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COMPLICATIONS OF ANTIRETROVIRAL THERAPY (GA MCCOMSEY, SECTION EDITOR)

Factors Associated With Insulin Resistance in Adults With HIV Receiving Contemporary Antiretroviral Therapy: a Brief Update

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Abstract

Purpose of Review This narrative review summarizes recent data on factors associated with insulin resistance (IR) in adults with HIV, including contemporary antiretroviral therapy (ART).

Recent Findings IR remains common in persons with HIV, even those receiving contemporary ART. Generalized and abdominal obesity and ectopic fat are correlates of IR, and emerging data have identified associations with biomarkers of inflammation and immune activation. Small studies suggest associations between mitochondria and IR. In ART-naïve individuals, IR increased within 4 weeks of starting ART in persons receiving contemporary boosted protease inhibitors or an integrase inhibitor.

Summary The importance of IR in non-diabetic persons with HIV will continue to grow as the population ages and obesity increases. Non-invasive estimates of IR appear to perform well in persons with HIV, but clinically relevant cutoffs are uncertain. Unexpected metabolic effects of newer HIV integrase inhibitors have been reported; thus, careful observation for and studies of IR are still warranted.

Keywords HIV · Antiretroviral therapy · Insulin resistance · Hyperglycemia · Integrase inhibitors

Introduction

Since the earliest days of antiretroviral therapy (ART), metabolic complications have been common and vexing effects of HIV treatment. Mitochondrial toxicities of early nucleoside reverse transcriptase inhibitors (NRTI) were often expressed in metabolically active adipose, muscle, and hepatic tissue [1–4]. After their introduction in the mid-1990s, protease inhibitors (PI) were quickly recognized as causing additional, overlapping metabolic complications [5], including insulin resistance (IR) and diabetes [6–8]. Contemporary ART is more effective and better tolerated than older ART. Nonetheless, metabolic complications and downstream cardiovascular disease (CVD) risk persist in persons with HIV [9]. Insulin resistance predicts future CVD in adults without HIV [10]. Recent studies have identified associations between IR and coronary stenosis by computed tomography angiography in men with and without HIV in the Multicenter AIDS Cohort Study (MACS) [11••], and between IR and cognitive performance in the Women's Interagency Health Study (WIHS) that differed by HIV status [12].

This brief narrative review will focus on risk factors for IR in non-diabetic adults with HIV treated with contemporary ART regimens, emphasizing data from the last 5 years. A comprehensive discussion of the pathophysiology of IR is beyond the scope of this review, but readers are referred to other recent HIV- and non-HIV-focused reviews [13•, 14•, 15, 16] for additional information. For a detailed review of IR and diabetes related to older ART, the reader is directed to an earlier review [17]. The present review focuses on adults with HIV, but there are also recent data characterizing IR in children and adolescents with HIV [18–23], a particularly metabolically vulnerable population often exposed to ART early in life. Finally, since pharmacologic treatment of IR is addressed in recent reviews noted above, and there are no current treatment recommendations other than use of the insulin sensitizer metformin for some persons at exceptionally high risk for diabetes [24], this area is not addressed here.

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Measurement and Definitions of Insulin Resistance

Discussion of IR in any context or population must begin with a definition. In its simplest form, it is a decreased ability of insulin to stimulate glucose uptake in a target tissue—resistance to insulin. With respect to pathophysiology, IR is understood to be a precursor to development of type 2 diabetes when an individual is no longer able to produce sufficient insulin to overcome this resistance. The more pragmatic question is how to identify IR based on available measurement tools? The hyperinsulinemic-euglycemic clamp procedure (originally described in 1979 [25]) is considered the "gold standard" for determining whole-body insulin sensitivity [26]. It has been used to measure IR in small studies of persons with HIV [27–30], including clinical intervention trials [31–33], but is impractical for larger studies due to cost and need for time-intensive and invasive procedures. Indirect estimates of IR have been used much more widely in clinical studies of persons with and without HIV. These include oral glucose tolerance testing (OGTT) and mathematical modeling estimates from simultaneous fasting blood glucose and insulin concentrations: the homeostasis model assessment (HOMA) [34] and the quantitative insulin sensitivity check index (QUICKI) [35]. These latter methods have been shown to correlate well with euglycemic clamp [26], including in studies using both HOMA and clamp measures in persons with HIV where results were comparable [36, 37]. They reliably and relatively easily estimate insulin sensitivity in non-diabetic individuals and populations, but cutoffs defining clinically relevant IR (and associating it with adverse clinical outcomes) are less clear. The Matsuda index uses mean plasma glucose and insulin concentrations during a 2-h OGTT to obtain a more dynamic estimate of IR [38], but has been used infrequently in studies of persons with HIV.

Functional imaging modalities that have been available for many years continue to generate interest due to their potential to directly or indirectly image in vivo tissue glucose disposition. These include ^{1}H-magnetic resonance spectroscopy (MRS) to quantitate intramyocellular lipid (IMCL) content in skeletal muscle, and ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET). IMCL quantitation by MRS correlates with muscle biopsy and with whole-body insulin sensitivity in some populations [39]. FDG-PET imaging is based on tissue glucose metabolism, and has been utilized to assess skeletal muscle and whole-body glucose uptake [39]. Enhanced dynamic PET techniques can image glucose transport defects that correlate with IR by euglycemic clamp in non-diabetic persons [40], and a recent report demonstrated feasibility of integrated PET-MR for quantifying tissue specific and whole-body IR [41]. These modalities have also been utilized and correlated with measures of IR in small studies of persons with HIV [42–46]. While tantalizing, limited availability, high cost, and radiation exposure make these modalities impractical outside of research settings.

For all of the reasons above, prevalence and incidence of IR are difficult to ascertain. The prevalence of IR (HOMA- IR > 2.35) in normoglycemic adults was estimated to be 32% in the general US population from 1999 to 2002 [47]. In populations with HIV, recent estimates of IR prevalence range from approximately 20% (defined as HOMA-IR ≥ 3.8) in persons on contemporary ART [48] to as high as 50% in an Austrian cohort where IR was more liberally defined as HOMA-IR > 2.0 (or > 2.6 in women > 35 years old) [49]. Two very recent studies provide additional information on the incidence of pre-diabetes among persons with HIV, defined as either abnormal fasting glucose or impaired glucose tolerance by OGTT. One is a meta-analysis of 44 studies with > 1500 person-years of follow-up. The pooled incidence rate and cumulative incidence of pre-diabetes were 125/1000 person years and 15%, respectively [50••]. A small longitudinal study followed 104 non-diabetic men with HIV for a mean of almost 12 years. The incidence rate and cumulative incidence of pre-diabetes in this study were lower (24/1000 person-years) and higher (32%), respectively [51•], highlighting potential differences in study eras, populations, body composition, ART exposure, or other contributing factors. Obviously, lack of a standard definition of IR precludes rigorous epidemiologic assessment, but also limits clinical and translational studies of risk factors and interventions.

Risk Factors for Insulin Resistance Common to Persons With and Without HIV

Insulin resistance is closely related to obesity. As adipose derangement develops in any population, adverse effects on glucose disposal and IR would be expected. Indeed, as noted previously, the earliest descriptions of PI-associated lipodystrophy often included IR [6]. With increasing recognition of obesity and abnormal adiposity persisting and contributing to adverse outcomes in persons with HIV [52•, 53, 54], even those on contemporary ART, one would expect IR to follow. In both of the recent studies cited above [50••, 51•], increasing age and obesity (either BMI or abdominal fat gain) were among the most consistent risk factors for incident pre-diabetes.

In addition to whole-body or regional (i.e., visceral or subcutaneous) fat and the well-established association between IR and hepatic fat [55], a potential emerging risk factor for IR is ectopic fat [56], including skeletal muscle (i.e., IMCL) and pericardial fat, the latter having been recently characterized longitudinally in persons with HIV [57•]. Adipose-derived plasminogen activator inhibitor (PAI)-1, a regulator of vascular and tissue fibrinolysis, is associated with IR and diabetes in persons without HIV [58]. Circulating PAI-1 was also negatively and independently associated with whole-body IR measured by the

Matsuda index and HOMA in recent studies of non-diabetic adults with HIV [59, 60]. Not surprisingly, but recently quantified more rigorously, lower physical activity is associated with IR in persons with and without HIV [61, 62].

Recent observations have identified associations between HMG-CoA reductase inhibitor (statin) exposure and both new onset diabetes and altered insulin sensitivity in persons without HIV [63, 64]. Statins are used frequently in persons with HIV for treatment of dyslipidemia, and any abnormal glucose homeostasis in persons with HIV might be expected to also increase any statin-associated risk of IR. This was seen in an analysis of a 96-week randomized clinical trial of rosuvastatin in 147 non-diabetic persons with HIV, where HOMA-IR increased significantly in persons randomized to rosuvastatin versus placebo [65]. There was no increased risk of clinical diabetes observed in the study.

Risk Factors for Insulin Resistance Potentially Unique to or Accentuated in Persons With HIV

As alluded to above, and reviewed extensively elsewhere [17], multiple ART components induce IR by various mechanisms in a class- and even drug-specific manner. HIV infection causes chronic immune activation and inflammation, even when plasma viral replication is suppressed by the immune system [66] or ART [67]. Inflammation and immune activation are also components of obesity, metabolic syndrome, and CVD, and have been associated with IR in persons with and without HIV [53, 68, 69].

While the extent to which and mechanisms by which HIV infection induces IR independent of ART requires further study, a recent analysis from the MACS affirmed that HIV infection was independently associated with having a HOMA-IR in the highest tertile (OR 2.46) after adjustment for age, race, BMI, and other metabolic risk factors [11••]. Other recent data from persons with HIV have identified associations between higher HOMA-IR and monocyte subsets from peripheral blood that were also independent of immunologic status and traditional diabetes risk factors [60]. In a small study of dietary renin-angiotensin-aldosterone system (RAAS) manipulation in persons with and without HIV, high aldosterone levels were associated with IR independent of visceral adipose tissue or adiponectin levels [70]. Mounting evidence over the last several years has highlighted the potential contribution of an impaired gut microbial barrier and translocated bacterial products to sequelae of chronic inflammation and immune activation in persons with HIV [71, 72]. Acute hyperinsulinemia during OGTT in persons with and without HIV was associated with increases in soluble CD14, a marker of monocyte activation related to lipopolysaccharide (LPS) [73]. Other recent studies have reported correlations between higher IR (by OGTT) and plasma LPS level in persons on ART [74], and between the presence of bacterial DNA products and elevations of hemoglobin A1c over time [75]. Not unexpectedly, the same sequelae of chronic HIV infection that may drive other end-organ effects, like immune activation driven by impaired gut permeability, likely contribute to IR.

Genetic Risk Factors for Insulin Resistance

While the strong familial risks of IR and type 2 diabetes suggest a heritable component, like most metabolic conditions they are considered complex phenotypes with respect to determining genetic risk. This is particularly true for IR given the nature of its measurement, lack of clarity regarding disease-defining cutoff values, and limited knowledge of the biological "continuum" of IR from normal glucose disposal to overt diabetes. Nonetheless, recent large genome-wide association studies (GWAS) of glucose homeostasis (summarized in a recent review [76]) have identified several candidate loci associated with HOMA-IR and OGTT in ethnically diverse populations of persons without HIV. Few studies to date have examined genetics of IR in persons with HIV. Recent small cross-sectional analyses in persons with HIV and hepatitis C virus (HCV) coinfection have reported associations between an IL28 receptor alpha gene single-nucleotide polymorphism (SNP) and IR (defined as HOMA-IR ≥ 3.0), and between a SNP in the fat mass and obesity-associated protein (FTO) gene and HOMA-IR ≥ 2.5 [77, 78].

Because of the role of mitochondrial dysfunction in altered glucose homeostasis and IR generally [79, 80], and specifically in HIV [81], and the legacy of ART-related mitochondrial toxicity, our group and others have been interested in relationships between host mitochondrial DNA (mtDNA) variation and diabetes-related outcomes in persons with HIV, including IR. Multiple small studies over the last decade have reported associations between shared patterns of SNPs in mtDNA, called haplogroups, and metabolic outcomes in persons with HIV [82]. A small study from Spain among persons coinfected with HIV and HCV reported that persons having mtDNA haplogroup U (found in persons of European ancestry) were significantly more likely to have IR defined as HOMA-IR ≥ 3.8 [83]. Larger analyses of mtDNA haplogroups and IR (led by the author and collaborators) in both MACS and WIHS are underway.

Our group has also examined mtDNA variants and metabolic biomarkers, including HOMA-IR, in analyses using data from small subgroups of ART-naïve participants in AIDS Clinical Trials Group (ACTG) studies A5142 and A5202 [84, 85]. Among 39 persons starting ART with one of three randomized class-sparing regimens in A5142 (described in detail elsewhere [86]), serum adiponectin (an adipose-

derived adipokine associated with glucose homeostasis and IR) was higher at baseline but decreased to a greater extent after 24 weeks of ART among persons with a non-synonymous mtDNA mutation in mitochondrial complex I (m.10398A > G). In a small subgroup ($N = 6$) of these, we also observed a greater increase in HOMA-IR at week 24 in persons belonging to mtDNA haplogroup U than those having other haplogroups [84]. This difference was consistent with findings from the Spanish HIV/HCV cohort [83].

We have gone on to perform analyses including adipose measurements of mitochondrial function in participants from another ACTG metabolic substudy (A5224s) randomized to receive contemporary ART (NRTI tenofovir DF [TDF]/emtricitabine [FTC] or abacavir [ABC]/lamivudine [3TC] plus either atazanavir/ritonavir [ATV/r] or efavirenz [EFV]) [87, 88]. Again, among a small subset of participants of European ancestry ($N = 12$), the m.10398G mutation was associated with lower adiponectin after 96 weeks of ART in this study. Additionally, decreased mitochondrial complex I and IV activity in adipose tissue was associated with increased HOMA-IR [85], to our knowledge, the first time such a relationship has been observed in persons with HIV.

Contemporary ART and Insulin Resistance, With a Focus on Integrase Strand Transfer Inhibitors

While the role of chronic HIV infection and associated inflammation and immune activation in metabolic effects has been increasingly appreciated [9], ART remains a contributing factor. An analysis focused on the most common currently used NRTI combinations (ABC/3TC and TDF/FTC) from ACTG study A5224s found no significant differences in fasting glucose, insulin, or HOMA-IR between these NRTIs arms over 96 weeks of treatment in 269 non-diabetic, ART-naïve persons [89]. The contemporary ritonavir-boosted PI, DRV/r, has been associated with an increased risk of CVD in data from the Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) Study [90, 91•]. In a small phase 4 study, both of the contemporary ritonavir-boosted PI DRV/r and ATV/r given once daily with TDF/FTC demonstrated similar modest increases in insulin sensitivity by euglycemic clamp over 48 weeks [92]. Over the last 5 years, preferred initial ART regimens for most people with HIV in US treatment guidelines have shifted from primarily non-NRTI (NNRTI) and PI-based to integrase strand transfer inhibitor (INSTI)-based regimens [93]. This is due to an excellent profile of potency and tolerability for INSTI, including few serious adverse effects observed in clinical trials of treatment-naïve persons [94–98].

ACTG study A5260s was a large metabolic substudy of a randomized clinical trial comparing ATV/r, DRV/r, and the first INSTI, raltegravir (RAL), all with the NRTI combination TDF/FTC, in treatment-naïve adults with HIV [99]. In an analysis focused on IR [100••], 324 participants had a median baseline (pre-ART) HOMA-IR of 0.59, and 10% of these predominantly young (median age 36 years) male (90%) participants had a HOMA-IR > 2.5 before ART. Higher baseline BMI and older age correlated with higher baseline HOMA-IR as expected. By week 4 of ART, HOMA-IR increased by a median of 2-fold, and—somewhat surprisingly—the HOMA-IR increase did not differ between the PI and RAL arms. By week 4, 22% of participants had HOMA-IR > 2.5. Given such a rapid increase, the authors hypothesized that the early HOMA-IR changes were independent of fat changes. While not significantly correlated at baseline, at later time points (weeks 48 and 96), HOMA-IR was consistently associated with plasma levels of sCD163, a marker of innate immune (monocyte) activation also associated with IR in the general population [101]. A single case report has described new onset diabetes following a switch from the NNRTI EFV to RAL with ABC/3TC [102].

Studies of metabolic effects of another INSTI, elvitegravir (EVG), have been confounded somewhat by the addition of cobicistat (COBI), and cytochrome P450 3A4-inhibitor used for pharmacologic boosting that has similar effects on metabolic measures as its older prototype, ritonavir. The exception was less of an increase in serum triglycerides with EVG/COBI versus ATV/r [95]. Overall, coformulated EVG/COBI had less or similar effects on metabolic parameters in ART-naïve participants compared to ritonavir-boosted PI or the NNRTI EFV, but glucose and insulin levels were not reported in these trials [95, 96]. A small study of healthy volunteers examined IR using euglycemic clamp before and after 14 days of treatment with TDF/FTC coformulated with EVG/COBI or in combination with the boosted PI DRV/r or the older coformulated PI lopinavir/r. Glucose disposal rate decreased with lopinavir/r, but was not significantly changed with exposure to DRV/r or EVG/COBI [103]. The lack of persons with HIV and the short exposure time are notable limitations of these data.

A common clinical scenario over the last several years has been switching virologically suppressed patients from NNRTI- or PI-based ART to INSTI-based ART regimens. Several clinical trials have confirmed the safety and efficacy of various INSTI switch strategies [104], and these are addressed in US treatment guidelines [93]. Dolutegravir (DTG) is a newer INSTI, is part of several preferred initial ART regimens for most people with HIV, and is often a component of regimens to which patients on older ART are switched. Based on anecdotal reports from local providers and a small published study [105], our research group recently analyzed data in our clinic population. We reported an unexpected weight increase in persons switched from coformulated TDF/FTC/EFV to any INSTI that was greatest in those switched to ABC/3TC/DTG, and not seen in persons switching to regimens including a boosted PI [106]. In addition, a non-significant

increase in hemoglobin A1c was observed among 26 persons who switched to an INSTI compared to those who remained on TDF/FTC/EFV. A recent case report of hyperglycemia in a patient on DTG [107] describes a clinical scenario also observed by local providers. The authors of this case report provide an extensive review of data on hyperglycemia from published clinical trials of DTG, package inserts, and clinicaltrials.gov. While hyperglycemia (> 125 mg/dL) was uncommon in trials where it was reported, the authors note that it was not reported in the VIKING-3 trial of treatment-experienced persons on twice-daily DTG [108], but is the most common treatment-emergent laboratory abnormality from VIKING-3 in the DTG package insert, with a reported rate of 14% [109]. In a phase 2 randomized controlled trial of the newest INSTI bictegravir (FDA approved February 7, 2018) versus DTG (each combined with tenofovir alafenamide [TAF]/FTC) in ART-naïve persons with HIV, 4/32 (13%) randomized to DTG and 5/64 (8%) randomized to bictegravir had grade 2 or higher elevations in fasting glucose levels (> 125 mg/dL) during 24 weeks of follow-up [110]. The phase 3 clinical trial of coformulated bictegravir/TAF/FTC versus ABC/3TC/DTG reported similarly rare grade 3 or 4 glycosuria events (4/314 and 3/315, respectively), and median increases in fasting glucose of 4 mg/dL in both arms of the study at week 48 [111]. The 48-week phase 3 trial of coformulated bictegravir/TAF/FTC versus DTG plus TAF/FTC also reported rare glucosuria (2/320 and 6/325, respectively). Grade 3–4 fasting hyperglycemia (> 250 mg/dL) occurred in 1/320 (< 1%) randomized to bictegravir versus 7/325 (2%) randomized to DTG, with a median change in fasting glucose at week 48 of 2 versus 4 mg/dL, respectively, a small but statistically significant difference (p = 0.0435) [112].

Mechanisms by which INSTI might have metabolic effects are not known. As noted above, Fong et al. reported a case of diabetes attributed to RAL, and postulate a possible effect of INSTI on bioavailable magnesium that alters muscle insulin signaling [102]. Several in vitro studies have reported neutral effects of RAL in primary adipocytes [113–115]. However, one of these found that both EVG and EFV impaired expression of adipogenesis-related genes compared with RAL, and EVG induced pro-inflammatory cytokines to a lesser extent than EFV, but more than RAL [114]. No published data on effects of DTG or bictegravir on adipocytes are available. Interestingly, DTG also has a known drug-drug interaction between the anti-diabetic medication metformin via inhibition of metformin renal excretion by organic cation transporter 2 [116, 117]. Dose reduction of metformin is recommended when used concomitantly with DTG. Given inter-individual pharmacokinetic variation, addition of DTG in a diabetic person on metformin might alter glucose control independent of any direct DTG effects. This would not explain disrupted glucose homeostasis in non-diabetic persons with HIV.

Conclusions

As the general population and those with HIV grow older and obesity rates increase, IR will likely grow in frequency and importance as a marker of diabetes and CVD risk. With new mechanisms of action and cellular targets, even the newest and best ART may have unexpected metabolic effects, including IR. One might speculate that older persons with chronic HIV and some degree of tissue/organ-specific immune activation, fat dysregulation/accumulation, and/or toxicity due to prior ART exposure could be more vulnerable to any metabolic effects upon switching to new ART. These effects might not be as prominent in younger persons with a shorter duration of HIV and no prior ART exposure.

To address knowledge gaps regarding IR in persons with HIV, several approaches in addition to expanding our understanding of fundamental pathophysiology are needed. Unified definitions and validated cutoffs to guide risk stratification and targeted prevention and treatment of IR will be critical. HIV-specific cutoffs would be ideal, but as with other areas of preventive health, simply utilizing guidelines from the general population when they are available will be a good start. Relatively inexpensive "low-hanging fruit" for refining our understanding of risk factors for IR would be including fasting glucose and insulin levels as part of ART clinical trials and prospective cohort studies, and assessing HOMA and/or QUICKI as part of study protocols and a priori analysis plans. Focused metabolic substudies that include IR as part of randomized clinical trials, like A5260s [100••], can be invaluable. As we care for patients in the meantime, best practices should include providing wise counsel and supportive environments for a healthy diet and physical activity that are cornerstones of weight control and normoglycemia, maintaining a high index of suspicion for IR (and for unexpected metabolic effects of new ART), and being ready to implement interventions for IR that slow or prevent development of diabetes when they are available.

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Compliance with Ethical Standards

Conflict of Interest The author declares that he has no competing interests.

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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- •• Of major importance

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