HIV and Metabolic, Body, and Bone Disorders: What We Know From Low- and Middle-Income Countries

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Abstract: Globally, the HIV epidemic is evolving. Life expectancy for HIV-infected individuals has been extended because of more effective and more widely available antiretroviral therapy. As a result, chronic noncommunicable diseases (NCDs) have become important comorbid conditions. In particular, HIV-infected persons are increasingly at risk of developing metabolic (diabetes, dyslipidemias), body composition (lipodystrophy, overweight/obesity) and bone mineral density abnormalities. We have summarized the published epidemiological and clinical literature regarding these HIV-NCD comorbidities in low- and middle-income countries (LMICs). We found important gaps in knowledge. Specifically, there are few studies that use standardized methods and metrics; consequently, prevalence or incidence data are not comparable. There are very little or no data regarding the effectiveness or cost-effectiveness of clinical monitoring or therapeutic interventions for metabolic disorders in HIV-infected individuals. Also, although NCDs continue to grow in the HIV-negative population of most LMICs, there are few data comparing the incidence of NCD comorbidities between HIV-infected and HIV-negative populations. To address these gaps, we describe potential research and capacity development priorities for the future.

Key Words: diabetes and dysglycemia, dyslipidemia, overweight and obesity, lipodystrophy, bone mineral density abnormalities, low- and middle-income countries

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INTRODUCTION

Treatment with effective antiretroviral therapy (ART) has transformed the course of disease for those infected with HIV. In many parts of the world, HIV-infected individuals now experience longer life expectancy than previously, but with that, also long-term exposure to ART toxicities and chronic inflammation. Extended life expectancy, together with increasingly contemporary lifestyles (poor diet quality and sedentary activity patterns), predispose HIV-infected persons to developing chronic noncommunicable diseases (NCDs) like diabetes mellitus (DM), cardiovascular disease (CVD), and cancers.1,2 Although HIV-NCD comorbidities are increasingly common and documented in high-income countries (HICs),3,4 little is known about the epidemiology, treatments, or outcomes of HIV-NCD comorbidities, and the capacity (human, financial, and infrastructural resources)5 needed to address these comorbidities in low- and middle-income countries (LMICs).

In this article, we summarize the published literature on metabolic (DM, dyslipidemias), body composition (lipodystrophy, overweight/obesity), and bone mineral density (BMD) abnormalities among HIV-infected persons with a focus on relevance for LMICs. These conditions are burdensome in their own right, requiring regular monitoring and treatment, but more importantly, they increase the risk for disabling, and often fatal, complications such as heart disease, chronic kidney disease, and fractures. Improving these metabolic parameters has been shown to improve CVD outcomes in longitudinal studies from HICs.6 For each group of disorders, we summarize the available epidemiological and clinical data (Table 1) and identify important data gaps. We conclude by conveying potential research and capacity development opportunities that would help address these HIV-NCD comorbidities in LMICs.

DIABETES AND DYSGLYCEMIA

Epidemiology

The estimated prevalence of DM among HIV-infected people is generally higher in HIC cohorts (range, 1.9%21 to 14.9%24) than in LMICs. Yet, the absolute number of persons living with HIV-DM is greater in LMICs, and given the high prevalence of young HIV-infected people in these countries, their average age is lower. A South African study of HIV-infected persons reported newly diagnosed DM in 3.4% who were ART-naive and in 2.2% who were on ART for ≥6 months.7 A multicountry cohort study from South America showed DM prevalence in HIV-infected persons ranged from 0.8% in Colombia to 6.5% in Brazil.17 Pre-DM, which precedes and predicts DM, is relatively more common, noted among 18.5% and 23.5% of ART-naive and ART patients, respectively, in South Africa7 and 16% of ART patients in...
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<td>Subjects with lipodystrophy have increased glucose and cholesterol levels. Glucose concentrations are also elevated in nonlipodystrophic HIV-positive subjects.</td>
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<td>Lipodystrophy and the metabolic syndrome were commonly and rapidly observed. A high prevalence (34%-37%) of IFG was demonstrated.</td>
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<td>Lipo</td>
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<td>Lipo</td>
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<td>Assess effect of ART initiation of anthropometry</td>
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<td>Lipo</td>
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<td>819</td>
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<td>CS</td>
<td>Prevalence of dyslipidemia</td>
<td>Hypertriglyceridemia and low HDL were common abnormalities seen in a large HIV-positive population.</td>
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<tr>
<td>Lipids</td>
<td>Armstrong et al</td>
<td>Tanzania</td>
<td>12,513</td>
<td>12,513</td>
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<td>CS</td>
<td>Prevalence of dyslipidemia</td>
<td>A high prevalence of dyslipidemia was seen in HIV-infected patients in a low-income setting. TGs increased and HDL and LDL decreased with loss of immune function.</td>
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<td>Lipids</td>
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<td>1240</td>
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<td>Prevalence of dyslipidemia</td>
<td>Hypertriglyceridemia and low HDL was seen in patients with HIV.</td>
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<td>Lipids</td>
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<td>172</td>
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<td>Prevalence of dyslipidemia</td>
<td>Dyslipidemia was common in patients with HIV and became more severe with increasing immunodeficiency.</td>
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<td>Lipids</td>
<td>Fourie et al[14]</td>
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<td>600</td>
<td>300</td>
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<td>Prevalence of dyslipidemia</td>
<td>Dyslipidemia but not metabolic syndrome was common in ART-naïve HIV subtype C patients</td>
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<td>De Araujo et al, 2010</td>
<td>Brazil</td>
<td>189</td>
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<td>CS</td>
<td>Prevalence of dyslipidemia</td>
<td>Hypercholesterolemia and hypertriglyceridemia were associated with PI-based ART</td>
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<td>Albuquerque et al</td>
<td>Brazil</td>
<td>257</td>
<td>257</td>
<td>0</td>
<td>CS</td>
<td>Prevalence of dyslipidemia</td>
<td>High prevalence of high TG, high LDL, and low HDL was seen in ARV-treated patients with HIV</td>
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<td>Lipids</td>
<td>Lazzaretti et al, 2005</td>
<td>Brazil</td>
<td>90</td>
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<td>RCT</td>
<td>Incidence of dyslipidemia</td>
<td>Patients initiating HAART developed dyslipidemia at a high rate. Dietary modification reduced this effect</td>
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<td>Lipids</td>
<td>Ceccato et al[16]</td>
<td>Brazil</td>
<td>620</td>
<td>620</td>
<td>0</td>
<td>L</td>
<td>Change in prevalence of dyslipidemia</td>
<td>Prevalence of dyslipidemia/lipodystrophy almost tripled (11.3%–32.4%) with HAART initiation</td>
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<tr>
<td>Lipids</td>
<td>Cahn et al[17]</td>
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<td>4010</td>
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<td>Prevalence of dyslipidemia</td>
<td>Prevalence of dyslipidemia was as high as 80% in a HAART-treated population</td>
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<td>Lipids</td>
<td>Adewole et al, 2010</td>
<td>Nigeria</td>
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<td>130</td>
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<td>CS</td>
<td>Prevalence of dyslipidemia</td>
<td>Higher TG and LDL and lower HDL were seen in patients with HIV compared with controls</td>
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<td>Change in lipid levels</td>
<td>Cholesterol and TG increased with HAART initiation</td>
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<td>Lipids</td>
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<td>Changes in lipid levels</td>
<td>Initiation of HAART therapy led to a normalization of lipid profile in children with an increase in HDL and decrease in LDL</td>
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<td>PI-naive children switched to double-boosted PI therapy had increases in LDL and TGs</td>
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<td>24</td>
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<td>Change in prevalence of dyslipidemia</td>
<td>Of patients initiating PI-based ART, 62.5% developed hypercholesterolemia and 79.2% developed hypertriglyceridemia</td>
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<td>Lipids</td>
<td>Strehiou et al, 2012</td>
<td>South Africa</td>
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<td>Changes in lipid levels</td>
<td>LPV/r regimens initiated in ART-naïve patients led to increases LDL and HDL. Switching to an NVP-containing regimen increased HDL further</td>
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<td>HIV-positive children and adolescents treated with PI-containing HAART had increased TG compared with seronegative controls</td>
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<td>Lipids</td>
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<td>Prevalence of hypercholesterolemia increased from 12.1% to 21.1% and hypertriglyceridemia increased from 29.5% to 37.6% in the second year of treatment with stavudine</td>
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<td>Obesity (8.3%) and overweight (34.2%) highly prevalent, 5.2% malnourished. Obesity more frequent in women and similar to general population</td>
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<td>Obesity</td>
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<td>Factors associated with progression to overweight/obesity</td>
<td>Progression rate to overweight/obesity was 19% over average 4.12 years. Men more likely to progress to overweight, women to obesity</td>
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<td>Obesity</td>
<td>Hurley et al21</td>
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<td>230</td>
<td>230</td>
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<td>Assess anthropomorphic changes and perceptions over 12 mo after starting ART</td>
<td>Overweight/obesity in 21%/12% at baseline, 36%/22% at 12 mo, increased weight gain associated with desire to gain weight</td>
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<td>Osteopenia</td>
<td>Aydin et al, 2013</td>
<td>Turkey</td>
<td>126</td>
<td>126</td>
<td>0</td>
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<td>Prevalence of low BMD treated and untreated HIV patients</td>
<td>High rate of low BMD. Osteopenia and osteoporosis rates were 53.9% and 23.8%, respectively</td>
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<td>Osteopenia</td>
<td>Masyeni et al, 2013</td>
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<td>Factors influencing BMD in ARV-naive patients</td>
<td>Patients with higher HIV stage had higher risk of low BMD. Osteopenia and osteoporosis were diagnosed, respectively, in 35.6% and 8.2%</td>
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<td>Osteopenia</td>
<td>Puthanakit et al, 2012</td>
<td>Thailand</td>
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<td>Prevalence of low BMD in perinatally HIV-infected adolescents</td>
<td>One-fourth of HIV-infected Thai adolescents have osteopenia</td>
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<td>Prevalence of low BMD in ART-treated HIV-infected patients</td>
<td>In a resource-limited setting, HIV-infected patients on ART exhibit lower BMD than their age, and sex-matched uninfected counterparts</td>
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<td>Osteopenia</td>
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<td>Prevalence of low BMD treated and untreated HIV patients</td>
<td>Prevalence of osteopenia and osteoporosis was 59% and 22%, respectively, in HIV-infected individuals on therapy compared with rates of 15% and 0%, respectively, in HIV-negative individuals</td>
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*Observational or intervention studies conducted in LMICs that examined the relationship between HIV status or therapy and selected noncommunicable cardiovascular and pulmonary diseases based on published data between 1996 and present.

CS, cross-sectional; HAART, highly active antiretroviral therapy; HIV+ , seropositive with HIV; HIV− , negative for HIV; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; L, longitudinal; Lipo, lipodystrophy; NR, not reported; RCT, randomized controlled trial.
As the global prevalence of DM increases in the coming 15–20 years (from 382 million in 2013, to a projected 592 million in 2035), more studies are needed to identify effective DM prevention strategies in HIV-infected persons.

Risk Factors

Whether HIV infection itself increases an individual’s risk of developing dysglycemia (pre-DM or DM) remains controversial. Large observational cohort studies from HICs offer the only known data sources to investigate the relationship. The US Multicenter AIDS Cohort Study reported a fourfold higher DM incidence [rate ratio (RR), 4.1; 95% confidence interval (CI): 1.9 to 9.2] among HIV-infected persons using ART compared with HIV-negative persons, adjusting for age and body mass index (BMI). Two other cohort studies observed no significant association between HIV and DM risk. A large cohort study in Denmark comparing DM incidence among HIV-infected and HIV-negative persons reported a higher DM rate among HIV-infected persons being treated with older antiretroviral (ARV) drugs between 1996 and 1998 (RR, 3.2; 95% CI: 1.4 to 7.4), but not during 1999–2009 (RR, 1.0; 95% CI: 0.8 to 1.3). Population-based longitudinal measurements of incident dysglycemia from LMICs are needed among persons with and without HIV to improve our understanding of the associations between HIV, ART, and dysglycemia.

Factors associated with incident dysglycemia among HIV-infected persons include traditional risks (eg, physical inactivity, increasing age, waist-to-hip ratio, and obesity) as well as specific HIV and treatment-associated risks (eg, lipoatrophy). Currently, an estimated 13% of HIV-positive individuals on ART in sub-Saharan Africa are aged 50 years or older. With continued expansion of ART use, life expectancy and dysglycemia are expected to increase. Cumulative exposure to ART (and to specific ARVs) is associated with increased dysglycemia in HIV-infected persons. For example, the Danish cohort reported higher DM incidence (RR, 1.8; 95% CI: 1.2 to 2.8) in those ever exposed to stavudine compared with patients never exposed. Data from South Africa also show that exposure to efavirenz was associated with dysglycemia (odds ratio, 1.7; 95% CI: 1.2 to 2.5) after adjusting for age, sex, and CD4 count. There are almost no data from LMICs regarding the role of body composition (eg, overweight, obesity, or lipodystrophy), nutrition, lifestyle factors, concomitant infections (eg, hepatitis C), and common non-ARV medications (eg, statins) to aid our understanding of dysglycemia emergence in HIV-infected persons.

Knowledge and Implementation Gaps

Several key knowledge gaps remain regarding HIV and dysglycemia. Current observational data are insufficient to infer whether HIV-infected persons truly have a higher incidence of dysglycemia than the general non-HIV-infected population, and whether this risk is mediated by the virus itself, persistent systemic inflammation, or solely some aspect of ARVs (eg, interruption). Regardless of the causal pathways, the coprevalence of HIV-dysglycemia is expected to increase in LMICs, signifying a growing need for clinical capacity to screen, diagnose, and treat HIV-DM. Accurate identification of dysglycemia currently requires laboratory services and typically testing on 2 separate occasions. Point-of-care HbA1c analyzers currently exist and may become the standard of care, but in most LMICs, they are currently cost prohibitive and not validated in persons with chronic infections or anemia. Screening may be more cost-effective through low-cost approaches (eg, risk tests) to identify subgroups at greatest risk, although more data are needed to devise these risk scores. Finally, many unanswered questions remain regarding treatment of HIV-dysglycemia. Comparative effectiveness trials of treatment regimens in this population and studies of drug interactions are needed to compare effectiveness, benefits, and harms of different treatment options.

**DYSLIPIDEMIAS**

**Epidemiology**

The risk of CVD events in HIV-infected persons has led to an enhanced focus on abnormal serum lipids or dyslipidemia. Many individual studies and reviews have summarized the prevalence and risk of dyslipidemias in HIV-infected persons in HICs. Most studies are cross-sectional, but some have been longitudinal, describing lipid changes after ART regimen initiation; however, none have included HIV-negative comparison groups. Studies have used multiple ART drug classes and followed participants for varying durations. The relationships between dyslipidemias and ART adherence (specific regimens and cumulative exposure), concurrent CVD risk factors (smoking, exercise), and underlying comorbidities among persons with HIV in LMICs have not been studied.

Dyslipidemia also occurs in ART-naive HIV-infected patients. Increased triglyceride (TG) and reduced total low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol subfractions are common, especially in those with more advanced HIV disease and greater levels of immunosuppression. In addition, studies have reported more atherogenic lipoprotein composition (eg, higher proportions of small, dense LDL particles) in HIV-infected persons.
Most of these were HIC studies, often in populations where obesity and overweight are more common.

The literature from LMICs is scant and subject to methodological concerns similar to those described above. Cross-sectional studies among ART-naïve HIV-infected persons in Cameroon, Tanzania, and South Africa generally show normal LDL levels (88–100 mg/dL). Dyslipidemias (low HDL and high TG) are observed more commonly among patients with longer ART exposure, as shown in a few South American studies. Longitudinal studies of patient lipid levels 6–29 months after ART initiation report variable degrees of elevation of TG and both LDL and HDL cholesterol. There is variation in the use of fasting and nonfasting lipid testing across studies, which affects the accuracy of TG values. However, nonfasting specimens are more practical to collect from patients who live far from clinics or cannot take time off work repeatedly for blood tests.

Risk Factors

The etiology of dyslipidemias in HIV-infected persons is complex and may be related to HIV infection itself, ART, inflammation, genetic factors, age, obesity, lipodystrophy, DM, and liver disease; all of these relationships remain poorly understood.

Regarding ART and lipid metabolism, there are broad differences in lipid effects among ARV drug classes and even among agents within a class. The pathogenesis of ART-induced dyslipidemia is complex and incompletely understood, although it broadly involves interference with key intracellular processes regulating lipid and glucose metabolism [for protease inhibitors (PIs)], mitochondrial function [for nucleoside reverse-transcriptase inhibitors (NRTIs)], and genetic vulnerability. Observational data from LMICs regarding ART and lipids have limitations because HIV-infected patients are often on heterogeneous regimens, there are local differences in drug availability, and prescription practices are changing over time. For example, the NRTI stavudine, now rarely prescribed in the United States due to toxicities, has been widely used in LMICs and is the NRTI most likely to lead to elevated TG and total cholesterol. Another widely used agent in LMICs, nevirapine, has beneficial lipid effects, and switch studies (from PI to nonnucleoside reverse-transcriptase inhibitor regimens) have resulted in lipid profile improvements. Many newer agents, including the PIs atazanavir and darunavir, and the integrase inhibitor raltegravir, have lesser or no effects on lipid metabolism but have limited availability in LMICs. Many studies have shown that within and between drug classes, substitutions can lead to improved lipid levels.

Treatment

There have been no randomized clinical trials to establish the optimal treatment of ART-associated dyslipidemia. Treatment guidelines from HICs for HIV-infected patients mirror recommendations for the general HIV-negative population. Guidelines promote lifestyle modification as initial therapy. If lifestyle modification is insufficient, or if the initial degree of dyslipidemia is severe, lipid-lowering agents are indicated. However, a study auditing treatment regimens reported that HIV-infected patients do not adhere and respond as well to lipid-lowering therapy as HIV-negative patients do. To treat elevated LDL cholesterol, pravastatin, atorvastatin, or rosuvastatin are generally recommended to minimize drug interactions with ART. For hypertriglyceridemia, fibrin acid analogs (gemfibrozil or fenofibrate) are indicated. Niacin and fish oils may offer some additional benefit. In summary, the best treatment approach involves controlling other CVD risks, choosing ARVs with better lipid profiles, and adding lipid-lowering drugs when clinically indicated. Many of these agents are available in more developed LMICs like South Africa, but availability in many other LMICs may be limited.

Knowledge and Implementation Gaps

Despite a number of studies, little is known about dyslipidemia in LMICs. Lipid changes seen in late-stage, untreated HIV infection or after ART initiation are likely similar in LMICs compared with HICs, but this assumption needs to be empirically confirmed. More data are needed to clarify the mechanisms of dyslipidemia, especially the persistence of low HDL in treated patients. Most importantly, longitudinal studies are needed to document CVD event risk attributable to dyslipidemia and other conditions among HIV-infected persons.

The cost-effectiveness and optimal frequency of lipid monitoring in ART patients has not been established in LMICs, and specific therapeutic thresholds and targets for each of the lipid subfractions are not defined. Among individuals without chronically elevated lipids, it remains unclear whether aggressive lipid-lowering therapy should be indicated. There are no data documenting adherence to lipid-lowering therapies, drug interactions, or clinical outcomes after correcting HIV-associated dyslipidemias in LMICs.

BODY COMPOSITION CHANGES

Lipodystrophy

Lipodystrophy refers to changes in body fat distribution encompassing both lipo hypertrophy and lipoatrophic. Lipohypertrophy is commonly characterized by increased abdominal visceral fat, dorsocervical fat pad (buffalo hump), and/or breast enlargement, whereas lipoatrophy is characterized by subcutaneous fat wasting of the face, extremities, and/or buttocks. These body composition changes can occur separately or overlap in the same patient; and they have been associated with lower quality of life, depression, and decreased ART adherence. Lipodystrophy is also associated with dyslipidemias and insulin resistance.

Epidemiology

Prevalence reports of lipodystrophy vary widely in HICs with high ART access—from 10% to over 80% depending on the definitions used. Prevalence reports from LMICs similarly range widely from 7% to 65%. Reports from LMICs are limited by varying definitions (self-report, clinical

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examination, or objective measurement). One study described its population’s lipoatrophy prevalence as 49.5% or 65% depending on whether an objective definition based on measurable characteristics or a broader clinical definition was used. Similarly, another study described prevalence as 7% or 49% depending on the definitions used.6 It is important to note that data regarding lipoatrophy from HICs come from individuals with a higher average BMI than are observed among HIV-infected individuals in LMICs.

Risk Factors
ART is commonly noted as a risk factor for lipodystrophy. Lipohypertrophy has been associated with ART, total body fat, older age, and female gender.63 Exposure to the thymidine analog NRTIs, stavudine and zidovudine, has been implicated in lipoatrophy through inhibition of mitochondrial polymerase gamma.64–67 Even in studies with widely varying definitions of lipoatrophy, stavudine usage is consistently associated with it.61,62,69 In the largest of these studies, the prevalence of lipoatrophy was significantly (P = 0.02) higher: 31.4% in stavudine versus 10.3% in zidovudine-containing regimens.62

Finally, it is important to note that observed fat increases after initiation of ART can also signify a return to health and are not solely indicative of lipohypertrophy. For example, an LMIC study compared 12-month changes in skinfold measurements: arm, hip, thigh, and/or waist circumference; and fat mass (bioelectric impedance) between HIV-infected persons initiating ART and HIV-negative controls. The study found increased measurements in patients using ART, but these were no higher than in HIV-negative controls.70

Treatment
Therapeutic options for lipohypertrophy include exercise, surgical interventions, and medication, with the goals of decreasing discomfort, lowering cardio-metabolic risk, and cosmetic improvement. Metformin has been shown to be beneficial as have recombinant growth hormone and recombinant growth-hormone releasing factor.74 Side effects include dysglycemia, fat loss in those with concomitant lipoatrophy (which has direct cosmetic effects and indirect effects on adherence), and rapid reaccumulation after stopping therapy.75–77

Lipoatrophy treatment options include switching to alternative NRTIs, which can attenuate lipohypertrophy modestly, or changing to regimens with lower risks of lipoatrophy but higher risks of dyslipidemia.82,83 Trials evaluating thiazolidinediones for lipoatrophy have been conflicting and their use has been limited by concern for adverse effects.91–93 Evaluations of leptin (small studies) and uridine (mixed results) have been inconclusive.94–97 Surgical options (injectable fillers and autologous fat transplantation) are expensive.98

Knowledge and Implementation Gaps
In addition to associations with lower quality of life, depression, and decreased ART adherence, lipoatrophy can be stigmatizing to patients.54 Lipoatrophy seems to be less common in HICs, where thymidine analog usage has decreased substantially, than in LMICs.99,100 However, further studies are needed, as LMIC populations may have very different genetic, environmental, dietary, and socioeconomic exposures whose interaction may affect body composition. The few effective treatment options available are all cost prohibitive worldwide.

Overweight/Obesity
Early in the HIV epidemic, the primary weight-related concern was wasting. Established data from HICs and now-emerging data from LMICs show that overweight/obesity (defined by BMI of 25–29.9 kg/m2 and ≥30 kg/m2, respectively) is becoming more prominent than wasting among HIV-infected individuals.19,20,101 Several recent US studies show that HIV-infected persons on ART gain weight.3,102–106 Among this group, women, African Americans, and those with a higher BMI at ART initiation are at greater risk of becoming overweight/obese.

Pharmacologic treatment with agents like stavudine and didanosine can lead to a paradoxical decline in weight after virologic control is achieved because of the development of lipoatrophy.107 The use of these agents has become uncommon in most HICs. In parallel, overweight and obesity in the HIV-infected population, which signals a return to health, has reached levels observed in the general population. Retrospective data from Brazil showed a similar pattern over the course of 7 years after the initiation of ART; the combined prevalence of overweight/obesity among these participants increased from 35.9% to 44.4%, compared with a prevalence of 40.6% in the general adult population. Among 177 individuals in South Africa starting ART, the proportions of participants classified as overweight or obese both increased after 12 months: the overweight from 21% to 36% and the obese from 12% to 22%.21 In this study, despite high rates of overweight and obesity, the majority of participants perceived their weight as “just right,” reinforcing reports that in some cultures, higher weight is a desired state and can be associated with wealth (adequate food) or good health, while low weight can be associated with wasting and sickness and be stigmatizing.21,108

In summary, growth in overweight/obesity in the general population is being mirrored in the HIV-infected population, at least in part because of restored health. More data are needed to understand if and how these body composition changes affect long-term health outcomes (eg, cardiovascular and chronic kidney diseases and mortality).35,109

BMD ABNORMALITIES
Bone disorders are common sequelae of HIV infection. In HICs, close to 50%–60% of HIV-infected adults are osteopenic (low BMD) and an additional 15% are osteoporotic (low BMD and distorted micro-architecture with high fracture risk).110,111

Epidemiology
Available data, although limited, indicate that HIV-induced skeletal abnormalities are equally troubling in LMICs.18,22 For example, a study of 142 HIV-infected Argentinians aged 20–45 years using ART showed an osteopenia prevalence of 59% among the study group, compared with 15% in HIV-negative individuals, and an osteoporosis
Data from HICs suggest that fracture risk, especially among younger age groups. Consequently, there are concerns that in the aging HIV population, the synergistic effects of ART and age-related skeletal damage could precipitate fractures.

### Risk Factors
The pathophysiology underlying HIV-associated bone abnormalities is incompletely understood. Common comorbidities with HIV infection such as renal impairment, hypogonadism, and hypovitaminosis-D all predispose to bone catabolism, and this may be perpetuated by lifestyle factors. The virus itself contributes to skeletal damage through altered immune B-cell function as well as enhanced bone resorption. ART-induced bone effects seem to occur through immune reconstitution, direct suppressive effects on bone cells, and/or alteration of vitamin D metabolism by certain drugs. Teasing apart the relative contributions of these various mechanisms is currently a focus of intense research that should be extended to individuals from LMICs.

### Treatment
Chemotherapies to address osteoporosis can be associated with disabling side effects. Bisphosphonates, although available and affordable in LMICs, cannot be used for more than 5 years due to the risk of atypical femoral fractures. Teriparadite, a stimulant of osteoblastic bone formation, is not clearly understood and are currently being investigated in both HICs and LMICs. The utility of denosumab, a long-acting monoclonal antibody that blocks bone resorption, and the benefit of aggressive osteoporosis lifestyle modification remain inadequately evaluated. Antiresorptive prophylaxis has also been proposed to block the bone loss mediated by ART-induced immune reconstitution. Although not approved for use in the United States, strontium ranelate is widely available in LMICs and could be an effective antosteoporotic agent for those with HIV, as it increases deposition of new bone by osteoblasts while at the same time reducing osteoclastic bone resorption. However, recent concerns regarding increased CVD risk with the use of strontium ranelate suggest that safety needs to be carefully evaluated.

### Knowledge and Implementation Gaps
Many unanswered questions remain regarding HIV and BMD. For example, when should screening for osteoporosis begin, and what tools should be used? Most guidelines emphasize screening at age 65 and do not recognize HIV infection as a risk factor. Available diagnostic tools also have limitations. Dual energy x-ray absorptiometry (DXA) scan is imperfect, as it averages the density of all bone types without accounting for differences between cortical and trabecular bone losses. Also, half of all fragility fractures are missed by DXA scan, especially among younger age groups (<55 years), among whom DXA-computed BMD bears no correlation with fracture risk. An alternative to DXA is the high-resolution peripheral quantitative computed tomography. The use of either DXA or tomography tools in LMICs may be limited by cost, availability, and training. Cost-effective screening tools with better discriminatory properties, particularly for the younger population, would greatly enhance early detection of skeletal decline in HIV infection.
DISCUSSION: GAPS AND RESEARCH PRIORITIES

This review highlights important gaps in our knowledge about HIV-associated metabolic and bone comorbidities in LMICs. In particular, existing LMIC data (Table 1) are derived from heterogeneous populations and report a variety of metrics collected using different measurement tools.

Epidemiological data from LMICs regarding prevalence and incidence of these HIV-NCD comorbidities, their associated clinical end points (eg, myocardial infarction, renal disease, fractures), and their associated mortality rates are scarce. One such analysis comparing an urban setting in Botswana with urban Tennessee shows that age- and sex-adjusted incidence of CVD events and mortality was actually higher in Botswana. However, there is a conspicuous absence of HIV-negative comparison groups to assess the relative risk of metabolic abnormalities and complications among HIV-infected persons (Table 1). Expanding knowledge in these areas may provide significant insights into (1) the prevalence, incidence, and predictors of HIV-NCD comorbidities among different HIV infection phenotype(s) in HIC and LMIC settings, (2) the evolution of these comorbidities in the time course of HIV infection and its treatment, and (3) whether currently recommended treatment thresholds and targets for these metabolic abnormalities are appropriate, effective, and cost-effective for HIV-infected persons (Table 3). There is an urgent need for this research in LMICs as current output is minimal, management guidelines are lacking, and it is unknown which interventions provide greatest benefits, particularly when working with limited resources. Research capacity itself is limited and therefore an emphasis on training should be considered in plans going forward.

Health services research will provide a better understanding of clinical practice patterns and how adherence, detection, and monitoring of disease impact morbidity and mortality in LMICs. There are a number of inexpensive point-of-care tools for monitoring metabolic (eg, capillary glucose testing) and body compositional changes (eg, tape measure), but there are no data that demonstrate the value of these tools in practice. Both epidemiological and health services data need to be incorporated into the larger picture of integrated care in LMICs (Table 3). Using pre-existing HIV clinic infrastructure may be an ideal and efficient opportunity to address these associated comorbidities and enhance population health. Implementation research is needed to understand what

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CT, computed tomography; GACD, global alliance for chronic diseases; IeDEA, International epidemiologic Databases to Evaluate AIDS; QOC, quality of care.
common benefits could be achieved (eg, approaches to achieving high adherence to combination ARV drug therapies could aid adherence to cardio-metabolic therapies), what capacity is needed to integrate care, and what the potential scalability is of this model. Identifying these processes and resources would help stakeholders assimilate the model into routine practice across LMICs. In addition, clinical and scientific capacity needs to be developed to address these care and research needs.

Of course, limited resources may be an impediment. Secondary analyses of existing databases of HIV-infected and HIV-negative populations may offer an efficient avenue, although uniformity of metrics used and data collection procedures must be taken into account. High-quality research will have important implications for practice patterns, programs, policies, and ultimately health outcomes related to these disabling HIV-NCD comorbidities. In the words of Dr. Paul Farmer, “... it seems to me that making strategic alliances across national borders to treat HIV among the world’s poor is one of the last great hopes of solidarity across a widening divide.”

REFERENCES


19. Ali et al. Systems and capacity to address these care and research needs.


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