REVIEW ARTICLE

Diabetes and HIV: What Do We Know?

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ABSTRACT

Context The acquired immunodeficiency syndrome (AIDS) has become one of the biggest pandemics since 1981. According to the Joint United Nations Program on HIV/AIDS (UNAIDS), in 2018, 38 million people worldwide were living with HIV. In parallel to this scenario, the prevalence and mortality of diabetes have increased in recent decades. Thus, it would be pertinent to know if the risk factors for the development of diabetes mellitus to which people with HIV/AIDS are exposed are the same as those of the non-infected population. According to autopsy studies conducted at the São Paulo Death Verification Service, University of São Paulo, HIV-infected patients in the pre-HAART era (Highly Active Antiretroviral Therapy) presented histological changes in the exocrine pancreas, although in the endocrine pancreas these were not significant. In the post-HAART era, the exocrine pancreas continued to present histological changes, but in this population, they also occurred in the endocrine pancreas and were particularly important in the islets of Langerhans. **Objective** We seek to address the relationship between the use of HAART for the treatment of HIV/AIDS and the possible impacts on the pancreas. **Methods** Horizontal review by the Prisma method, bibliographic search in PubMed and Google Scholar. **Results** Was observed an association between the development of diabetes mellitus and the use of HAART, mainly with the oldest protease inhibitors from 1997-2004. **Conclusion** Although diabetes mellitus is a multifactorial pathology, antiretrovirals have played an important role in increasing the prevalence of diabetes mellitus in the population undergoing HIV/AIDS treatment.

INTRODUCTION

The acquired immunodeficiency syndrome (AIDS) has become one of the biggest pandemics since 1981. It is estimated that in 2018, around 770,000 people have died of AIDS-related diseases worldwide [1]. According to the World Health Organization (WHO), in low-income countries, HIV/AIDS was among the top ten causes of death in 2016 [2]. The prevalence and mortality of diabetes have increased in recent decades. Approximately 422 million people worldwide live with diabetes, which is also the direct cause of 1.6 million deaths per year [3]. In 2016, diabetes was among the top ten causes of death in the world according to the WHO [2]. Given this scenario of high prevalence of diabetes mellitus in the population, it is pertinent to know if the same risk factors are valid for the group of people with HIV/AIDS.

The acquired immunodeficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV), which destroys cells of the immune system, specifically CD4 T lymphocytes, weakening the immunity and predisposing the individual to various infections. However, having HIV does not necessarily imply the development of AIDS, as there are several strains of the virus [4].

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According to the Joint United Nations Program on HIV/AIDS (UNAIDS), in 2018, approximately 38 million people were living with HIV worldwide, of which 23.3 million had access to antiretroviral therapy [5]. According to the World Health Organization, in 2018, there were 766,000 people with HIV in Brazil who knew of their diagnosis and 593,000 of them were receiving ART [6]. Over 95% of new HIV infections occurred in Eastern Europe and Central Asia. Some groups are considered populations at risk for HIV infection: the risk is 22 times higher among men who have sex with men; 22 times higher among people who inject drugs; 21 times higher among sex workers and 12 times higher for transsexual people [5]. Although there is no cure for HIV, treatment can be performed with antiretroviral drugs/antiretroviral therapy (ART), which emerged in the 1980s and reduce viral replication, consequently decreasing the viral load. In Brazil, ART was introduced in the National Health Service (Brazilian SUS) in November 1996, which made Brazil one of the model countries for HIV treatment, as it is universal and free.

There are several classes of antiretroviral drugs:

- Nucleoside reverse transcriptase inhibitors (NRTIs)
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Protease inhibitors (PI)
- Fusion inhibitors (FI)
- Integrase inhibitors (II)

Nucleoside reverse transcriptase inhibitors (NRTIs) act by competing with HIV reverse transcriptase. In addition, they make the DNA chain created by the HIV

virus defective within the body's defense cells, preventing the virus reproduction. Examples are Abacavir (ABC), Lamivudine (3TC), Tenofovir (TDF), Zidovudine (AZT). [8, 9] Non-nucleoside reverse transcriptase inhibitors (NNRTIs) prevent virus reproduction by directly blocking the enzyme reverse transcriptase. Unlike NRTIs, they do not act by template-competitive reverse transcriptase. Examples are Efavirenz (EFZ) and Nevirapine (NVP) [7, 8]. Protease inhibitors (PI) interfere with the last stage of viral replication by blocking the protease enzyme and preventing the production of new cells infected with HIV. Examples are Atazanavir (ATV), Darunavir (DRV) and Ritonavir (RTV) [7, 8]. Fusion inhibitors (FI) block the HIV virus entry into defense cells, preventing its fusion with the host cell. An example is Enfuvirtide (T20) (T20) [7, 8]. Integrase inhibitors inhibit virus replication and act on its ability to infect new cells. They prevent the action of the integrase enzyme, which is responsible for inserting HIV DNA into human DNA. Examples are Dolutegravir (DTG) and Raltegravir (RAL). Initial therapy always includes three drugs in total: two nucleoside reverse transcriptase inhibitors associated with a non-nucleoside reverse transcriptase inhibitor or a ritonavir-enhanced protease inhibitor (PI/r). Both schemes have level of evidence 1 and degree of recommendation A, although the preferred scheme is 2NRTI + 1 NNRTI [9].

Diabetes Mellitus

Diabetes is a chronic disease in which the body develops insulin resistance or does not produce insulin satisfactorily. The lack of full insulin action causes a state of hyperglycemia that in the long run, can trigger changes in some organs, blood vessels and nerves [10].

Diabetes is generally classified into type 1, type 2 and gestational. Type 1 diabetes mellitus usually manifests in childhood or adolescence and may occur in adulthood. It usually occurs due to a failure of the immune system that attacks pancreatic beta cells, impairing insulin secretion [11]. The development of type 2 diabetes mellitus is multifactorial and involves genetic, environmental and behavioral factors, although at first, it is caused by decreased sensitivity of target tissues to the effect of insulin, triggering the so- called insulin resistance. Inadequate insulin secretion can lead to insulin resistance and the deficit in glucose uptake can cause eventual beta cell failure. Thus, the patient usually develops type 2 diabetes mellitus due to a genetic predisposition associated with a sedentary lifestyle, obesity, smoking and a change in insulin functioning and secretion [12]. Genetic influence is the main predisposing factor to the occurrence of type 1 diabetes. In type 2 diabetes, some factors increase the risk, such as diagnosis of prediabetes, high blood pressure, dyslipidemia, obesity, polycystic ovary syndrome, sleep apnea and having had gestational diabetes. People with diabetes are subject to some chronic complications that can be prevented with proper glycemic control. Possible complications include kidney disease, disease in the feet and lower limbs, skin and callus changes, retinopathy and neuropathy [13].

HIV and Pancreas

The pancreas The pancreas is formed by two main types of tissue: acinar cells are the exocrine cells of the pancreas and the islets of Langerhans form the endocrine pancreas. Acinar cells secrete digestive juice in the duodenum and the islets of Langerhans secrete insulin and glucagon directly into the blood. The islets have three main cell types: alpha, beta and delta cells, which differ in color and morphology. Alpha cells secrete glucagon, beta cells secrete insulin and amylin, and delta cells secrete somatostatin [14]. The main pathologies affecting the pancreas are acute pancreatitis, chronic pancreatitis and pancreatic cancer.

Treatment As HIV directly affects the pancreas, the seropositive population is more likely to develop pancreatic diseases compared to the general population. The incidence of acute pancreatitis in HIV-positive patients can reach 40%, a very high value compared to the 2% incidence in the general population. After the introduction of antiretrovirals in 1996, the occurrence of acute pancreatitis caused by drugs increased, even though the main etiology is still alcoholic, as in the general population [15]. A study showed that protease inhibitors may cause pancreatitis secondary to hyperlipidemia. Nucleoside analogue reverse transcriptase inhibitors showed several side effects, including myelotoxicity and acute pancreatitis. Drugs such as didanosine, zalcitabine and stavudine are possible causes of acute and chronic pancreatitis [15]. Although there are other etiologies for the onset of pathologies in the pancreas in HIV-positive individuals, drug-induced pancreatitis caused by antiretrovirals should always be investigated as one of the possible diagnoses [15].

HIV and pancreas__A cross-sectional study was conducted from June 2006 to December 2009 with 20 patients diagnosed with AIDS and undergoing HAART. After these patients died, an autopsy was performed at the São Paulo Death Verification Service - University of São Paulo. The results were compared with those of another study from year 1995, in which the pancreas of 109 adult patients with AIDS but without HAART treatment were evaluated; in this case, 39 out of the 109 patients used AZT [16]. The pancreas of patients was analyzed histologically, evaluating acinar cells, changes in the stroma, intralobular and interlobar pancreatic ducts and the islets of Langerhans [16]. According to the study, most patients receiving HAART did not have dysplasia, while 67 patients not receiving HAART presented some degree of change. Regarding atrophy, the number of cases was higher in patients receiving HAART (2 out of 20 patients) than in those not receiving (3 out of 109 patients). In addition, the group receiving HAART showed changes in the islets that did not appear in the group without HAART [16]. According to these two autopsy studies from 1995 and 2006-2009, HIV-infected patients in the pre-HAART era had histological changes in the exocrine pancreas: acinar and parenchymal atrophy, reduction of zymogen granules

and nuclear dysplasia. However, the endocrine pancreas showed no significant changes. In that same study in the post-HAART era, the exocrine pancreas continued to present histological changes such as parenchymal atrophy and reduction of zymogen granules, although in this population the endocrine pancreas was affected with important changes in the islets of Langerhans [16]. Thus, a relationship between the use of HAART and the development of some histological changes in the endocrine pancreas not seen before the use of this therapy was found. Therefore, a question was raised: could this change in the islets of Langerhans have clinical repercussions in the patient?

Objective Based on the analysis of autopsy studies, the aim of this study is to correlate the histological findings of a pancreas under the effect of antiretrovirals and its possible clinical manifestations, especially diabetes.

METHODOLOGY

This horizontal review by the Prisma method addresses the relationship between the use of HAART for HIV treatment and the impacts on the endocrine pancreas. The articles were selected by an independent reviewer, then evaluated by a senior editor, and they both determined the inclusion and exclusion criteria together. The included publications had participants aged over 18 years, addressed the relationship of diabetes in humans with HIV/AIDS, at least part of participants should be receiving HAART, preferably with a large sample space and a long study period.

Articles including participants under the age of 18 years, studies on animal models, and those not addressing the relationship between HIV/AIDS and diabetes were considered ineligible. On 22 August 2020, the words "HIV and diabetes mellitus" were searched in Pubmed; 570 articles appeared and six were selected. On 15 September 2020, the words "HAART + diabetes mellitus" were searched in PubMed; 55 articles were found and two were selected. On 30 September 2020, two articles mentioned in "Recommended First-Line Antiretroviral Therapy Regimens and Risk of Diabetes Mellitus in HIV-Infected Adults in Resource-Limited Settings" were selected.

On 10 October 2020, the words "Diabetes mellitus and HIV risk" were searched in PubMed; 226 results appeared and two articles were selected.

On 27 October 2020, two articles cited in "Is There Sufficient Evidence for a Causal Association between Antiretroviral Therapy and Diabetes in HIV-infected Patients? A Meta-Analysis" were searched.

On 11 November 2020, Google Scholar was accessed and the words "HIV ART+ diabetes mellitus" were searched; approximately 233,000 results were found and two articles were selected. The eligibility criteria were applied on the previously selected texts; four out of 18 articles on the theme "use of HAART and development of diabetes mellitus" were excluded and 14 remained for an analysis. According to the 14 selected publications, some questions were raised to assist in the search for the relationship between the use of HAART and the development of diabetes **Figure 1.**

Was there a relationship between the development of diabetes mellitus and the use of HAART?

In 11 out of 14 articles, some relationship between the development of diabetes mellitus and the use of HAART was found. In three articles, was found no relationship between the treatment and the occurrence of diabetes mellitus. According to an article, the main cause of development of diabetes in patients with HIV/AIDS is iatrogenic due to the use of HAART. Despite the benefits of using antiretrovirals, they can lead to metabolic changes such as insulin resistance, diabetes, dyslipidemia and lipodystrophy. Thus, diabetes can be four times more common in men with HIV receiving HAART than in men without HIV [17]. In most publications, a strong relationship between the development of diabetes mellitus and receiving HAART was shown, especially when older drugs were used. The most relevant antiviral drugs to the development of diabetes mellitus were first-generation PIs. Former NRTIs, mainly stavudine and didanosine may increase the risk of developing diabetes mellitus, probably by causing insulin resistance [17, 18].

The incidence of diabetes mellitus was also higher among the population with HIV being treated than in the population without treatment thus, the development of diabetes mellitus was higher after the introduction of treatment [19, 20].The prevalence of diabetes among patients receiving HAART is a cause for concern, as, according to some authors, several high-risk conditions and cardiovascular diseases have a worse prognosis in patients

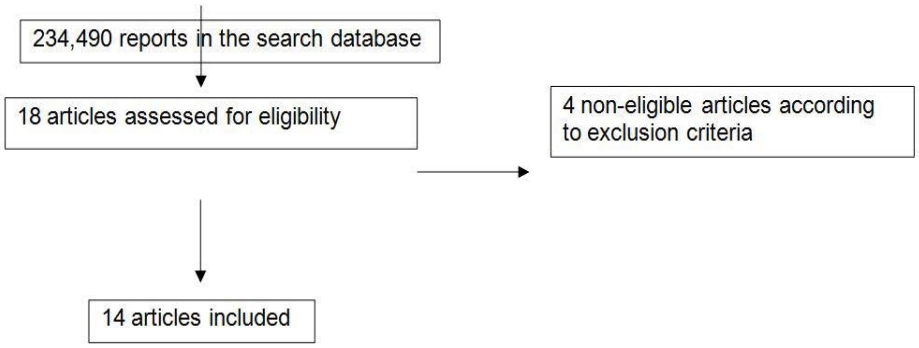

Figure 1. The relationship between the use of HAART and the development of diabetes.

with HIV/AIDS and diabetes [19]. Some authors found a relationship between the time of exposure to HAART and the increase in blood glucose; such an association was seen only in patients who used HAART for more than 18 months [21].

Although HIV infection may not be an independent determining factor for the development of diabetes mellitus, pre-existing comorbidities such as systemic arterial hypertension, obesity and dyslipidemia have shown to be risk factors. Furthermore, the combination of antiretrovirals, especially PIs, can significantly increase the incidence of diabetes mellitus [22]. According to a study conducted in Cameroon, the use of HAART could predispose to the onset of diabetes directly through insulin resistance caused by lipodystrophy or indirectly by interfering with traditional risk factors such as BMI and blood pressure [19].

Lipodystrophy can be caused by both HIV infection and HAART. It is an abnormal distribution of fat in the body that can also change the metabolism and cause dyslipidemia and insulin resistance. There is an increase in inflammatory cytokines such as TNF (tumor necrosis factor) that may predispose to the onset of insulin resistance [23]. Since there is a higher prevalence of diabetes mellitus in the general population, HIV-positive people will consequently be subject to the same increase. In addition, the higher survival of these people implies a longer use of HAART, further predisposing to the development of diabetes mellitus.

Throughout life, people infected with HIV are exposed to the same conditions as the rest of the population and probably the treatment and action of viruses itself may be factors that increase the risk of developing diabetes [24, 19]. Some studies in which no association was found between the development of diabetes mellitus and the use of HAART, was found a relationship between the use of PIs and the occurrence of metabolic syndrome. As in this case metabolic syndrome may be a risk factor for the development of diabetes mellitus, participants should be monitored for longer to determine that in fact there is no relationship between the use of PIs and diabetes mellitus [25]. Finally, in a study conducted in the Asian-Pacific region, the use of HAART was not an additional risk factor for the development of diabetes among HIV-positive people. Most participants who developed diabetes used NNRTIs and there was no relationship with the use of PIs and the onset of diabetes. In this case, participants with HIV were subject to the same risk factors as the general population [26].

Is the development of diabetes mellitus in patients receiving HAART related to any comorbidity?

In 8 out of the 14 articles analyzed, the existence of comorbidities was related to the development of diabetes mellitus. Family history of diabetes, weight gain, lipodystrophy, advanced age, BMI, systemic arterial hypertension, advanced age, pre-existing metabolic syndrome and hepatitis C coinfection have shown to be risk factors for the development of diabetes mellitus in patients using HAART. In addition, people with low CD4 counts and long infection time have also had a higher risk of developing diabetes mellitus [19, 20, 23, 27]. In a study conducted in Cameroon, the duration of HIV infection was not a determining factor for the development of diabetes, although the other traditional risk factors previously presented were relevant [25]. As mentioned earlier, HIV and hepatitis C coinfection is common and the latter is associated with the development of insulin resistance and diabetes by increasing hepatic steatosis and TNF alpha. Thus, people over 40 years of age with hepatitis C have a three times higher risk of developing diabetes compared to people without hepatitis C [19].

In addition to the effect of HAART on the development of insulin resistance and diabetes mellitus, chronic inflammation caused by HIV infection itself can accelerate the development of comorbidities such as diabetes mellitus [21]. In some studies, no association was found between family history of diabetes mellitus, smoking, hepatitis C coinfection, characteristics of HIV and ethnic origin and the occurrence of diabetes mellitus among people infected with HIV [20].

Does the development of diabetes mellitus in patients receiving HAART have any prevalence between genders?

According to studies, only 4 articles related gender to the prevalence of diabetes mellitus in patients with HIV. In a study, the occurrence of diabetes mellitus was higher among men than among women [23]. In two articles, it was more prevalent among women [21, 27]. In another study, there was no prevalence between genders [20]. Thus, the prevalence between genders is controversial.

Was there any difference between the use of more recent or older antivirals for the development of diabetes mellitus?

People who started treatment between 1997-2004 were 50 times more likely to develop diabetes mellitus than those who started between 2005-2009. Such a fact shows the higher frequency of diabetes in patients who started treatment with first-generation antiretrovirals. Before the use of HAART, the occurrence of diabetes mellitus in people infected with HIV was not so frequent. However,the incidence increased after introduction of this treatment [26].

In general, participants who used older antiretrovirals (years 1996, 1997) had more diagnoses of diabetes mellitus than participants who used the newer drugs (from 2010). The main related drug is PI, and in some articles, was found an association with NRTIs.

Was the risk of developing diabetes mellitus higher with the use of PIs?

Protease inhibitors act on the metabolism of adipose tissue by generating oxidative stress that alters the

secretion, differentiation and action of adipocytokines. Another possible action for this drug would be as noncompetitive inhibitors of GLUT4 in adipose tissue and reduction of insulin secretion due to apoptosis of the pancreatic beta cell [27]. Three articles showed a higher occurrence of diabetes mellitus among patients using PIs compared to other antiretrovirals. Protease inhibitors increase insulin resistance and reduce insulin secretion by interfering with GLUT4, although not all PIs have the same metabolic effect and must be assessed individually [19, 26, 27].

The mechanism of PIs differs between drugs. Indinavir causes insulin resistance and blocks GLUT 4 with no effect on lipid metabolism. Lopinavir and ritonavir do not reduce insulin sensitivity and increase free fatty acids and triglycerides [19]. Patients treated for 12 weeks with nelfinavir, indinavir, liponavir showed changes in the first phase of insulin secretion with reduced beta cell action. Each antiretroviral in the PI class should be studied individually to know its metabolic effects and in the case of developing diabetes, select the most appropriate treatment [19].

After the introduction of first-generation PIs in 1996, the prevalence of diabetes mellitus in patients with HIV increased. In these patients, the peak incidence of DM was 1999-2000 and for patients who had never received previous treatment, the peak was 2001-2002. There was a reduction in the incidence of diabetes mellitus after 2000 with the use of new antiretrovirals [20]. In one study, was demonstrated a relationship between the use of PIs and the development of metabolic syndrome in HIV-infected patients. Even though there was no association between the use of PIs and the development of diabetes mellitus, it is important to remember that metabolic syndrome is a precursor to diabetes mellitus thus, a long-term follow-up may be necessary to better determine whether or not there is an association between PIs and DM [27].

Note that NRTIs also increase the risk of developing diabetes because they cause insulin resistance, lipodystrophy and mitochondrial dysfunctions, although such effects are only seen in individuals treated for a long period. Thus, PIs present acute metabolic changes while NRTIs have a cumulative effect. The combined use of PIs with NRTIs poses an extra risk for the development of diabetes [19].

Does the increase in life expectancy/quality of life with the use of HAART have any association with the development of diabetes mellitus?

In some studies, the use of HAART alone was not determinant for the development of diabetes mellitus among patients with HIV. In this sense, diabetes mellitus would actually be a consequence of several factors.

One of the contributing points raised was that the use of HAART has improved life expectancy and nutritional status. Thus, individuals living longer would use HAART for longer, prolonging exposure to the same risk factors for developing diabetes mellitus than the general population. In other words, they would be developing comorbidities associated with aging and higher life expectancy [19, 24, 28].

DISCUSSION

Despite the benefits of HAART, its prolonged use is associated with mitochondrial changes and complications such as dyslipidemia, lactic acidosis, pancreatitis, lipodystrophy and dysglycemia. With the evolution of drugs efficacy, the main cause of morbidity and mortality of people infected with HIV is changing from opportunistic infections to chronic diseases such as diabetes mellitus, hypertension and dyslipidemia [24]. After the analysis of articles, was observed an association between the development of diabetes mellitus and the use of HAART, especially the oldest PIs from 1997-2004. Even though diabetes mellitus is a multifactorial pathology, antiretrovirals have played an important role in increasing the prevalence of diabetes mellitus in the population being treated for HIV.

The higher prevalence of diabetes mellitus in patients with HIV undergoing treatment may be associated with a histological alteration of the endocrine pancreas found in an autopsy study of HIV-infected patients using HAART. In this autopsy, the islets of the pancreas underwent changes in number and size and presented dysplasia. These changes were more frequent in patients using HAART than in patients not using it. Another analysis of the exocrine pancreas showed a reduction in zymogen granules in more than 50% of acinar cells in patients who died of HIV without treatment. In these cases, the islets of Langerhans were also completely preserved. That is, in patients who did not receive HAART treatment, the endocrine pancreas was normal, whereas patients with treatment had changes in the islets of Langerhans. This histological finding corroborates the clinical findings that patients using HAART had a higher prevalence of development of diabetes mellitus than patients without any treatment.

Diabetes mellitus is a multifactorial disease that can be associated with family history of diabetes, weight gain, lipodystrophy, advanced age, high BMI, systemic arterial hypertension, advanced age, pre-existing metabolic syndrome and hepatitis C coinfection. However, the use of HAART is a possible determining factor for the histological alteration of the endocrine pancreas that progresses to clinical manifestations, culminating in the onset of diabetes mellitus.

CONCLUSION

HIV/ AIDS and diabetes are chronic diseases that directly affect the quality of life of patients and predispose to the appearance of other conditions. The prevalence of diabetes has increased in recent decades and people living with HIV/ AIDS are susceptible to the same risk factors as the general population. In addition, the treatment of HIV/ AIDS with the use of ART caused histological changes in the endocrine pancreas, predisposing to the onset of diabetes

in this group. Thus, by knowing the additional risk factors to which the population with HIV/AIDS receiving HAART is exposed, a more accurate monitoring and screening for the development of diabetes can be performed in this group of society.

Conflicts of Interest

The authors report no conflict of interest.

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