

HIV and diabetes



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Practice Points

- The introduction of combined antiretroviral therapy has resulted in an improved life expectancy for those infected with HIV.
- Antiretroviral therapy drugs, particularly first-generation protease inhibitors, have been associated with the development of glucose metabolism disorders including Type 2 diabetes.
- HIV and its treatment have been associated with the development of lipodystrophy, which can be difficult to manage, with marked insulin resistance being a prominent feature.
- Structured care for all patients with HIV should include routine screening for metabolic complications including diabetes.
- Diabetes is diagnosed in HIV-infected patients in the same way as for patients without HIV.
- Once a diagnosis of diabetes has been made in patients with HIV, management needs to include screening for complications, which is carried out routinely in diabetes clinics.
- The management of metabolic complications of HIV and its treatment may benefit from having the diabetologist's input into the routine care of patients with HIV.

SUMMARY Patients with HIV can now expect an improved life expectancy following the introduction of combined antiretroviral therapy. However, patients with HIV are at risk of developing metabolic complications, including the development of insulin resistance and diabetes, that are associated with specific antiretroviral drugs. HIV services may need to adapt, if they have not already done so, to ensure that patients are screened regularly for diabetes. Once a diagnosis of diabetes is made, routine screening for the complications associated with diabetes should take place and efforts should be made to improve glycemic control. How this is delivered will depend on the number of factors within any given healthcare system (e.g., manpower, teaching of the patients, and nurses and physicians in charge of HIV patients, and the need for a multidisciplinary approach) and the prevalence of diabetes within a locality's HIV population.

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It is estimated that 34 million people worldwide are infected with HIV [101]. With the introduction of antiretroviral therapy (ART) and a global public health drive to reduce the impact of HIV, many more infected individuals can expect a life expectancy that is no longer curtailed by opportunistic infection and AIDS-related complications. However, with improved treatment and prognosis, it has been recognized that there is an association between HIV infection, and its treatment, and disorders of glucose metabolism, including a possible increased incidence and prevalence of Type 2 diabetes. This presents a significant challenge to those tasked with establishing structured clinical services to manage patients with HIV in both developed and developing nations, and for clinicians worldwide making treatment decisions for individual patients.

HIV: background & the introduction of combined ART

AIDS was first reported in the USA in 1981 [1] and was subsequently shown to be the consequence of HIV infection. The following 10–15 years saw HIV lead to patients developing increasingly severe immunosuppression, the development of AIDS and inevitable death. The late 1980s/early 1990s saw the introduction of ART, initially with zidovudine (3-azido-3-deoxythymidine), a nucleoside reverse transcriptase inhibitor initially developed as an anticancer drug, but this did not slow down the rise in the number of cases. This was at least in part due to the development of drug resistance, which was recognized as early as 1989, to the only drug at that time licensed for the treatment of HIV [2].

A major development in the treatment of HIV came between 1995 and 1996, with the advent of combined ART, also referred to in the literature as highly active ART, which is a combination treatment using three or more agents. The aim of treatment was full suppression of HIV to undetectable levels in the blood, resulting in less viral resistance, improved immune recovery and markedly improved prognosis [3]. Recent evidence confirms that combined ART decreases the number of new cases when the viral load is suppressed [4].

Drugs used to treat HIV

HIV is a ssRNA retrovirus that uses the enzyme reverse transcriptase during its replication cycle to convert RNA to dsDNA, which is then incorporated into the host cell DNA. There is no cure

for HIV infection, but there are a number of different drugs that slow or stop disease progression and are now licensed for use in HIV (Table 1). In addition to nucleoside reverse transcriptase inhibitors (NRTIs), there are also non-NRTIs, protease inhibitors, integrase inhibitors and drugs that act by inhibiting the HIV virus from entering the host cells (Figure 1). The initiation of ART should be left to specialists in the management of HIV because, while early treatment is no doubt of benefit, the treatment regimens are complex, some of the drug treatments have been specifically associated with the development of disorders of glucose metabolism and some drugs are known to have the potential to result in significant drug–drug interactions. To complicate matters further, ART involves more than one potential combination treatment; for example, two NRTIs (tenofovir and emtricitabine) and either a non-NRTI (e.g., efavirenz), a boosted protease inhibitor (atazanavir/ritonavir or darunavir/ritonavir) or the integrase inhibitor raltegravir. Additionally, guidelines that are regularly updated need to be applied in the clinical setting, under expert supervision, with drug adherence being an important aspect of successful treatment [5,6,102,103].

Diabetes & disorders of glucose metabolism: prevalence in HIV

Prior to the introduction of combined ART as a routine treatment for HIV, diabetes prevalence was reported to be 2.0–2.6% in treatment-naïve diabetes subjects [7,8]. A number of cases of rapid-onset diabetes have been reported following first-generation protease inhibitor initiation [9–11]. A longer-term study has shown a fourfold increase in the relative risk of incident diabetes (10% of ART patients vs 3% in HIV-negative controls over 4 years), but this cohort study predates combined ART, following male patients between 1984 and 1991 [12]. There are two large epidemiological data sets: the Data Collection on Adverse Events of AntiHIV Drugs study followed 33,389 HIV infected patients over an average of 3.8 years with a diabetes prevalence at baseline of 2.9% and incidence of 5.72 cases/1000 patient-years at follow-up [13]; and the Swiss HIV cohort, which followed 8444 patients with a diabetes prevalence at baseline of 4% and an estimated incidence of 3.12 cases/1000-patient years at follow-up, giving a prevalence of 7% at 3 years [14]. These cohort studies also included patients treated

Table 1. Drugs for treating HIV infection and risk of diabetes.

Drug class	Examples	Risk of insulin resistance/diabetes
Nucleoside/nucleotide reverse transcriptase inhibitors	Zidovudine	Yes (includes lipoatrophy [†])
	Didanosine	Yes (includes lipoatrophy [†] especially combined with stavudine)
	Lamivudine	Yes (includes lipodystrophy)
	Stavudine	Yes (includes lipoatrophy [†])
	Abacavir	No
	Tenofovir	No
	Emtricitabine	No
Non-nucleoside reverse transcriptase inhibitors	Nevirapine	No
	Efavirenz	No
	Etravirine	No
	Rilpivirine	No
Protease inhibitors	Saquinavir	Less likely
	Ritonavir	Yes
	Indinavir	Yes
	Nelfinavir	Yes
	Fosamprenavir	Yes
	Lopinavir plus ritonavir	Yes
	Atazanavir	Less likely
	Tipranavir	Yes
	Darunavir	Yes
Fusion and entry inhibitors	Enfuvirtide	No
	Maraviroc	No
Integrase inhibitor	Raltegravir	No

[†]Especially in combination with protease inhibitors.
Information taken from the British National Formulary [106].

with older ARTs, and more recent evidence is questioning whether there is an increased incidence of diabetes in HIV-infected individuals on newer ARTs. In a large Danish HIV cohort (n = 4984) with matched noninfected controls followed between 1996 and 1999, the risk of diabetes was higher for HIV-infected patients (adjusted incident rate ratio: 3.24; 95% CI: 1.42–7.39), whereas in the period between 1999 and 2010 there was no increased risk (adjusted incident rate ratio: 0.90; 95% CI: 0.72–1.13) [15]. This seems to suggest that the association with HIV infection may simply be a consequence of using older ARTs.

HIV-specific risk factors for developing diabetes

There does not appear to be an association between duration of HIV or CD4 count, and the risk of developing diabetes [16]. However, there are HIV-specific factors that influence the risk of developing diabetes, including which drugs patients are treated with and whether or not they develop the complication of lipodystrophy.

■ Drug treatments

The effect of drug treatments in HIV can manifest in two ways; as a consequence of increased weight and improvement in well-being after initiating therapy; and the specific effects of certain drugs on aspects of glucose metabolism. Healthy volunteer studies have been used to assess individual drugs' potential to cause disturbances in glucose metabolism, assess whether there is a dose-dependent effect and whether certain combinations of treatment are more likely to result in diabetes. Observational studies in HIV-infected cohorts have defined specific drugs associated with disturbances in glucose metabolism and proposed the mechanisms behind this. **Table 1** summarizes those drugs known to have an effect on glucose metabolism. In general, the older-generation drug therapies have a stronger association with disorders of glucose metabolism [17].

■ Lipodystrophy

Lipodystrophy occurs in HIV-infected patients who are being treated with antiretroviral

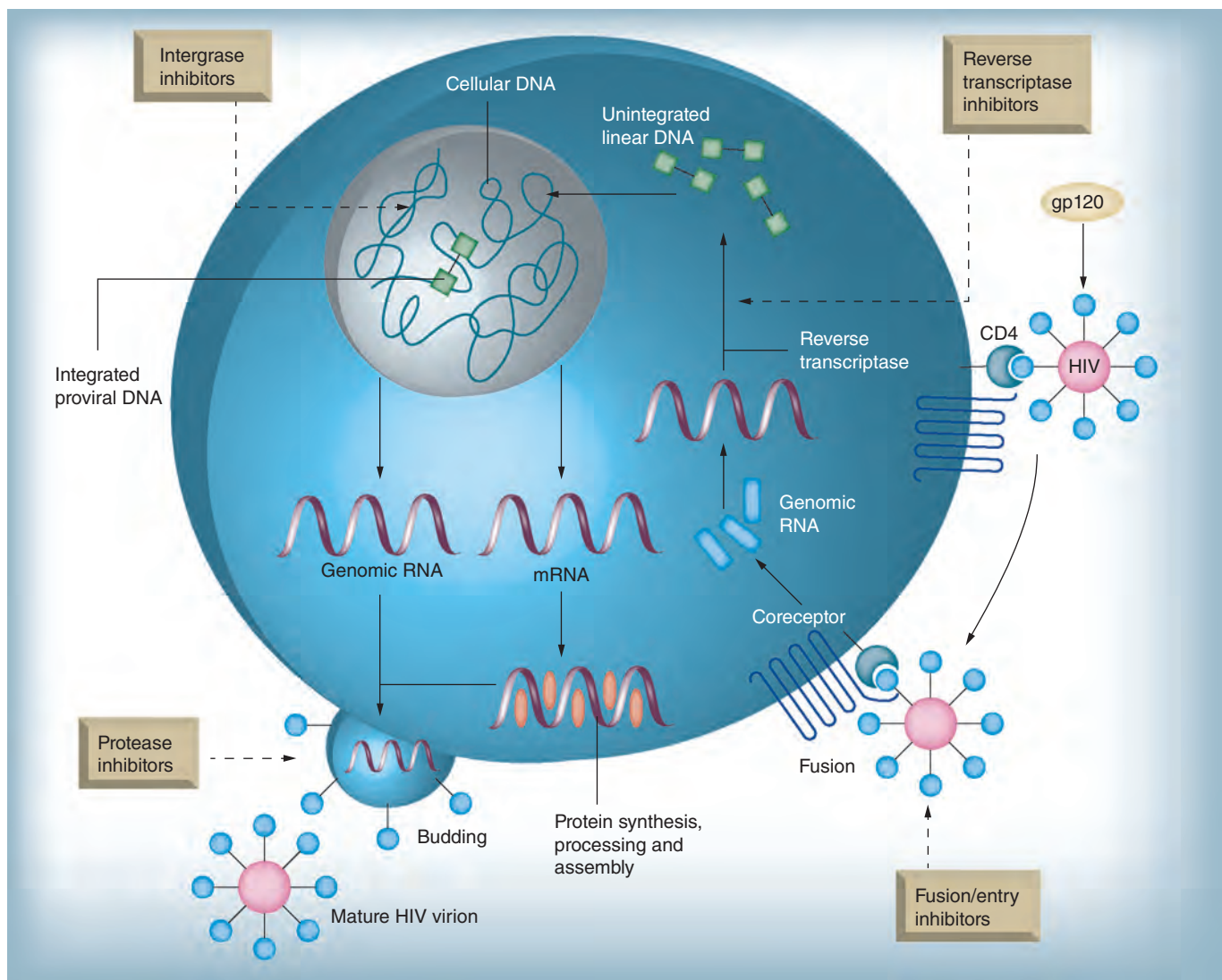


Figure 1. Mechanism of action of HIV drugs. Adapted with permission from [41].

medications. This can be defined as abnormal central fat accumulation (lipohypertrophy) or diffuse loss of fat tissue (lipoatrophy), which is more noticeable in certain areas such as the face. Patients affected may suffer from one or the other, or a mixture of both. The recognition of abnormal fat redistribution was first described in 1998 [18]. At that time, a number of protease inhibitors were in widespread use and one study reported that 74 out of 116 patients (64%) receiving protease inhibitors for an average of 14 months displayed lipodystrophy as opposed to only one out of 32 (3%) protease inhibitor-naïve patients [19]. However, lipodystrophy has also been shown to be associated with NRTIs, especially stavudine and zidovudine [20].

■ **Obesity & usual risk factors for impaired glucose tolerance & Type 2 diabetes**

The standard risk factors for the development of disorders of glucose metabolism are the same for those infected with HIV. These include advancing age, high BMI, a greater waist-to-hip ratio and certain ethnic backgrounds or cultures. Advancing age, in particular, contributes to the increased prevalence of diabetes, which is particularly relevant as the HIV-infected patient cohorts get older [21]. In the Swiss HIV cohort study, patients had a longer duration of HIV infection at baseline and more patients were on antiretroviral therapy. The prevalence of diabetes at baseline was 2.1% for those <50 years of age, 7% in those 50–64 years and 16.2% in those >65 years [14].

Other risk factors for developing diabetes in patients with HIV

■ Hepatitis C coinfection

Hepatitis C coinfection is often seen in patients with HIV and is associated with increased insulin resistance [22], but there remains some doubt as to whether it confers an increased risk of developing diabetes – early studies suggesting this to be the case have not been replicated [23].

■ Sex

Most studies in HIV populations have predominantly male participants. The Women's Interagency HIV Study reported a diabetes incidence of 2.8% over 3 years in protease inhibitor recipients versus 1.2% in ART-naïve and 1.4% in HIV-uninfected participants [24]. HIV-uninfected women were more likely to be overweight or obese (33 vs 23% in the HIV-infected women), but had half the rate of incident diabetes, implying that HIV-infected women have a greater risk at a lower BMI.

Measuring insulin resistance & monitoring for diabetes in HIV

Given that the main reason patients with HIV develop diabetes is through insulin resistance, it would be potentially beneficial if patients could be screened for this. The gold standard for checking insulin resistance is to use euglycemic clamp studies that look at the amount of glucose required to maintain blood glucose levels in patients with an insulin infusion. This technique has been used in research projects to show the degree of insulin resistance in patients with HIV [25], the association with specific HIV drugs [26] and the strong association with lipodystrophy [27]. However, from a practical point of view, this is not easily translated into normal clinical practice, and indirect methods of measuring insulin resistance derived from blood insulin and glucose concentrations under fasting conditions (steady state) or after an oral

glucose load (dynamic) are also not easily carried out in the clinic and are less accurate [28]. National guidelines suggest that the diagnosis of diabetes should be established using routine tests for blood glucose and HbA1c (**Box 1**), particularly in those patients with associated risk factors, including the presence of features of the metabolic syndrome, patients on specific therapies known to be associated with insulin resistance, those with a hepatitis C coinfection and those with a family history of diabetes [5].

Management of hyperglycemia in HIV

In a retrospective cohort study looking at glycemic management in 286 HIV-infected patients and 858 age- and sex-matched HIV-uninfected controls, it was found that HIV-infected patients achieve a significantly smaller reduction in HbA1c with an absolute mean difference of 0.17% (95% CI: 0.28–0.06; $p = 0.003$) compared with the overall group, with an adjusted absolute mean reduction in HbA1c of 1.04% (95% CI: 0.87–1.22) during the first year of therapy [29]. This seems to suggest that those diabetes patients with HIV have more difficulty controlling hyperglycemia. Unsurprisingly, on subgroup analysis, the poor response is seen in those HIV patients on protease inhibitor-based regimens, probably mediated through increased insulin resistance. However, other studies suggest that glycemic control in HIV patients is no more difficult to achieve than in HIV-uninfected patients with diabetes [30,31]. The HIV-infected patients in both studies ($n = 216$ and 142 , respectively) achieved comparable American Diabetes Association HbA1c targets as the non-HIV-infected diabetes patient population. In both of these studies, patients were on a variety of treatments, and there is some evidence that dietary intervention, metformin and glucose sensitizers work in patients with HIV and diabetes [32–34].

Box 1. Diagnosing diabetes and screening in the HIV clinic

Diagnosing diabetes

- Diabetes symptoms (i.e., polyuria and polydipsia) plus random venous plasma glucose ≥ 11.1 mmol/l, fasting blood glucose ≥ 7.0 mmol/l, 2-h plasma glucose ≥ 11.1 mol/l after 75-g oral glucose tolerance test
- No symptoms: need an additional positive test on another day; HbA1c > 48 mmol/mol (6.5%)

In the HIV clinic

- Screen for diabetes prior to starting treatment, assessing risk from history (e.g., diabetes symptoms), history of gestational diabetes, family history of diabetes, examination (increased BMI) and random blood glucose prior to treatment
- Repeat screening at 3–6 months then annually thereafter

Cardiovascular risk & management of risk factors

The National Health and Nutrition Examination Survey data were analyzed to obtain prevalence estimates of vascular risk factors by HIV status in adults aged 20–49 years and showed a significant association with diabetes mellitus, but also a borderline significant association with hypertension [35]. In another US healthcare database study, patients with HIV were found to have a significantly higher prevalence of hypertension (21.2 vs 15.9%), diabetes (11.5 vs 6.6%) and dyslipidemia (23.3 vs 17.6%) than the non-HIV-infected group [36]. In this study, there was also a higher rate of acute myocardial infarction (AMI) in HIV-infected women (the unadjusted AMI rates per 1000 person-years were higher for HIV patients among women – 12.71 vs 4.88 for HIV- vs non-HIV-infected women – but not for men – 10.48 vs 11.44 for HIV- vs non-HIV-infected men). This study has limitations, including incomplete data on smoking, but it suggests that it is important to ensure that individual patients with HIV have their vascular risk assessed and any abnormalities should be acted upon if this is considered beneficial. The risk of AMI in HIV-infected patients has also been reported in a large cohort study with >97% of patients being male [37]. After correcting for all the standard Framingham risk factors in HIV-positive patients and controls, infection with HIV is associated with a 50% increased risk of AMI (hazard ratio: 1.48; 95% CI: 1.17–1.66). Further data from the Swiss HIV Cohort Study suggest that some of the increased risk is associated with poorly controlled blood pressure [38].

Individual patient management

When considering the treatment of the individual with HIV, the initial concern needs to be about ensuring adequate monitoring, commencement of combined ART at the appropriate time, adherence to treatment and regular follow-up. In addition to checking various parameters, such as CD4 count, along with physical well-being, it is now an important part of longer follow-up to ensure that individuals are screened for metabolic complications such as diabetes and this is reflected in a number of different guidelines [5,6]. The other metabolic complications of HIV and its treatment, including effects on lipids, are beyond the scope of

this review, but must be borne in mind when considering treatment options for the individual patient. Once a diagnosis of diabetes is established, it is important to have a structured approach to patient management with dietary interventions followed by consideration of drug treatment to manage hyperglycemia. This may prove challenging, particularly in the presence of marked insulin resistance. Additionally, the management of hyperglycemia needs to be viewed in the context of overall cardiovascular risk with attention given to other modifiable risk factors.

Systems for managing diabetes in developed nations

The complexity of management of patients with HIV and diabetes leads many to recommend specialist clinics [39], preferably with both a diabetes and HIV physician present, as well as the diabetes multidisciplinary team. As with all patients with diabetes, lifestyle measures, diet and exercise, education and medical management should be considered at every opportunity. The treatment is likely to be led by a diabetes team, with additional focus on cardiovascular risk and monitoring of complications. Similarly, HIV physicians should receive training and information on screening and management of diabetes in their population of patients. However, studies have shown that even in well-resourced settings, patients with HIV and diabetes do not always have their cardiovascular risk appropriately screened, resulting in undertreatment [13,17]. A focused clinical setting with structured goals for screening and treatment may improve the overall management of the variety of needs.

In terms of diagnosis, the same WHO definition for diabetes is used in those with and without HIV, but there are no set international criteria for monitoring and testing, with a variety of recommendations in different countries guided by different organizations. It has been recommended that all those starting protease inhibitors have their fasting blood glucose checked, and prior to commencing any ART, a thorough family history is carried out [40]. There is a continued need to evaluate risk and intervene, give advice on choice and avoidance of certain ARTs, and yearly screening (at a minimum) for risks and complications. How this is delivered locally will depend on the local prevalence of diabetes in those with HIV. **Box 1** outlines the diagnostic

criteria and a suggested screening schedule for managing patients diagnosed with diabetes.

Systems for managing HIV in developing nations

Of all patients with HIV/AIDS, 69% live in sub-Saharan Africa, with many more in other low- and middle-income countries [104]. The ongoing changes and developments in resource-poor countries are leading to a change in lifestyle, a growing population with obesity and an increase in general population risk factors for developing Type 2 diabetes. At the end of 2012, just under 10 million people living with HIV in low- and middle-income countries had access to appropriate treatment. With the revised WHO guidelines in 2013, almost 26 million people will meet criteria for starting medication. This is due to a change in the recommended CD4 count that triggers the commencement of treatment; the new guidelines state that all those with a CD4 count of less than 500 cells/mm³ should commence ART regardless of their stage of disease [105].

There is a long way to go before each and every one of these patients get the appropriate drugs they need, but many factors are leading to improved accessibility of these drugs thanks to changes in political understanding, funding, education and aid organizations. These changes, coupled with an open license for many of the older ARTs means that many of these drugs are now available at competitive prices.

However, secondary to the increase in accessibility of these older drugs is the potential to expose an increased number of individuals to metabolic side effects, including the development of diabetes. The highest risk of metabolic effects from ARTs lies mainly with the protease inhibitors, particularly the older more established ones and some NRTIs, including stavudine, as already outlined. These medications are no longer first-line choices, and WHO recommends avoiding them where possible. New ARTs developed by large pharmaceutical companies are being added

into WHO guidelines for second- and third-line recommendations. These medications do not carry the same metabolic risks as older ARTs. However, due to patents and licenses, these medications are often expensive and may not be readily available outside of the USA/Europe. This, in turn, may put many millions of HIV-infected people at risk of developing diabetes secondary to their medication, among a population with a growing general population risk of diabetes.

Conclusion & future perspective

Diabetes and complications of glucose metabolism are associated with HIV infection and treatment. This is probably due to the increased insulin resistance seen in aging populations in combination with some factors specific for this patient group, including the use of combined ART and the association of some drugs with the development of lipodystrophy. In practice, avoiding or moving away from drugs that have been associated with disorders of glucose metabolism may reduce the prevalence of diabetes in the HIV-infected patient population, but this remains a challenge and requires services equipped to identify those with diabetes. This applies to both developed and developing nations, but the latter may be particularly problematic because of the availability and use of older ARTs. Even if identified appropriately, the management of hyperglycemia may not be easy to achieve for individual patients, particularly if insulin resistance is a prominent feature, and services may benefit from the input of specialists in diabetes.

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