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Research Article

Incidence of primary hypertension in a population–based cohort of HIV–infected compared with non–HIV–infected persons and the effect of combined antiretroviral therapy

Avnish Tripathi, MD, PhD, MPH[a,*], Jeanette M. Jerrell, PhD[b], Thomas N. Skelton, MD[a], Myrna A. Nickels, MD[a], and Wayne A. Duffus, MD, PhD[c]

[a]*Division of Internal Medicine, Department of Medicine, University of Mississippi School of Medicine, Jackson, MS, USA;* [b]*Department of Neuropsychiatry and Behavioral Science, University of South Carolina School of Medicine, Columbia, SC, USA; and* [c]*Division of Infectious Diseases, Department of Medicine, University of South Carolina School of Medicine, Columbia, SC, USA*

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Abstract

Literature remains scarce on the impact of antiretroviral medications on hypertension in the HIV population. We used the South Carolina Medicaid database linked with the enhanced HIV/AIDS system surveillance database for 1994–2011 to evaluate incident hypertension and the impact of combination antiretroviral therapy (cART) in HIV/AIDS population compared with a propensity– matched non–HIV control group. Multivariable, time–dependent survival analysis suggested no significant difference in incidence of hypertension between the HIV group and the non–HIV control group. However, subgroup analysis suggested that among the HIV–infected group, months of exposure to both non–nucleoside reverse transcriptase inhibitors (adjusted hazard ratio, 1.52; 95% confidence interval, 1.3–1.75) and protease inhibitors (adjusted hazard ratio, 1.26; 95% confidence interval, 1.11–1.44) were associated with an increased risk of incident hypertension after adjusting for traditional demographic and metabolic risk factors. In people with HIV/AIDS, prolonged exposure to both protease inhibitor–based and non–nucleoside reverse transcriptase inhibitor–based cART may increase the risk of incident hypertension. J Am Soc Hypertens 2015;9(5):351–357.

Keywords: Enhanced HIV/AIDS surveillance; medicaid; non-nucleoside reverse transcriptase inhibitors; protease inhibitors.

Introduction

Over the last two decades, there has been substantial improvement in treatment of persons living with HIV infection, especially with the use of combination antiretroviral therapy (cART).[1,2] However, there are increasing concerns regarding elevated morbidity and mortality due to the cardiometabolic adverse effects of long–term cART use in this clinical population,[3,4] as indicated by a heightened prevalence of traditional cardiovascular risk factors such as diabetes mellitus, hypertension, and smoking.[3] The relationship between highly active antiretroviral therapy (HAART) and hypertension has not been well–studied.[5] Conflicting results have been reported for the association between ART and blood pressure (BP),[6] and for the association between HAART and the prevalence of hypertension.[7,8] So there remains a need to further examine the relationship between HIV infection, cART, and hypertension in different population subgroups.[9]

cART appears to have a minimal to modest impact on BP, which may be partially mediated by metabolic changes occurring with this treatment, but non–nucleoside reverse transcriptase inhibitors (NNRTIs) have been associated with a lower risk of incident hypertension in previous

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*Corresponding author: Avnish Tripathi, MD, PhD, MPH, Division of Internal Medicine, Department of Medicine, University of Mississippi School of Medicine, 2500 N State St, Jackson, MS 39216. Tel: +1 601.984.5601; Fax: +1 601.984.6601.

E-mail addresses: atripathi@umc.edu, tripathi.avnish@gmail.com

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research.[8,10,11] Increased BP has been found to be associated with lipodystrophy,[12] providing additional evidence that HAART and hypertension may be linked via pathways involving lipodystrophy or other metabolic disorders.[13] More recent studies focusing on the newer cART medications, control of the HIV infection, co–morbid conditions including hepatitis co–infections,[14,15] and incident hypertension are needed.

In this study, we examined the incidence rates and factors associated with development of hypertension in a large retrospective, longitudinal cohort of HIV–infected persons and a matched non–HIV–infected comparison group. We employed marginal structural models with time–dependent comorbid conditions, concomitant medications, and viro–immunologic status to examine the temporal association of two major classes of antiretroviral drugs, PIs and NNRTIs, with development of hypertension.

Methods

Study Participants

The study population included HIV–infected persons ≥18 years who were served through the South Carolina (SC) Medicaid system from January 1, 1994 through December 31, 2011. Exclusion criteria included death within 6 months of entry in cohort, those who had less than 30 days between the first and last visit in the cohort, and evidence of cocaine use because of the known direct and indirect cardiometabolic adverse effects and increased overall mortality. The final case (HIV–infected) cohort was 6816 persons. A propensity score 1:1 matching procedure[16] was used to randomly select non–HIV–infected persons matched on age at entry in study cohort, race/ethnicity, gender, total months of enrollment, and year of entry in the cohort, yielding a total study cohort of 13,632 persons. The Medicaid data obtained (ie, medical service utilization and pharmacy fills/refills) were linked with the enhanced HIV/AIDS Reporting System (eHARS) surveillance database.[17] This study was approved by the SC Department of Health and Human Services Research Committee and the SC Department of Health and Environmental Control Institutional Review Board.

Case Ascertainment

HIV–infected persons were categorized as cART–treated if they received antiretroviral drugs for at least 30 days or more, whereas those who did not receive any antiretroviral medications or received for less than 30 days were categorized as cART–naïve. The incidence of hypertension was ascertained by at least two visit claims for a primary International Classification of Diseases (ICD) Ninth Revision Clinical Modification diagnostic code of 401.0, 401.1, 401.9, 402.91,405.11, 405.19, 405.09, 405.91, 405.99, or 440.1, which were at least 30 days apart, and not within 6 months (washout period) of the first date of enrollment. A 6–month washout period after entry into Medicaid helps to mitigate misclassification of a prevalent condition as incident. Persons who had diagnoses of hypertension within the washout period, hereby regarded as pre–existing, were excluded from further analysis, yielding a total of N = 2777 cases of incident hypertension. A similar methodology was used to ascertain other relevant cardio–metabolic conditions and covariates including diabetes mellitus, dyslipidemia, obesity/overweight, tobacco use, and hepatitis B or C virus co–infections (HBV; HCV).

Multivariable Analyses

Time–dependent proportional hazards analysis was used to estimate the risk of incident hypertension among cART–naïve HIV–infected, cART–treated HIV–infected, and non–HIV–infected persons, with diabetes mellitus, dyslipidemia, obesity, HBV, and HCV as time–dependent independent covariates; that is, the status of an individual could change from absence to presence of the disorder as updated for each person–month. The fixed independent variables included gender, age at enrollment, race/ethnicity, year of enrollment categories, and total number of months of follow–up. Over the study observation period of 1994–2011, therapeutic efficacy and side effects profile of antiretroviral medications changed dramatically. Furthermore, during this period, guidelines for HIV/AIDS also witnessed several changes. We controlled for this potential selection bias by forcing the inclusion of age at enrollment, year of enrollment, and total months of follow–up into each multivariable analysis. The year of enrollment variable was categorized into 4–year periods until 2010 (1994–1997, 1998–2001, 2002–2005 [used as the reference category], 2006–2009, and 2010–2011). To explore the association of incident hypertension and PI– and NNRTI–exposure updated for each person–month of observation, and viro–immunologic control using the nearest available CD4+ T–cell count and log viral load data for each person–month with development of hypertension, a subgroup analysis was performed only among HIV–infected persons. Backward elimination methods using a cutoff *P*–value of 0.05 were used to obtain parsimonious models. In the multivariable Cox proportional hazards models, interaction terms with a time variable were included if the proportional hazards condition was not met. SAS software, version 9.2 (SAS Institute, Cary, NC) was used for all analyses.

Results

Participant Characteristics

The total study sample was comprised of 13,632 persons: their median age was 39 years (interquartile range