International Journal of Cardiology 220 (2016) 400–407

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

A plausible causal link between antiretroviral therapy and increased blood pressure in a sub-Saharan African setting: A propensity score-matched analysis

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ARTICLE INFO

Article history:
Received 30 April 2016
Accepted 25 June 2016
Available online 27 June 2016

Keywords:
HIV
Antiretroviral therapy
Blood pressure
Causality
Propensity score matching

ABSTRACT

Background: The transition from association to causation could represent a fundamental step for taking preventive action against hypertension and its complications, especially among HIV-infected persons on antiretroviral therapy in sub-Saharan African countries.
Methods: 406 consecutive HIV-infected adults attending a tertiary HIV clinic in semi-urban Nigeria were prospectively recruited between August and November 2014. These participants were stratified by antiretroviral treatment status. A propensity score matching model was fitted to examine the causal average treatment effects on the treated (ATT) of antiretroviral therapy on blood pressure. Propensity score matching entailed using nearest neighbour matching with a calliper width of 0.2 to achieve similarity in the baseline characteristics between participants naïve and exposed to antiretroviral therapy.
Results: Matching HIV-infected patients naïve and exposed to antiretroviral therapy on the propensity score yielded a total of 303 participants — 229 antiretroviral-exposed and 74 antiretroviral-naïve — matched without any residual differences in the baseline characteristics between both groups of patients. In this propensity score-matched sample, the estimated ATT for the effects of antiretroviral therapy on systolic (7.85 mm Hg, 95% CI 3.72 to 15.68) and diastolic blood pressure (7.45 mm Hg, 95% CI 4.99 to 13.61) were statistically significant ($P < 0.001$ for each).
Conclusions: There is a high probability that the epidemiological association between antiretroviral therapy and increased blood pressure be causal in nature among people living with HIV in sub-Saharan African settings. HIV-infected patients commencing antiretroviral treatment in these settings may require regular hypertension screening and other cardiovascular risk assessments.

1. Introduction

Approximately two-thirds of HIV-infected patients receiving antiretroviral treatment develop adverse cardio-metabolic effects, including changes in blood pressure [1,2]. Essentially, antiretroviral drugs induce vascular endothelial changes that impair the production of biological markers known to regulate blood pressure, such as nitric oxide [3–5]. However, while the association of antiretroviral therapy with increased blood pressure has been reported in a previous meta-analysis of observational studies [5], the evidence to ascertain whether this epidemiological association is causal in nature is limited. This dearth of evidence on causality might be attributed to the highly observational nature of available studies on the subject [5,6]. Although it is widely acknowledged that randomised controlled trials provide a higher level of evidence suggestive of causality, compared to observational studies;

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http://dx.doi.org/10.1016/j.ijcard.2016.06.210
0167-5273/

there is a growing interest in using observational data to infer or rule out causal effects, especially when it is not practical to perform a controlled experiment [7–10].

As modern-day epidemiology continues to evolve, the interpretations of causality continue to expand, above and beyond the simple direct relationships that satisfy "Hill's Criteria of Causation" [11–13]. Statistical methods, such as propensity score analyses, have become quite fundamental in testing causal hypotheses [7–9]. Of note, the concept of the propensity score originated from the need to examine cause–effect relationships in cases where controlled experiments were not feasible [7], such as studies investigating the effects of antiretroviral therapy on blood pressure changes in people living with HIV [5,6]. Much like the analysis of a randomised controlled trial, propensity score analyses yield a balanced distribution of the baseline characteristics between patients exposed and naïve to treatment based on the probability of treatment assignment, the objective of which is to estimate the causal average treatment effect of said treatment on an outcome [7–9]. However, this statistical concept has not been applied to the epidemiological association between antiretroviral therapy and increased blood pressure: to our knowledge, no study has examined the average treatment effect (or any other causal parameter) of antiretroviral therapy on increased blood pressure. Unfortunately, the statistical methods in previous studies that have examined this association have been limited to standard regression techniques, which are seldom used for causal inferences [5,6].

Therefore, it was essential to address this gap in the current body of evidence, as the transition from association to causation may potentially guide preventive action with regard to antiretroviral-associated hypertension, especially among people living with HIV in the sub-Saharan African region where the burden of HIV infection is greatest [14], and antiretroviral treatment coverage rates continue to increase exponentially [15].

2. Methods

2.1. Study design and setting

Between August and November 2014, we prospectively recruited patients attending the Benue State University Teaching Hospital HIV clinic in Nigeria. The teaching hospital is one of two tertiary health institutions in the state serving approximately 500,000 residents in the state's capital, Makurdi [16]. Approximately 50 patients visit the outpatient HIV clinic weekly, including new enrollees and patients returning for follow-up visits. During the study period, over 700,000 people were reported to be living with HIV in Benue state, accounting for 5.6% of the resident population [17], and enrolment into care usually coincided with the date HIV-infection was first diagnosed.

Benue has consistently recorded one of the higher prevalence rates of HIV among all 36 states in Nigeria. High levels of socio-economic deprivation and close proximity to neighbouring states with somewhat comparable HIV prevalence rates are speculated to contribute substantially to the HIV disease epidemic in Benue [18].

2.2. Participants

Four hundred six (406) patients were sampled consecutively from the outpatient HIV clinic between August and November 2014. To participate in the study, patients had to be HIV-infected; no less than 18 years old; naïve or exposed to highly active antiretroviral therapy (HAART); and able to communicate in English or Nigerian Pidgin. We excluded HIV-infected patients diagnosed with opportunistic infections, children and adolescents, pregnant and lactating mothers, patients with persistent decline in CD4 cell counts or with clinically symptomatic HIV infection while on antiretroviral therapy for no less than three months (antiretroviral treatment failure) [19]. Patients with suboptimal adherence to follow-up visits at the clinic were also excluded because such patients were unlikely to have adequate antiretroviral adherence levels, which conflicted with our definition of HAART-exposure. Patients were considered HAART-exposed if they had received regularly a combination of two nucleoside reverse transcriptase inhibitors with one non-nucleoside reverse transcriptase inhibitor (2NRTI + 1NNRTI), or two nucleoside reverse transcriptase inhibitors with one protease inhibitor (2NRTI + 1PI) for no less than three months. HIV-infected patients were considered naïve to HAART if they never received antiretroviral treatment. A control group of HIV-negative individuals to compare baseline characteristics was recruited at the same time from the medical outpatient department and hospital staff members.

2.3. Data collection

Research staff were trained to administer the World Health Organisation (WHO) STEPS instrument, which has been validated for chronic disease risk factor surveillance in low- and middle-income settings [20]. Demographic data included age, gender, educational status and occupational grade. Other data obtained using the stepwise approach to surveillance instrument included lifestyle data (such as smoking status, drinking status, and self-reported physical activity) and family history of hypertension. Clinical characteristics, including baseline systolic and diastolic blood pressure measurements taken around the time of enrollment into the HIV clinic, CD4 cell counts assessed within the last three months, antihypertensive treatment taken within the last two weeks, and duration of HIV infection were obtained from the patients' medical records. Body mass index and waist circumference were measured using standard protocols. We also obtained data on other behavioural correlates of blood pressure. For instance, data on sleep quality were obtained using the Pittsburgh Sleep Quality Index (PSQI) questionnaire; a patient with a PSQI score of 5 or more was considered to have poor sleep quality, whereas good sleep quality was defined as a PSQI score of less than 5 [21]. The Centre for Epidemiologic Studies Depression Scale (CES-D) was used to assess for presence of depressive symptoms, which was indicated by a CES-D score of 16 or greater [22]. Physical and mental health-related quality of life (HRQL) scores were estimated for each participant using the Short Form-12 (SF-12) questionnaire [23].

The study outcomes were systolic and diastolic blood pressure. Blood pressure was measured using the Omron M10 IT Blood Pressure Monitor. The average of the first two blood pressure readings taken no less than 20 min apart was recorded as the patient's blood pressure. A third blood pressure reading was taken in cases where the disparity was substantial (≥5 mm Hg) between the first two systolic or diastolic blood pressure readings [24]. Hypertension was diagnosed when patient's recorded blood pressure was ≥140/90 mm Hg or the current use of antihypertensive medication [24]. To ensure quality control, blood pressure measurements were taken by trained study nurses.

2.4. Ethics

Informed consent was obtained from each participant. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected *a priori* by the University of Warwick Biomedical and Scientific Research Ethics Committee (REGO-2014-711) and the Benue State University Teaching Hospital Health Research Ethics Committee (NHREC/08/11/2013B).

2.5. Statistical methods

2.5.1. Descriptive statistics

All data were analysed using Stata version 14 for Windows (Stata Corp, College Station, Texas). The null hypothesis was tested against a two-sided alternative hypothesis at significance level of 5%. For all continuous variables (*e.g.* age, body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, blood glucose concentration, physical activity in minutes per week, PSQI score, CES-D score, SF-12 physical and mental component scores), the means with standard deviations were compared between HAART-exposed and HAART-naïve HIV-infected patients, and HIV-negative individuals. The means (with standard deviations) for CD4 cell count, baseline systolic blood pressure, baseline diastolic blood pressure, and duration of HIV infection were compared between HAART-exposed and HAART-naïve HIV-infected patients only. Mean HAART duration (with standard deviation) was reported for HAART-exposed patients. Statistical significance of the comparisons were determined using the *t*-test.

Similarly, the frequencies and proportions of categorical variables (*e.g.* gender, age group, educational attainment, occupational grade, drinking status, smoking status, physical activity categories, PSQI categories, depression status, overweight/obesity status, central obesity status, family history of hypertension, diabetes mellitus status, and hypertension status) were compared between HAART-exposed and HAART-naïve HIV-infected patients, and HIV-negative individuals. For categorical variables, statistical significance of the comparisons between these patient groups were determined using the Chi-square test or Fisher's exact test where necessary.

2.5.2. Propensity score matching

A propensity score model was fitted to estimate propensity scores for each participant, and to yield a balanced distribution of baseline characteristics between HAART-exposed and HAART-naïve patients, conditional on the estimated propensity scores [7]. The propensity score model is much like a logistic regression model where a dichotomous variable, which is the treatment status (or exposure criterion), is regressed on a number of observed baseline covariates [7,8]. In fitting our propensity score model, we included a total of 20 baseline covariates: age, sex, educational status, occupational grade, smoking status, drinking status, physical activity level (continuous), body mass index (continuous), waist circumference (continuous), blood glucose concentration, antihypertensive treatment, PSQI (categorical), CESD (categorical), physical and mental HRQL, family history of hypertension, CD4 count (continuous), HIV infection duration, baseline systolic and diastolic blood pressure. Subsequently, a propensity score matching model — now including the study outcomes and a variable denoting the propensity score — was fitted to examine the causal average effects of antiretroviral therapy on systolic and diastolic blood pressure.

Propensity score matching entailed using nearest neighbour matching with a calliper width of 0.2, which has been recommended as most suitable for observational studies in