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Metabolic Syndrome in HIV/HCV Co-infected Patients

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Abstract

Purpose of review We review the scope and burden of metabolic syndrome in HIV/HCV co-infected patients, risk factors, and potential mechanisms driving the increased cardio-metabolic risk in this population, and discuss relevant clinical considerations for management in the era of highly effective antiretroviral therapy (ART) and curative anti-HCV direct-acting antivirals.
Recent findings HIV/HCV co-infected patients are at elevated risk of metabolic syndrome, attributed to (1) patient-specific factors, (2) viral-mediated effects, and (3) ART exposure. Risk factors for cardio-metabolic disorders are common in this population and include poor socioeconomic conditions, substance use, cardiovascular comorbidities, and liver/kidney disease. Chronic HIV/HCV infection induces an inflammatory and immune-activated state in the host leading to alterations in glucose and lipid metabolism. Selection of life-saving ART must carefully consider the differential metabolic risk associated with each drug class and agent, such as dyslipidemia, hyperglycemia and insulin resistance, weight gain, and hypertension. Emerging evidence supports metabolic derangements in chronic HCV may be improved by viral eradication with direct-acting antivirals; however, additional study in HIV/HCV co-infected patients is needed.
Summary Future research programs should aim to better characterize metabolic syndrome in HIV/HCV co-infected patients with the goal of improved screening, treatment, and prevention.

Opinion statement

Persons with HIV are living longer due to highly effective antiretroviral therapy (ART). Age-related non-AIDS comorbidities (e.g., cardiovascular and metabolic disorders) increasingly account for morbidity and mortality in this population. Chronic HCV is independently associated with dyslipidemia, hepatic steatosis, and insulin resistance. The role of curative anti-HCV direct-acting antiviral (DAA) therapy in reversing metabolic derangements is being actively investigated. Less is known regarding how HIV co-infection may influence HCV-induced metabolic sequelae and potential recovery with DAAs after viral cure. However, evidence consistently supports that compared with mono-infected counterparts, patients with HIV/HCV co-infection are at increased risk of metabolic syndrome, which predisposes to the development of type 2 diabetes and cardiovascular disease. This is likely multifactorial due to patient-specific factors, direct effects of chronic HIV/HCV infection on glucose and lipid metabolism, and cardio-metabolic toxicities associated with long-term ART use. Newer antiretrovirals, particularly integrase strand transfer inhibitors and tenofovir alafenamide, have been associated with weight gain and dyslipidemia, respectively. Additional investigation of the mechanisms—both viral- and ART-mediated—driving metabolic syndrome in HIV/HCV co-infection is needed; in addition to the potential for metabolic reversal following DAA therapy. Finally, further studies evaluating appropriate screening modalities and intervals, prevention tools, and therapeutics are needed to inform the clinical management of metabolic syndrome in patients with HIV/HCV co-infection.

Introduction

Persons with HIV (PWH) with access to care are aging. Those treated with antiretroviral therapy (ART) experience a near-normal life expectancy compared with the general population [1]. According to the most recent Centers for Disease Control and Prevention surveillance data, persons aged ≥ 65 years had the largest percentage increase in prevalence of HIV diagnoses from 2012 to 2016 (56%; from 104.4 to 162.6 per 100,000 persons) [2]. Age-related non-AIDS comorbidities increasingly account for morbidity and mortality in PWH [3–5]. Most commonly, comorbidities include cardiovascular disease (CVD), metabolic disorders, hepatic and renal disease, and psychiatric illnesses [3, 6, 7].

In the USA, approximately 25–30% of PWH are co-infected with hepatitis C virus (HCV), accounting for roughly one million individuals [8]. It is well-established that patients with HIV/HCV co-infection experience an accelerated natural history of liver disease with increased complications and fatality, when compared with HIV or HCV mono-infected patients [9–12]. There is emerging evidence that HIV/HCV co-infected individuals also suffer from increased cardio-metabolic risk [13–16]. Chronic HCV infection is associated with a multitude of metabolic complications: dyslipidemia, hepatic steatosis, insulin resistance (IR), and chronic kidney disease (CKD) [17, 18]. Exactly how HCV may exacerbate the risk of cardio-metabolic comorbidities in PWH warrants further characterization. The advent of curative direct-acting antiviral (DAA) therapy has revolutionized the management of HCV infection for both HCV mono- and HIV/HCV co-infected patients [19, 20]; and the metabolic impacts of achieving HCV cure after DAA treatment are under active investigation [21].

The National Cholesterol Education Program Adult Treatment Panel III definition of "metabolic syndrome" (alternatively, "insulin resistance syndrome" or "syndrome X") is the co-occurrence of (1) hyperglycemia, (2) dyslipidemia, (3) hypertension, and (4) abdominal obesity [22], all of which coalesce to promote the development of type 2 diabetes mellitus (T2DM) and CVD. Metabolic syndrome is uniquely prevalent in aging PWH [6, 23, 24] and in persons with chronic HCV [17, 25]. Accordingly, it is plausible that HIV/HCV co-infection compounds metabolic derangements in these

individuals. The development of metabolic syndrome in HIV/HCV co-infection is likely multifactorial, influenced by (1) patient-specific factors, (2) HIV and HCV viral-mediated effects, and (3) ART exposure.

In this article, we review the scope and burden of metabolic syndrome in HIV/HCV co-infected patients, risk factors, and potential mechanisms driving the increased cardio-metabolic risk in this population, and discuss relevant clinical considerations for management in the era of highly effective and tolerable ART and curative anti-HCV DAA therapy.

The scope and burden of metabolic syndrome in HIV/HCV co-infection

Data on the prevalence and incidence of "metabolic syndrome" by formal definition are limited in HIV/HCV co-infected patients. However, extrapolations can be made from reports of metabolic syndrome in PWH or those with chronic HCV, as well as studies examining the syndrome's individual diagnostic components or clinical endpoints (i.e., T2DM, CVD) in the context of HIV/HCV co-infection.

The prevalence of baseline metabolic syndrome in 881 PWH initiating ART in the Initio trial was 7.8–8.5%, depending on the criteria used [26]. The incidence during 3 years of follow-up was 8 to 12 cases per 100 person-years. Whereas only incident metabolic syndrome was associated with the development of CVD (HR 2.73, 95% CI 1.07–6.96), both baseline and incident metabolic syndrome increased the risk of T2DM (HR 4.34, 95% CI 1.83–10.25; and HR 4.89, 95% CI 2.22–10.78, respectively) [26]. Data from the Women's Interagency HIV Study (WIHS) revealed a higher prevalence of metabolic syndrome in HIV-seropositive than HIV-seronegative women (33% vs. 22%, respectively; aOR 1.79, 95% CI 1.48–2.16) [23]. This increased risk was attributed to dyslipidemia rather than higher blood pressure, glucose, or waist circumference. According to the D:A:D multi-cohort study and a recent trends analysis of claims data, the prevalence of metabolic syndrome in PWH is increasing over time [3, 24], which has significant and complex implications for the care management of this aging population.

A retrospective evaluation of 2003 to 2012 National Health and Nutrition Examination Survey (NHANES) data among patients with HCV found the prevalence of T2DM and metabolic syndrome to be 18% and 35%, respectively [18]. The association between chronic HCV infection and diabetes risk is unequivocal and interconnected [27]: HCV results in hyperinsulinemia and IR [28], and T2DM accelerates liver fibrosis leading to cirrhosis [29]. Hepatic steatosis and fibrosis, both implicated in chronic HCV, are associated with metabolic syndrome and likely compound HCV-induced glucose abnormalities, further elevating metabolic risk in this population [30]. The link between chronic HCV and the metabolic outcome of CVD is less clear, though the evidence overall suggests an association with higher rates of cardiovascular events and death [31, 32].

In a cross-sectional analysis of the ICONA study, HIV/HCV co-infected patients with HCV viremia had a threefold higher risk of diabetes than PWH [33]. In this study, the following metabolic comorbidities were independently associated with diabetes in the setting of co-infection: body mass index (BMI) ≥

30 kg/m^2, hypertension, hypercholesteremia, and hypertriglyceridemia [33]. Older age, HIV viremia, and degree of liver fibrosis also increased diabetes risk in HIV/HCV co-infected patients. In terms of HCV modifying the cardiovascular risk in PWH, studies have yielded conflicting results, especially when controlling for potential confounders [15, 16, 34, 35]. Acute myocardial infarction (AMI) and cerebrovascular event incidences were higher among 6136 HIV/HCV co-infected veterans (4.2 and 12.5 events per 1000 person-years, respectively) compared with those HIV mono-infected (3.4 and 11.1 events per 1000 person-years, respectively) [35]. However, the greater risk of AMI in co-infected veterans was not statistically significant after adjusting for age, hypertension, T2DM, and duration of ART.

Risk factors associated with metabolic syndrome in HIV/HCV co-infection

Metabolic syndrome in HIV/HCV co-infected patients arises from the interplay of traditional and nontraditional risk factors that are overrepresented compared with the general population: poor socioeconomics, substance use, cardiovascular comorbidities (e.g., dyslipidemia), and liver/kidney disease. Additionally, exposure to ART and direct viral-mediated effects of chronic HIV/HCV further elevate cardio-metabolic risk in the aging co-infected population.

Patient-specific factors

The development of metabolic syndrome in the general population is associated with age, race/ethnicity, and increased body weight [36, 37]. Other risk factors in NHANES included smoking, low household income, high carbohydrate diet, and physical inactivity [38], factors especially prevalent in HIV/HCV co-infected individuals. Metabolic syndrome is also associated with hepatic steatosis, fibrosis, and cirrhosis [39], along with CKD and microalbuminuria [40], comorbidities common to those with HIV/HCV co-infection. In terms of traditional cardiovascular risk, evidence is strongest for overrepresentation of dyslipidemia in PWH compared with the general population; however, emerging data suggest other metabolic components are likely also more common in PWH; the role of HCV co-infection is less clear. Patient-specific factors contributing to the development of metabolic syndrome in HIV/HCV co-infection are summarized in Table 1.

Substance use

Rates of smoking in PWH are nearly twice as high than in the general population: 42% and 20% of > 4000 PWH reported current and former cigarette use, respectively, compared with 21% and 22%, respectively, of nearly 28,000 US adults without HIV [41]. Concurrent substance use with marijuana and cocaine is common in PWH and both have been associated with CVD risk in this population [42, 43]. Furthermore, the effects of tobacco and cocaine use have proven more deleterious in PWH, contributing to higher mortality and worsened subclinical coronary atherosclerosis, respectively, compared with the general population [42, 44]. Drug use including smoking is also more common in

Table 1. Patient-specific factors contributing to the development of metabolic syndrome in HIV/HCV co-infection

Risk category	Viral infection	Risk factors
Socioeconomics	**HIV/HCV**	Low household income High carbohydrate diet Physical inactivity
Substance use	**HIV/HCV**	Tobacco (increased CVD risk and mortality) Marijuana (increased CVD risk) Cocaine (subclinical coronary atherosclerosis)
Liver disease	**HIV**	• Accelerated natural history of HCV-liver disease • Alcoholic fatty liver disease • Non-alcoholic fatty liver disease • Drug-induced hepatoxicity • Opportunistic infections • AIDS cholangiopathy
	HCV	• Natural history: steatosis >> fibrosis >> cirrhosis • Hepatic decompensation • Hepatocellular carcinoma
Kidney disease	**HIV/HCV**	• Non-recovered acute kidney injury • Hypertension • Diabetes mellitus
	HIV	• HIV-associated nephropathy • Immune-complex mediated glomerulonephritis • Thrombotic microangiopathy • ART-associated nephrotoxicity
	HCV	• Mixed cryoglobulinemia syndrome • Membranous nephropathy • Polyarteritis nodosa
Cardiovascular comorbidities	**HIV/HCV**	Dyslipidemia Elevated blood pressure Impaired glucose tolerance Increased waist-to-hip ratio

ART antiretroviral therapy, *CVD* cardiovascular disease

HCV-infected than HCV-uninfected persons [45]. Given a clear predisposition to all four metabolic syndrome components, it is well-founded that the high prevalence of polysubstance abuse by persons with HIV/HCV co-infection exacerbates cardio-metabolic risk.

Liver and kidney disease

A recent trend analysis using cross-sectional MarketScan research data from 64,398 PWH evaluated prevalent non-AIDS comorbidities between 2003 and 2013. The most common comorbidities were hypertension (31–76%), hyperlipidemia (22–50%), and diabetes (11–37%) (ranges reflect payer source) [3]. Compared with HIV-negative matched controls, the proportions of PWH with HCV infection, liver disease, and renal impairment were significantly greater [3]. HIV infection accelerates the natural history of HCV-mediated liver disease, resulting in higher rates of fibrosis progression, hepatic decompensation, and hepatocellular carcinoma [9–12]. It should also be noted that PWH are at increased risk of hepatic steatosis independent of viral hepatitis. For example, other etiologies of chronic liver disease include alcoholic- and non-alcoholic fatty liver disease, drug-induced liver injury, opportunistic infections, and AIDS cholangiopathy [46].

HIV and HCV are independently associated with CKD [47]. Studies of PWH have consistently shown the risk of CKD increases dramatically (i.e., 90%) in the presence of HCV co-infection [35, 48]. In a study of > 20,000 veterans with HIV, those with HIV/HCV co-infection had significantly higher rates of CKD and mortality, even when adjusting for degree of kidney impairment [49]. According to NHANES data, metabolic syndrome significantly increases the risk of CKD and microalbuminuria in a "dose-dependent" fashion based on the number of metabolic components [40]. The high prevalence of metabolic comorbidities in HIV/HCV co-infection may exacerbate renal complications and death in this patient population.

Traditional cardiovascular risk

Data from two large, prospective US cohorts of women and men with and without HIV (the WIHS and the Multicenter AIDS Cohort Study [MACS], respectively) estimated 10-year risk of developing CVD by the Framingham risk score equations [50]. Compared with seronegative controls, men and women with HIV more frequently had reduced levels of high-density lipoprotein (HDL) cholesterol and elevated triglycerides [50], a finding consistent with a similar cohort of French men and women [51]. In the WIHS/MACS study, ART exposure, being overweight, and having a low income predicted CVD risk in PWH [50]. While HIV-associated dyslipidemia can be exacerbated by ART, it is also present in ART-naïve individuals [52]. In 50 men whom HIV-seroconverted in the MACS, significant declines in mean serum total cholesterol, HDL, and low-density lipoprotein (LDL) cholesterol were observed for several years after HIV infection [53]. Subsequent ART initiation was associated with increased total and LDL cholesterol but minimal change in HDL cholesterol levels.

Chronic HCV is also associated with dyslipidemia [17]. Acquisition of HCV infection has been shown to lead to hypolipidemia, including a progressive decline in triglycerides and total, HDL, and LDL cholesterol levels independent of BMI and liver fibrosis [54]. Further, some data suggest HCV co-infection may confer protection against HIV-associated dyslipidemia, a finding supported by a lower observed use of lipid-lowering agents in co-infected patients [55, 56].

Findings from the MACS following 5578 men over 19 years revealed an association between systolic hypertension and prolonged ART use, controlling for age, BMI, and smoking [57]. Interestingly, the odds of systolic hypertension were similar in ART-naïve men and those with ART exposure < 2 years compared with HIV-seronegative men. Recently, an association between hypertension and higher waist-to-hip ratio among PWH has also been suggested [58, 59]. In the Veterans Aging Cohort Study, baseline and incident T2DM after ART initiation were lower in PWH compared with HIV-seronegative controls; however, weight gained in the first year after initiating ART was associated with greater risk of T2DM in PWH [60]. While ART is a major driver of cardio-metabolic risk in PWH and those with HCV co-infection, viral-mediated effects also contribute—the roles of each are discussed below.

ART impact on metabolic syndrome in HIV/HCV co-infection

The preponderance of evidence supports an increased cardio-metabolic risk in ART-exposed compared with ART-naïve PWH [13, 61, 62]. However, the benefits of ART such as HIV virologic control, immunologic recovery, decreased inflammation and immune activation, and prolonged longevity undoubtedly outweigh treatment-associated risks [63–65]. While an exhaustive analysis of ART is beyond the scope of this review, it is important to note its global impact on metabolic syndrome and the differential impact of select classes and agents on metabolic events in HIV/HCV co-infection.

ART and lipodystrophy syndrome

The HIV-associated lipodystrophy syndrome is characterized by lipoatrophy and/or fat accumulation. Clinical presentation is heterogeneous and estimated prevalence ranges from 10 to 80% [66, 67]. While the development of lipoatrophy is primarily attributed to thymidine analogue nucleoside reverse transcriptase inhibitors (e.g., stavudine, zidovudine), no specific antiretroviral agent or class has been implicated in fat accumulation [68]. Other possible contributors to lipodystrophy syndrome include lower fat mass at baseline, HIV disease severity (lipoatrophy), female sex, elevated baseline triglycerides, higher body fat percentage (fat accumulation), and increased age (lipoatrophy and fat accumulation) [69]. Both lipoatrophy and fat accumulation have been associated with abnormal glucose and lipid metabolism, even in the absence of frank obesity [70]. Notably, lipodystrophy and associated metabolic complications may be worsened by HCV co-infection. In a cross-sectional analysis of patients with comparable age, CD4 count, HIV viral load, and duration of ART, lipoatrophy was more prevalent in HIV/HCV co-infected versus HIV mono-infected patients (41% vs. 14%, $p = 0.003$) [71]. In multivariable analysis, IR, BMI, triglycerides, and peripheral fat wasting were associated with HCV co-infection.

Metabolic effects of ART

Evaluating the pathogenesis driving atherosclerosis in HIV, Piconi et al. demonstrated pro-thrombotic and inflammatory mediators were lower, and metabolic factors (i.e., serum cholesterol and lipoproteins) higher, in ART-treated than ART-naïve PWH [65]. Data from the MACS and WIHS cohorts found that ART exposure induces an atherogenic lipoprotein profile in men and women with HIV, respectively [53, 72]. As mentioned previously, studies have suggested that HCV co-infection may blunt ART-associated hypercholesterolemia [55, 56, 73]. While the most prominent ART-induced metabolic derangement is dyslipidemia, elevated risks of hypertension and diabetes have also been reported, even when controlling for possible lipid effects [74–76]. Important clinical considerations for cardio-metabolic risk by ART class are summarized in Table 2, and a focused discussion on the most recent data follows.

Nucleoside reverse transcriptase inhibitors

Tenofovir disoproxil fumarate (TDF) is associated with lower lipid levels than tenofovir alafenamide (TAF) and abacavir [77•, 78, 79]. However, TDF use has been associated with kidney function decline, proximal renal tubulopathy (leading to proteinuria and phosphate wasting), and reduced bone mineral density (BMD). While abacavir use has fewer nephrotoxic and deleterious BMD effects than TDF, it has been associated with increased risk of cardiovascular events (including AMI) in some, but not all, observational studies [80–82]. Switching the nucleoside reverse transcriptase inhibitors (NRTI) backbone component from TDF to TAF given renal and bone safety advantages is increasingly common. While TAF-associated rises in triglyceride, total and LDL cholesterol levels (due to decreased plasma tenofovir levels) may be reversed by switching back to TDF [83], long-term follow-up studies assessing lipid changes on cardio-metabolic clinical outcomes are needed.

Protease inhibitors

Hypercholesteremia and hypertriglyceridemia are common with use of protease inhibitors (PIs), though effect varies by individual PI [84]. Observational cohort studies have found an association between some PIs and an increased risk of cardiovascular events [81]; however, this has not been seen with atazanavir [85, 86]. It is speculated that the indirect hyperbilirubinemia observed with atazanavir use may be cardioprotective; however, further study is needed, especially considering possible alteration by HCV co-infection [87, 88].

Non-nucleoside reverse transcriptase inhibitors

Use of non-nucleoside reverse transcriptase inhibitors (NNRTIs), including efavirenz, has been associated with increased LDL and total cholesterol levels, compared to those of ART-naïve PWH; however, this is counterbalanced by increased HDL levels [89]. The overall favorable lipid profile associated with NNRTIs appears most pronounced for rilpivirine and the newest agent in this class, doravirine, as demonstrated in randomized clinical trials of ART-naïve patients comparing initiation of either to efavirenz [90, 91].

Table 2. Summary of recommended antiretroviral regimens by drug class and potential metabolic considerations for persons with HIV/HCV co-infection

	Impact on Lipids	Cardiovascular disease	Liver disease	Kidney disease	PK drug interactions
Nucleoside Reverse Transcriptase Inhibitors (NRTI)					
ABC/3TC	–	(X)	(X) in CTP B, C	–	–
TAF/FTC	↓	–	Active against Hepatitis B	–	–
TDF/FTC	↑	–	Active against Hepatitis B	(X)	–
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI)					
DOR	–	–	–	–	–
EFV	↓	–	–	–	Many DDIs possible*
RPV	–	–	–	–	(X) with acid-lowering agents
Protease Inhibitors (PI)					
ATV/c, ATV/r	↓	↑	Increases indirect hyper-bilirubinemia	May cause nephrolithiasis	(X) with acid-lowering agents
DRV/c, DRV/r	↓	(X)	–	–	Many DDIs possible*
Integrase Strand Transfer Inhibitors (INSTI)					
BIC	–	–	–	–	(X) coadministration with polyvalent cations
DTG	–	–	–	–	(X) coadministration with polyvalent cations
EVG/c	↓	–	–	–	Many DDIs possible*
RAL	–	–	–	–	(X) coadministration with polyvalent cations

3TC Lamivudine, *ABC* Abacavir, *ATV* Atazanavir, *BIC* Bictegravir, *CTP* Child Turcotte Pugh, *c* Cobicistat, *DDIs* drug-drug interactions, *DOR* Doravirine, *DRV* Darunavir, *DTG* Dolutegravir, *EVG* Elvitegravir, *FTC* Emtricitabine, *PK* pharmacokinetic, *r* Ritonavir, *RAL* Raltegravir, *RPV* Rilpivirine, *TAF* Tenofovir Alafenamide Fumarate, *TDF* Tenofovir Disoproxil Fumarate
Symbols: (X) = avoid use; (–) = no reported association; ↑ = may benefit; ↓ = may worsen
*Suggest referencing a medication interaction tool (i.e., https://www.hiv-druginteractions.org/)

Integrase strand transfer inhibitors

While the newest ART class has favorable effects on lipids, results from two recently published open-label, phase 3, randomized clinical trials in Africa, ADVANCE [92••] and NAMSAL [93], have intensified concerns regarding metabolic risk associated with integrase strand transfer inhibitor (INSTI) use. In both trials, significantly more weight gain was observed with dolutegravir-containing compared with efavirenz-based regimens (5–6 vs. 2–3 kg, respectively); especially when combined with TAF and in female patients [92••]. Data from 1118 WIHS participants (2008–2017) demonstrated women on ART who switched to or added an INSTI not only gained significantly more weight but also experienced increases in BMI, body fat, and blood pressure, compared with women who remained on non-INSTI ART [94].

HIV and HCV viral-mediated effects on metabolic syndrome

The ongoing viral replication of chronic HIV/HCV infection induces an inflammatory and immune activated state in the host, leading to alterations in glucose and lipid metabolism [14]. Resultant metabolic complications—often exacerbated by ART—include hepatic steatosis, IR, dyslipidemia, and visceral adiposity, which ultimately increase the risk of T2DM and CVD in HIV/HCV co-infected patients. Proposed viral mechanisms driving the development of metabolic syndrome are reviewed here and summarized in Fig. 1.

Hepatic steatosis

HCV core protein, a key modulator of viral and cellular gene expression, has been shown to disrupt lipid metabolism and play a significant role in the development of hepatic steatosis [95]. Upon hepatocyte invasion, HCV core protein facilitates viral replication and assembly. The replication complex co-locates near hepatocyte lipid droplets, allowing HCV core protein to directly interfere with intracellular lipid metabolism by overcoming host machinery. This leads to decreased expression of peroxisome proliferator activating receptor-alpha/gamma and activation of sterol regulatory element-binding protein, ultimately triggering lipogenesis [96]. Pathways exploited by HCV core protein also impair lipid degradation and export, exacerbating hepatic steatosis [96].

In a study evaluating PWH with elevated aminotransferases by liver biopsy, 75% had evidence of steatosis; of whom, 32% were graded moderate to severe [97]. ART duration ≥ 12 months was the greatest risk factor. When compared with HCV mono-infection, HIV/HCV co-infection hastens the trajectory of chronic liver disease as measured by prevalence, severity, and necro-inflammatory scores of steatosis [95]. While the exact mechanism of accelerated hepatic fibrosis progression is unknown, HIV viremia likely plays a significant role. In a study of 274 HIV/HCV co-infected patients, those with any degree of HIV viremia had significantly faster progression than those virologically suppressed; however, when those virologically suppressed were compared with 382 HCV mono-infected patients, rates of fibrosis progression were comparable [98].
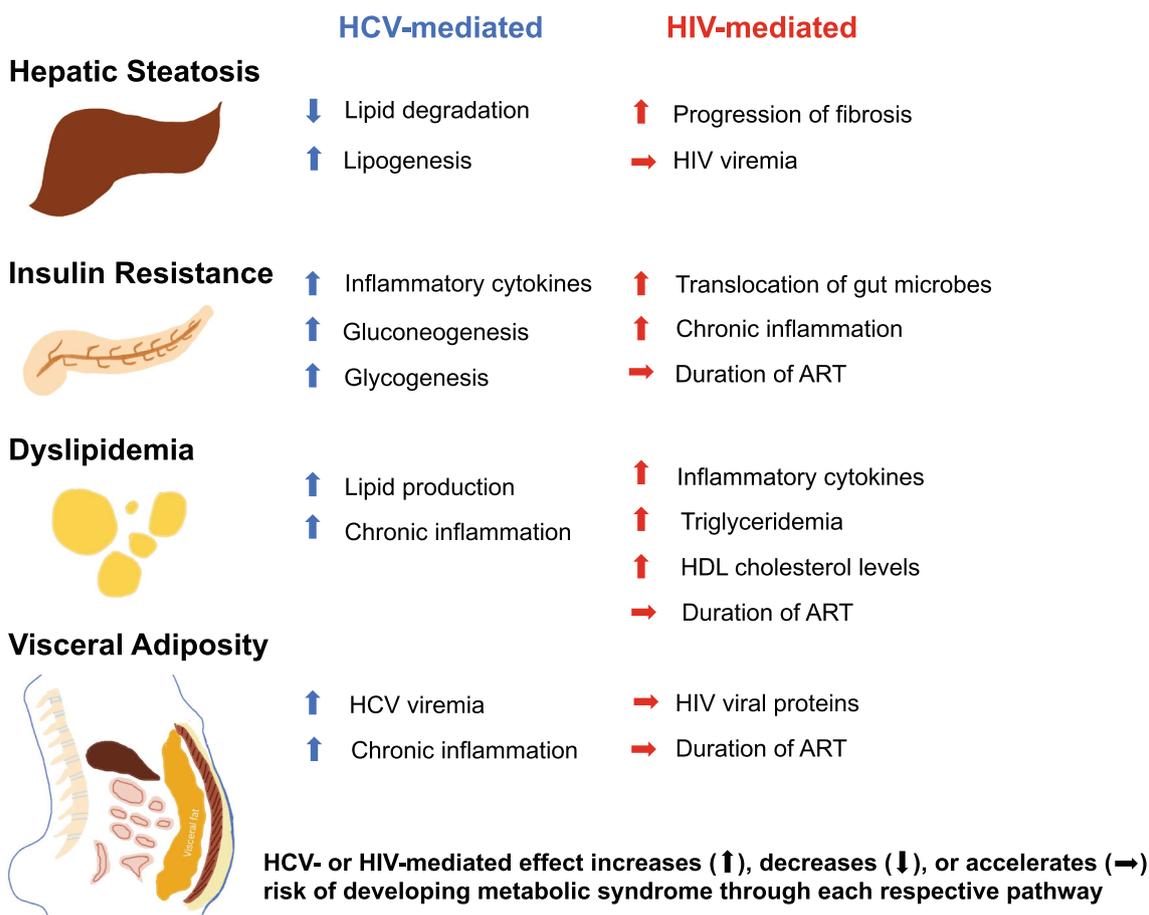
	HCV-mediated	HIV-mediated
Hepatic Steatosis	⬇ Lipid degradation	⬆ Progression of fibrosis
	⬆ Lipogenesis	➡ HIV viremia
Insulin Resistance	⬆ Inflammatory cytokines	⬆ Translocation of gut microbes
	⬆ Gluconeogenesis	⬆ Chronic inflammation
	⬆ Glycogenesis	➡ Duration of ART
Dyslipidemia	⬆ Lipid production	⬆ Inflammatory cytokines
	⬆ Chronic inflammation	⬆ Triglyceridemia
		⬆ HDL cholesterol levels
		➡ Duration of ART
Visceral Adiposity	⬆ HCV viremia	➡ HIV viral proteins
	⬆ Chronic inflammation	➡ Duration of ART

HCV- or HIV-mediated effect increases (⬆), decreases (⬇), or accelerates (➡) risk of developing metabolic syndrome through each respective pathway

Fig. 1. Summary of mechanisms by which chronic HCV and HIV infection increase, decrease, or accelerate the risk of metabolic syndrome mediated by hepatic steatosis, insulin resistance, dyslipidemia and visceral adiposity. (*ART* antiretroviral therapy).

Insulin resistance

Inflammatory states, such as those seen in chronic viral infection, facilitate the interaction of hepatocytes and adipocytes with extracellular mediators (e.g., cytokines, free fatty acids). This initiates a signaling cascade leading to inhibition of insulin action and generation of IR through enhanced glycogenesis, gluconeogenesis, and hepatic glucose production [99]. Chronic HCV promotes an inflammatory state mediated by host and viral factors (i.e., the production of interferon-gamma/tumor necrosis factor-alpha [TNF-a] and HCV core protein, respectively). In turn, TNF-a mediates chronic activation of monocytes/macrophages and can lead to elevated homeostatic model assessment of IR (HOMA-IR) levels and hepatic steatosis [99].

In PWH, NRTI exposure was independently associated with lactate production; however, this relationship was attenuated when adjusting for HOMA-IR levels, suggesting IR may drive this association [100]. NRTIs are implicated in mitochondrial toxicity and formation of reactive oxidative species; this downregulates adiponectin and increases lactate production in adipocytes,

culminating in IR [101]. Translocation of gut microbes may also contribute to HIV-associated development of IR. Depletion of gut-associated lymphoid tissue during primary HIV infection increases epithelial permeability and microbial translocation, thereby activating toll-like receptor-4 and the NF-kB pathway. Downstream inflammatory signaling activates release of interferon-gamma and lipopolysaccharides, ultimately promoting IR and atherogenesis [102•, 103].

Reid et al. found that sCD163, a marker of monocyte/macrophage activation, may play a significant role in mediating the development of IR through inflammation triggered by gut translocation in the setting of HIV/HCV co-infection [102•]. The authors speculate that the association between co-infection and greater HOMA-IR is likely facilitated by viral and non-viral factors affecting sCD163, and further investigation is needed.

Dyslipidemia

HIV infection promotes dyslipidemia and atherogenesis through direct viral effects and ART use. HIV viremia increases inflammatory cytokines (e.g., TNF-a, interferon-alpha, interleukins, steroid hormones), which induce hypertriglyceridemia [104]. HIV replication modifies HDL cholesterol levels through upregulating cholesteryl ester transfer protein activity, stimulating atherogenesis [105]. In terms of ART, PIs directly stimulate hepatic triglyceride synthesis and decrease lipolytic activity, resulting in increased very-LDL secretion and decreased circulating HDL [106]. Similarly, the mechanism driving NNRTI-associated dyslipidemia appears related to increased apoA1 production promoting capacity for lipoprotein secretion, whereas NRTIs stimulate lipid production indirectly through mitochondrial toxicity [107].

In contrast, HCV is associated with hypolipidemia as previously discussed [54]. Pathways whereby HCV contributes to atherogenesis include chronic inflammation, direct vascular invasion, disruption of lipid metabolism, and increased IR [108]. When compounded with HIV-associated lipid effects, co-infected patients experience an increased risk of atherosclerosis and CVD.

Visceral adiposity

Both HIV- and HCV-associated chronic inflammation independently stimulate visceral adipose tissue accumulation, which likely plays a role in the development of obesity. A study of 236 HCV-infected patients showed that a higher visceral adiposity index was associated with degree of HCV viremia, severity of steatosis, and necroinflammation [109]. HIV viral proteins (i.e., Vpr, Tat) have been implicated in affecting adipogenesis through increased inflammatory cytokine expression thereby affecting adipose tissue distribution in PWH. ART may further enhance visceral adiposity development by increasing systemic inflammation and altering expression of mitochondrial DNA and transcription factors regulating lymphocyte proliferation, differentiation, and activation [110, 111].

There are limited studies on the effect of HIV/HCV co-infection on visceral adiposity. A cross-sectional analysis comparing co-infected men and women with those HIV mono-infected suggested that amounts of

subcutaneous and visceral adipose tissue are comparable between groups, though subtle differences by gender and ART status may exist [112]. The authors speculate that HIV commonly precedes HCV infection; therefore, HCV has minimal additional contribution to preexistent HIV viral- and ART-mediated effects on adiposity (e.g., mitochondrial toxicity and systemic inflammation).

Clinical considerations for management of metabolic syndrome in HIV/HCV co-infection

The landscape for managing HIV/HCV co-infected patients has vastly changed in the era of highly efficacious and tolerable ART as well as curative anti-HCV DAA therapy [19, 20]. This cohort is now aging and the cornerstone of management hinges on addressing senescent-related comorbidities and sequelae of chronic viral infection and therapy-associated side effects. The safety and efficacy of DAAs allows for treatment of co-infected patients in the same way as HCV mono-infected patients [19] and confers a mortality benefit in ART-treated PWH [113•]. Below we discuss important clinical considerations for the management of metabolic syndrome in HIV/HCV co-infected patients, including cardio-metabolic screening and risk mitigation, recognizing relevant drug-drug interactions (DDIs), and possible metabolic improvement after DAA-induced HCV eradication.

Screening and monitoring of metabolic syndrome

Given the increased baseline risk of metabolic syndrome in PWH and in those with chronic HCV, it is imperative to screen for metabolic comorbidities during initial clinical assessment, prior to ART initiation. Primary Care Guidelines for the management of PWH recommend evaluation of renal or hepatic dysfunction with a comprehensive metabolic panel, viral hepatitis testing, and screening for dyslipidemia (fasting lipid panel) and impaired glucose tolerance (either hemoglobin A1c or fasting blood glucose) prior to and 1–3 months after starting ART [114]. Additionally, blood pressure and body weight (including BMI) should be measured at the initial clinic visit and each follow-up appointment. Furthermore, it is crucial to screen for comorbid substance use disorders with standardized instruments such as the AUDIT-C and counsel on harm reduction where appropriate [115].

Many recommendations for cardio-metabolic screening in PWH are based on clinical guidelines for the general population. However, data demonstrating the burden of metabolic comorbidities in PWH approximates that of HIV-seronegative persons aged 10 years older support the need for earlier screening in PWH [116]. Appropriate intervals for reassessing metabolic derangements in PWH are unknown, and data to specifically inform guidance on screening and monitoring of metabolic syndrome in HIV/HCV co-infection are lacking. An opportunity for preventive intervention before the onset of metabolic disease may be assessing trends in routinely collected clinical data. For example, Rhee et al. found that at least two measurements of random plasma glucose > 130 mg/dL

was nearly 95% specific for T2DM onset within 5 years [117].

Metabolic consequences of drug-drug interactions

Selecting an ART regimen poses several important host and virologic considerations, including presence of HCV co-infection [118]. Specific metabolic effects by ART class are discussed previously and summarized in Table 2. Additionally, critical pharmacokinetic DDIs involving the cytochrome P450 enzyme system, specifically the CYP3A4 enzyme, are relevant in managing HIV/HCV co-infected patients given potential for metabolic consequences. Ritonavir and cobicistat, included in PI- and INSTI-based ART as a strategy to increase or "boost" antiretroviral exposure and accommodate once daily dosing, both strongly inhibit CYP3A4. It is therefore critical to recognize either pharmacologic "booster" in an ART regimen when selecting anti-HCV DAA or lipid-lowering (i.e., HMG-CoA reductase inhibitor or "statin") therapy given possible DDIs. The potent inhibition of CYP3A4 by ritonavir or cobicistat can also lead to significantly higher levels of certain anti-psychotic drugs and worsen associated metabolic toxicities. A medication interaction tool should be used to review potential DDIs before initiating ART and/or DAAs with other concomitant medications (i.e., https://www.hiv-druginteractions.org/).

Metabolic reversal with HCV clearance after DAA therapy

There is emerging literature describing recovery of metabolic impairment in patients who achieve HCV cure after DAA treatment [21]; however, reports in HIV/HCV co-infected individuals are lacking. In the era of interferon-free DAA therapy with HCV eradication rates of 94–100% [19], improvements in HCV-associated alterations in glucose and lipid metabolism are attributed to viral clearance.

In a prospective case-control study of 133 HCV-infected patients with advanced fibrosis though not T2DM, DAA-induced HCV clearance improved IR and glycemic control [119]. In 2435 veterans with T2DM, a significantly greater drop in hemoglobin (mean decrease of 0.98%) and reduced need for insulin was observed 1 year after DAAs in those who achieved sustained virologic response versus treatment failure [120]. A proposed mechanism is that HCV eradication by DAAs enhances insulin sensitivity; however, studies are conflicting on whether this occurs in peripheral and/or hepatic tissue [121, 122]. Further, HCV-associated hypolipidemia and intra-hepatic lipid accumulation has been shown to normalize after DAA therapy initiation, resulting in significantly improved steatosis [123]. In a cohort of liver-transplant recipients, DAA-based eradication of recurrent HCV infection resulted in a decreased need for treatment of diabetes and hypertension by 38% and 22% from baseline, respectively [124]. The effects of HCV clearance by DAA treatment on clinical metabolic outcomes show promise in HCV mono-infected patients though data are needed in PWH.

Clinical approach to metabolic modification in HIV/HCV co-infected patients

Clinicians caring for HIV/HCV co-infected patients should utilize regular clinic visits as opportunities to reduce modifiable metabolic risk factors including (1) brief assessment and evidence-based intervention for substance use disorders; (2) counseling to minimize unhealthy weight gain; (3) aggressive

pharmacotherapy management of hypertension, diabetes, and dyslipidemia; (4) prioritizing HCV cure with DAA therapy; and (5) periodic re-assessment of ART regimen in virologically suppressed PWH to consider whether a different (potentially two-drug [125]) regimen may be associated with lower cardio-metabolic risk over time [125]. Ideally, multi-disciplinary teams comprising addiction psychiatrists, dieticians, clinical pharmacy specialists, and health coaches in addition to nurses, advanced practice practitioners, and physicians should be employed to care for this aging cohort of HIV/HCV co-infected patients at high-risk of metabolic syndrome.

Conclusions

Persons with HIV/HCV co-infection are aging due to the success of ART and accordingly, suffer from an increased risk of metabolic syndrome and subsequent development of T2DM and CVD. Traditional and non-traditional cardio-metabolic risk factors are overrepresented in co-infected patients compared with the general population: poor socioeconomics, substance use, cardiovascular comorbidities, liver, and kidney disease. Direct viral-mediated effects of chronic HIV/HCV infection and toxicities associated with long-term ART exposure further compound risk by altering host glucose and lipid metabolic pathways. HCV eradication by DAA therapy may improve metabolic comorbidities; however, additional study in HIV/HCV co-infection is needed. Future research programs should aim to better characterize metabolic syndrome in HIV/HCV co-infected patients with the overall goal of improved screening, treatment, and prevention. This will require additional investigation into optimal screening modalities and intervals, comorbidity reduction, viral effects on host metabolism, and safer ART regimens.

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Compliance with ethics standards

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Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
•   Of importance
••   Of major importance

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