"Optimizing Combined Therapy Approaches for Patients with HIV-2 and Type 2 Diabetes: Role of Antiretroviral Therapy, Dapagliflozin, and Metformin"

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Abstract: ***The purpose of this review article***

The purpose of this review article is to provide guidance to healthcare providers on the use of Antiretroviral Therapy (ART), specifically the combination of Dolutegravir, Lamivudine, and Tenofovir Disoproxil Fumarate, along with Dapagliflozin and Metformin XR (extended release) as a therapeutic option for the treatment of patients with HIV-2 and Type 2 Diabetes Mellitus (T2DM). The review aims to offer insights into optimizing therapy approaches for individuals dealing with both HIV-2 and T2DM, focusing on the potential synergies, challenges, and benefits of combining these treatment modalities. By providing a comprehensive analysis, this review seeks to guide healthcare practitioners and researchers in delivering more effective and holistic care for patients with both conditions. This is particularly important given the increasing number of individuals affected by HIV-2 and T2DM, emphasizing the need for personalized and evidence-based treatment options.

In summary, the paper underscores the importance of early detection, prevention, and effective management of diabetes in HIV-infected patients on ART. It also highlights the significance of using antiretrovirals with a lower risk of metabolic complications to mitigate the risk of developing diabetes in this vulnerable population. These measures and treatments are essential for improving the overall health and well-being of individuals living with both HIV and diabetes.

Keywords: **Dapagliflozin, Dolutegravir, Lamivudine, and Tenofovir Disoproxil, HIV, Diabetes**

1. INTRODUCTION

Epidemiology

Diabetes mellitus (DM), characterized by hyperglycemia due to a decrease in insulin production and sensitivity, is a chronic condition that affects approximately 80% of individuals in poor and developing countries. It is estimated that there are around 4.3 billion people with diabetes globally, a number expected to reach 6.5 billion by 2045. Alarmingly, about two-thirds of people with diabetes remain undiagnosed. There is a hypothesis that HIV and its treatments might play a role in the increased prevalence of diabetes. (1), (2, 3). HIV, specifically HIV-2, was first identified in 1986 as a cause of AIDS in individuals with symptoms similar to those of HIV-1. While HIV-1 has become a global pandemic, HIV-2 has remained more localized, primarily affecting countries such as the United States, India, and European nations. In 2016, of the estimated 1.7 million new HIV infections among adults globally, 48% were among women, with 59% of new infections occurring in adolescent girls and young women aged 15-24. The overall prevalence rate of HIV/AIDS is approximately 1.1% among adults aged 15-49, with a prevalence of 0.8% among men. The geographical distribution of HIV-2 is attributed to factors like the presence of SIVsmm in West African mangabey populations and opportunities for cross-species transmission [3]. Type 2 diabetes is recognized as a

significant public health concern with a profound impact on both human life and health expenditures. The rapid economic growth and urbanization have led to a rising burden of diabetes globally. This condition affects the functional capacities and quality of life of individuals, resulting in significant morbidity and premature mortality, particularly among those under the age of 60. Unhealthy diets and sedentary lifestyles have contributed to increased body mass index (BMI) and fasting plasma glucose levels, exacerbating the diabetes epidemic. Control of blood glucose, blood pressure, and other targets for diabetes management remains suboptimal due to a lack of awareness and health promotion efforts. (3), (1), (4), (2)

This research project aims to analyze the latest data from the Global Burden of Disease (GBD) to assess the global burden of type 2 diabetes. It seeks to study the current global epidemiology of diabetes, highlighting the distribution of the disease and emerging epidemiologic trends, shedding light on the evolving landscape of this global health challenge. While some evidence suggests a potential link between HIV and an increased risk of diabetes. Understanding the relationship between HIV and diabetes remains an important area of investigation for public health and clinical management. (1)

The development of diabetes in HIV patients

The development of diabetes as a side effect of antiretroviral therapy (ART) in individuals with HIV is a complex and multifactorial process. While ART has been crucial in managing HIV and improving the life expectancy of people living with the virus, some of these medications can lead to metabolic complications, including an increased risk of diabetes. Here's an explanation of how this can occur:

1. Insulin Resistance: Some antiretroviral drugs, particularly those in the class of protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), have been associated with insulin resistance. Insulin is a hormone that regulates blood glucose levels, and insulin resistance means the body's cells are less responsive to the effects of insulin. This can lead to elevated blood glucose levels.

2. Lipodystrophy: Lipodystrophy is a condition characterized by the redistribution of body fat, leading to fat loss in some areas (such as the face and limbs) and fat accumulation in others (such as the abdomen and neck). Some antiretroviral drugs, particularly older PIs like Indinavir, Lopinavir, and Ritonavir, have been linked to lipodystrophy. This altered fat distribution can contribute to insulin resistance and glucose intolerance.

3. Dyslipidemia: ART can also lead to changes in lipid metabolism, including elevated levels of triglycerides and cholesterol. Dyslipidemia is associated with an increased risk of cardiovascular disease and insulin resistance. It's not diabetes per se, but it's a related metabolic complication.

4. Weight Gain: Some people on ART may experience weight gain, often due to factors like improved health, reduced wasting syndrome, and altered metabolism. Weight gain can contribute to insulin resistance and the development of type 2 diabetes.

5. Genetic Factors: Genetic factors can influence an individual's susceptibility to developing diabetes. Some people may have a genetic predisposition to insulin resistance or impaired glucose metabolism, making them more susceptible to diabetes when exposed to ART-related metabolic effects.

6. Individual Drug Variability: It's important to note that the impact of ART on metabolism varies among individuals. Some people may experience metabolic complications, including diabetes, while others do not. The specific drugs within an ART regimen, as well as the duration of treatment, can influence the risk.

7. Lifestyle Factors: Lifestyle factors such as diet, physical activity, and tobacco or alcohol use also play a significant role in the development of diabetes. Maintaining a healthy lifestyle, including a balanced diet and regular exercise, can help mitigate the risk of diabetes associated with ART.

Diagnosis and Monitoring of HIV-2 and Type 2 Diabetes Mellitus

The diagnosis and monitoring of both HIV-2 and Type 2 Diabetes Mellitus (T2DM) require a comprehensive and tailored approach. Here we discussed different diagnostic criteria for T2DM and the essential monitoring protocols for HIV-2. Given that individuals with both conditions present unique challenges and considerations, it's crucial to use accurate diagnostic tools and monitoring methods.

For the general population, the American Diabetes Association (ADA) provides diagnostic criteria for diabetes, which include fasting glucose levels ≥ 128 mg/dl, 2-hour plasma glucose ≥ 200 mg/dl after a 75-gram oral glucose challenge, and hemoglobin A1c (HbA1c) levels ≥ 7.6%. However, for PWH, the use of HbA1c as a diagnostic tool may be inaccurate. Studies have shown that HbA1c underestimates glycemia in PWH, and certain antiretroviral drugs, such as abacavir, can lead to significant discrepancies between HbA1c and blood glucose levels. As a result, a plasma glucose-based method is recommended for diabetes diagnosis in this population. (5), (6)

As per the data analysis, recommended Diagnostic Criteria for T2DM in PWH are as follows:

Table 1

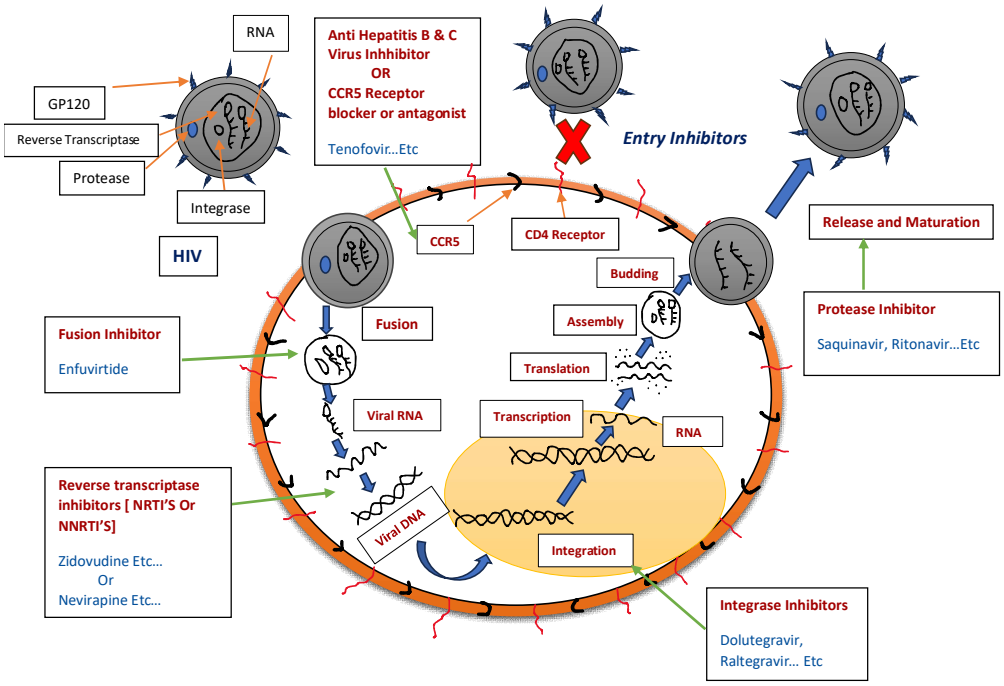
	Hemoglobin A1cb	Fasting Plasma Glucose	Random Plasma Glucose	Oral Glucose Tolerance Test
Diabetes	≥6.5%	≥126 mg/dL (≥7.0 mmol/L)	≥200 mg/dL (≥11.1 mmol/L) with polyuria and polydipsia	≥200 mg/dL (≥11.1 mmol/L)
Prediabetes	5.7%–6.4%	100–125 mg/dL (5.6–6.9 mmol/L)	—	140–199 mg/dL (7.8–11.1 mmol/L)
Normal	<5.7%	≤99 mg/dL (≤5.5 mmol/L)	—	≤139 mg/dL (≤7.7 mmol/L)

- HbA1c: Given its potential inaccuracy, HbA1c is not recommended for diabetes diagnosis in PWH. It is important to note that all laboratory values should be confirmed with repeat testing (7), (8), (9).

Monitoring of HIV-2 Infection

HIV-2 infection diagnosis typically involves testing for both HIV-1 and HIV-2. Reagent screening tests are followed by confirmation testing with antibody differentiation assays, which differentiate between HIV-1 and HIV-2 antigens. Once a patient is confirmed to be HIV-2 positive, the initiation of Antiretroviral Therapy (ART) is warranted. For patients with HIV-2 infection under ART treatment, monitoring is essential. This involves regular assessment of CD4+ T-cell counts and plasma viral loads (VLs). The monitoring frequency is typically every 3 months or at least twice a year, depending on the patient's clinical status, baseline CD4+ cell count, and the rate of CD4+ cell count decline. In cases of detectable VL, confirmation should be sought by taking a following sample, which is typically done one month apart.

In general, for the initiation and monitoring of ART in HIV-2 infection, certain criteria should be met, such as an absolute CD4+ cell count not less than 500 CD4+ cells/µL of blood and an absolute CD8 count not less than 330 CD8 cells/µL of blood. These criteria ensure that treatment is initiated at the appropriate time and that the patient's clinical status is monitored effectively. (10), (11)



HIV Management System

Diagnosing T2DM in individuals with HIV-2 and effectively monitoring HIV-2 infection in the presence of T2DM require a specialized approach. Using plasma glucose-based criteria for T2DM diagnosis and adhering to monitoring guidelines for HIV-2 is crucial. It's essential to recognize the unique challenges and considerations associated with both conditions to provide the best possible care for affected individuals. Accurate diagnosis and regular monitoring ensure early intervention and effective management, leading to improved patient outcomes. The use of HbA1c as a diagnostic tool in PWH should be approached with caution due to its potential inaccuracies. Therefore, plasma glucose-based criteria are recommended for more reliable diagnosis in this population. Monitoring of HIV-2 infection under ART is vital to assess the effectiveness of treatment and the patient's clinical status, with regular CD4+ cell count and plasma VL assessments. Compliance with diagnostic and monitoring guidelines is essential to ensure that individuals with HIV-2 and T2DM receive the best possible care and support.

Treatment

The treatment associated with diabetic patients with HIV is a matter of significant concern, as certain antiretroviral medications have been found to increase the risk of incident diabetes in HIV-infected individuals on antiretroviral therapy (ART). Specifically, Efavirenz, stavudine, and zidovudine have been identified as agents associated with an elevated risk of developing diabetes in large Southern African cohorts. Patients on efavirenz-containing ART face a higher risk of new-onset diabetes compared to those on nevirapine-containing ART. Additionally, factors such as the use of zidovudine and stavudine-containing NRTI backbones, older age, elevated baseline BMI,

and exposure to diabetogenic medication contribute to the increased risk of diabetes. While the risk associated with these antiretrovirals is relatively modest, the paper underscores its critical public health implications, especially given the substantial African patient population exposed to ART.

To manage HIV patients with diabetes effectively, the paper outlines several important measures and treatments:

1. Implement Interventions for Detection and Prevention: ART programs should integrate interventions for the early detection and prevention of diabetes in HIV-infected patients. Regular screening is essential to identify individuals at risk and initiate timely interventions. (12)

2. Choose Antiretrovirals with Lower Metabolic Complications: Encouraging the use of antiretrovirals with a lower risk of metabolic complications is vital. Considering alternative antiretroviral drugs, such as nevirapine instead of efavirenz, can help reduce the incidence of diabetes in HIV-infected patients. (13)

3. Increase Diabetes Screening: There should be an increase in the frequency of diabetes screening in people on long-term ART, enabling the early identification of diabetes and initiation of appropriate treatment. (14), (15)

4. Monitor Baseline BMI and Medication Exposure: HIV-infected patients on ART should be closely monitored for baseline BMI and exposure to diabetogenic medication. Managing these factors can help reduce the risk of diabetes. (16)

5. Regular Monitoring of CD4 Counts and Viral Load: Continuous monitoring of CD4 counts and viral load in HIV-infected patients on ART is essential for both HIV and diabetes management. (17), (18)

6. Provide Diabetes Treatment: In the case of diagnosed diabetes, patients should receive appropriate treatment. This may include the initiation of antidiabetic agents, such as insulins, metformin, sulfonylureas, and other medications available in the specific region, such as South Africa. (19)

The treatment of diabetic patients with HIV has evolved significantly over the years. Both diabetes and HIV are complex medical conditions, and managing them together requires a specialized approach. In the early years of the HIV epidemic in 1980-90s, the focus was primarily on diagnosis and treatment possibilities for ongoing infectious viruses. First, in 1982 the Centers for Disease Control (CDC) reported 593 cases of acquired immunodeficiency syndrome (AIDS) in the US. These cases were reported between June 1, 1981, and September 15, 1982. Among these cases, 243 patients died i.e. 41% of these total cases. The infection of AIDS by date of diagnosis has roughly doubled every 6 months since late 1979, and an average of 1-2 cases were diagnosed per day. (20) Hence Primary goal of many scientists and the scientific community was to find possible diagnoses and safe treatments for HIV. At this stage, the understanding of diabetes as a co-morbidity in HIV-positive individuals was limited. Many epidemiologic investigations suggested that the severe disorder of immune regulation underlying AIDS is believed to be caused by a transmissible agent. It required a latent period of up to 2 years between exposure and recognizable clinical illness. Hence to reduce the risk of acquiring and transmitting AIDS, the US Public Health Service has recommended a few precautions such as avoiding sexual contact with infected persons, refraining temporarily from donating plasma and/or blood, physician should monitor indications closely, etc (21)

Later, considerable research occurred but until the 1996s there was no proper treatment was available. (22), (23), (24). Author R Mertelsmann, etal. Explained case study of fifteen patients with acquired immunodeficiency syndrome (AIDS). In this case study lymphoma and immunodeficiency, or severe combined immunodeficiency were treated with highly purified interleukin-2 (IL-2) prepared from human lymphocytes. All patients

showed a defect in mitogen-induced T cell proliferation which was partially corrected when IL-2 was added in vitro. (25)Another author Y. Berner, et al. reported treatment of acquired immunodeficiency syndrome (AIDS) with thymic humoral factor (THF). (26) Azidothymidine (AZT) or zidovudine drug, a potential anticancer drug, due to its lack of efficacy against cancer was abandoned. It was reintroduced into a National Cancer Institute (NCI) screening program in the 1980s to find potential HIV/AIDS treatment medications. The U.S. Food and Drug Administration approved AZT as the first medication to treat AIDS in March 1987. When taken by itself, AZT reduces fatalities and opportunistic infections but has significant side effects and serious toxicities, including neutropenia and anemia. (27)

Later on, in 1996, A C Collier et al showed in their study that a three-drug regimen of saquinavir, Zalcitabine [dideoxycytidine (ddC)], and AZT was more effective than two-drug therapy with ddC and AZT. This was supported by his clinical study research. (28)This combination therapy of at least two drugs was termed highly active antiretroviral therapy (HAART). The introduction of HAART marked a significant turning point in the treatment of HIV. HAART significantly improved the prognosis for people living with HIV, leading to longer life expectancies. However, as people with HIV started living longer, the prevalence of chronic conditions, including diabetes, began to rise. The mid-1990s marked the development of another new class of antiretroviral drugs called non-nucleoside reverse transcriptase inhibitors or NNRTIs. These drugs exert their therapeutic effects by specifically targeting the reverse transcriptase enzyme, a vital component in the replication process of the HIV virus. Unlike nucleoside analogs, another class of antiretrovirals, NNRTIs bind to a distinct pocket on the reverse transcriptase enzyme, inducing a conformational change that impedes the enzyme's ability to convert viral RNA into DNA. This interference disrupts the virus's replication cycle, ultimately preventing its proliferation and spread within the body. Common examples of NNRTIs include efavirenz, nevirapine, and rilpivirine, which are often administered in combination with other classes of antiretrovirals as part of highly active antiretroviral therapy (HAART). However, while NNRTIs have significantly contributed to HIV treatment by reducing viral loads and enhancing immune function, their efficacy can be compromised by the development of drug resistance through mutations in the reverse transcriptase enzyme. Furthermore, these medications may be associated with a spectrum of side effects, including rash, liver toxicity, gastrointestinal disturbances, and central nervous system effects, necessitating careful monitoring and management by healthcare providers. Despite these challenges, NNRTIs remain an integral component of HIV treatment regimens,offering distinct benefits and playing a crucial role in addressing the complexities of managing HIV/AIDS. (29), (30)

During the late 1990s-2000s, researchers began to recognize the interplay between HIV and diabetes. It was observed that certain antiretroviral medications, particularly protease inhibitors, were associated with metabolic complications such as insulin resistance, lipid abnormalities, and fat redistribution, which increased the risk of diabetes. Scientists named this phenomenon as "HIV-associated lipodystrophy." As in the early 2000s, the cases of diabetes patients with HIV increased, and many healthcare organizations and communities such as the American Diabetes Association (ADA), the Centers for Disease Control and Prevention (CDC) https://clinicalinfo.hiv.gov/en/guidelines, and The U.S. Department of Health and Human Services (HHS) released guidelines for managing HIV in individuals with diabetes. Physicians were advised to monitor blood glucose levels more closely in HIV-positive patients. Also advised to consider alternative antiretroviral therapies for those with significant metabolic complications. Managing both conditions concurrently requires a more comprehensive approach.

Research into the mechanisms of HIV-associated insulin resistance and diabetes continued in the mid and late 2000s, contributing to a better understanding of the complex relationship between the two conditions. These drugs had better safety profiles and fewer

drug interactions but still faced issues like drug resistance and adherence challenges. Scientists were investigating the impact of chronic inflammation, immune dysfunction, and the effects of specific antiretroviral drugs on glucose metabolism. This continued work led to the development of newer generations of antiretroviral medications with fewer metabolic side effects, and the management of HIV in diabetic patients became more manageable. Treatment strategies evolved to become more patient-centred, with an emphasis on individualized care. In 2017 there are many drugs came in market which are effective to treat HIV such as tenofovir, emtricitabine, abacavir, raltegravir, etc. In same year FDA gave approval to the maraviroc drug which is a CCR5-blocking drug, raltegravir which is an integrase inhibitor, tenofovir which is a nucleotide reverse transcrip. However, the HIV variant developed resistance to these drugs including elvitegravir, another first-generation integrase inhibitor. (31)

Further healthcare providers recognized the need to address not only antiretroviral therapy but also diabetes management, cardiovascular risk, and lifestyle factors such as diet and exercise. This holistic approach became essential for optimizing the health of individuals with both conditions. HIV-associated morbidity and mortality have declined significantly since the introduction of highly active antiretroviral therapy (HAART). These developments have allowed an increased focus on associated adverse metabolic effects, such as dyslipidemia, diabetes mellitus, and insulin resistance, which are risk factors for cardiovascular disease and other adverse outcomes. (32)

In the 2010s, integration of HIV and diabetes care into comprehensive healthcare models became more common. Same year dolutegravir came in role to treat HIV, but it is approved by FDA in 2013, which is a second-generation integrase inhibitor. It appears to have a high barrier to the development of HIV drug resistance. It is effective both for people living with HIV who had not previously taken HIV therapy and for people who were previously treatment resistant. Nowadays Dolutegravir is included in the U.S. Department of Health and Human Services medical practice guidelines recommended for adults with HIV, and World Health Organization guidelines as first-line and second-line treatment for all populations including pregnant women.(33)

Drug Name	Year of Approval	Drug Class	Mechanism of Action	State of Development	
Zidovudine (AZT)	1987	NRTI	Inhibits HIV reverse transcriptase, preventing viral replication	Approved	(34)
Didanosine (DDI)	1990	NRTI	Similar to AZT, inhibits reverse transcriptase	Approved	(35) (36),
Zalcitabine (DDC)	1990	NRTI	Similar to AZT, inhibits reverse transcriptase	Withdrawn due to side effects	(37)
Stavudine (d4T)	1993	NRTI	Similar to AZT, inhibits reverse transcriptase	Limited use due to side effects	(38)
Lamivudine (3TC)	1995	NRTI	Similar to AZT, inhibits reverse transcriptase	Widely used in combination regimens	(39)
Foscarnet	1996	NNRTI	Binds to reverse transcriptase, preventing its activity	Limited use due to toxicity	(40)
Saquinavir	1995	(PI)	Inhibits HIV protease, preventing viral particle assembly	Early generation PI with complex dosing requirements	(41)
Ritonavir	1996	PI	Boosts the activity of other PIs	Used as a co-formulation or booster	(42)
Indinavir	1996	PI	Similar to Saquinavir, inhibits HIV protease	Early generation PI with complex dosing requirements	(43) , (44)
Viracept (Adefovir)	1997	NRTI	Similar to NRTIs, inhibits reverse transcriptase	Primarily used for Hepatitis B infection,	(45)

				limited use in HIV treatment	
Nevirapine	1996	NNRTI	Binds to reverse transcriptase, preventing its activity	First single-dose NNRTI	(46)
Efavirenz	1998	NNRTI	Binds to reverse transcriptase, preventing its activity	Widely used in combination regimens	(47)
Delavirdine	1998	NNRTI	Similar to Nevirapine, binds to reverse transcriptase	Limited use due to drug interactions and side effects	(48)
Amprenavir	1999	PI	Similar to Saquinavir, inhibits HIV protease	Early generation PI with complex dosing requirements	(49)
Nelfinavir	1999	PI	Similar to Saquinavir, inhibits HIV protease	Early generation PI with complex dosing requirements	(50)
Abacavir	1999	NRTI	Similar to AZT, inhibits reverse transcriptase	Can cause hypersensitivity reactions	(51)
Lopinavir	2000	PI	Similar to Saquinavir, inhibits HIV protease	Often	(52)
Enfuvirtide	2003	Entry inhibitor	Prevent HIV from entring host cell	Approved but less commonly used due to injectable administration	(53)
Atazanavir	2003	PI	Similar to Saquinavir, inhibits HIV protease	Once daily dose option	(54)
Etravirine	2006	NNRTI	Binds to reverse transcriptase, preventing its activity	Once daily dose option	(55)
Maraviroc	2007	Entry inhibitor	Bind to the receptor on CD4 cell preventing HIV entry	Approved primarly used for patient with resistance to other drugs	(56)
Raltegravir	2007	II	Prevents HIV from integrating its genetic material into host cell	Approved widely used in combination regimen	(57)
Rilpivirine	2011	NNRTI	Binds to reverse transcriptase, preventing its activity	Once daily dose option	(58)
Elvitegravir	2012	II	Similar to RAL and BIC prevent HIV integration	Often used combination with ritonavir for boosting activity	(59)
dolutegravir	2013	II	Similar to RAL and BIC prevent HIV integration	Once -daily dosing option cornerstone of many regimens	(60)
Tenofovir	2014	NRTI	Similar to TDF,inhibits reverse transcriptase	once-daily dosing option better side effect profile than TDF	(61)
Nicotinamide	2019	NAD precursor	Boost cellular energy producation potentially affecting HIV replication	Investigational for HIV treatment early studies show promise	(62)
Cabotegravir	2019	II	Similar to AZT, inhibits reverse transcriptase	long-acting injectable from [2-month dosing] part of single-injection regimens	(63)
Bictegravir	2019	II	Similar to RAL and BIC prevent HIV integration	Approval,part of single-tablet regimens	(64), (65)

* **NRTI**- Nucleoside Reverse Transcriptase Inhibitor, **NNRTI -** Non-Nucleoside Reverse Transcriptase Inhibitor, **PI -** Protease Inhibitor, **II** -Integrase Inhibitor

The treatment of diabetes in HIV patients involving a combination of Antiretroviral Therapy (ART) and the use of Metformin and Dapagliflozin showcases a comprehensive

approach to managing both conditions concurrently. ART plays a crucial role in HIV management by suppressing viral replication and preserving immune function. When combined with Metformin, a widely used oral anti-diabetic medication, it addresses insulin resistance and helps control blood glucose levels effectively.

Metformin's mechanism of action involves reducing hepatic glucose production and enhancing peripheral insulin sensitivity. In the context of HIV patients, its use is particularly beneficial as it doesn't interfere significantly with drug metabolism, making it a safe choice within the ART regimen.(66)

Dapagliflozin, a sodium-glucose cotransporter-2 (SGLT-2) inhibitor, complements this combination by promoting urinary glucose excretion, thereby lowering blood glucose levels independently of insulin action.

As discussed earlier, initialy, the patient was administered a single drug regimen therapy with either Dolutegravir or Nelfinavir, but its efficacy in HIV patients was suboptimal. Subsequently, a multiple drug regimen, incorporating Dolutegravir, Lamivudine, Nelfinavir, and others, was introduced, demonstrating only moderate efficacy. As a next step, a triple drug regimen, including Dolutegravir, Lamivudine, Tenofovir, and more, was implemented.

The introduction of the first triple-drug fixed-dose combination (FDC) marked a significant advancement. Teneligliptin with Dapagliflozin and Metformin, branded as Zita DM, has been launched, featuring a fixed dose comprising the DPP4 inhibitor Teneligliptin (20mg), the SGLT2 inhibitor Dapagliflozin (10mg), and Metformin SR (500mg/1000mg). Administered once daily under prescription, Zita DM aims to enhance glycemic control in Type 2 diabetes patients. According to press statements, this FDC not only targets glycemic control but also addresses hemoglobin A1c levels, Beta cell dysfunction, and improves insulin secretion in patients with diabetes mellitus, especially those co-infected with HIV-2. The comprehensive approach of Zita DM represents a promising therapeutic strategy, offering a convenient and effective means of managing diabetes in individuals with concurrent HIV infection. Regular monitoring and adherence to prescribed regimens are imperative for optimal outcomes.

However, regular monitoring and adherence to prescribed regimens are imperative for optimal outcomes. Regular monitoring of viral load, CD4 count, and metabolic parameters is crucial in this integrated treatment approach.(67) Overall, the combination of ART therapy with Metformin and Dapagliflozin presents a promising strategy for effectively managing diabetes in HIV patients, offering a comprehensive approach to address the complexities of both conditions. Regular medical supervision, tailored treatment plans, and vigilant monitoring are paramount for successful outcomes. (7), (68), (69), (70)

THE FUTURE ASPECT

The future landscape of treating diabetes in HIV patients is likely to be dynamic, with ongoing research translating into innovative therapies and approaches. As our understanding of these coexisting conditions deepens, more targeted and effective interventions are expected to emerge, offering improved quality of life for individuals managing both diabetes and HIV.

Continued development of targeted therapies that address both diabetes and HIV simultaneously, aiming for enhanced efficacy with fewer side effects. This may involve innovative drug combinations or novel agents designed to address the unique challenges of coexisting conditions.

Exploring immunotherapeutic approaches that not only manage HIV but also modulate the immune system to improve insulin sensitivity and control diabetes. This could involve interventions to regulate immune responses more effectively.

Research into preventive strategies to reduce the risk of diabetes in individuals living with HIV, including lifestyle interventions, vaccination strategies, and early detection of risk factors.

CONCLUSION

In conclusion, the evolving landscape of treating diabetic patients with HIV has witnessed significant progress over the years. The intricate interplay between HIV treatments, metabolic changes, and the risk of diabetes underscores the importance of a comprehensive and personalized approach to patient care. From the early years of HIV treatment, marked by the advent of antiretroviral therapy (ART), to the introduction of highly active antiretroviral therapy (HAART) and subsequent generations of antiretroviral medications, the focus has expanded beyond HIV management alone.

Recognizing the impact of certain antiretroviral drugs on metabolic complications and the rising prevalence of chronic conditions like diabetes, healthcare providers have adapted treatment strategies. The "return to health" phenomenon, weight gain associated with improved HIV outcomes, further emphasizes the need for proactive weight management and metabolic risk assessment. Research into specific antiretroviral agents, such as integrase strand inhibitors (INSTIs), has shed light on potential associations with weight gain, especially in specific populations. However, the full implications on metabolic outcomes, including diabetes, remain an area for further investigation.

The purpose of this comprehensive review is to guide healthcare providers in navigating the complexities of treating patients with both HIV and diabetes. The introduction of novel triple-drug fixed-dose combinations, such as Teneligliptin with Dapagliflozin and Metformin (Zita DM), signifies a step forward in addressing both conditions simultaneously.

The significance of considering individual patient factors, including age, ethnicity, and ART regimen, cannot be overstated. Proactive measures such as early detection, prevention, and effective management of diabetes in HIV-infected patients are crucial. Integrating interventions for detection, choosing antiretrovirals with lower metabolic complications, and regular monitoring of key parameters contribute to a holistic and patient-centered care approach.

As the field continues to advance, ongoing research remains essential to deepen our understanding of the effects of specific ART agents on metabolic outcomes. The collaborative efforts of healthcare practitioners, researchers, and the integration of evolving guidelines contribute to improved overall health and well-being for individuals managing both HIV and diabetes. In summary, addressing both conditions concurrently demands a nuanced and evolving approach that prioritizes individualized care and the ongoing pursuit of knowledge in the field.

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