Diabetologia (2023) 66:1162–1164
https://doi.org/10.1007/s00125-023-05904-9

LETTER

A large portion of diabetes cases in sub-Saharan African populations with HIV represent drug-induced diabetes

Petr Heneberg [1]

Received: 1 February 2023 / Accepted: 27 February 2023 / Published online: 23 March 2023

Keywords AIDS · Antiretroviral therapy · Drug-induced diabetes · Environmental exposure · HIV · Infectious diseases · Protease inhibitors · Sub-Saharan Africa · Type 2 diabetes mellitus

Abbreviations
ART Antiretroviral therapy
NRTI Nucleoside reverse transcriptase inhibitor

To the Editor: I have read with great interest the review by Goedecke and Mendham and subsequent correspondence from Christensen et al on the causes of type 2 diabetes in sub-Saharan African populations published in *Diabetologia* [1, 2]. The authors correctly point out that type 2 diabetes is more prevalent among people affected by severe infectious diseases, such as tuberculosis and/or HIV infection. People with these diseases often have persistent dysglycaemia. Christensen et al noted that dysglycaemia occurs despite treatment [2]. However, treatment for HIV infection should not be expected to decrease the incidence of new cases of dysglycaemia. The treatment itself is an essential and problematic factor from the point of view of a diabetologist. Although infectious diseases themselves have the potential to enhance insulin resistance and unmask an underlying beta cell deficiency, some therapies for infectious diseases may contribute to the onset of insulin resistance and dysglycaemia, as previously exemplified [3].

Goedecke and Mendham argue that insulin resistance in sub-Saharan African populations with HIV may be secondary to hyperinsulinaemia resulting from increased insulin secretion or reduced insulin clearance [1]. These may be two independent steps that lead to the same disease. Tuberculosis and/or HIV infection may stimulate primary hyperinsulinaemia, whereas antiretroviral therapy (ART) may later stimulate insulin resistance or facilitate its manifestation following priming by the infectious insult. A major increase in type 2 diabetes prevalence among patients with HIV is associated with the onset of ART [4]. ART is subject to rapid development [5]; guidelines are frequently updated, and different countries follow different guidelines that, in part, reflect their financial status. However, I noticed that the differences in side effects of ARTs were rarely reflected in studies that were not conducted by HIV specialists. The analysis of pools of sub-Saharan African patients with HIV did not reveal differences in diabetes incidence and prevalence between those treated with ART and those not treated with ART [6] because of the lack of differentiation between the prescribed ARTs. When the patients were stratified according to the therapy used, the association between ART and type 2 diabetes onset became obvious.

The best-known examples of the association between ART and type 2 diabetes are the cases of type 2 diabetes that manifested after the administration of first-generation protease inhibitors (indinavir, ritonavir and nelfinavir) [7]. Protease inhibitors were introduced in 1995, and their introduction alone decreased the mortality rate of patients with advanced HIV infection from 30% to 8%, but led to a massive increase in the incidence of new-onset type 2 diabetes cases among treated patients [7]. Protease inhibitors likely cause type 2 diabetes due to activation of the mitochondrial apoptotic pathway in beta cells [8]. They cause peripheral lipoatrophy, visceral adiposity, hyperlipidaemia, insulin resistance, hyperglycaemia and type 2 diabetes, which manifest in a striking 60–80% of patients with HIV treated with first-generation protease inhibitors [9], and they dysregulate metabolism even in HIV-seronegative individuals.

Although other ARTs were initially considered safe concerning the development of metabolic disorders, the

✉ Petr Heneberg
petr.heneberg@lf3.cuni.cz

[1] Third Faculty of Medicine, Charles University, Prague, Czech Republic

reverse is now thought to be true. Multiple nucleoside reverse transcriptase inhibitors (NRTIs) and integrase strand transfer inhibitors (INSTIs) induce gains in adipose tissue [10]. In particular, the first-generation NRTIs (stavudine and zidovudine) have strong pro-diabetic effects. Many effects, such as the body fat repartition effects induced by NRTIs, last for many years after treatment with the respective compounds are discontinued [10].

In sub-Saharan Africa, ART became available in 2002 but it had only 10% coverage of people living with HIV in 2007. This increased to 37% in 2012 and 79% in 2021 (Fig. 1) [11]. Between 2002 and 2021, ART therapy coverage dramatically

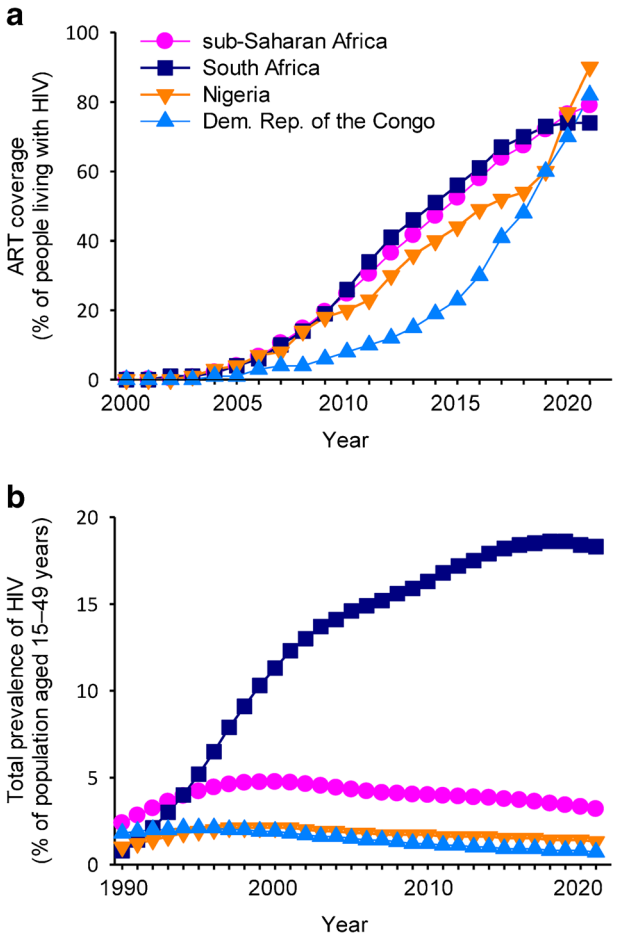

Fig. 1 Trends in (**a**) ART coverage and (**b**) prevalence of HIV in sub-Saharan Africa. The data are shown for all sub-Saharan African countries combined, and specifically for South Africa, Nigeria and the Democratic Republic of Congo. ART coverage is expressed as a percentage of people living with HIV in 2000–2021. The prevalence of HIV is expressed as a percentage of the population aged 15–49 years in 1990–2021. The data represent estimates of the Joint United Nations Programme on HIV and acquired immune deficiency syndrome (AIDS), which are openly available [11]. Dem. Rep., Democratic Republic; UNAIDS, Joint United Nations Programme on HIV/AIDS

improved across most sub-Saharan countries, including South Africa, Nigeria, and the Democratic Republic of the Congo (Fig. 1a). Therefore, most sub-Saharan African patients with HIV are currently on ART. Hence, most recently diagnosed individuals with diabetes and HIV are exposed to both HIV infection and ART. Due to economic reasons, patients with HIV are often treated with ART compounds that are already out of use in the developed world [12]. In 2009, the prevailing first-line treatment regimens consisted of various combinations of stavudine, lamivudine, zidovudine, nevirapine and efavirenz [13]. Of these, stavudine strongly stimulates the development of lipoatrophy, central fat gain, elevated HOMA-IR and diabetes [12]. Similar but weaker effects are known for zidovudine and efavirenz. Only lamivudine and nevirapine are without evidence for negative metabolic effects. Moreover, patients who fail to positively respond to first-line treatment are treated with a combination of ARTs boosted with a protease inhibitor, typically lopinavir and ritonavir [12]. As mentioned above, treatment with ritonavir is associated with the development of type 2 diabetes and lipodystrophic syndrome [13]; this compound is a GLUT4 inhibitor. Of the more recently used first-line regimens, which include zidovudine, efavirenz and nevirapine, all alter lipid profiles, and zidovudine and efavirenz induce type 2 diabetes and stimulate increases in HOMA-IR [14].

Therefore, we call for more attention to the role of treatment regimens in the onset and progression of type 2 diabetes in sub-Saharan African populations with HIV. Diabetes that develops in sub-Saharan African populations with HIV is probably a disease with heterogeneous causes. Some patients develop diabetes associated only with HIV infection or with concomitant tuberculosis infection [15]. In contrast, other patients manifest diabetes only after treatment with various ARTs, thereby being primed by the infectious insult and manifesting the disease after the subsequent drug insult. Drug-induced diabetes and hyperglycaemia have a delay in occurrence, which can be anything from hours to months, or even years after drug initiation [16]. Ideally, baseline glucose levels should be determined before commencing ART. Routine checks should be performed every 3–4 months during the first year of the therapy and less frequently during follow-up years. Caution is needed when using HbA_{1c} as a proxy for blood glucose control as patients with HIV may have increased turnover of red blood cells and, therefore, have falsely lower HbA_{1c} levels [17]. Should the role of ART be confirmed in the increased risk of diabetes in those with HIV, a large portion of diabetes cases in sub-Saharan African populations with HIV should be considered to represent drug-induced diabetes.

Data availability All relevant data are available within the article.

Funding The work was supported by the Charles University project Cooperatio 39 and by the Czech Health Research Council project NU23-06-00045. The study sponsor/funder was not involved in the design of the letter; the collection, analysis and interpretation of data; or writing the report; and did not impose any restrictions regarding the publication of the report.

Author's relationships and activities The author declares that there are no relationships or activities that might bias, or be perceived to bias, his work.

Contribution statement The author was the sole contributor to this paper.

References

1. Goedecke JH, Mendham AE (2022) Pathophysiology of type 2 diabetes in sub-Saharan Africans. Diabetologia 65:1967–1980. https://doi.org/10.1007/s00125-022-05795-2
2. Christensen DL, Hjort L, Mpagama SG, Ramaiya KL (2023) Environmental exposures are important for type 2 diabetes pathophysiology in sub-Saharan African populations. Diabetologia 66: 777–779. https://doi.org/10.1007/s00125-022-05867-3
3. Assan R, Perronne C, Assan D et al (1995) Pentamidine-induced derangements of glucose homeostasis. Determinant roles of renal failure and drug accumulation. A study of 128 patients. Diabetes Care 18:47–55. https://doi.org/10.2337/diacare.18.1.47
4. Duncan AD, Goff LM, Peters BS (2018) Type 2 diabetes prevalence and its risk factors in HIV: a cross-sectional study. PLoS ONE 13:e0194199. https://doi.org/10.1371/journal.pone.0194199
5. Chaudhuri S, Symons JA, Deval J (2018) Innovation and trends in the development and approval of antiviral medicines: 1987-2017 and beyond. Antiviral Res 155:76–88. https://doi.org/10.1016/j.antiviral.2018.05.005
6. Prioreschi A, Munthali RJ, Soepnel L et al (2017) Incidence and prevalence of type 2 diabetes mellitus with HIV infection in Africa: a systematic review and meta-analysis. BMJ Open 7:e013953. https://doi.org/10.1136/bmjopen-2016-013953
7. Palella FJ, Delaney KM, Moorman AC et al (1998) Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med 338:853–860. https://doi.org/10.1056/NEJM199803263381301
8. Zhang S, Carper MJ, Lei X, Cade WT, Yarasheski KE, Ramanadham S (2009) Protease inhibitors used in the treatment of HIV+ induce beta–cell apoptosis via the mitochondrial pathway and compromise insulin secretion. Am J Physiol Endocrinol Metab 296:E925–E935. https://doi.org/10.1152/ajpendo.90445.2008
9. Hadigan C, Meigs JB, Corcoran C et al (2001) Metabolic abnormalities and cardiovascular disease risk factors in adults with human immunodeficiency virus infection and lipodystrophy. Clin Infect Dis 32:130–139. https://doi.org/10.1086/317541
10. Lagathu C, Béréziat V, Gorwood J et al (2019) Metabolic complications affecting adipose tissue, lipid and glucose metabolism associated with HIV antiretroviral treatment. Expert Opin Drug Saf 18: 829–840. https://doi.org/10.1080/14740338.2019.1644317
11. The World Bank (2023). World Bank open data. Available from: https://data.worldbank.org/. Accessed: 21 February 2023
12. Beck EJ, Vitoria M, Mandalia S, Crowley S, Gilks CF, Souteyrand Y (2006) National adult antiretroviral therapy guidelines in resource-limited countries: concordance with 2003 WHO guidelines? AIDS 20:1497–1502. https://doi.org/10.1097/01.aids.0000237365.18747.13
13. Wester CW, Bussmann H, Koethe J et al (2009) Adult combination antiretroviral therapy in sub-Saharan Africa: lessons from Botswana and future challenges. HIV Ther 3:501–526. https://doi.org/10.2217/hiv.09.35
14. Mbébi Enoné JP, Ida Penda C, Bruno Ebong S et al (2019) First-line antiretroviral treatment and virological response among HIV adult patients at an accredited HIV care center, Cameroon. Transl Med Commun 4:8. https://doi.org/10.1186/s41231-019-0040-9
15. Menon S, Rossi R, Dusabimana A, Zdraveska N, Bhattacharyya S, Francis J (2020) The epidemiology of tuberculosis-associated hyperglycemia in individuals newly screened for type 2 diabetes mellitus: systematic review and meta-analysis. BMC Infect Dis 20: 937. https://doi.org/10.1186/s12879-020-05512-7
16. Zheng Z, Liu Y, Yang J et al (2021) Diabetes mellitus induced by immune checkpoint inhibitors. Diabetes Metab Res Rev 37:e3366. https://doi.org/10.1002/dmrr.3366
17. Glesby MJ, Hoover DR, Shi Q et al (2010) Glycated haemoglobin in diabetic women with and without HIV infection: data from the Women's Interagency HIV study. Antivir Ther 15:571–577. https://doi.org/10.3851/IMP1557