

# Diabetes and HIV

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J Soc Health Diab 2019;7:45–49

## Abstract

In India, the prevalence of HIV infection among adults (15–49 years) is estimated at 0.26%. The total number of people living with HIV (PLHIV) in India was estimated at 21.17 lakhs in 2015. There has been a declining trend in the mortality rate of HIV-infected patients on antiretroviral therapy (ART). With HIV becoming a chronic manageable disease, metabolic complications like diabetes mellitus (DM) and dyslipidemia are coming to the forefront. Generally, protease inhibitors (PI) are implicated in metabolic derangement; however, nucleoside reverse transcriptase inhibitors (NRTI) like stavudine can also cause diabetes. Among HIV-infected patients, the prevalence of diabetes is reported to range from 2 to 19%, so there is strong case for screening of diabetes among HIV-infected cases. The South Asian Consensus Guidelines recommend that both fasting and postprandial glucose values should be checked at screening and during monitoring of therapy. National AIDS Control Organization (NACO) recommends fasting plasma glucose with value  $\geq 126$  mg% diagnostic of diabetes mellitus. HbA1c may underestimate the degree of hyperglycemia in HIV-infected individuals and may not be a good diagnostic tool. Lifestyle modification is recommended as part of treatment. Metformin should be used with caution in HIV patients. Concomitant use of metformin with non-nucleoside reverse transcriptase inhibitors (NNRTI) can cause lactic acidosis. Thiazolidinediones should be the drug of choice in HIV, particularly in patients with lipodystrophy. Insulin secretagogues (meglitinides and sulfonylureas) are safe but may not be effective in the presence of severe insulin resistance. There are concerns regarding the use of gliptins in HIV-infected patients as they have molecular targets on immune cells. Insulin should be the drug of choice for HIV-infected patients with marked hyperglycemia (HbA1c  $> 9\%$ ), ketonuria, severe liver disease, or severe kidney disease. SGLT2 inhibitor may increase the risk of urinary tract infection and genital mycotic infections in HIV-infected diabetics. Regarding the use of ART among HIV patients with diabetes, NACO guidelines recommend that Tenofovir, lamivudine, and efavirenz should be used as first-line ART for all new patients, except known cases of severe diabetes, severe hypertension, or renal disease. Tenofovir, lamivudine, and lopinavir/ritonavir should be used as first line in women ever exposed to single dose Nevirapine in the past and also for all confirmed HIV-2 or HIV-1 & 2 coinfecting patients. HIV infected with diabetes mellitus and microalbuminuria or proteinuria need Abacavir-based regimen (Abacavir + Lamivudine + Efavirenz). There is some suggestion that PI-based regimens should be avoided in patients at high risk of developing diabetes, for example, those with a history of gestational diabetes, positive family history of diabetes, or impaired glucose tolerance on screening.

## Keywords

- ▶ PLHIV and diabetes
- ▶ ART and metabolic derangement
- ▶ management of HIV dysglycemia

## Introduction

In India, the prevalence of HIV infection among adults (15–49 years) was estimated at 0.26% (0.22–0.32%) in 2015, with 0.30% among males and 0.22% among females. The total number of people living with HIV (PLHIV) in India was estimated at 21.17 lakhs in 2015. The number of AIDS-related deaths (ARD) started to show a declining trend from 2007, with the annual number of AIDS-related deaths declining by 54%. In 2015, an estimated 67.6 (46.4–106.0) thousand people died of AIDS-related causes in India.<sup>1</sup> Thus, HIV infection has become a chronic manageable disease and as patients continue to live longer, metabolic complications like dyslipidemia, changes in body composition, insulin resistance, and glucose intolerance have emerged. Viral coinfection and adverse effects of treatment may place HIV-infected patients at increased risk of developing diabetes.

## Epidemiology

The multicenter AIDS cohort study showed a 14% incidence of diabetes mellitus (DM) in people living with AIDS (PLWHA) exposed to antiretroviral therapy (ART), which was four times higher than that found amongst HIV-seronegative controls.<sup>2</sup> From 1997 to 2012, there was a 4.2-fold increased prevalence of diabetes among HIV-infected patients in Spain compared with a 1.56-fold increase among non-HIV-infected patients.<sup>3</sup> In the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study, diabetes was diagnosed in 744 patients (incidence rate of 5.72 per 1,000 person-years of follow-up).<sup>4</sup>

There have been several studies from India. A study from New Delhi reported a 2.1% prevalence of DM among patients on ART. The study also reported metabolic syndrome in 19.1% (according to International Diabetes Federation [IDF] criteria) and 25% (adult treatment panel [ATP] III).<sup>5</sup> A study from Bangalore evaluated 60 patients who had HIV infection for  $\geq 12$  months, out of which 30 patients were ART-naive and 30 on ART. A high prevalence of metabolic syndrome was observed in patients with HIV (26.7%) using ATP III criteria and was more prevalent in the ART-treated group (43.3%;  $p = 0.028$ ). Diabetes was diagnosed in one patient who was ART-naive and among six patients who were on ART.<sup>6</sup> Metabolic syndrome was also reported in 20% of HIV-positive patients from Allahabad.<sup>7</sup>

A study of 201 HIV infected patients (142 males and 59 females) in Imphal, despite the incidence of dysglycemia and dyslipidemia being higher in patients on second-line ART, failed to show a statistically significant difference from those on first-line ART.<sup>8</sup> In another study from Imphal, 47 patients were evaluated at baseline and after 6 months following initiation of protease inhibitor (PI)-based therapy (second-line ART) following failure with first-line drugs not adhering to NACO guideline 2008. After 6 months of treatment, 19.1% developed DM.<sup>9</sup>

In a smaller study by Mittal et al, evaluating 27 cases on PIs for at least 6 months, 13 drug-naive patients reported

no significant difference among the patients who were on PI-based ART and the treatment-naive patients with regard to their fasting blood sugar.<sup>10</sup>

Among Indian HIV-infected patients, around 2 to 19% of them develop DM.

## ART and Risk of Diabetes Mellitus

It was earlier felt that nucleoside reverse transcriptase inhibitors (NRTIs) were less likely to cause metabolic abnormalities and PIs were mainly implicated. However, in a study which analyzed 130151 person-years of exposure has shown that these drugs, too, increase the risk of diabetes. Exposure to stavudine has the highest risk; zidovudine also increases the risk.

With median follow-up at 9.6 years, an increased incidence of diabetes was associated with exposure to didanosine during the first year or stavudine during the first 2 years of treatment. A decreased incidence was associated with exposure to nelfinavir. A high-incidence of diabetes was also associated with longer use of didanosine (between 2 and 3 years). Exposure to the PIs lopinavir, saquinavir, or atazanavir was not associated with diabetes. DM was also less likely among those ever treated using emtricitabine, tenofovir, abacavir, efavirenz, nevirapine, or darunavir. However, in one study, efavirenz increased the risk of incident diabetes.

Proposed mechanisms include insulin resistance, lipodystrophy, and mitochondrial dysfunction. These mechanisms may be evident only in HIV-infected persons treated for long periods of time with NRTIs. PI has been shown to decrease glucose uptake by inhibiting the transport function of GLUT-4 in vitro and reduce insulin sensitivity in vivo. PI therapy not only reduces insulin sensitivity but also impairs the  $\beta$ -cell response to this reduction in insulin sensitivity.

- Although PIs are mainly incriminated, NRTIs (mainly stavudine) can also cause diabetes.
- Among PIs, lopinavir, saquinavir, or atazanavir, were not associated with diabetes.
- Among the commonly used ARTs, tenofovir, abacavir, and nevirapine, are less likely to cause diabetes.

## Lipid Abnormalities

Among 788 HIV-infected adults in the lipodystrophy case definition study, 451 were afflicted with lipodystrophy. There was a high-prevalence of lipid disturbances: 39% had hypercholesterolemia and 56% had hypertriglyceridemia.<sup>11</sup>

There was significant increase in total cholesterol, triglyceride, and LDL-cholesterol after 6 months of ART<sup>5</sup> and also after switching to second-line ART from first-line ART.<sup>9</sup>

- Lipid abnormalities can be seen as early as 6 months of ART and there is a higher prevalence of dyslipidemia among those on second-line ART.

## Statin Use and Diabetes

Statin use was associated with a nonsignificant increase in the risk of DM. In a HIV outpatient study (HOPS) of 4692 patients, 590 (12.6%) initiated statin therapy and 355 (7.2%) developed DM. Statin use was associated with a modestly increased risk of incident DM in an HIV-infected population, similar to existing data for the general population. However, in patients with increased risk for atherosclerotic cardiovascular disease, the use of statins is warranted, as the benefit outweighs the benefit.

- Similar to the available data among HIV-negative patients, statin therapy can increase the risk of diabetes but among patients with high-risk of atherosclerotic cardiovascular disease, the benefit of statin therapy may outweigh the risk.

## Diagnosis

The South Asian Consensus Guidelines recommend that both fasting and postprandial glucose values should be checked at screening and during monitoring of therapy.<sup>11</sup> NACO recommends fasting plasma glucose (FPG) with value  $\geq 126$  mg/dL diagnostic of DM.<sup>12</sup> A recent study from USA has shown that using oral glucose tolerance test (OGTT) detects more cases of DM than using FPG or A1C. A1C may underestimate the degree of hyperglycemia in HIV-infected individuals and may not be a good diagnostic tool. Discordance between glycemic level and HbA1c have been reported in patients with lower CD4 count and those treated with NRTI, specifically abacavir.

- Both fasting and postprandial glucose values should be used to diagnose diabetes among HIV-infected cases.
- HbA1c may underestimate the degree of hyperglycemia and is not a good tool.

## Management of Diabetes in HIV

The South Asian Consensus Guidelines recommend dietary modification, physical activity, and psychosocial support in patients with diabetes and HIV. The guidelines states metformin should be used with caution in HIV patients. There are reports of lactic acidosis with concomitant use of metformin with NNRTIs as both drugs hinder oxidative phosphorylation.

The mechanism of action of thiazolidinedione should make them drugs of choice in HIV. The possibility of a slight increase in subcutaneous fat makes them the preferred drug class in patients with lipodystrophy.<sup>13</sup>

Insulin secretagogues (meglitinides and sulfonylureas) are safe, but may not be effective in the face of severe insulin resistance. However, amongst the oral agents, they have a faster onset of action and may be used in appropriate doses, provided there is no ketonuria. The meglitinides can address the defect in first-phase insulin secretion, which is seen with certain PIs, and may be an appropriate choice.

A study of 2,454 HIV-infected patients and 8,892 HIV-uninfected patients compared the glycemic effectiveness of oral diabetic medications among patients with

and without HIV infection. Metformin was the most commonly prescribed medication ( $n = 5,647$ , 50%), followed by sulfonylurea ( $n = 5,554$ , 49%) and thiazolidinedione ( $n = 145$ , 1%). There was no significant difference in the change in HbA1c level among the three groups of new users after adjustment for potential confounders. HIV infection was not significantly associated with glycemic response ( $p = 0.24$ ).<sup>14</sup>

There are concerns regarding the use of gliptins in HIV-infected patients as they have molecular targets on immune cells; however, a small study revealed no changes in CD4 count or HIV RNA among HIV-infected patients treated with sitagliptin. Saxagliptin interacts with cytochrome P450 3A4/5 inhibitors like ritonavir, and saxagliptin dose should be reduced when used along with ritonavir.

Insulin should be the drug of choice for HIV-infected patients with marked hyperglycemia (HbA1c  $> 9\%$ ), severe liver disease, or severe kidney disease. With severe osmotic symptoms or ketonuria, it is mandatory to use insulin. Also, in patients with acute super-added infections, insulin would be the preferred drug.

Glucagon like peptide-1 receptor agonists, possibly by improving weight control, body fat distribution, and cardiovascular markers, may be a valuable tool in the treatment of HIV-associated type 2 diabetes. Gliflozins may theoretically increase the risk of urinary tract infection and genital mycotic infections in HIV-infected diabetics because of their immune-compromised state.

- Lifestyle modification is recommended as part of treatment.
- Metformin should be used with caution in HIV patients. Concomitant use of metformin with NNRTIs can cause lactic acidosis.
- Thiazolidinedione should be the drug of choice in HIV, particularly in patients with lipodystrophy.
- Insulin secretagogues (meglitinides and sulfonylureas) are safe but may not be effective in the face of severe insulin resistance.
- There are concerns regarding the use of gliptins in HIV-infected patients as they have molecular targets on immune cells.
- Insulin should be the drug of choice for HIV-infected patients with marked hyperglycemia (HbA1c  $> 9\%$ ), ketonuria, severe liver disease, or severe kidney disease.
- Gliflozins may increase the risk of urinary tract infection and genital mycotic infections in HIV-infected diabetics.

## ART Treatment Among Diabetics or Those Prone to DM

Revised NACO ART regimen 2016 advocates the use of tenofovir, lamivudine, and efavirenz as the first-line ART for all new patients, except known cases of severe diabetes, severe hypertension or renal disease, confirmed HIV-2 or HIV-1 & coinfecting, or women with past history of single dose exposure to Nevirapine. Tenofovir, Lamivudine and lopinavir/ritonavir is used as first line in women ever

exposed to single dose nevirapine in the past and also for all confirmed HIV-2 or HIV-1 & 2 coinfecting patients.<sup>12</sup>

Patients with diabetic retinopathy and/or retinopathy are said to have severe diabetes and will have more chance of getting Tenofovir toxicity. HIV infected with DM and microalbuminuria or proteinuria need Abacavir-based regimen (abacavir + lamivudine + efavirenz).<sup>12</sup>

PI-based regimes should be avoided in patients at high risk of developing diabetes, for example, those with a history of gestational diabetes, positive family history of diabetes, or impaired glucose tolerance on screening. Indinavir should be avoided and replaced with less toxic drugs.

- Tenofovir, lamivudine, and efavirenz should be used as first-line ART for all new patients except known case of severe diabetes, severe hypertension, or renal disease.
- Tenofovir, lamivudine, and lopinavir/ritonavir should be used as first line in women ever exposed to single dose nevirapine in the past and also for all confirmed HIV-2 or HIV-1 & 2 coinfecting patients.
- HIV infected with DM and microalbuminuria or proteinuria need Abacavir-based regimen (abacavir + lamivudine + efavirenz).
- PI-based regimes should be avoided in patients at high risk of developing diabetes, for example, those with a history of gestational diabetes, positive family history of diabetes, or impaired glucose tolerance on screening.

## Authors' Recommendations

1. Among Indian HIV-infected patients, around 2 to 19% develop diabetes. Patients on PIs have the highest risk but NRTI (mainly stavudine) can also cause diabetes. Screening for diabetes mellitus is strongly recommended among patients on ART.
2. Both fasting and postprandial glucose values should be used to diagnose diabetes among HIV-infected cases. A1C may underestimate the degree of hyperglycemia and is not a good tool.
3. Lipid abnormalities can be seen as early as 6 months of ART and there is higher prevalence of dyslipidemia among those on second-line ART, so lipid profile should be done after 6 months of ART and then annually.
4. Statin therapy can increase the risk of diabetes but among patients with high-risk of atherosclerotic cardiovascular disease, statins should not be withheld as the benefit of statin therapy outweighs the risk.
5. Lifestyle modification is recommended as part of treatment of diabetes.
6. Metformin should be used with caution in HIV patients. Concomitant use of metformin with NNRTI can cause lactic acidosis.
7. Thiazolidinediones should be the drug of choice in HIV, particularly in patients with lipodystrophy.
8. Insulin secretagogues (meglitinides and sulfonylureas) are safe but may not be effective in the face of severe insulin resistance.

9. There are concerns regarding the use of gliptins in HIV-infected patients as they have molecular targets on immune cells.
10. Insulin should be the drug of choice for HIV-infected patients with marked hyperglycemia (HbA1c > 9%), ketonuria, severe liver disease, or severe kidney disease.
11. SGLT2 inhibitors may increase the risk of urinary tract infection and genital mycotic infections in HIV-infected diabetics.
12. Tenofovir, lamivudine, and efavirenz should be used as first-line ART for all new patients, except known case of severe diabetes, severe hypertension, or renal disease.
13. Tenofovir, lamivudine, and lopinavir/ritonavir should be used as first line in women ever exposed to single dose nevirapine in the past and also for all confirmed HIV-2 or HIV-1 & 2 coinfecting patients.
14. HIV infected with DM and microalbuminuria or proteinuria need Abacavir-based regimen (abacavir + lamivudine + efavirenz).
15. PI-based regimes should be avoided in patients at high-risk of developing diabetes, for example, those with a history of gestational diabetes, positive family history of diabetes, or impaired glucose tolerance on screening.

## Conflict of Interest

None declared.

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