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The Effects of Protease Inhibitors on Metabolic Complications and Lipodystrophy in Human Immunodeficiency Virus-Infected Patients

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Abstract: Problem statement: Highly Active Antiretroviral Therapy (HAART)-associated metabolic complications include lipoatrophy (loss of Subcutaneous Adipose Tissue (SAT) and insulin resistance. The risk of Diabetes Mellitus (DM) in Human Immunodeficiency Virus (HIV)-infected patients receiving Highly Active Antiretroviral Therapy (HAART) especially protease inhibitors has not been well defined. **Approach:** We conducted an analysis in the Hospital of Rajeev Gandhi Institute of Medical Sciences (RIMS), Adilabad district of Andhra Pradesh to determine the prevalence and incidence of DM in the cohort of HIV-infected and HIV seronegative men. Prevalence analysis included 1278 men (710 HIV seronegative and 568 HIV infected, 411 receiving protease inhibitors) with fasting glucose concentration determinations at baseline. **Results:** Fifty-seven (14%) of the 411 HIV-infected men using protease inhibitors at the baseline visit had prevalent DM compared with 33 (5%) of the 711 HIV-seronegative men (prevalence ratio = 4.6; adjusted for age and body mass index). The rate of incident DM was 4.7 cases per 100 person-years among HIV-infected men using protease inhibitors compared with 1.4 cases per 100 person-years among HIV seronegative men (rate ratio = 4.11; adjusted for age and body mass index), during the 4 year observation period, based on a median follow-up of 2.3 years. **Conclusion:** The incidence of DM in HIV-infected men with exposure of protease inhibitors was greater than 4 times that of HIV-seronegative men, representing a risk that is higher than previous estimates.

Key words: Lipoatrophy, highly active antiretroviral therapy, protease inhibitors and diabetes mellitus

INTRODUCTION

Since the advent of Highly Active Antiretroviral Therapy (HAART) in the mid-1990s, abnormalities in glucose homeostasis have been reported with increasing frequency in persons infected with Human Immunodeficiency Virus (HIV) (Justman *et al*., 2003; Mehta *et al*., 2003; Nightingale, 1997; Carr *et al*., 1993; Dybul *et al*., 2002). Insulin resistance has been described in 41 (61%) of 67 Protease Inhibitor (PI)-treated, HIV-infected patients (Tsiodras *et al*., 2000) and impaired glucose tolerance was observed in 25 (35%) of 71 HIV-infected patients using HAART (Walli *et al*., 1998). Prevalence estimates of Diabetes Mellitus (DM) are lower. In a cross-sectional study, 28 (6%) of 493 HIV-infected patients had DM (Walli *et al*., 2001; Saves *et al*., 2002).

Prospective data estimating the incidence of DM are beginning to emerge (Mehta *et al*., 2003; Nightingale, 1997). In the Women's Interagency HIV Study, 20 (3% or 2.8 cases per 100 person-years) of the 609 HIV-infected women receiving a PI-containing HAART regimen were diagnosed as having DM during 2.9-year median follow-up period (Krishnaswamy *et al*., 2000). In that study, case ascertainment was determined by self-reports at semiannual visits. Without the use of Fasting Glucose (FG) concentration determinations, however, the true incidence of DM is likely to be underestimated.

Estimates of the incidence of DM and fasting hyperglycemia based on active surveillance using recommended diagnostic techniques are needed. In this prospective study, we sought to determine the prevalence and incidence of DM in a well-characterized cohort of HIV-seronegative and HIV-infected men with heterogeneous exposure to antiretroviral therapies.

MATERIALS AND METHODS

Study participants: We conducted an analysis in the Hospital of Rajeev Gandhi Institute of Medical

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Sciences (RIMS), Adilabad district of Andhra Pradesh, India. About 5622 homosexual and bisexual men between 2006 and 2008 enrolled in Hospital of RIMS. Prevalence analysis included 1278 men (710 HIV seronegative and 568 HIV infected, 411 receiving protease inhibitors) with fasting glucose concentration determinations at baseline. This study visits consist of a detailed interview, physical examination and collection of biological specimens, including serologic HIV antibody tests on HIV-seronegative men. Beginning in April 2006, the biological specimens obtained included a fasting serum sample.

Of the 5622 men enrolled in Hospital of RIMS, 1857 HIV-seronegative men were administratively censored in 2006 and 1750 had died by April 1, 2007, leaving 2015 men. Of these 1773 (88%) were observed between April 1, 2007 and March 31, 2008 and 1627 had at least 1 blood specimen drawn including 1278 fasting (≥8 h) serum samples on which the glucose concentration was determined. The visit at which a participant had an initial FG concentration determination was defined as the index visit. At the index visit, the prevalence of DM was determined, defined as an FG concentration of 126 mg dL^{-1} (7 mmol L^{-1}) or higher, self-reported DM, or self-reported use of an antidiabetic medication (i.e., insulin, sulfonylureas, thiazolidinediones, biguanides, meglitinides, or α-glucosidase inhibitors). Age, Body Mass Index (BMI) (calculated as weight in kilograms divided by the square of height in meters), waist-hip ratio, educational attainment and total cholesterol level were ascertained for all participants.

The study population for incident analysis was composed of 680 of 1278 men. Of the 1278 men, 970 had an FG concentration of 98 mg dL^{-1} (5.4 mmol L^{-1}) or less at the index visit. Of these 970, 705 had follow-up data. The exclusion of those with self-reported DM (n = 22) or self-reported use of an antidiabetic medication at the index visit (n = 3) yielded the 680 men used in the analysis. The FG concentration cutoff point of 98 mg dL^{-1} (which is the lower boundary of the definition of fasting hyperglycemia (i.e., 100 mg dL^{-1}) (Kaslow *et al*., 1987) minus about 1 SD for the glucose assay (i.e., 1.8 mg dL^{-1} {0.09 mmol L^{-1}})) was chosen to ensure that the incident study population excluded men with prevalent hyperglycemia.

End point ascertainment: Two end points were examined in the incident study population. First, the date of incident DM was defined as the midpoint between the date of the last visit seen free of DM and the date of the first visit seen with DM. Incident DM was defined as an FG concentration of 126 mg dL^{-1} (7 mmol L^{-1}) or higher, self-reported DM, or current self-reported use of antidiabetic medication. All FG concentrations were measured by the combined hexokinase/glucose-6-phosphate dehydrogenase method (Gupta *et al*., 2003) using serum samples that had been stored at -80°C. The definition of DM as an FG concentration of 126 mg dL^{-1} or higher is consistent with the guidelines of the Indian Diabetes Association (2004) and Bondar and Mead (1974).

The second end point was a combination of incident DM and incident hyperglycemia and was used in the exploratory analyses of the effects of specific antiretroviral medications and disease stage. The date of incident hyperglycemia was defined as the midpoint of the date of the last visit seen with an FG concentration of 100 mg dL^{-1} (5.5 mmol L^{-1}) or less and the date of the first visit seen with an FG concentration between 100 and 125 mg dL^{-1} (5.5 and 6.9 mmol L^{-1}). The date of the combined end point was the first of incident DM or incident hyperglycemia. This combined end point, which included both clinically significant hyperglycemia and DM (Kaslow *et al*., 1987), was constructed to improve the precision of these analyses by increasing the number of events.

Assessment of exposure to antiretroviral therapy: The primary exposures of interest were HIV infection and antiretroviral therapy use. We classified men into the following 3 groups: (1) HIV seronegative, (2) HIV infected not using HAART and (3) HIV infected using HAART. We combined HIV-infected men not using HAART (i.e., 103 who were antiretroviral free, 5 using monotherapy and 49 using combination therapy at the index visit) because of the small number of men and similar event rates. To create time-varying exposure categories, men were classified at each semiannual visit according to HIV serostatus and self-reported use of antiretroviral therapy in the prior 6 months.

Based on the results of prior studies (Tsiodras *et al*., 2000; Krishnaswamy *et al*., 2000), we explored the effect of the individual PIs most frequently used at the index visit on the rate of the combined end point by stratifying the HIV-infected HAART group by exposure to ritonavir, nelfinavir mesylate, saquinavir mesylate and indinavir sulfate. To explore the effect of disease severity on the rate of the combined end point among men exposed to HAART at the index visit, we compared men with a CD4 cell count greater than 300 cells mm^{-3} to men with nadir CD4 cell counts of 300 cells mm^{-3} or less. CD4 cell counts greater than 300 cells mm^{-3} represented approximately the upper quartile of values.

Statistical analysis: The Prevalence Ratio (PR) and 2-sided 95% CIs for DM was calculated using a modified Poisson regression (Noor *et al*., 2001; Harrell, 2001) that allowed adjustment for age and BMI measured at the index visit. Age and BMI were modeled as restricted cubic splines with knots at the 5th, 50th and 95th percentiles, thereby creating a smoothly joined piecewise polynomial that allowed for a flexible association between each covariate and the end point (Zou, 2004).

For the analysis of incident DM (or the combined end point), person-time for each participant was calculated from the date of the index visit to the date of incident DM (or the date of the combined end point) or censoring at the last observed visit free of the end point, whichever came first. Incidence rates were obtained by dividing the number of end points by the number of person-years contributed to a specific category.

RESULTS

Prevalence of DM: The 1278 men who were alive and under follow-up and had at least 1 FG concentration determination between April 1, 2007 and March 31, 2008, had a slightly higher BMI than the entire 5622 men enrolled in Hospital of RIMS in 2006 (Table 1). Compared with the 411 HIV-infected men receiving HAART, the 710 HIV-seronegative men were older, had a slightly higher BMI and a lower total cholesterol level and were more likely to have a college degree but were otherwise similar. Of the 411 HIV-infected men receiving HAART at the index visit, 110 were receiving more than 1 PI (including 13 who were receiving lopinavir therapy), 207 were receiving 1 PI (105 were receiving indinavir; 68, nelfinavir; 15, saquinavir; 13, amprenavir and 6, ritonavir) and 94 were not receiving a PI (40 of 94 had never reported use of a PI). Of the same 411 HIV-infected men receiving HAART, 6 were receiving more than 1 Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI), 178 were receiving 1 NNRTI (92 were receiving efavirenz; 73, nevirapine and 13, delavirdine mesylate) and 227 were not receiving any NNRTI (187 of 227 had never reported NNRTI use).

Prevalent DM was more common among the HIV-infected group receiving HAART compared with the HIV-seronegative group (14% Vs 5%) (Table 2). Because the HIV-infected group receiving HAART were younger and had a lower BMI than the HIV-seronegative group, the PRs of DM increased after adjustment for these factors (PR for DM = 4.64; 95% CI, 3.03-7.10). The HIV-infected men not using HAART had an increased risk of prevalent DM relative to the HIV-seronegative group after adjustment for age and BMI (Table 2).

Incidence of DM: The 680 men in the incidence analysis had characteristics similar to the overall study group of 1278 men shown in Table 1 (data not shown). Of these 680, 38 developed DM, 458 completed follow-up without DM and 184 (27%) were lost to follow-up. At the index visit, 261 of 319 HIV-infected men were receiving antiretroviral therapy. Of these 261, 255 provided adherence data and 222 (87%) reported regimen adherence of 95% or more of the time. The 229 HIV-infected men using HAART at the index visit had a higher rate of incident DM than the 361 HIV-seronegative men (RR = 4.11; 95% CI, 1.85-9.16; Table 3) after adjustment for age and BMI (Table 3). The associations of a 5-unit increase in BMI and age on the rate of incident DM were 1.34 (95% CI, 0.91-1.96) and 1.31 (95% CI, 1.04-1.64), respectively.

Effect of specific PI use and CD4 cell count: Of the 680 men in the incidence analysis, 209 developed the combined end point of DM or hyperglycemia, yielding an adjusted RR of 1.64 (95% CI, 1.21-2.33) in the HIV-infected group using HAART compared with the HIV-seronegative group. Only ritonavir was significantly associated with an increased rate of the combined end point (RR = 1.70; 95% CI, 1.08-2.68) relative to men not using ritonavir, adjusting for age, BMI, CD4 cell count and cumulative use of Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and NNRTIs. Classification of exposure to the PIs as "ever or never" use did not change our inferences (data not shown).

Table 1: Characteristics of 1278 men at the index visit between April and October 2008*

Characteristic	Current study population (N = 1278)	HIV-seronegative (n = 710)	HIV-seronegative (n = 710)	HIV-infected using HAART (n = 411)	p-value**
Age (years)	48	50	50	46	<.001
Body mass index***(BMI)	26	26	26	25	<.001
Waist-hip ratio	0.95	0.94	0.94	0.95	0.17
Total cholesterol level (mg dL^{-1})	202	201	201	210	<.001
Glucose level (mg dL^{-1})	90	90	90	91	0.08
CD4 count (cells mm^{-3})	NA	NA	NA	211	NA
Duration of receiving HAARTS****	NA	NA	NA	3.26	NA

HAART: Highly Active Antiretroviral Therapy; HIV: Human Immunodeficiency Virus; *: Data are given as medians; **: Compared HIV-infected receiving HAART group with the HIV-infected group; ***: Calculated as weight in kilograms divided by the square of height in meters; ****: Years from initiation of HAART to the data of index visit

Table 2: Prevalence of diabetes mellitus among 1278 men at the index visit between April and October 2008

Diabetes mellitus*		
Patient group	No. of patients (%)	PR (95% CI)**
Overall (N = 1278)	101 (8)	NA
HIV seronegative (n = 710)	33 (5)	1
HIV infected not using HAART (n = 157)	11 (7)	2.21 (1.12-4.38)
HIV infected using HAART (n = 411)	57 (14)	4.64 (3.03-7.10)

CI: Confidence Interval; HAART: Highly Active Antiretroviral Therapy; HIV: Human Immunodeficiency Virus; NA: Not Applicable, PR; Prevalence Ratio; *: Fasting glucose level of 126 mg dL^{-1} or higher; **: Prevalence ratio

Table 3: Incidence of diabetes mellitus among 680 men between April 2006 and March 2008

Patient group (n = 680)	No. of end points	Peron-years	Rate per 100 Person-years (95% CI)
Overall	38	1451.0	2.6 (1.9-3.6)
HIV seronegative	10	703.3	1.4 (0.8-2.6)
HIV infected not using HAART	4	236.3	1.7 (0.6-4.5)
HIV infected using HAART	24	506.8	4.7 (3.2-7.1)

CI: Confidence Interval; HAART: Highly Active Antiretroviral Therapy; HIV: Human Immunodeficiency Virus; NA: Not Applicable

Among the 229 HIV-infected men using HAART, the 157 with a CD4 cell count of 300 cells mm^{-3} or less at the index visit developed the combined end point at a significantly increased rate compared with the 72 with a nadir CD4 cell count greater than 300 cells mm^{-3} (RR = 1.67; 95% CI, 1.00-2.80, adjusted for age, BMI and duration of HAART (<2 years Vs >2 years).

DISCUSSION

We report that during a 3-year follow-up period in the Hospital of RIMS, 24 (10%) of 229 HIV-infected subjects receiving HAART developed DM compared with 10 (3%) of 361 HIV-seronegative men. After adjustment for BMI and age, this difference represents a greater than 4-fold increase in the risk of incident DM among HIV-infected subjects receiving HAART.

These findings support and extend previously observed increases in both prevalent and incident fasting hyperglycemia and DM among HIV-infected patients receiving HAART. Initial reports estimated a 5-7% cumulative incidence of DM in HIV-infected patients receiving HAART (Mehta *et al*., 2003; Nightingale, 1997; Cox and Oakes, 1984), but these studies were relatively small, were based on retrospective record review and used less rigorous ascertainment techniques, such as random blood glucose values (Nightingale, 1997; Cox and Oakes, 1984). In addition, the lack of an internal comparison group in many of the initial studies precluded accurate estimates of relative risk. Justman *et al*. (2003) recently reported a relative risk of incident self-reported DM of 2.0 (95% CI, 1.0-4.1) when HIV-infected women receiving a PI were compared with an HIV-seronegative subgroup prospectively followed in the Women's Interagency HIV Study.

Antiretroviral medications likely play a causative or permissive role in the pathogenesis of hyperglycemia in HIV-infected patients (Justman *et al*., 2003; Mehta *et al*., 2003; Krishnaswamy *et al*., 2000). In present study, we explored the association of several specific PIs with the risk of incident hyperglycemia and DM. Only ritonavir use was significantly associated with an increased risk of a combined end point of DM or hyperglycemia. In vitro evidence suggests that ritonavir is associated with both the development of insulin resistance (Harrell, 2001; Ramachandran *et al*., 2002, Lee *et al*., 2004) and impaired β-cell function (Murata *et al*., 2000). In clinical studies and in healthy volunteers, administration of ritonavir-containing regimens has been linked to worse glucose homeostasis (Dufer *et al*., 2004). Because 94% of men in our study who were receiving ritonavir therapy were also receiving at least 1 other PI, it is unclear if the effect is due to ritonavir per se or the combination of PIs. Given the few end points, however, these results require independent replication.

Human immunodeficiency virus-related factors may be important in the development of metabolic abnormalities in HIV-infected patients. Severity of HIV disease, as estimated by the nadir CD4 cell count, has been associated with increased risk of lipoatrophy (Martinez *et al*., 2004 and Wu and Ke, 2000), combined lipodystrophy (Lichtenstein *et al*., 2003), and cardiovascular disease (Mauss *et al*., 2002; David *et al*., 2002). In the present study, HIV-infected men with lower CD4 cell counts had an increased risk of incident glucose abnormalities compared with those with higher CD4 cell counts. The possibility that confounding factors, such as more diabetogenic antiretroviral regimens in the more severely ill patients, contributed to this finding cannot be excluded. To assess the contribution of disease-related factors in the pathogenesis of hyperglycemia and DM in the setting of HAART, HIV-infected patients not exposed to HAART are an essential comparison group. In present study, the small size of this group precluded a thorough analysis.

CONCLUSION

The present study had several additional limitations. First, owing to the semiannual visit schedule, our end points were based on a single FG

concentration measurement and were not confirmed by a duplicate measurement on a subsequent day as suggested by the Indian Diabetes Association (2004) and Bondar and Mead (1974). Also, since 1278 of the original 5622 Hospital of RIMS participants were included in the study, it is possible that selection biases may have influenced our results. In addition, incident rates may have been slightly underestimated because of the intermittently missing FG concentration data.

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