I nuovi farmaci antidiabetici nelle persone che vivono con l'infezione da HIV.

Novel anti-diabetic drugs in people living with HIV.

Marco Mirani

Endocrinology, Diabetology and Andrology Unit, IRCCS Humanitas Research Hospital, Rozzano, (MI), Italy

Autore per la corrispondenza:

Marco Mirani
Endocrinology, Diabetology and Andrology Unit, IRCCS Humanitas Research Hospital Rozzano, (MI), Italy

marco.mirani@humanitas.it

Keywords:
HIV, type 2 diabetes, People living with HIV, Cardiovascular risk, Anti-diabetic drugs

Potenziali conflitti di interesse: nessuno

JHA 2023; 8(2): 31-35

DOI: 10.19198/JHA31553

Riassunto

L'infezione da virus dell'immunodeficienza umana (HIV) e la terapia antiretrovirale (ART) sono noti fattori di rischio indipendenti per lo sviluppo di disturbi metabolici come la lipodistrofia, la dislipidemia e l'insulino-resistenza, comportando un rischio maggiore per lo sviluppo del diabete mellito di tipo 2. Con la crescente efficacia dell'ART, la sieropositività dell'HIV sta diventando una malattia cronica, con una percentuale progressivamente crescente di persone anziane che vivono con l'HIV (PLWH), esponendole a un carico significativo di morbilità legate all'età, incluso il diabete. Date queste premesse, i PLWH dovrebbero essere considerati soggetti ad alto rischio cardiovascolare e il diabete coesistente dovrebbe essere adeguatamente trattato.

In questa review viene discussa l'importanza di una diagnosi rapida e di un trattamento appropriato del diabete di tipo 2 nei PLWH, analizzando la letteratura disponibile sull'effetto dei farmaci antidiabetici in questa popolazione selezionata, concentrandosi sui nuovi farmaci con comprovati benefici cardiovascolari.

Abstract

Human Immuno-deficiency Virus (HIV) infection and antiretroviral therapy (ART) are known independent risk factors for the development of metabolic disorders such as lipodystrophy, dyslipidemia and insulin resistance, bearing a greater risk for the development of type 2 diabetes mellitus. With the growing effectiveness of ART, HIV seropositivity is becoming a chronic disease, with a progressively increasing proportion of elderly people living with HIV (PLWH), exposing them to a significant age-related burden of morbidities, including diabetes. On these premises, PLWH should be considered subjects at high cardiovascular risk and coexisting diabetes should be properly treated.

In this review the importance of a rapid diagnosis and an appropriate treatment of type 2 diabetes in PLWH is discussed, analyzing the available literature on the effect of anti-diabetic drugs in this selected population, focusing on the novel drugs with proven cardiovascular benefits.

Introduction

The remarkable achievements obtained with the combination antiretroviral therapy (cART) to treat human immunodeficiency virus (HIV) infection have prolonged the life expectancy and has led to the emergence of several age-related chronic conditions, including diabetes mellitus (DM).

Diabetes is a cardiovascular (CV) risk factor and, together with obesity and age, contributes to the already significant risk for developing CV disease among PLWH.

In the last decade new anti-diabetic treatment, such as Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs) and Sodium Glucose cotransporter 2 inhibitors (SGLT2-Is) have been made available, which have not only glucose-lowering effect but share proven CV benefits (1). In this scenario, it is crucial that even a special population such as PLWH with diabetes may take advantage of these new effective treatments.

Epidemiology

The prevalence and incidence of DM are heterogeneous in the literature, with disparities due to different cohorts in terms of sex, age, weight, HIV duration, and treatments.

In Italy an observational, cross-sectional analysis showed a higher prevalence of DM in an HIV infected population (4.1%) compared to healthy subjects (2.1%) (2), while a more recent study con-

	Yes	No
Worsening of insulin resistance	Indinavir	Lopinavir, Ritonavir
Worsening of lipid metabolism	Lopinavir, Ritonavir	Indinavir
Blocks GLUT-4 transporter	Indinavir, Ritonavir	Amprenavir, Atazanavir
Alteration of insulin secretion and beta-cell function	Nelfinavir, Indinavir, Lopinavir, Saquinavir	

Table 1. Summary of the described mechanisms underlying the detrimental effect of different protease inhibitors (PIs) on glucose and lipid metabolism (4, 5); GLUT-4: glucose transporter type 4.

ducted among 4,366 participants by the CISAI Study Group reported an incidence of diabetes of 1.26 cases/100 PYFU (3), which is slightly higher compared to the incidence in the general population.

Studies directly focused on incident cases of diabetes on ART showed conflicting results, with some large observational studies founding a neutral effect of exposure to INSTIs (4), or rather a role of protease inhibitor (PI) class (5), while in a study performed on US health insurance data, an association between INSTIs and DM incidence was found (6).

Weight gain has likely impacted diabetes incidence, as shown by The USA Veterans Aging Cohort Study and The D:A:D cohort study (7,8).

Even modest weight gain in cART recipients increases the risk of metabolic comorbidities and suggests that efforts should be aimed at preventing weight gain in healthy weight people living with HIV infection or addressing overweight or obesity.

Effect of antiretroviral treatment (ART) drugs on glucose and lipid metabolism

The most important classes of drugs used in ART are protease inhibitors (PI) and reverse transcriptase inhibitors (RTIs), divided into nucleoside and non-nucleoside RTIs (NRTI and NNRTI respectively).

PIs have various metabolic effects, which can vary the therapeutic choices.

The detrimental effect on glycemic control and lipid metabolism is multi-faceted, with molecules like indinavir that affect both insulin resistance and glucose transportation **(Table 1)**.

A 2003 study from Woerle investigated the effect of treatment with several PIs (nelfinavir, indinavir, lopinavir, saquinavir) in the first twelve weeks of treatment: fasting plasma glucose rose in all treated patients, insulin sensitivity decreased by approximately 50%, beta-cell function was reduced, and first-phase insulin release decreased by 25% (9).

PIs interfere with cellular retinoic acid-binding protein type 1 (CRABP 1), which modulates peroxisomal proliferator-activated receptor (PPARγ); its inhibition promotes adipocyte inflammation, release of free fatty acids, and insulin resistance.

Hyperglycemia resolves in almost all patients when PIs are discontinued (10).

NNRTIs have detrimental effects on glycemic control as well, and patients treated with these drugs (in particular stavudine, but also zidovudine and didanosine) have an increased risk of developing diabetes compared to untreated PLWH (11). Fleischman in 2007 investigated the effect of stavudine in PLWH, highlighting both insulin resistance and mitochondrial dysfunction as possible underlying mechanisms.

The combination of PIs and RTIs has an additive effect on the risk of developing type 2 diabetes mellitus (12).

Particular ART agents have been associated with weight gain. These include the integrase strand inhibitors (INSTIs), in particular dolutegravir, in combination with the NNRTI tenofovir alafenamide (TAF) (13).

Guidelines for diagnosis and follow-up

Available guidelines of the European AIDS Clinical Society *(https://www.eacsociety.org/guidelines/eacs-guidelines)* recommend screening these patients for diabetes 1) at HIV seropositivity diagnosis; 2) when ART is started; 3) 3 to 6 months after ART has been started.

It is recommended to evaluate fasting glucose and post-prandial glycemia with an oral glucose tolerance test (OGTT), hence insulin resistance is the predominant mechanism.

Glycated hemoglobin (HbA1c) should be avoided as a diagnostic tool in these patients. (14).

Anti-diabetic drugs in people living with HIV

In the last decade, numerous new molecules have been developed for the treatment of type 2 diabetes mellitus, but few data are available in the literature on the effect of these drugs in diabetic patients with HIV seropositivity.

Here the most recent available data from the literature on diabetes mellitus in PLWH are summarized.

Metformin

Metformin is the first-line drug of choice in type 2 diabetes mellitus, in the absence of specific contraindication (i.e. renal impairment, liver dysfunction, advanced heart failure).

It may lead to metformin-associated lactic acidosis (MALA) and as such should be avoided in combination with drugs such as stavudine, which also increases the risk of lactic acidosis, while abacavir, lamivudine, and tenofovir have less effect on lactate levels (15).

No adjustment to metformin is needed with the use of NNRTIs, PIs, or nucleoside reverse transcriptase inhibitors (NRTIs).

Caution should be warranted with INSTIs, as they can increase the area under the curve of metformin. A maximum dose of metformin 1000 mg daily is recommended for use with dolutegravir. No specific maximum dose of metformin is noted for bictegravir, but monitoring for adverse events of metformin is suggested (16).

Thiazolidinediones (TZD)

Pioglitazone, the unique glitazone on the market, has been associated with a reduction in cardiovascular events in a general population study of individuals with type 2 diabetes and a history of macrovascular disease.

On the other hand, adverse effects of pioglitazone include fluid retention and edema, increased risk of bone fractures, and some studies have described an association between pioglitazone and bladder cancer (17).

Due to thiazolidinedione positive action on insulin resistance and the redistribution of body fat, they were considered a candidate for the treatment of the HIV-associated lipodystrophy.

However, in different studies, no clear benefit of pioglitazone treatment has been shown for this complication (18).

Secretagogues

Sulfonylureas decrease A1c by 1–2%, associated side effects include weight gain and hypoglycemia. The last AMD-SID Italian guidelines recommend the de-prescription of sulfonylureas in the general type 2 diabetes population due to their negative risk-benefit profile. Specific consideration in the treatment of PLWH is the adverse effect of weight gain with sulfonylurea use, given that ART initiation is already a risk factor for weight gain.

No interactions between sulfonylureas and PIs, NNRTIs, NRTIs, or INSTIs have been reported (16).

Dipeptidyl peptidase-4 (DPP4) inhibitors

This class of medications is generally well tolerated, is not associated with hypoglycemia, and is considered weight neutral.

They act by inhibiting circulating soluble DPP4 (sDPP4) enzyme activity and prolonging the circulating half-life of GLP-1 and GIP, enhancing insulin secretion and action, but also on the DPP4 enzyme present in the CD26 cell surface receptor present on monocytes and T-lymphocytes, where it plays a role in pro-inflammatory signaling, immune regulation, and signal transduction (19). In a randomized clinical trial in PLWH and impaired glucose tolerance, sitagliptin reduced blood glucose and improved oral glucose insulin sensitivity; it also reduced plasma high-sensitivity C-reactive protein and C-X-C motif chemokine 10 (CXCL10) levels more than placebo (20). In patients with virologically suppressed HIV levels without glycemic alterations sixteen weeks of sitagliptin had no effect on sCD14 levels but showed a marked decline in CXCL10, suggesting an independent effect in reducing inflammation and immune activation in these patients (21).

Sodium-glucose transport protein 2 inhibitors (iSGLT2)

Several CV outcomes trials have demonstrated the benefit of this class of medications in reducing the composite primary outcome of non-fatal myocardial infarction, non-fatal stroke, and CV-related death in patients with type 2 diabetes.

Further, they reduce hospitalization for heart failure and delay the progression of chronic kidney disease (22). The currently available drugs on the market include empagliflozin, canagliflozin, dapagliflozin and ertugliflozin.

A recent report showed how in real life only 4% of diabetic patients with HIV are currently treated with iSGLT2, far less than the general population (23).
However, since the most frequently reported adverse effect of iSGLT-2 is genito-urinary tract infections, the use of these drugs in PLWH should be carefully monitored.

GLP-1 receptor agonists (GLP-1RAs)

To date, most of the international guidelines recommend the GLP-1 RAs for the treatment of type 2 diabetes patients at high cardiovascular risk, since data showed a reduction in the composite primary endpoint of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular-related death (24).
In addition, they induce a significant reduction of body weight, while adverse effects associated with their use include nausea and vomiting.
Even if there are no randomized controlled trials conducted in PLWH, but rather few case studies (25), considering their efficacy on glycemic control, CV benefits, and weight loss action, GLP-1 RA could potentially become the drug of choice in this specific population.

Insulin

The use of insulin is indicated if patients have poor glycemic control, as indicated by a hemoglobin A1c > 10% or blood glucose ≥ 300 mg/dL, symptoms of hyperglycemia, and hyper-catabolism.
In the case of comorbid conditions, acute illness, and contraindication to other antidiabetic drugs, insulin use is always a safer alternative. Disadvantages of insulin therapy include hypoglycemia and weight gain.

Conclusion

PLWH are a population at high risk for the development of type 2 diabetes mellitus, especially when undergoing combination ART.
The growing effectiveness of ART has led to a progressively increasing proportion of elderly PLWH, affected by a significant age-related burden of morbidities and increasing their cardiovascular risk. Scarce data are available in the literature about the real effectiveness of anti-diabetic drugs in PLWH and are mainly focused on older-generation drugs. However, in the last few years treatment of diabetes mellitus has progressively moved from the mere control of blood glucose ("treat to target") to the improvement of long-term CV events, kidney disease, and heart failure ("treat to benefit"). Therefore, data on novel anti-diabetic drugs, such as iSGLT2 and GLP-1RAs, are essential to guarantee also to PLWH an adequate standard of cure. ■

REFERENCES

1. Lin DS, Lee JK, Hung CS, Chen WJ. *The efficacy and safety of novel classes of glucose-lowering drugs for cardiovascular outcomes: a network meta-analysis of randomised clinical trials.* Diabetologia. 2021 Dec;64(12):2676-2686. doi: 10.1007/s00125-021-05529-w. Epub 2021 Sep 18.

2. Galli L, Salpietro S, Pellicciotta G, et al. *Risk of type 2 diabetes among HIV-infected and healthy subjects in Italy.* Eur J Epidemiol. 2012 Aug;27(8):657-65. doi: 10.1007/s10654-012-9707-5. Epub 2012 Jun 22.

3. Taramasso L, Squillace N, Ricci E, et al.; CISAI Study Group. *Incident diabetes in course of antiretroviral therapy.* AIDS. 2023 Mar 14. doi: 10.1097/QAD.0000000000003548. Epub ahead of print.

4. Rebeiro PF, Jenkins CA, Bian A, et al. *Risk of Incident Diabetes Mellitus, Weight Gain, and Their Relationships With Integrase Inhibitor-Based Initial Antiretroviral Therapy Among Persons With Human Immunodeficiency Virus in the United States and Canada.* Clin Infect Dis 2021; 73:e2234–e2242.

5. Justman JE, Benning L, Danoff A, et al. *Protease inhibitor use and the incidence of diabetes mellitus in a large cohort of HIV-infected women.* J Acquir Immune Defic Syndr 2003; 32:298–302.

6. O'Halloran JA, Sahrmann J, Parra-Rodriguez L, et al. *Integrase Strand Transfer Inhibitors are Associated with Incident Diabetes Mellitus in People with HIV.* Clin Infect Dis 2022; :ciac355.

7. Herrin M, Tate JP, Akgun KM, et al. *Weight Gain and Incident Diabetes Among HIV-Infected Veterans Initiating Antiretroviral Therapy Compared With Uninfected Individuals.* JAIDS 2016; 73:228-36.

8. Achhra AC, Mocroft A, Reiss P, et al. *Short-term weight gain after antiretroviral therapy initiation and subsequent risk of cardiovascular disease and diabetes: the D:A:D study.* HIV Medicine 2016; 17:255-68.

9. Woerle HJ, Mariuz PR, Meyer C, et al. *Mechanisms for the deterioration in glucose tolerance associated with HIV protease inhibitor regimens.* Diabetes. 2003 Apr;52(4):918-25. doi: 10.2337/diabetes.52.4.918.

10. Lee GA, Rao MN, Grunfeld C. *The Effects of HIV Protease Inhibitors on Carbohydrate and Lipid Metabolism.* Curr Infect Dis Rep. 2004 Dec;6(6):471-482. doi: 10.1007/s11908-004-0067-5.

11. De Wit S, Sabin CA, Weber R, et al. *Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. Incidence and risk factors for new-onset diabetes in HIV-infected patients: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. Diabetes Care.* 2008 Jun;31(6):1224-9. doi: 10.2337/dc07-2013. Epub 2008 Feb 11.

12. Fleischman A, Johnsen S, Systrom DM, et al. *Effects of a nucleoside reverse transcriptase inhibitor, stavudine, on glucose disposal and mitochondrial function in muscle of healthy adults.* Am J Physiol Endocrinol Metab. 2007;292(6):E1666-73. Epub 20070206. doi: 10.1152/ajpendo.00550.2006.

13. Venter WDF, Moorhouse M, Sokhela S, et al. *Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV.* N Engl J Med. 2019;381(9):803-15. Epub 20190724. doi: 10.1056/NEJMoa1902824.

14. Kim PS, Woods C, Georgoff P, et al. *A1C Underestimates Glycemia in HIV Infection.* Diabetes Care. 2009;32(9):1591–1593.

15. Kohli R, Shevitz A, Gorbach S, Wanke C. *A randomized placebo-controlled trial of metformin for the treatment of HIV lipodystrophy.* HIV Med. 2007;8(7):420-6. doi: 10.1111/j.1468-1293.2007.00488.x. PubMed PMID: 17760733.

16. *https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/drug-interactions-overview?view=full*

(accessed 31/5/2023)

17. Spence JD, Viscoli C, Kernan WN, et al. *Efficacy of lower doses of pioglitazone after stroke or transient ischaemic attack in patients with insulin resistance.* Diabetes Obes Metab. 2022 Jun;24(6):1150-1158. doi: 10.1111/dom.14687. Epub 2022 Mar 18.

18. Edgeworth A, Treacy MP, Hurst TP. *Thiazolidinediones in the treatment of HIV/HAART-associated lipodystrophy syndrome.* AIDS Rev. 2013 Jul-Sep;15(3):171-80.

19. Mulvihill EE, Drucker DJ. *Pharmacology, physiology, and mechanisms of action of dipeptidyl peptidase-4 inhibitors.* Endocr Rev. 2014;35(6):992-1019. Epub 20140912. doi: 10.1210/er.2014-1035.

20. Best C, Struthers H, Laciny E, Royal M, Reeds DN, Yarasheski KE. *Sitagliptin Reduces Inflammation and Chronic Immune Cell Activation in HIV+ Adults With Impaired Glucose Tolerance.* J Clin Endocrinol Metab. 2015;100(7):2621-9. Epub 20150504. doi: 10.1210/jc.2015-1531.

21. Dubé MP, Chan ES, Lake JE, et al. *A Randomized, Double-blinded, Placebo-controlled Trial of Sitagliptin for Reducing Inflammation and Immune Activation in Treated and Suppressed Human Immunodeficiency Virus Infection.* Clin Infect Dis. 2019;69(7):1165-72. doi: 10.1093/cid/ciy1051.

22. Brønden A, Christensen MB, Glintborg D, et al. *Effects of DPP-4 inhibitors, GLP-1 receptor agonists, SGLT-2 inhibitors, and sulfonylureas on mortality, cardiovascular and renal outcomes in type 2 diabetes: a network meta-analyses-driven approach.* Diabet Med. 2023 May 30:e15157. doi: 10.1111/dme.15157. Epub ahead of print. PMID: 37249579.

23. Butale B, Woolley I, Cisera K, Korman T, Soldatos G. *Under-utilisation of cardioprotective glucose-lowering medication in diabetics living with HIV.* Sex Health. 2022;19(6):580-2. doi: 10.1071/SH22070.

24. Marso SP, Daniels GH, Brown-Frandsen K, et al. *Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016;375(4):311-22.* Epub 20160613. doi: 10.1056/NEJMoa1603827.

25. Diamant M, van Agtmael M. *Liraglutide treatment in a patient with HIV and uncontrolled insulin- treated type 2 diabetes.* Diabetes Care. 2012;35(5):e34.