stages, especially among individuals with well-controlled or early-stage organ damage, in order to better characterize the reversibility of cardiometabolic trajectories over time. In addition, the role of widely used and emerging pharmacological therapies, including metformin, statins, mineralocorticoid receptor antagonists, GLP-1 receptor agonists, and SGLT2 inhibitors, should be systematically investigated for their potential to promote CKHM regression and modify disease progression (63). Future investigations should also aim to identify additional clinical, biological, and behavioral predictors of CKHM progression and regression, as well as to evaluate the long-term cardiovascular and metabolic outcomes associated with early and proactive intervention strategies.

CONCLUSIONS

CKHM syndrome in PWH is characterized by dynamic and predominantly progressive trajectories rather than a static accumulation of comorbidities. Older age, male sex, and longer HIV duration were associated with progression toward more advanced stages, whereas physical activity was associated with more favorable transitions, highlighting the potential influence of modifiable factors on disease evolution. By integrating cardiovascular, kidney, hepatic, and metabolic domains within a single longitudinal framework, CKHM staging may provide a clinically useful approach for identifying individuals at risk of adverse health trajectories before the onset of overt cardiovascular disease and for evaluating interventions aimed at promoting healthy ageing in PWH. In this context, early and integrated cardiometabolic management, together with lifestyle interventions such as physical activity, may help slow or partially reverse selected transitions. Overall, the CKHM framework offers a comprehensive model for HIV care that shifts the focus from the management of isolated comorbidities toward multiorgan prevention, long-term risk reduction, and the promotion of healthy ageing.

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LIST OF ABBREVIATIONS

ACC = American College of Cardiology

ACEi = Angiotensin-Converting Enzyme inhibitor

ADA = American Diabetes Association

ASCVD = Atherosclerotic Cardiovascular Disease

AHA = American Heart Association

AIDS = Acquired Immunodeficiency Syndrome

ARB = Angiotensin Receptor Blocker

ARNI = Angiotensin Receptor-Neprilysin Inhibitor

ART = Antiretroviral Therapy

BMI = Body Mass Index

BNP = B-type Natriuretic Peptide

CAC = Coronary Artery Calcium

CAD = Coronary Artery Disease

CD4 = Cluster of Differentiation 4

CI = Confidence Interval

CKD = Chronic Kidney Disease

CKHM = Cardiovascular-Kidney-Hepatic-Metabolic (Syndrome)

CKM = Cardiovascular-Kidney-Metabolic (Syndrome)

CMV = Cytomegalovirus

CROI = Conference on Retroviruses and Opportunistic Infections

CRP = C-Reactive Protein

CT = Computed Tomography

CVD = Cardiovascular Disease

CVRD = Cardiovascular-Renal Disease

DALY = Disability-Adjusted Life Year

DEXA = Dual-Energy X-ray Absorptiometry

DTG = Dolutegravir

EACS = European AIDS Clinical Society

EFV = Efavirenz

eGFR = Estimated Glomerular Filtration Rate

ESC = European Society of Cardiology

FTC = Emtricitabine

GIP = Glucose-dependent Insulinotropic Polypeptide

GLP-1 RA = Glucagon-Like Peptide-1 Receptor Agonist

HAART = Highly Active Antiretroviral Therapy

HbA1c = Glycated Haemoglobin

HCV = Hepatitis C Virus

HDL = High-Density Lipoprotein

HF = Heart Failure

HFpEF = Heart Failure with preserved Ejection Fraction

HFrEF = Heart Failure with reduced Ejection Fraction

HIV = Human Immunodeficiency Virus

HOMA-IR = Homeostatic Model Assessment of Insulin Resistance

HR = Hazard Ratio

IL-6 = Interleukin-6

IMT = Intima-Media Thickness

INSTI = Integrase Strand Transfer Inhibitors

KDIGO = Kidney Disease Improving Global Outcomes

LDL = Low-Density Lipoprotein

LMIC = Low- and Middle-Income Countries

LVEF = Left Ventricular Ejection Fraction

MACE = Major Adverse Cardiovascular Events

MASH = Metabolic dysfunction-Associated SteatoHepatitis

MASLD = Metabolic dysfunction-Associated Steatotic Liver Disease

MetS = Metabolic Syndrome

MHMC = Modena HIV Metabolic Clinic

MRA = Mineralocorticoid Receptor Antagonist

NACM = Non-AIDS Comorbidities

NCD = Non-Communicable Disease

NICM = Non-Infectious Comorbidities

NRTI = Nucleoside Reverse Transcriptase Inhibitors

NNRTI = Non-Nucleoside Reverse Transcriptase Inhibitors

PI = Protease Inhibitors

PWH = People With HIV

Q1/Q3 = First/Third Quartile

RAAS = Renin-Angiotensin-Aldosterone System

SCORE2 = Systematic Coronary Risk Evaluation 2

SD = Standard Deviation

SDOH = Social Determinants Of Health

SGLT2i = Sodium-Glucose Cotransporter-2 Inhibitors

SNAE = Serious Non-AIDS Event

TAF = Tenofovir Alafenamide

TDF = Tenofovir Disoproxil Fumarate

VAT = Visceral Adipose Tissue

WHtR = Waist-to-Height Ratio

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