Section: Medicine

Original Research Article

STUDY OF HYPERGLYCEMIA AMONG HIV INFECTED PATIENTS ON HIGHLY ACTIVE ANTIRETROVIRAL THERAPY

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Received *: 09/10/2024*
Received in revised form *: 22/11/2024*
Accepted *: 06/12/2024*

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DOI: 10.70034/ijmedph.2024.4.177

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2024; 14 (4); 965-971

ABSTRACT

Background: Highly active antiretroviral therapy (HAART) is the mainstay of treatment for those infected with Human immunodeficiency virus (HIV). The prospect of maintaining patients on long term HAART may be restricted by a heterogeneous collection of unexpected metabolic abnormalities including hyperglycemia. Patients on HAART are at increased risk of developing diabetes than those who are treatment naïve. Hyperglycemia has been mentioned as the side effect of protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors (NRTIs) and Integrase strand transfer inhibitors (INSTIs) have been shown to increase insulin resistance and reduce insulin secretion. NRTIs were also reported with increased risk of diabetes in a recent study, mechanism not well understood. The effects of HAART on glucose metabolism among PLHIV in Manipur remain largely unknown. The present study was conducted to evaluate the prevalence of hyperglycemia among HIV patients on HAART and to correlate hyperglycemia in different HAART regimens and according to the duration of anti retro viral therapy (ART).

Materials and Methods: A cross sectional study was conducted from 1st December, 2022 to 31st November, 2023 in the Department of Medicine, Regional Institute of Medical Sciences (RIMS) Hospital, Imphal, Manipur. HIV positive patients on HAART admitted in Medicine ward, attending Medicine OPD and CoE ART Centre, RIMS, Imphal were included in the study. All the routine examination was done as per NACO recommendation. Blood investigations included fasting blood sugar (FBS), kidney function test (KFT), complete blood count (CBC) and lipid profile. Data collected were analyzed using SPSS-version-26. A P value of <0.05 was taken as significant.

Results: A total of 151 patients who has received HAART for at least 6 months were enrolled. The mean age of patients in the study was 46.25 ± 10.8 years. Majority 105 (69.5%) were in HIV stage 1, maximum patients114(75.4%) had CD4 count in range 200-399 and most of them 122(80.8%), had undetectable viral load. The commonest ART regimen 128(84.8%) was TLD (Tenofovir, lamivudine, dolutegravir). Majority of the study subjects did not experience hyperglycemia (82.8%) and had FBS levels of normal range (70-125 mg/dL). Only 17.22% of individuals have FBS >125 mg/dL. There was a statistically significant association between hyperglycaemia and ART duration ($p < 0.001$) while not significant with the ART regimen ($p = 0.773$).

Conclusion: This study concludes the duration of ART treatment is associated with an increased risk of hyperglycaemia, with longer treatment durations

corresponding to higher rates of hyperglycaemia. The findings emphasize the need for vigilant metabolic monitoring and tailored ART regimens to mitigate the risk of hyperglycemia and related complications.
Keywords: Hyperglycemia, pre- diabetes, Diabetes Mellitus, HAART regimen.

INTRODUCTION

A Highly active antiretroviral therapy (HAART) is the mainstay of treatment for those infected with Human immune deficiency virus (HIV).[1] The main effect of HAART is to suppress viral replication, allowing the individual's immune system to recover and protecting from the development of AIDS (Acquired immunodeficiency syndrome) and death.[2] In recent years, provision of HAART to those in need has become an increasingly important and feasible global priority. However, the prospect of maintaining patients on long term HAART may be restricted by a heterogeneous collection of unexpected metabolic abnormalities including hyperglycemia and has become a major cause of morbidity and mortality among adults on HAART.[3] Impaired glucose metabolism such as, hyperglycemia during the course of HIV infection and its treatment has become a common condition.[4] The improvement in the diagnosis and management of patients living with HIV has led them to live long and develop diabetes mellitus. The increased risk of developing diabetes is related to HIV itself or its treatment.[5] Patients on HAART are at increased risk of developing diabetes than those who are treatment naïve.[6]

Hyperglycemia has been mentioned as the side effect of protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors (NRTIs) and Integrase strand transfer inhibitors (INSTIs) have been shown to increase insulin resistance and inhibit GLUT-4-mediated glucose transport, which lowers insulin secretion. It acutely and reversibly inhibits peroxisomal proliferator-activated receptor (PPAR) NRTIs were also reported with increased risk of diabetes in a recent study, mechanism not well understood.[7]

In Manipur, AIDS has become a new and significant public health issue, according to the Manipur state AIDS control organization. Manipur is one of the six high prevalence states in India and HIV prevalence rate among pregnant women attending ANC being 1.4% (sentinel surveillance 2006). Manipur with hardly 0.2% of India's population is contributing 8% of India's total HIV positive cases.[8]

There are very few studies based on the effects of HAART on glucose metabolism among PLHIV in Manipur. Hence, the present work was done to evaluate the prevalence of hyperglycemia among HIV patients on HAART.

MATERIALS AND METHODS

A cross sectional study was conducted at Regional Institute of Medical Sciences (RIMS) Hospital, Imphal from 1st December ,2022 to 31st November, 2023. HIV positive patients on HAART admitted in Medicine ward, attending Medicine OPD and CoE ART Centre, RIMS, Imphal were included in the study.

Inclusion Criteria: Included all patients age ≥18 yrs, HIV positive patients, those on HAART ≥6 months and participants who gave written consent.

Exclusion Criteria: Participants with diabetes mellitus, those on HAART < 6 months, patients on medications that affects glycemic status such as OHA (oral hypoglycemic agents), Beta-Blockers, Thiazide Diuretics, Corticosteroids, Phenytoin, Oral Contraceptives and Sex Hormones, Phenothiazines, conditions that are likely to produce transient hyperglycemia like patients with acute infections, pregnant, lactating women and those not giving consent were excluded from the study.

Sample size: The sample size was calculated using the formula:

n =4 x PQ/L2, Where n = sample size, P =Prevalence

The prevalence of hyperglycemia among patients on HAART was taken as 40.6% from a study done by Angsana et al,[9] on pre diabetes among HIV-infected individuals receiving antiretroviral therapy

L= Absolute Allowable error = 8. Therefore, n= 4 x 40.6 x (100-40.6)/8=151

Working definition

Alcoholic hyperglycemia,[10]

Pre-diabetes: Impaired fasting glucose. Fasting plasma glucose : 100- 125 mg/dl

Diabetes Mellitus: Fasting Plasma Glucose: ≥ 126 mg/dl

Fasting plasma glucose: Blood glucose level following a minimum of eight hours of fasting HAART regimen,[10] was classified according to current NACO guidelines: first line drugs included two NRTIs preferably Non-Thymidine (Tenofovir plus Lamivudine) and one INSTI, preferably Dolutegravir and Two NRTIs and one boosted protease inhibitor (PI) were among the second-line medications.

Study Procedures

A predesigned proforma which recorded age, sex, BMI, duration of HIV, ART Regimen, duration of current HAART Regimen, occupation, marital status and HIV Status of Partner. All the routine examination was done as per NACO recommendation. Blood investigations included fasting blood sugar level (FBS), kidney function test

(KFT), complete blood count (CBC) and lipid profile. A total confidentiality of patient's data was maintained throughout the study.

Statistical Analysis: Collected data was tabulated and analyzed by using SPSS (Statistical Package for the Social Sciences software) 26.0. A descriptive statistics like mean, median, SD, frequency, percentage was used. Chi-Square test was be used to see the association between variables. A P value of <0.05 was taken as significant.

Approval from ethics committee: Ethical approval for this study was obtained from Research Ethics Board, Regional Institute of Medical Sciences, Imphal [No. A/206/REB-Comm(SP)/RIMS/2015/904/242/2022]. Approval from Programme Director, COE, ART, RIMS, Imphal was also obtained.

RESULTS

A total of 151 patients who has received HAART for at least 6 months were included in this study. The baseline characteristics of the study subjects were shown in table 1. The mean age of patients in the study was 46.25 ± 10.8 years with a minimum of 18 years and maximum of 75 years, males 75(49.67%) and females 76(50.34%) were almost equal. Hypertension was present in 134(88.7%) patients and lipid profile was normal in most patients, 79(52.3%) had normal cholesterol. The distribution of fasting blood sugar (FBS) levels reveals that a significant portion of the studied population falls within the normal category, with 82.8% of individuals registering FBS levels of normal range (70-125mg/dL), i.e., they do not exhibit hyperglycaemia. Only 17.22% of individuals have FBS levels higher than 125 mg/dL identified as experiencing hyperglycaemia. To assess the relationship between ART duration and hyperglycaemia as given in table 2, a chi-square test of independence was conducted. The results indicate a statistically significant association between ART duration and hyperglycaemia ($\chi^2 = 25.066$, df = 3, $p < 0.001$). The frequency distribution shows that among individuals receiving ART for 6 months to 2 years, none exhibited hyperglycaemia. However, as the duration of ART increased, the prevalence of hyperglycaemia also increased significantly ($\chi^2 = 25.066$, df = 3, $p < 0.001$). Specifically, 9 out of 61 individuals (14.8%) in the 2 years to 4 years group, 9 out of 23 individuals (39.1%) in the 4 years to 6 years group, and 8 out of 20 individuals (40%) in the group receiving ART for over 6 years experienced hyperglycaemia. This suggests that the duration of ART treatment is associated with an increased risk of hyperglycaemia, with longer treatment durations corresponding to higher rates of hyperglycaemia. Most of the study subjects 105(69.5%), belonged to HIV stage 1, majority 114(75.4%) had CD4 count in range 200-399. Viral load was detectable only in 29(19.2%) patients while undetectable in 122(80.8%) patients.TLD was the most common regimen used 128(84.8%).

To analyze the relationship between the regimen and hyperglycaemia as shown in Table 3, a chi-square test of independence was performed. The results indicate that there is no statistically significant association between the regimen and hyperglycaemia ($\chi^2 = 3.277$, df = 6, $p = 0.773$). The frequency distribution shows that the majority of individuals across different regimens did not experience hyperglycaemia. Among those on the TLD regimen, 23 out of 128 individuals (17.97%) experienced hyperglycaemia, while only a small number of individuals in other regimens reported hyperglycaemia.

Table 1: Baseline characteristics of the study subjects (N = 151)

Characteristics	Study subjects (n, %)
Age (in years)	
10-19	2(1.33%)
20-29	10(6.63%)
30-39	19(12.59%)
40-49	62(41.06%)
50-59	45(29.81%)
60-69	12(7.95%)
70-79	1(0.67%)
Gender	
Male	75(49.67%)
Female	76(50.34%)
Weight (kg)	
40-49	35(23.2%)
50-59	73(48.3%)
60-69	16(10.6%)
70-79	8(5.3%)
80-89	19(12.6%)
Hypertension	
Yes	134(88.7%)
No	17(11.3%)
Hyperglycemia	
Yes	26(17.2%)
No	125(82.8%)
Total cholesterol (mg/dl)	
Desirable :<200	79(52.3%)

Borderline high: 200-239	55(36.4%)
High :≥240	17(11.3%)
LDL range (mg/dl)	
Optimal: <100	6(4%)
Near optimal :100-129	27(17.9%)
Borderline high :130-159	40(26.5%)
High 160-189	34(22.5%)
Very high : ≥190	44(29.1%)
ART duration (in years)	
6 months – 2years	47(31.1%)
2-4	61(40.4%)
4-6	23(15.2%)
≥6	20(13.2%)
ART regimen	
TLD	128(84.8%)
AL + EFV	2(1.3%)
ZL + DTG	2(1.3%)
TLE	4(2.6%)
AL + DTG	9(6%)
ABC+ 3TC + DTG	5(3.3%)
ABC + 3TC + AZT	1(7%)
HIV stages	
1	105(69.5%)
2	32(21.2%)
3	13(8.6%)
4	1(0.7%)
CD4 count range	
0-199	11(7.29%)
200-399	57(37.75%)
400-599	57(37.75%)
600-799	18(11.93%)
800-999	5(3.32%)
1000-2000	3(1.99%
Viral Load range (copies/mL)	
Detectable	29(19.2%)
Undetectable (TND)	122(80.8%)

TLD – Tenofovir, Lamivudine, Dolutegravir, AL+ EFV – Abacavir, Lamivudine, Efavirenz
ZL + DTG – Zidovudine, Lamivudine, Dolutegravir, TLE – Tenofovir, Lamivudine, Efavirenz
AL + DTG – Abacavir, Lamivudine, Dolutegravir, ABC + 3TC + DTG – Abacavir, Lamivudine, Dolutegravir, ABC + 3TC + AZT –Abacavir, Lamivudine, Zidovudine

Table 2: Distribution of the patients in terms of ART Duration Vs Hyperglycaemia (N = 151)

ART Duration	Hyperglycaemia		Total	χ^2	P value
	No	Yes			
6 months - 2 years	47	0	47	25.066	<0.001
2 years - 4 years	52	9	61		
4 years - 6 years	14	9	23		
≥6 years	12	8	20		
Total	125	26	151		

Table 3: Distribution of the patients in terms of Treatment Regimen Vs Hyperglycaemia (N = 151)

REGIMEN	Hyperglycaemia		Total	χ^2	P value
	No	Yes			
TLD	105	23	128	3.277	0.773
AL+EFV	1	1	2		
ZL +DTG	2	0	2		
TLE	4	0	4		
AL +DTG	8	1	9		
ABC +3TC +DTG	4	1	5		
ABC +3TC +AZT	1	0	1		
Total	125	26	151		

DISCUSSION

The present study offers a comprehensive examination of the demographic and clinical characteristics of 151 HIV patients, providing valuable insights into the current landscape of HIV management. The mean age of the cohort was 46.25 years, with the 40-49 age group being the most represented (41.06%). This demographic profile is consistent with national estimates where HIV prevalence is observed significantly among adults aged 15-49 years, with a similar gender distribution in the infected population.[8] This finding is consistent with other study of Guaraldi et al,[11] that highlight a shift in the age distribution of HIV patients towards older age groups, reflecting the

success of antiretroviral therapy (ART) in extending life expectancy.

A significant majority of the participants (84.8%) were on the Tenofovir, Lamivudine, and Dolutegravir (TLD) regimen, reflecting current clinical guidelines that favour this combination for its efficacy and tolerability.[12] There is variation among different studies about the prevalence of diabetes and hyperglycemia in patients of HIV patients who are on HAART. The current study reports a 17.22% prevalence of hyperglycemia, identified by FBS levels higher than 125 mg/dL. Tsiodras et al,[13] observed a 5% cumulative incidence of new-onset hyperglycemia over five years in patients on protease inhibitors (PIs). Dever et al,[14] Brown et al,[15] and Angsana Phuphuakrat et al,[9] collectively highlighted the varied and significant prevalence of hyperglycemia and DM among HIV patients on HAART.

In this study, the ART duration varied from 6 months to more than 6 years, with most patients receiving treatment for 2-4 years (40.4%). A noteworthy finding was that 82.8% of our patients had normal FBS levels, despite the longer duration on ART being significantly associated with hyperglycemia ($\chi^2 = 25.066$, $p < 0.001$). This indicates that while most patients maintained normal glycemic levels, the risk of hyperglycemia increases with prolonged ART. This finding aligns with multiple studies indicating prolonged HAART use, especially involving PIs, increases the risk of insulin resistance and hyperglycemia.[16,15] The association between the duration of ART and hyperglycemia has been extensively studied, highlighting significant correlations, which were consistent with the findings by Tsiodras etal,[13] and Abebe et al.[17] Herrin et al,[18] found that weight gain in the first year following ART initiation was associated with a higher risk of DM, indicating that early changes post-ART could predict long-term metabolic outcomes. emphasized that first-line HAART was associated with elevated glucose levels compared to untreated patients, reinforcing the impact of ART duration on hyperglycemia. Belay et al,[16] conducted a meta-analysis revealing that prolonged ART use increased the prevalence of diabetes, with factors like HDL-C levels, hypertension, and body mass index (BMI) further exacerbating the risk.

In the current study, there was no significant association between the treatment regimen and hyperglycemia ($\chi^2 = 3.277$, $p = 0.773$) suggests that factors beyond the specific drug regimen, such as duration of therapy and individual patient factors, play a crucial role in metabolic complications which was at par with the studies done by Domingos H et al,[19] and Ademuyiwa et al.[20] The current study's findings contrast with several verified studies that have explored the relationship between HAART regimens and metabolic outcomes. Meena et al,[21] observed significant increases in FBS and insulin resistance among patients on second-line HAART regimens containing PIs, suggesting a metabolic impact associated with PIs. Similarly, Tsiodras et al,[13] documented independent associations between PIs and hyperglycemia, hyperlipidemia, and lipodystrophy, underscoring the metabolic effects of these medications in HIV-infected individuals. The correlation between HAART regimens and metabolic abnormalities like hyperglycemia had been reported by many studies,[17,22] while others have highlighted the impact of HAART on factors such as dyslipidemia and cardiovascular risk).[23,24] Abebe et al,[17] and Dorey-Stein et al,[22] found that the prevalence of hyperglycemia was higher in the HAART group compared to the non-HAART group. These findings suggest that certain HAART regimens may indeed contribute to metabolic abnormalities like hyperglycemia.

ART affects hyperglycemia directly by impairing cellular glucose uptake,[25] or indirectly by central obesity and/or peripheral lipoatrophy.

Nucleoside reverse transcriptase inhibitors (NRTIs)

Among the NRTIs, zidovudine, stavudine and didanosine were the culprits having higher risk of DM significantly on long term follow up . Among the NRTIs now in use, didanosine and stavudine have the largest correlation with mitochondrial toxicity, as determined by inhibition of the mitochondrial DNA polymerase. Notably, these two medications are also substantially linked to DM.[26]

Protease inhibitors (PIs)

Patients recieving PIs in 80% of patients develop insulin resistance, and leading to overt diabetes in individuals who are genetically predisposed.[27,28] Pathogenesis may be explained by PIs directly impairing signaling of insulin at pharmacologic doses in tissues which are insulin responsive.[25,29] On discontinuation of PIs, there is reversal of hyperglycemia and glucose returns to normal.[30] The most important culprit among then PIs is Indinavir and therefore should not be used as a first-line choice.[31]

However, research using a variety of cell lines, such as 3T3-L1 adipocytes and L6-myotubes in rats, indicates that PIs abruptly inhibit the cellular glucose-transport mechanism.[25,32,33,34,35] According to the theory, PIs prevent the manufacture of cis-9-retinoic acid and the peroxisome proliferator-activated receptor type-g (PPAR-g) heterodimer, which are mediated by cellular retinoic acid binging protein 1(CRABP-1) and cytochrome P450-3A. Triglyceride storage is decreased and lipid release is increased as a result of the inhibition, which also slows the rate at which pre-adipocytes differentiate into adipocytes and speeds up adipocyte apoptosis. Hyperlipidemia and insulin resistance would arise from PIs binding to lipoprotein receptor related protein (LRP), which would hinder endothelial triglyceride clearance and hepatic chylomicron uptake.[36,37] Additionally, PIs influence insulin signaling through threonine (Thr) 308/Serine (Ser) 473-Akt, interaction of the P85 subunit of phosphatidylinositol 3-kinase (PI3-kinase)38, and/or

insulin-receptor substrate (IRS)-1 phosphorylation.[39,38]

Short-term and long-term exposure may have different mechanisms underlying the effects of PI. Short-term exposures seem to primarily impact the glucose-transport system.[25,25,33,34] while longer-term exposures show effects on insulin signaling at the level of IRS-1,[38] PI3-kinase,[40] and/or AKT 1.[38] Long-term exposure to PIs appears to have varying effects on glucose-stimulated insulin production from beta cells in addition to causing peripheral insulin resistance.[40] According to clinical research, indinavir, lopinavir/ritonavir, and amprenavir treatments result in insulin resistance and decreased glucose tolerance.[41-44] PIs also inhibit GLUT-4-mediated glucose uptake in 3T3-L1 adipocytes in a dose-dependent manner, and the development of central/visceral obesity causes insulin resistance, which is acute and reversible.

The current study's finding suggests that the specific HAART regimen may not be a significant predictor of hyperglycemia in this particular cohort or setting. This discrepancy could stem from differences in sample sizes, patient demographics, duration of ART exposure, or variations in metabolic monitoring protocols across studies. It highlights the complexity of metabolic outcomes in HIV-infected individuals treated with HAART and underscores the need for further research to clarify the underlying mechanisms and identify potential risk factors associated with specific treatment regimens.

CONCLUSION

Hyperglycemia following HAART therapy is a real challenge. More than the type of regimen, the duration of prolonged use of HAART is directly affecting the emergence of significant hyperglycemia. Subsequently, all HAART regimen should be customized and efforts should be made to prescribe for shorter duration in all possible cases. Further research should focus on long-term outcomes of newer ART regimens and strategies to optimize metabolic health in this population.

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