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Cardiometabolic health in people with HIV: expert consensus review

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Objectives: To develop consensus data statements and clinical recommendations to provide guidance for improving cardiometabolic health outcomes in people with HIV based on the knowledge and experience of an international panel of experts.

Methods: A targeted literature review including 281 conference presentations, peer-reviewed articles, and background references on cardiometabolic health in adults with HIV published between January 2016 and April 2022 was conducted and used to develop draft consensus data statements. Using a modified Delphi method, an international panel of 16 experts convened in workshops and completed surveys to refine consensus data statements and generate clinical recommendations.

Results: Overall, 10 data statements, five data gaps and 14 clinical recommendations achieved consensus. In the data statements, the panel describes increased risk of cardiometabolic health concerns in people with HIV compared with the general population, known risk factors, and the potential impact of antiretroviral therapy. The panel also identified data gaps to inform future research in people with HIV. Finally, in the clinical recommendations, the panel emphasizes the need for a holistic approach to comprehensive care that includes regular assessment of cardiometabolic health, access to cardiometabolic health services, counselling on potential changes in weight after initiating or switching antiretroviral therapy and encouraging a healthy lifestyle to lower cardiometabolic health risk.

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Conclusions: On the basis of available data and expert consensus, an international panel developed clinical recommendations to address the increased risk of cardiometabolic disorders in people with HIV to ensure appropriate cardiometabolic health management for this population.

Introduction

The availability of highly effective ART has transformed HIV from a terminal illness into a chronic condition requiring long-term clinical management.[1] Thus, a major contemporary goal for the care of people with HIV is to ensure that they live long and healthy lives.[2] Healthcare providers have advocated for the addition of good health-related quality of life to the UNAIDS treatment targets for people with HIV, including the management of comorbidities, mental health, self-perceived quality of life, fatigue and addressing HIV-associated stigma.[3]

Maintaining optimal cardiometabolic health and body composition is important to achieving good health. Cardiometabolic health encompasses a spectrum of parameters (e.g. blood pressure, body weight, lipids) that influence an individual's likelihood of developing cardiometabolic disease.[4] Body composition comprises fat, lean mass, and bone quantity and quality, and affects multiple domains of metabolic health. Metabolic diseases are multifactorial and are linked to anthropometric changes, in particular ectopic fat accumulation.[5,6] In clinical settings, weight and body composition assessment provides an opportunity to discuss metabolic health status.

Traditional and HIV-associated risk factors contribute to the higher burden of comorbidities in people with HIV,[7] including those related to metabolic health and body composition. For example, a systematic review and meta-analysis ($N = 8\,848\,569$) reported that people with HIV had a 1.8-fold increased risk of heart failure compared with the general population.[8] In a population-based matched cohort study in the UK, people with HIV had a 1.5-fold greater risk of cardiovascular disease (CVD) and a 1.3-fold greater risk of type 2 diabetes compared with people without HIV.[9] An analysis of the TREAT Asia HIV Observational Database projected that incidence of CVD will double in people with HIV in Asia between 2019 and 2028.[10]

Numerous studies have evaluated cardiometabolic health and body composition in people with HIV, and clinical guidelines have been issued. However, given the rapid evolution of data and development of ART, comprehensive practical guidance aimed at improving cardiometabolic outcomes in this population is needed. Here, on the basis of a literature review and professional experience, an international panel of experts developed consensus data statements and identified data gaps, culminating in a set of clinical recommendations to support the management of cardiometabolic health in people with HIV.

Methods

Targeted literature review

A targeted literature review was performed using PubMed to search for articles evaluating cardiometabolic health and body composition in people with HIV published between January 2016 and April 2022. This date range was selected to include contemporary data on metabolic health in people with HIV. Topics included weight change; metabolic syndrome and lipids; diabetes, insulin resistance, glucose and fatty liver disease; cardiac health and bone health. Articles were filtered by title and abstract text for relevance and study quality. Overall, 281 reports formed the basis of the targeted literature review (see Supplementary Methods (available as Supplementary data at *JAC* Online) for additional details). This targeted literature review was used to draft a set of data statements to initiate the consensus process.

Table 1. Members of the expert panel

Name	Affiliation(s)	Country
Rachel L. Batterham	University College London; University College London Hospitals Biomedical Research Centre	UK
Roger J. Bedimo	VA North Texas Health Care System; University of Texas Southwestern Medical Center	USA
Ricardo S. Diaz	Federal University of São Paulo	Brazil
Giovanni Guaraldi	University of Modena and Reggio Emilia	Italy
Janet Lo	Massachusetts General Hospital	USA
Esteban Martínez	Hospital Clinic and University of Barcelona	Spain
Grace A. McComsey	Case Western Reserve University	USA
Ana Milinkovic	ViiV Healthcare; Chelsea and Westminster Hospital; Imperial College London	UK
Toshio Naito	Juntendo University Faculty of Medicine	Japan
Sebastian Noe	MVZ Karlsplatz	Germany
Donal O'Shea	University College Dublin School of Medicine	Ireland
Roger Paredes	Hospital Universitari Germans Trias i Pujol	Spain
Jonathan M. Schapiro	Sheba Medical Center	Israel
Mark S. Sulkowski	Johns Hopkins University School of Medicine	USA
François Venter	University of the Witwatersrand	South Africa
Laura Waters	Central and North West London NHS Foundation Trust	UK

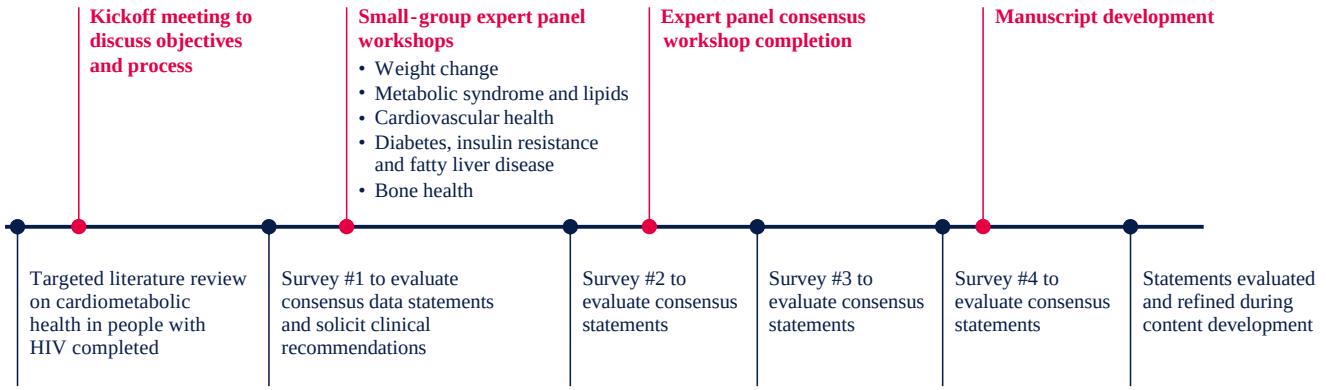

Figure 1. Timeline of the modified Delphi process to achieve consensus. Initially, a targeted literature review on cardiometabolic health in people with HIV was completed, which provided the foundation for initial draft consensus data statements. The expert panel evaluated the draft statements and proposed additional clinical recommendations in the first online survey and a series of small-group workshops. Revised consensus data statements and clinical recommendations were then evaluated in a second online survey and a subsequent workshop that included the complete expert panel. Two additional surveys (surveys 3 and 4) were conducted to evaluate the consensus statements. Statements were further evaluated and revised during content (poster and manuscript) development. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

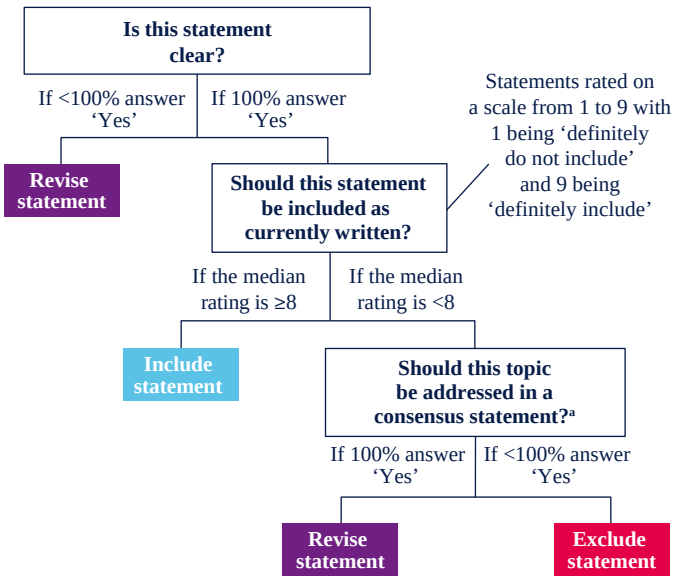

Figure 2. Decision tree for evaluating consensus statements. Question 1 assessed whether a statement was clear (understandable) and was rated as yes or no. If any expert responded no to Question 1, the statement was revised for clarity. Question 2 assessed whether a statement should be included as currently written and was rated on a scale from 1 to 9. A statement had to receive a median rating ≥8 to be included as currently written. A third question asked whether the topic should be addressed in a consensus statement. If any expert responded that the topic should not be addressed, then the statement was excluded. If 100% of experts voted to address the topic, the statement was revised based on their feedback and resurveyed. The experts could also provide their feedback and propose new statements in response to free-form questions in each survey. [a]If a topic was evaluated by 100% of experts to address in a consensus statement, then the topic was no longer polled. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

Consensus process

An international panel of 16 HIV and cardiometabolic health experts agreed to engage in the consensus process (Table 1). The panel was selected based on publication records, geographic representation, and availability. A modified Delphi method[11] composed of online surveys and virtual workshops was used to achieve consensus (Figure 1). A decision tree composed of three questions was used to evaluate consensus for each statement (Figure 2). Feedback from all members of the panel was evaluated and votes from each member were treated equally. To reduce the risk of bias, all survey responses were anonymous.

Initially, a set of consensus data statements and data gaps was generated based on the targeted literature review. In the first online survey, the expert panel evaluated the draft consensus statements, provided feedback for the data statements, and proposed additional data statements and a set of clinical recommendations. Subsequently, revised data statements and clinical recommendations were evaluated in a series of small-group virtual workshops addressing cardiometabolic health topics, each including four to five experts (Table S1). Additional data statements and clinical recommendations were also proposed during each workshop. The draft consensus data statements and clinical recommendations from the small-group workshops were subsequently evaluated in a second online survey. After survey 2, statements were reorganized and those addressing similar topics were grouped together where appropriate. The results of the second survey were then evaluated by the entire panel in a large virtual workshop. After the large workshop, the panel evaluated data statements and clinical recommendations in two additional online surveys. All online surveys were provided to all members of the panel. All statements that had achieved consensus through survey 4 were included. Statements that did not achieve consensus by survey 4 were revised on the basis of panel feedback and incorporated into the manuscript text but not considered to have achieved consensus. Additional feedback on the wording of statements was obtained during manuscript development. All members of the panel reviewed and approved the manuscript.

To ensure that the consensus statements were not limited by the parameters used for the initial targeted literature review, additional references were provided by the panel and additional literature searches were conducted to inform the evolving consensus statements.

Role of the study sponsor

ViiV Healthcare was the consensus sponsor. ViiV Healthcare identified the expert panel and hosted the workshop meetings. To reduce the risk of bias, a third party (MedThink SciCom, Raleigh, NC, USA) managed the surveys and guided the workshop discussions on the content of the statements. One member of the panel became an employee of ViiV Healthcare during the consensus process; their input was treated equally to that of the other members. The study sponsor reviewed the manuscript but did not have any influence on the consensus statements.

Consensus statements

Overview

Overall, 10 data statements, five data gaps and 14 clinical recommendations reached consensus. Four proposed statements did not achieve consensus, with each receiving a median rating of 7 (Table S2). Survey completion, workshop attendance, and statement evolution are presented in Tables S3–S5. Notably, the expert panel rejected all statements related to metabolic syndrome due to a concern that metabolic syndrome as a composite endpoint does not provide value beyond its individual components.

Consensus data statements and summary of evidence

Consensus data statements are listed in Table 2. In the data statements, the panel describes increased risk of cardiometabolic health concerns in people with HIV compared with the general population, known risk factors that contribute to cardiometabolic health outcomes, and the potential impact of ART on cardiometabolic health.

Weight change

Overweight and obesity are major causes of worsened health globally and have become more prevalent over time in both people with HIV and the general population

Summary of evidence: Globally, obesity has nearly tripled between 1975 and 2021.[12] Obesity increases the risk of developing multiple life-limiting chronic conditions,[13] and between 1990 and 2017, global deaths attributable to high BMI have more than doubled.[14] Among people with HIV, obesity has increased at a rate comparable to that of the general population.[6,15]

Weight gain is expected in some people with HIV after antiretroviral therapy initiation, in part, due to a 'return to health'

Summary of evidence: Untreated HIV is associated with weight loss, and after ART initiation, weight gain may occur due to a 'return to health' resulting from immune reconstitution and viral suppression.[16–18] Greater increases in weight, lean mass and fat mass have been reported in people with HIV initiating ART with low $CD4^+$ cell count or high viral load.[18–20] Weight gain of 4.5 to 6.8 kg (10–15 pounds) after ART initiation in people with HIV with normal baseline BMI was associated with reduced mortality.[16]

Weight gain is more pronounced after initiation of tenofovir alafenamide and second-generation integrase strand transfer inhibitors when compared with older antiretroviral agents (mainly tenofovir disoproxil fumarate and efavirenz)

Summary of evidence: In large cohort studies of treatment-naive people with HIV initiating ART, second-generation integrase strand transfer inhibitors (INSTIs) were associated with greater weight gain compared with cobicistat-boosted elvitegravir and NNRTIs.[21–26] Similarly, studies of ART-naive people with HIV initiating treatment have reported greater weight gain with use of tenofovir alafenamide versus lamivudine, tenofovir disoproxil fumarate or abacavir.[24,25,27] It was noted that efavirenz and tenofovir disoproxil fumarate have been independently associated with weight suppression,[17] although this statement did not reach consensus.

Demographic characteristics including female sex and, in US studies, black race have been associated with more pronounced weight gain thus far

Summary of evidence: In large cohort studies of ART-naive people with HIV initiating treatment, greater weight gain was observed in women and, in the USA, black people.[23,25,28,29]

Cardiovascular health

Cardiovascular disease risk is higher in people with HIV compared with the general population

Summary of evidence: Results from meta-analyses support greater CVD risk in people with HIV compared with the general population.[8,30–32] In large cohort studies, people with HIV had a higher risk of cardiovascular events including myocardial infarction, stroke, ischaemia, heart failure and sudden cardiac death compared with people without HIV.[9,33–39]

Traditional risk factors for cardiovascular disease apply to people with HIV

Summary of evidence: Traditional risk factors for CVD including smoking, excess adiposity, diabetes, dyslipidaemia, hypertension, and male sex apply to people with HIV and some, such as smoking, are more prevalent.[36,37,39–46] Non-traditional risk factors for CVD, including alcohol use disorders, depression, and hepatitis C virus co-infection, are more common in people with HIV.[40] More recently, hepatic steatosis was also associated with higher cardiovascular risk in individuals with BMI <25 kg/m^2 (versus ≥25 kg/m^2), those with BMI <30 kg/m^2 (versus ≥30 kg/m^2) and those aged <60 years (versus ≥60 years).[42,47]

Untreated HIV and some antiretroviral agents (abacavir, ritonavir-boosted darunavir and lopinavir) have been associated with increased cardiovascular disease risk

Summary of evidence: Untreated HIV is associated with increased risk of CVD.[40,48,49] Untreated HIV can lead to $CD4^+$ T-cell depletion, greater intestinal permeability, microbial translocation and cholesterol metabolism alterations, which can promote inflammation and atherogenesis. Low $CD4^+$ cell count, particularly <200 cells/mm^3, has been associated with increased risk of clinical CVD.[37–39,46] Furthermore, in cohort studies that included

Table 2. Consensus data statements

Weight change
1. Overweight and obesity are major causes of worsened health globally and have become more prevalent over time in both people with HIV and the general population
2. Weight gain is expected in some people with HIV after antiretroviral therapy initiation, in part, due to a 'return to health'
• Weight gain is more pronounced after initiation of tenofovir alafenamide and second-generation INSTIs when compared with older antiretroviral agents (mainly tenofovir disoproxil fumarate and efavirenz)
3. Demographic characteristics including female sex and, in US studies, black race have been associated with more pronounced weight gain thus far
Cardiovascular health
1. Cardiovascular disease risk is higher in people with HIV compared with the general population
• Traditional risk factors for cardiovascular disease apply to people with HIV
• Untreated HIV and some antiretroviral agents (abacavir, ritonavir-boosted darunavir and lopinavir) have been associated with increased cardiovascular disease risk
Type 2 diabetes, insulin resistance, non-diabetic hyperglycaemia and MAFLD
1. Short-term data suggest that the prevalence of type 2 diabetes is similar or greater in people with HIV compared with individuals without HIV
2. Risk factors for insulin resistance and type 2 diabetes are multifactorial and include traditional and non-traditional factors. Identified risk factors include the following:
• Older age
• Increased waist circumference
• Higher body mass index
• Sedentary lifestyle
• Diet
• Family history of type 2 diabetes
• Race
3. MAFLD is an important component of metabolic health in people with HIV
• Male sex, physical inactivity, higher body mass index and type 2 diabetes have been identified as being associated with higher likelihood of hepatic steatosis and older age with higher likelihood of hepatic fibrosis
Bone health
1. Abnormal bone health is a potential concern for all people with HIV
• Compared with individuals without HIV, people with HIV have greater bone loss as reflected by decreased BMD and increased risk of fractures
• Identified risk factors associated with reduced BMD in people with HIV include traditional and HIV-specific risk factors such as the following:
◦ Older age
◦ Female sex
◦ Hypogonadism
◦ Menopause
◦ Low $CD4^+$ cell count
◦ Exposure to antiretroviral therapy regimens including tenofovir disoproxil fumarate and boosted protease inhibitors
◦ Tobacco use
◦ Heavy alcohol use
2. Initiating antiretroviral therapy is associated with decreases in BMD regardless of antiretroviral therapy type
• Vitamin D supplementation attenuates decreases in BMD after antiretroviral therapy initiation
3. Compared with other antiretroviral agents, use of tenofovir disoproxil fumarate is associated with greater decreases in BMD, which can be exacerbated by concomitant use of a boosted protease inhibitor
• Switching from a regimen that includes tenofovir disoproxil fumarate to one that does not is associated with improved BMD

large numbers of women, low $CD4^+$ cell count was associated with atherosclerosis.[45,50]

Antiretroviral agents including abacavir, ritonavir-boosted darunavir and lopinavir have been associated with a modest increase in risk of CVD. Large cohort studies and systematic reviews and meta-analyses have reported an association between abacavir exposure and increased risk of CVD, including myocardial infarction. Risk of CVD from recent abacavir exposure ranged

from an incidence rate ratio of 1.40 (95% CI, 1.20–1.64) to a relative risk of 1.71 (95% CI, 1.39–2.10).[32,51–53] A pooled analysis of people with HIV enrolled in clinical trials reported a lower incidence of cardiovascular events among individuals on abacavir (relative rate, 0.62 per 1000 person-years; 95% CI, 0.39–0.98).[54] Cumulative exposure to ritonavir-boosted lopinavir was associated with higher risk of myocardial infarction in a study of the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) cohort (relative rate, 1.13; 95% CI, 1.05–1.21) and a systematic review and meta-analysis (relative risk, 1.19; 95% CI, 1.03–1.39).[32,52] Exposure to ritonavir-boosted darunavir was associated with increased incidence of cardiovascular events in the D:A:D cohort (adjusted incidence rate ratio, 1.59 per 5 years; 95% CI, 1.33–1.91).[55]

Type 2 diabetes, insulin resistance, non-diabetic hyperglycaemia and metabolic-associated fatty liver disease

Short-term data suggest that the prevalence of type 2 diabetes is similar or greater in people with HIV compared with individuals without HIV

Summary of evidence: Large cohort studies have reported a higher prevalence of type 2 diabetes in people with versus without HIV.[56–58] However, a large cohort study and a systematic review and meta-analysis reported no significant differences in incidence and odds of type 2 diabetes, respectively, in people with versus without HIV.[59,60] Two large cohort studies reported numerically higher prevalence or incidence of type 2 diabetes in people with versus without HIV.[34,61]

Risk factors for insulin resistance and type 2 diabetes are multifactorial and include traditional and non-traditional factors

Summary of evidence: Several studies reported older age as a risk factor for type 2 diabetes in people with HIV.[62–65] People with HIV of black race or with a family history of type 2 diabetes had a higher incidence of prediabetes or type 2 diabetes.[65] Cardiometabolic health characteristics including increased waist circumference and higher BMI have been associated with increased risk of developing insulin resistance or type 2 diabetes in people with HIV.[62,66] In the general population, unhealthy diet and lack of physical activity have been associated with increased risk of type 2 diabetes.[67–69] Hepatitis C virus co-infection and HIV-related inflammation and lipodystrophy are non-traditional risk factors that can increase the risk of insulin resistance and diabetes in people with HIV.[70]

Metabolic-associated fatty liver disease is an important component of metabolic health in people with HIV

Summary of evidence: The expert panel supported recently published diagnostic criteria for metabolic-associated fatty liver disease (MAFLD),[71,72] which are evidence of hepatic steatosis plus any of the following: overweight or obesity, type 2 diabetes or metabolic dysregulation. MAFLD is caused by systemic metabolic dysfunction that affects the liver downstream. Although data are currently limited, approximately one-third of people with HIV met criteria for MAFLD in two studies.[73,74]

Male sex, physical inactivity, higher body mass index and type 2 diabetes have been identified as being associated with higher likelihood of hepatic steatosis and older age with higher likelihood of hepatic fibrosis

Summary of evidence: Identified risk factors associated with a higher likelihood of hepatic steatosis include physical inactivity,[75] type 2 diabetes[76,77] and male sex.[75–78] Across five studies, higher BMI was associated with increased likelihood of hepatic steatosis, including in one study that enrolled only women with HIV.[73,75,77–79] Three large cohort studies reported an association between older age and higher likelihood of hepatic fibrosis.[76,80,81]

Bone health

Abnormal bone health is a potential concern for all people with HIV: compared with individuals without HIV, people with HIV have greater bone loss as reflected by decreased bone mineral density and increased risk of fractures

Summary of evidence: Compared with people without HIV, people with HIV have a greater risk of bone loss, including decreased bone mineral density (BMD), an important risk factor for fractures,[82] and increased fracture risk. A meta-analysis reported that people with HIV had a higher prevalence and incidence of fractures compared with people without HIV.[83] Another meta-analysis reported that people with HIV had higher odds of developing osteopenia or osteoporosis at the lumbar spine and hip compared with people without HIV.[84] Compared with women without HIV, women with HIV had lower BMD in a cross-sectional study[85] and greater bone loss in a prospective study.[86]

Identified risk factors associated with reduced bone mineral density in people with HIV are traditional and HIV-specific

Summary of evidence: Traditional risk factors for reduced BMD and fractures apply to people with HIV and include demographic characteristics such as older age[82,87–93] and female sex,[89,92,94,95] vitamin D deficiency,[92,96,97] and hypogonadal states (e.g. lower testosterone levels in men[92,96,98] and menopause in women[85,86,92]). Notably, one study reported greater risk of BMD loss in people with versus without HIV who transitioned from pre- to post-menopause.[86] Modifiable risk factors associated with lower BMD include tobacco use[88,90,96,97] and heavy alcohol consumption.[96,97] Additional factors or conditions associated with reduced BMD and/or increased fracture risk in people with HIV and the general population include adrenal insufficiency, haemophilia, gastrointestinal malabsorption, glucocorticoid use, emphysema, opiate use, dietary calcium deficiency, primary hyperparathyroidism, Cushing's syndrome, renal phosphate wasting, idiopathic hypercalciuria, celiac sprue, multiple myeloma and mastocytosis.[96,97,99]

HIV-related parameters and co-infections contribute to lower BMD in people with HIV. Lower nadir $CD4^+$ cell count is associated with decreased BMD.[82,93,94] Chronic hepatitis C virus co-infection has been associated with reduced BMD and increased risk of fractures.[82,85,92,100]

Table 3. Data gaps

Data gaps
1. The causative effect(s) mediating weight gain with tenofovir alafenamide and second-generation INSTIs are not yet understood
2. In the future, well-designed studies, controlled for confounders, are needed to rigorously assess the following:
• The prevalence of weight change in people with HIV on newer antiretroviral therapy regimens compared with the general population
• The consequences of weight change after initiating or switching antiretroviral therapy regimens
• The impact of antiretroviral therapy on body composition including subcutaneous and visceral fat and intramuscular adipose tissue
• The impact of antiretroviral therapy regimens on MAFLD
• The effects of contemporary antiretroviral therapy on insulin resistance in relation to weight gain
• The pathogenesis of atherosclerotic cardiovascular disease in people with HIV
• The impact of HIV disease and/or antiretroviral therapy on bone health
3. Additional studies are needed to improve risk stratification and to characterize and optimize prevention and treatment of cardiovascular disease in people with HIV
4. Well-designed studies evaluating impact of lifestyle interventions, including the impact of diet changes, on cardiometabolic parameters such as type 2 diabetes in people with HIV are needed
5. Behavioural and biomedical interventions supportive of improved bone health in the general population should be assessed in people with HIV

Initiating antiretroviral therapy is associated with decreases in bone mineral density regardless of antiretroviral therapy type

Summary of evidence: A meta-analysis reported that ART-experienced versus ART-naive people with HIV had higher odds of osteopenia and osteoporosis at the lumbar spine and total hip.[84] In the START study, immediate versus deferred initiation of PI- or NNRTI-based ART (83.7% on tenofovir disoproxil fumarate) was associated with decreases in BMD.[101] Other studies reported lower trabecular bone score in ART-experienced versus ART-naive people with HIV[93] and an association between longer ART duration and lower BMD.[91]

Across antiretroviral agents, studies have generally reported a decrease in BMD after ART initiation. People with HIV naive to ART initiating tenofovir disoproxil fumarate and individuals without HIV using tenofovir disoproxil fumarate for pre-exposure prophylaxis (PrEP) had decreases in BMD.[90,94,95,102,103] Initiation of NNRTIs or boosted PIs in ART-naive people with HIV has been associated with decreased BMD.[104–106] Initiation of second-generation INSTIs in ART-naive people with HIV has been associated with significantly decreased BMD, numerically decreased BMD or numerically increased BMD depending on study and site investigated (e.g. hip, spine or femoral neck).[107,108]

Vitamin D supplementation attenuates decreases in bone mineral density after antiretroviral therapy initiation

Summary of evidence: A systematic review and meta-analysis of people with and without HIV using tenofovir disoproxil fumarate as part of ART or PrEP, respectively, reported that vitamin D supplementation was correlated with improved BMD.[109] A randomized, double-blind, placebo-controlled study assessing vitamin D and calcium supplementation in ART-naive people with HIV initiating efavirenz/emtricitabine/tenofovir disoproxil fumarate reported smaller declines in total hip and lumbar spine BMD in participants receiving high-dose vitamin D and calcium.[110] An analysis of people with HIV taking dolutegravir-based ART in the prospective observational SCOLTA Project found that vitamin D supplementation was associated with improved BMD.[107]

Compared with other antiretroviral agents, use of tenofovir disoproxil fumarate is associated with greater decreases in bone mineral density, which can be exacerbated by concomitant use of a boosted protease inhibitor

Summary of evidence: A systematic review and meta-analysis reported greater decreases in lumbar spine, total hip, and femoral neck BMD with tenofovir disoproxil fumarate-containing ART versus ART without tenofovir disoproxil fumarate.[111] In a prospective study and a sub-study of a phase 3, randomized, open-label trial, treatment-naive people with HIV who initiated tenofovir disoproxil fumarate-containing ART had decreases in BMD at the hip and spine.[95,112] In studies of people without HIV taking PrEP, use of tenofovir disoproxil fumarate-containing PrEP was associated with decreased BMD at the hip and lumbar spine and with a statistically significant increase in the incidence of osteoporosis or osteopenia.[102,103,111,113] Regimens containing pharmacokinetic enhancers can intensify the negative effect of ART, including tenofovir disoproxil fumarate, on bone health.[112] A meta-analysis of clinical trial data found that when tenofovir disoproxil fumarate versus tenofovir alafenamide was administered as part of a boosted regimen, tenofovir disoproxil fumarate was associated with decreased BMD and higher risk of fractures; however, differences were attenuated in comparisons in which both agents were included in an unboosted regimen.[114]

Switching from a regimen that includes tenofovir disoproxil fumarate to one that does not is associated with improved bone mineral density

Summary of evidence: Several studies reported improvements in hip and spine BMD after a switch from a regimen with tenofovir disoproxil fumarate to one without,[115–120] although there is a lack of data suggesting improvement in bone quality.

Data gaps

The expert panel identified key cardiometabolic health data gaps (Table 3). For weight change, data gaps include the need for more

studies investigating the causative effects mediating weight gain with tenofovir alafenamide and second-generation INSTIs, studies evaluating weight change in people with HIV using newer ART regimens compared with weight change in the general population and studies assessing the consequences of weight change on cardiometabolic health. With respect to cardiovascular health, the expert panel recommended additional research into the pathogenesis of atherosclerotic CVD in people with HIV and studies on risk stratification and characterizing and optimizing prevention and treatment of CVD in people with HIV. The panel identified the need for more studies evaluating the impact of contemporary ART regimens on insulin resistance in relation to weight gain and the effect on MAFLD. Regarding bone health, the panel recommended more studies investigating the impact of HIV and/or ART on bone health and studies in people with HIV investigating behavioural and biomedical interventions supportive of improved bone health in the general population, such as bone-loading physical activity, smoking cessation and dietary changes.[121–124] The panel noted that additional research is needed investigating cardiometabolic health and body composition in important groups of people with HIV including cisgender women initiating hormone replacement therapy, transgender individuals initiating gender-affirming hormonal therapy and transgender men transitioning into menopause.

Clinical recommendations

The expert panel developed clinical recommendations to provide supportive advice to healthcare providers treating people with HIV (Table 4). The panel acknowledged that some recommendations may not be feasible to implement in all care settings and recommended that they should be implemented if at all possible and in alignment with local treatment guidelines. For example, some low- or middle-income countries may not have access to some assays or a network of healthcare providers who are able to provide comprehensive care. Nonetheless, the goal was to outline a gold standard for the management of cardiometabolic health and body composition in people with HIV.

General cardiometabolic care

The expert panel agreed that comprehensive care should be provided to people with HIV, including appropriate referral pathways and/or guidance to provide adequate care for clinically relevant weight changes. During interactions with patients, healthcare providers should discuss weight and lifestyle in a non-stigmatizing and empathetic manner while being mindful of the perceptions that people with HIV have regarding their weight. Supportive advice related to healthy eating, physical activity, stress management, substance use management and improving sleep quality should be provided. Healthcare providers should also seek to understand barriers to healthy eating and adequate physical activity.

Cardiometabolic health assessments

To monitor cardiometabolic health, the expert panel recommended that healthcare providers assess weight, BMI, waist-to-height or waist-to-hip ratio, blood pressure and fasting lipids and glucose (if possible) at the first visit, annually and after ART initiation or switch. They also recommended assessing and discussing alcohol and substance use and smoking.

The panel underscored the importance of MAFLD as a cardiometabolic health concern in people with HIV. Elevated alanine transaminase levels may suggest MAFLD, especially among individuals with type 2 diabetes or visceral adiposity. Elastography can aid in further evaluating liver health, including assessing fibrosis and steatosis, if available.

The panel stressed that fragility and sarcopenia are concerns in adults ageing with HIV and recommended screening for sarcopenia using handgrip strength and walking speed. Sarcopenia is diagnosed by the documentation of low muscle mass and either low muscle strength or low physical performance.[125,126] Specifically, individuals with walking speed <0.8 m/s and low handgrip strength should undergo muscle mass testing. Many factors contribute to sarcopenia, with lack of physical activity considered one of the most important.[127] Cardiometabolic disorders including diabetes and obesity may also adversely affect skeletal muscle, potentially worsening sarcopenia.

ART and cardiometabolic health

The impact of ART on cardiometabolic health is one aspect that should be considered in the context of individualized treatment. Before initiating or switching ART, people with HIV should be counselled on the possibility of weight change. Although the statement did not achieve consensus, the expert panel noted that when initiating ART, in addition to traditional considerations including those related to HIV and drug–drug interactions, the choice of ART should account for cardiometabolic factors such as risk of cardiometabolic disorders and patient concerns, awareness and engagement regarding weight. Furthermore, the impact of ART on weight should be contextualized for each individual considering known parameters including ART history; HIV markers such as high viral load and low $CD4^+$ cell count; family history of obesity and/or other cardiometabolic diseases; concurrent metabolic conditions; concomitant medications that may affect weight; substance use disorders; mental health disorders; socioeconomic, cultural and lifestyle parameters and food access. ART-naive people with HIV with low baseline $CD4^+$ cell count and high baseline viral load may experience greater weight gain after ART initiation.[25,26,29]

Understanding the potential for drug–drug interactions between antiretroviral agents and medications prescribed for the treatment or prevention of cardiometabolic-related disorders is critical for the optimal management of both HIV and cardiometabolic health. For example, statins, which decrease low-density-lipoprotein cholesterol, have the potential for drug–drug interactions when used with boosted antiretroviral agents and older NNRTIs.[128] It is necessary to titrate statin dosing and monitor closely for side effects when co-prescribing statins with boosted antiretroviral agents. Insufficient lipid control with co-administration of PIs and statins has been reported in people with HIV.[129] Antidiabetic glucagon-like peptide 1 (GLP-1) receptor agonists (RAs) decrease HbA_{1c} and weight, including in people with HIV.[130,131] Because they inhibit gastric secretion, GLP-1 RAs have the potential to reduce ART absorption.[128] Thus, monitoring of viral load after initiation of GLP-1 RAs is important. For details on drug–drug interactions with therapies for metabolic

Table 4. Clinical recommendations

General cardiometabolic care
1. Comprehensive care should be provided to people with HIV and include access to services to help address good health and long-term well-being • HIV services should have appropriate referral pathways and/or guidance to provide adequate care for clinically relevant weight changes such as obesity or cachexia, if at all possible 2. Healthcare providers should discuss weight and lifestyle in a non-stigmatizing empathetic manner • Appreciating the perceptions that people with HIV have regarding changes in their weight is important 3. Supportive advice related to healthy eating, physical activity, stress management, and improving sleep quality should be provided 4. Healthcare providers should seek to understand barriers to healthy eating and adequate physical activity
Cardiometabolic health assessments
1. Healthcare providers are recommended to assess the following parameters at the first visit, annually and after antiretroviral therapy initiation or switch: • Weight • Body mass index • Waist-to-height ratio or waist-to-hip ratio • Blood pressure • Fasting lipids and glucose 2. Diet, alcohol, substance use and smoking should be assessed and discussed, and any concerns should be treated with evidence-based interventions 3. MAFLD is a concern for people with HIV • Elevated alanine transaminase levels may suggest MAFLD, especially among individuals with type 2 diabetes or visceral adiposity. Elastography can further evaluate liver health by measuring fibrosis and steatosis 4. Fragility and sarcopenia are concerns in adults ageing with HIV and can be assessed using handgrip strength and walking speed
Antiretroviral therapy and cardiometabolic health
1. The impact of antiretroviral therapy on cardiometabolic health is one aspect that should be considered in the context of individualized treatment • Counsel people with HIV on the possibility of weight change before initiating or switching to a new antiretroviral therapy regimen 2. Weight change is multifactorial and the impact of antiretroviral therapy on weight should be contextualized for each individual. The following known parameters should be considered: • Antiretroviral therapy history • HIV markers including high viral load and low CD4+ cell count • Family history of obesity and/or cardiometabolic diseases • Concurrent metabolic conditions • Concomitant medications that may affect weight • Substance use disorders • Mental health disorders • Socioeconomic, cultural and lifestyle parameters • Food access
Cardiovascular health
1. Considering the increased risk in people with HIV, cardiovascular health should be assessed routinely and management individualized accordingly • Risk calculators for cardiovascular health in the general population should be used in people with HIV; however, they may underestimate the risk of cardiovascular events in people with HIV
Bone health
1. It is important to screen for osteoporosis in people with HIV given the increased risk of metabolic bone disease. Osteoporosis is asymptomatic until fractures occur • Bone health should be assessed in people with HIV using fracture risk assessment tools at a frequency recommended by available HIV guidelines ◦ Dual-energy X-ray absorptiometry can aid in evaluating bone health, if available • Review the impact of current antiretroviral therapy and other medications on bone health and modify if appropriate 2. Lifestyle interventions can improve bone health and are encouraged for all people with HIV, including the following: • Smoking cessation • Decreased alcohol consumption • Weight-bearing and resistance physical activity

Continued

Table 4. *Continued*

Bone health
• Balanced diet with adequate calcium intake • Vitamin D supplementation
3. In people with HIV with decreased BMD or history of fracture, create an individual management plan, aiming to reduce pain, prevent disability and improve quality of life • In the event of a fracture or established osteoporosis, refer to available guidelines for additional details on management

Table 5. Example identified risk factors associated with osteoporosis and/or fractures[96,97]

Category	Risk factors
Demographic	Older age, female sex
Lifestyle and nutrition	Smoking, opioid use, excess alcohol consumption, vitamin D deficiency, low dietary calcium, risk of falls, long-term immobilization, low body mass
Non-ART medications	Corticosteroids, glitazones, excess thyroxine, proton pump inhibitors
HIV-specific	Nadir $CD4^+$ cell count, ART initiation (especially tenofovir disoproxil fumarate and a boosted protease inhibitor), duration of HIV, chronic immune activation, chronic hepatitis C virus co-infection
Medical conditions	Malabsorption, celiac sprue, hypogonadism (early menopause, low testosterone, pre-menopausal oligomenorrhea), hyperthyroidism, hyperparathyroidism, adrenal insufficiency, renal phosphate wasting, Cushing's syndrome, multiple myeloma, mastocytosis, haemophilia, sickle cell disease, chronic kidney disease, chronic metabolic acidosis, depression, emphysema

disorders, please see the review by Gutierrez *et al.*[128] Drug–drug interactions with antiretroviral agents can also be queried using the University of Liverpool HIV drug interaction checker (https://www.hiv-druginteractions.org/).

Cardiovascular health

Considering the increased risk in people with HIV, cardiovascular health should be assessed routinely and management individualized accordingly. Risk calculators for cardiovascular health in the general population are recommended for use in people with HIV; however, they tend to underestimate risk in this population.[132,133]

Although the statement did not reach consensus, the expert panel noted that there may be an elevated risk of CVD in groups of people with HIV not normally considered at high risk in the general population, including those who are younger with BMI <30 kg/m^2,[46,134] transgender,[135,136] perimenopausal,[137] have long-standing HIV[138] or who have substance use disorders.[139]

Results from the phase 3 randomized REPRIEVE study of pitavastatin calcium versus placebo in people with HIV on stable ART with low-to-moderate risk of atherosclerotic CVD were noted as important, although the study was published after the consensus process was completed.[140] Pitavastatin calcium versus placebo was associated with reduced risk of major adverse cardiovascular events (hazard ratio, 0.65; 95% CI, 0.48–0.90; $P=0.002$).

Bone health

The expert panel emphasized the importance of screening for osteoporosis in women with HIV who are post-menopausal and men with HIV aged >50 years given the increased risk of metabolic bone disease. Osteoporosis is asymptomatic until fractures occur. Bone health should be assessed in people with HIV using fracture risk assessment tools at a frequency recommended by available HIV guidelines. If available and feasible to use, dual-energy X-ray absorptiometry is the gold standard for evaluating bone health. As certain antiretroviral agents can negatively affect bone health, it is recommended that healthcare providers review the impact of ART on bone health and modify when appropriate.

The expert panel noted that assessing risk factors for bone health is important, although this statement did not achieve consensus. Key risk factors for osteoporosis and/or fractures in people with HIV include demographics, HIV-specific factors, lifestyle characteristics and some medical conditions and medications (Table 5).[96,97] For a comprehensive list of risk factors for bone health in the general population, please see LeBoff *et al.*[99]

Lifestyle interventions that can improve bone health are encouraged in all people with HIV, including smoking cessation, decreased alcohol consumption, weight-bearing and resistance physical activity, a balanced diet with adequate calcium intake and vitamin D supplementation. In people with HIV with decreased BMD or history of fracture, create an individual management plan, aiming to reduce pain and risk of falls, prevent disability and improve quality of life. In the event of fracture or established osteoporosis, refer to available guidelines for additional details on management.

Although the statement did not achieve consensus, the expert panel noted the importance of routinely discussing concerns about falls with individuals at risk of falls. Falls are a major cause of fractures, disability, hospitalization and injuries, including fatal injuries, in adults aged ≥65 years.[141] It was remarked that

assessing risk of falls is particularly important in people with HIV because of the increased risk of bone loss, accelerated process of ageing[142] and impact of polypharmacy on fall risk.[143,144]

Discussion

Maintaining optimal cardiometabolic health and body composition are important to achieving good health and well-being in people with HIV. Although a large body of research has investigated cardiometabolic health and clinical guidelines have been developed, there remained a need for comprehensive practical guidance to support cardiometabolic health in people with HIV. Using a modified Delphi method,[11] an international panel of HIV and cardiometabolic health experts drafted a set of consensus data statements, identified data gaps and developed clinical recommendations.

Professional experience supported by scientific evidence resulted in a set of consensus data statements that confirmed the increased risk of cardiometabolic health and body composition concerns in people with HIV compared with the general population, the role of traditional and HIV-specific risk factors in this increased risk, and the importance of choice of ART regimen. These statements provided a foundation for evidence-based clinical recommendations. Identified data gaps provide a guide for future research that will yield fruitful data supportive of improved cardiometabolic health and body composition in people with HIV.

The expert panel's clinical recommendations emphasize the importance of providing comprehensive care to people with HIV as part of a multidisciplinary team; assessing cardiometabolic health at an appropriate frequency; considering the impact of ART, including ART adherence, on cardiometabolic health and providing care with the awareness that people with HIV have an increased risk of cardiometabolic health concerns. Given the impact of HIV-specific risk factors and ART regimen on cardiometabolic health and body composition, it is essential that healthcare providers consider these factors when providing care for people with HIV. Additionally, care of people with HIV should be individualized, considering unique patient characteristics and needs.[145,146] People with HIV who are ageing have a heightened risk of non-communicable diseases and comorbidities (e.g. frailty); therefore, it is especially important that this group receives comprehensive and multidisciplinary care that incorporates cardiometabolic health and body composition.[147] Healthcare providers are encouraged to be mindful of these recommendations and existing clinical guidelines to ensure appropriate cardiometabolic health management for people with HIV. Given the complex interplay between HIV, traditional risk factors, impact of ART regimen and cardiometabolic health and body composition, a multidisciplinary care model (e.g. working together with endocrinologists and cardiologists) is strongly encouraged for the care of people with HIV, where possible. Implementing these recommendations requires a flexible approach that considers context and available resources.

There are some limitations to acknowledge. Few experts from low- or middle-income countries were represented in the panel, and some of the clinical recommendations may not be feasible to implement outside high-income countries. Participation was <75% for two surveys and one of the small-group workshops; however, all members of the panel attended a consensus workshop to review workshop outputs, in addition to reviewing and approving the final manuscript. Although the consensus process was designed to reduce risk of bias from the study sponsor, some of the statements discuss antiretroviral agents developed by the study sponsor and its competitors.

Conclusions

The guidance proposed here highlights the importance of reshaping the model of care for people with HIV towards a holistic and comprehensive approach involving a multidisciplinary team of care providers. As new high-quality data emerge to address key data gaps and yield novel insights into cardiometabolic health and body composition in people with HIV, it is critical that healthcare providers remain informed of study findings and that clinical guidelines are shaped by emerging information. The clinical management of people with HIV remains an evolving process combining high-quality research, professional experience from a multidisciplinary team, and consideration of unique patient characteristics to maximize health and well-being.

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Supplementary data

Tables S1 to S5 and Supplementary Methods are available as Supplementary data at *JAC* Online.

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