Antiretroviral medications associated with elevated blood pressure among patients receiving highly active antiretroviral therapy

Heidi M. Crane[a], Stephen E. Van Rompaey[a] and Mari M. Kitahata[a,b]

Objective: To examine the effect of antiretroviral agents and clinical factors on the development of elevated blood pressure (BP).

Methods: Observational cohort study of patients initiating their first HAART regimen. We evaluated mean BP prior to HAART and while receiving HAART in relation to antiretroviral classes and individual agents, and demographic and clinical characteristics including change in body mass index (BMI) while on HAART. We used logistic regression analysis to examine factors associated with elevated BP [≥ 10 mmHg increase in systolic BP (SBP), diastolic BP (DBP) or new diagnosis of hypertension].

Results: Among 444 patients who had 4592 BP readings, 95 patients developed elevated SBP ($n = 83$), elevated DBP ($n = 33$), or a new diagnosis of hypertension ($n = 11$) after initiating HAART. In multivariate analysis, patients on lopinavir/ritonavir had the highest risk of developing elevated BP [odds ratio (OR), 2.5; $P = 0.03$] compared with efavirenz-based regimens. When change in BMI was added to the model, increased BMI was significantly associated with elevated BP (OR, 1.3; $P = 0.02$), and the association between lopinavir/ritonavir and elevated BP was no longer present. Compared with lopinavir/ritonavir-based regimens, patients receiving atazanavir (OR, 0.2; $P = 0.03$), efavirenz (OR, 0.4; $P = 0.02$), nelfinavir (OR, 0.3; $P = 0.02$), or indinavir (OR, 0.3; $P = 0.01$) had significantly lower odds of developing elevated BP.

Conclusions: Treatment with lopinavir/ritonavir is significantly associated with elevated BP, an effect that appears to be mediated through an increase in BMI. Patients receiving atazanavir were least likely to develop elevated BP. The impact of antiretroviral medications on cardiovascular disease risk factors will increasingly influence treatment decisions.

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Introduction

The decline in mortality resulting from widespread use of highly active antiretroviral therapy (HAART) in the developed world has been accompanied by an increase in metabolic complications including dyslipidemia, impaired glucose metabolism, and body morphology abnormalities, which can result in significant morbidity among HIV-infected individuals [1–6]. The increasing prevalence of metabolic complications has raised concerns about the effect of HAART on patients' risk of cardiovascular disease. Hypertension is an important risk factor for cardiovascular disease, but little is known about the impact of HAART on blood pressure (BP).

From the Departments of [a]Medicine and [b]Health Services, University of Washington, Seattle, Washington, USA.
Correspondence to Heidi M. Crane, MD, MPH, Center for AIDS and STD Research, University of Washington, Harborview Medical Center, Box 359931, 325 9th Avenue, Seattle, WA 98104, USA.
E-mail: hcrane@u.washington.edu
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Previous studies examining the effect of HAART on BP have reported conflicting results [7–12]. One study suggested a lower risk of hypertension among HIV-infected patients receiving protease inhibitors (PIs) compared with HIV-uninfected individuals [13]. Other studies have shown an association between antiretroviral medications, in particular PIs, and the development of elevated BP [12,14,15]. A large cross-sectional study found that non-nucleoside reverse transcriptase inhibitor (NNRTI) or PI use was associated with hypertension, but this association did not persist after adjusting for baseline factors such as age [16]. Little is known about the effect of individual antiretroviral medications on BP. Seaberg and colleagues reported a higher prevalence of systolic hypertension (> 140 mmHg) associated with longer duration of HAART [9]. The investigators did not detect differences in risk of hypertension associated with individual medications but the study was limited by patient self-reported measurement of medication use.

We conducted this study of HIV-infected patients initiating their first HAART regimen to examine the associations between antiretroviral medications and elevated BP.

Methods

Study setting

This study was conducted on the University of Washington (UW) HIV cohort, a longitudinal observational study of HIV-infected patients who receive primary care in the UW Harborview Medical Center HIV clinic from 1 January 1995 to the present. The UW HIV clinic is the largest single provider of medical care to HIV-infected individuals in the northwestern US. Patients provide informed consent and are followed until death or relocation from the UW. To date, 2236 patients have been enrolled into the cohort, contributing over 9000 person-years of follow-up time, with loss to follow-up averaging 10%.

Study participants

All HIV-infected patients 18 years of age or older who were PI and NNRTI naive when they enrolled in primary continuity care and initiated their first HAART regimen between 1 June 1998 and 1 February 2005 were eligible for the study. Subjects were required to have at least 4 months of follow-up after initiating HAART, which was defined as antiretroviral medication regimens containing three or more drugs including either a PI or an NNRTI. In addition, patients had to have at least three BP values before initiating HAART, at least three BP values while on their initial HAART regimen, and no diagnosis of hypertension prior to instituting HAART. Data collection for this study ended 1 June 2005. The study was approved by the UW institutional review board.

Sources of data

The University of Washington HIV information system (UWHIS) captures longitudinal data on the UW HIV cohort and was the source of data for this study. The UWHIS integrates comprehensive clinical data from all outpatient and inpatient encounters including standardized HIV-related information collected at enrollment (initial clinic visit) regarding a patient's prior antiretroviral treatment and diagnosis history. Demographic, clinical, laboratory, medication, and socio-economic data are obtained from the UW electronic medical record and other institutional data sources. The majority of patients in the UW HIV cohort receive all their medications from the on-site pharmacy. Detailed prescription fill/refill data for all outpatient medications and inpatient discharge medications dispensed anywhere in the UW system are obtained directly from the UW pharmacy system. Laboratory data are downloaded directly from the UW laboratory medicine system and include results of all tests performed as part of routine clinical care. Clinician data entry is limited to documenting diagnoses addressed at each clinical encounter from a constrained web-based list of standardized diagnoses. Clinical patient data such as BP, height, and weight are routinely collected and integrated in the UWHIS.

Measurement of blood pressure

BP is measured at all clinic visits by nursing staff using a mercury sphygmomanometer. Although clinic protocol does not require a 5-min seated waiting period before measuring BP as is considered ideal [17], flow through the clinic results in patients being seated on average for at least 5 min before check-in.

Definition of outcomes

We evaluated the change in mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) and mean arterial pressure [MAP = (2 × DBP + SBP)/3] measured prior to initiating HAART and while receiving HAART. A change in mean SBP, DBP, or MAP of at least 10 mmHg was considered clinically significant. We evaluated mean BP measurement during two time periods to decrease the effect of variability of individual BP readings. A new diagnosis of hypertension confirmed by treatment with an antihypertensive medication was an additional end point for analysis. We examined an alteration in any BP endpoint as a combined outcome of elevated BP defined as a 10 mmHg or greater increase in SBP, DBP, or a new diagnosis of hypertension. We then examined each individual BP outcome. There were too few individuals who developed a new diagnosis of hypertension to examine this endpoint individually. We examined the development of isolated SBP (without an elevation in DBP), and an elevation in SBP accompanied by an elevation in DBP. We also examined elevated SBP or a new

diagnosis of hypertension, and elevated DBP or a new diagnosis of hypertension. We combined hypertension with elevations in SBP and DBP as an endpoint for analysis in order to examine patients experiencing the full spectrum of BP elevations.

Statistical analysis

We examined the association between development of BP outcomes and demographic characteristics (age, risk factor for HIV transmission, race, sex, family history of hypertension) and clinical characteristics [CD4+ cell count nadir, baseline HIV-1 RNA level, hepatitis C virus (HCV) infection indicated by either presence of HCV antibody or HCV RNA; and body mass index (BMI)]. We examined the association between BP outcomes and antiretroviral medications including individual medications and medication classes [nucleoside (-tide) reverse transcriptase inhibitors (NRTIs), NNRTIs, and PIs]. Antiretroviral medications were categorized into mutually exclusive and exhaustive groups. Patients receiving regimens with two PIs, boosted PI regimens, or regimens with both an NNRTI and a PI were grouped by their non-ritonavir PI. Patients receiving fosamprenavir were grouped with patients taking amprenavir, and patients receiving emtricitabine were grouped with patients taking lamivudine. We examined ritonavir use as a separate variable. We evaluated patients taking any dose of ritonavir together, and also categorized patients as either receiving full dose ritonavir (greater than 400 mg per 24-h period) or a boosting dose of ritonavir (400 mg or less per 24-h period). We calculated BMI using the traditional Quetelet index: weight divided by height squared (kg/m^2) [18]. Baseline BMI was categorized as underweight (< 18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese ($\geq$ 30 kg/m^2). Change in BMI was measured as the difference between BMI prior to receiving HAART, and the BMI at the final visit while receiving the initial HAART regimen or at the end of the study period, whichever came first.

We performed bivariate analysis of associations with development of BP outcomes using chi-squared tests for categorical variables and *t*-tests for continuous variables. We used multivariate logistic regression to examine independent predictors of the development of BP outcomes. Efavirenz and lopinavir/ritonavir were used in separate models as reference categories to examine the effects of individual PIs and NNRTIs on outcomes. NRTIs were never administered singly and so were examined as pairs. Effect modification was assessed with the use of interaction terms. We hypothesized that the effect of antiretroviral medications on development of BP outcomes was mediated, in part, through a change in BMI and tested this hypothesis by examining the effect of BMI on model results. Two-tailed P values of < 0.05 were considered significant for all statistical tests.

Results

Study entry criteria were met by 444 patients who had a total of 4592 BP readings. Mean age of study patients at first visit was 35 years, 84% were men, mean CD4+ cell count was 163 cells/μl, and 53% had a peak viral load $> 100\,000$ copies/ml (Table 1). Mean BMI for the study cohort was 24.1 kg/m^2 prior to initiation of HAART. At baseline, 7% of patients were underweight, 56% had a normal BMI, 27% were overweight, and 10% were obese.

Initial HAART regimens were evenly divided between patients receiving PI- ($n = 239$, 54%) and NNRTI-based regimens ($n = 237$, 53%); 32 patients (7%) received both a PI and an NNRTI (Table 2). A few patients received regimens containing two full dose PIs, (ritonavir combined with saquinavir, $n = 17$, 4%), or regimens with boosted PIs (lopinavir/ritonavir, $n = 47$, 11%; atazanavir with ritonavir, $n = 18$, 4%; amprenavir with ritonavir, $n = 4$, 1%). Study patients were on their initial HAART regimen for a mean of 13.5 months. Duration of initial HAART regimen did not differ by sex, race, HIV transmission risk factor, or HCV status.

The mean SBP measured among the study cohort during treatment with HAART was significantly higher compared with the mean SBP measured prior to initiating HAART (124.6 versus 121.6 mmHg; $P \leq 0.001$). The mean DBP during treatment with HAART and prior to initiating HAART were similar (74.1 versus 73.7 mmHg; $P = 0.5$). Mean SBP was significantly lower among women compared with men, both prior to initiating HAART (116.1 versus 122.4 mmHg; $P = 0.004$) and during treatment with HAART (118.9 versus 124.6 mmHg; $P = 0.006$). No statistically significant differences were observed in BP values based on risk factor for HIV acquisition, self-reported racial group, or HCV status.

Among the 444 patients in the study, 95 developed at least one of the BP endpoints and were classified as developing elevated BP. An increase in SBP of 10 mmHg or greater occurred in 83 individuals, 33 individuals developed an increase in DBP of 10 mmHg or greater and 11 had a new diagnosis of hypertension. Although we examined factors associated with the development of an increase in MAP, these results were similar to results obtained for DBP and are not described further.

In unadjusted analyses, age over 40 was significantly associated with development of the combined endpoint of elevated BP [odds ratio (OR), 1.7; 95% confidence interval (CI), 1.0–2.8; $P = 0.05$]. African-Americans tended to be more likely than whites to develop elevated BP (OR, 1.6; 95% CI, 0.9–2.6; $P = 0.09$). Patients with a CD4+ cell count ≤ 200 cells/μl were significantly more likely to develop elevated BP compared with patients with a CD4+ cell count > 200 cells/μl (OR,

Table 1. Demographic and clinical characteristics of 95 patients who developed elevated blood pressure (BP) while on their initial HAART regimen and 349 patients who did not.

Characteristic	Patients with elevated BP[a] $n = 95$ (%)	Patients without elevated BP $n = 349$ (%)	P values
Sex			
Male	85 (89)	287 (82)	
Female	10 (11)	63 (18)	0.08
Age (years)			
< 30	18 (19)	87 (25)	
30–40	42 (44)	167 (48)	
40–50	32 (34)	72 (21)	
≥ 50	3 (3)	23 (7)	0.03
Race			
White	47 (49)	212 (61)	
African-American	36 (38)	101 (29)	
Other	12 (13)	36 (10)	0.1
Risk factor for HIV transmission			
Men who have sex with men	55 (58)	166 (48)	
Injection drug use	21 (22)	93 (27)	
Heterosexual	14 (15)	74 (21)	
Other/unknown	5 (5)	16 (5)	0.3
CD4 cell count nadir cells/μl			
0–50	34 (36)	86 (25)	
51–200	38 (40)	127 (36)	
201–350	17 (18)	101 (29)	
> 350	6 (6)	35 (10)	0.03
Initial HIV-1 RNA level copies/ml ($n = 437$)			
$> 100\,000$	53 (57)	176 (51)	
30 000–100 000	24 (26)	87 (25)	
$< 30\,000$	16 (17)	81 (24)	0.4
Smoking			
No	36 (38)	115 (33)	
Yes	59 (62)	234 (67)	0.5
Hepatitis C virus infection			
No	85 (89)	290 (83)	
Yes	10 (11)	59 (17)	0.1
Protease inhibitors			
No	44 (46)	161 (46)	
Yes	51 (54)	188 (54)	0.9
Non-nucleoside (tide) reverse transcriptase inhibitor			
No	43 (44)	164 (47)	
Yes	52 (55)	185 (53)	0.7

[a]Elevated BP defined as a 10 mmHg increase in systolic blood pressure, diastolic blood pressure, or a new diagnosis of hypertension.

2.0; 95% CI, 1.2–3.3; $P = 0.009$). The mean BMI prior to initiating HAART in study subjects with a CD4+ cell count < 50 cells/μl was nearly 2 kg/m^2 lower than those with a CD4+ cell count ≥ 50 cells/μl (23.0 versus 24.8; $P = 0.003$). BMI measurements were available for 380 study patients (86%). An increase in BMI while receiving HAART was significantly associated with developing elevated BP (OR, 1.3 per kg/m^2 increase; 95% CI, 1.1–1.6; $P = 0.006$). No association was found between the development of elevated BP and baseline HIV-1 RNA level, family history of hypertension, baseline BMI, HIV risk factor, or smoking status.

Duration of initial antiretroviral regimen was shorter among patients on atazanavir-based regimens ($P = 0.01$) compared with those on efavirenz-based regimens. Patients on amprenavir-based regimens had the largest increase in BMI while on their initial HAART regimen (1.1 kg/m^2) compared with patients on efavirenz (0.5 kg/m^2), but this difference was not statistically significant. Patients on lopinavir/ritonavir were more likely to be older (37 versus 35 years; $P = 0.05$). Use of other antiretroviral medications did not differ by age, race, sex, duration of initial HAART regimen, change in BMI, hepatitis C status, or CD4+ cell count.

As a class, PI and NNRTI medications were not associated with the development of elevated BP in unadjusted analyses. However, when individual antiretroviral medications were examined, lopinavir/ritonavir was significantly associated with the development of elevated BP (OR, 3.0; 95% CI, 1.6–5.7; $P < 0.01$). In contrast, patients on atazanavir-based regimens showed a trend toward being less likely to develop elevated BP (OR, 0.3; 95% CI, 0.1–1.1; $P = 0.08$). Other antiretroviral medications, including ritonavir were not associated with the development of elevated BP in unadjusted analyses.

Table 2. Patients receiving each antiretroviral medication in their initial HAART regimen for the clinical cohort of 444 HIV-infected patients.

Class	Medication	Number (%)
Protease inhibitors		
	Nelfinavir	112 (25)
	Lopinavir	47 (11)
	Indinavir	34 (8)
	Atazanavir	24 (5)
	Saquinavir	17 (4)
	Amprenavir	5 (1)
	Ritonavir-full dose	17 (4)
	Ritonavir-boosting dose	69 (16)
NNRTIs		
	Efavirenz	159 (36)
	Nevirapine	78 (18)
NRTIs		
	Lamivudine	387 (87)
	Zidovudine	172 (39)
	Stavudine	167 (38)
	Tenofovir	79 (18)
	Didanosine	33 (7)
	Abacavir	25 (6)
	Zalcitabine	2 (< 1)

NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTIs, nucleoside (tide) reverse transcriptase inhibitors.

In multivariate analyses adjusting for age, race, sex, HCV status, and duration of initial HAART regimen (Table 3), patients receiving lopinavir/ritonavir-based regimens were more than twice as likely to develop elevated BP compared with patients on an efavirenz-based regimen (OR, 2.5; 95% CI, 1.1–5.7; $P = 0.03$), and patients receiving atazanavir-based regimens were less than half as likely to develop elevated BP, although this result was not statistically significant (OR, 0.4; 95% CI, 0.08–1.7; $P = 0.2$). Patients with a CD4+ cell count < 50 cells/μl were more than twice as likely to develop elevated BP compared with patients with a CD4+ cell count > 200 cells/μl (OR, 2.4; 95% CI, 1.2–4.8; $P = 0.02$). No effect modification was found when interactions between individual antiretroviral medications and CD4+ cell count, age, race, or sex were included in the model. We hypothesized that the impact of lopinavir/ritonavir on the development of elevated BP was mediated, in part, through an increase in BMI. When change in BMI was added to the multivariate model, increased BMI was significantly associated with developing elevated BP (OR, 1.4; 95% CI, 1.0–1.8; $P = 0.02$), and the association between lopinavir/ritonavir and BP was no longer present. However, the association between atazanavir and a lower risk of developing elevated BP was present after adjusting for change in BMI (OR, 0.1; 95% CI, 0.01–0.5; $P = 0.01$).

Patients receiving lopinavir/ritonavir were more than twice as likely to develop an elevation in SBP or a new diagnosis of hypertension (OR, 2.4; 95% CI, 1.0–5.6; $P = 0.04$) (Table 3). We compared the risk of developing elevations in SBP not accompanied by elevations in DBP with the risk of developing elevations in both SBP and DBP in fully adjusted models. Lopinavir/ritonavir was associated with over three times the risk of developing an isolated elevation in SBP (OR, 3.3; 95% CI, 1.3–8.5; $P = 0.01$), and not with an elevation in both SBP and DBP. A low CD4+ cell count was associated with over four times the risk of developing an elevation in both SBP and DBP (OR, 4.7; 95% CI, 1.6–14.1; $P = 0.005$).

Patients on atazanavir, efavirenz, nelfinavir, and indinavir had significantly lower adjusted odds of developing elevated BP compared with patients receiving lopinavir/ritonavir (Table 4). These results were similar when change in BMI was included in the model for all medications except for efavirenz, for which the change in risk was no longer statistically significant.

Patients who developed elevated BP were less likely to have received zidovudine (OR, 0.5; 95% CI, 0.3–0.8; $P = 0.007$), and more likely to have received tenofovir (OR, 1.9; 95% CI, 1.1–3.2; $P = 0.02$) in unadjusted analyses. We did not find an effect of other NRTIs on elevated BP. When we included NRTIs in the adjusted model, we found that tenofovir/lamivudine ($n = 67$) was associated with an increased risk of developing elevated BP (OR, 2.3; 95% CI, 1.0–5.2; $P = 0.046$) compared

Table 3. Adjusted odds ratios for factors associated with development of elevated systolic blood pressure (SBP) or new hypertension diagnosis, elevated diastolic blood pressure (DBP) or new hypertension diagnosis, or the development of the combined outcome of elevated blood pressure (BP) among patients on their first HAART regimen.

	Odds ratio (95% confidence interval; *P*)		
Variable	Elevated SBP or new diagnosis of hypertension	Elevated DBP or new diagnosis of hypertension	Elevated BP[a]
Efavirenz	1 (ref)	1 (ref)	1 (ref)
Lopinavir/ritonavir	2.4 (1.0–5.6; $P = 0.04$)	1.3 (0.4–3.7; $P = 0.6$)	2.5 (1.1–5.7; $P = 0.03$)
CD4+ cell count > 200 cells/μl	1 (ref)	1 (ref)	1 (ref)
CD4+ cell count 50–200 cells/μl	2.1 (1.1–4.1; $P = 0.03$)	1.8 (0.7–4.6; $P = 0.2$)	1.9 (1.0–3.7; $P = 0.05$)
CD4+ cell count < 50 cells/μl	2.4 (1.2–5.0; $P = 0.02$)	3.1 (1.2–7.9; $P = 0.02$)	2.4 (1.2–4.8; $P = 0.02$)

[a]Elevated BP defined as a 10 mmHg increase in SBP, DBP, or a new diagnosis of hypertension. All models adjusted for age, sex, race, hepatitis C virus status, CD4+ cell count, and duration of first antiretroviral regimen. No significant association was seen for nevirapine, nelfinavir, indinavir, atazanavir, or saquinavir. All patients receiving amprenavir developed DBP elevation.

Table 4. Adjusted odds ratios for variables associated with the development of elevated blood pressure among patients receiving their first HAART regimen with lopinavir/ritonavir as the reference.

Variable	Odds ratio (95% confidence interval; *P*) Elevated blood pressure
Lopinavir/ritonavir	1 (ref)
Atazanavir	0.2 (0.03–0.9; $P = 0.03$)
Efavirenz	0.4 (0.2–0.9; $P = 0.02$)
Nelfinavir	0.3 (0.1–0.8; $P = 0.02$)
Indinavir	0.3 (0.1–0.7; $P = 0.01$)
CD4+ cell count nadir > 200 cells/μl	1 (ref)
CD4+ cell count nadir 50–200 cells/μl	2.0 (1.1–3.7; $P = 0.03$)
CD4+ cell count nadir < 50 cells/μl	2.4 (1.2–4.7; $P = 0.01$)

All models adjusted for age, sex, race, hepatitis C virus status, and duration of first antiretroviral regimen. No effect found for amprenavir, nevirapine, saquinavir.

with zidovudine/lamivudine ($n = 145$) controlling for individual PIs, NNRTIs, race, sex, age, CD4+ cell count, duration of HAART regimen, and HCV infection. No significant effect was seen for the combination of stavudine/lamivudine ($n = 142$). When the change in BMI during HAART was also included, the association between tenofovir/lamivudine and the development of elevated BP was no longer significant (OR, 1.8; 95% CI, 0.6–5.6; $P = 0.3$).

Discussion

We found a two-fold increase in the risk of developing elevated BP among patients receiving lopinavir/ritonavir compared with those receiving efavirenz-based regimens. In addition, our results suggest that the increased risk associated with lopinavir/ritonavir was mediated, at least in part, through an increase in BMI. In contrast, patients receiving atazanavir-based regimens had a lower risk of developing elevated BP compared with patients receiving efavirenz or lopinavir/ritonavir even after adjusting for change in BMI. Regimens containing tenofovir/lamivudine were associated with an increased risk of developing elevated BP compared with those containing zidovudine/lamivudine controlling for other drugs in the regimen. We also found that patients with lower CD4+ cell counts were significantly more likely to develop an elevated BP while on HAART.

Antiretroviral medications

We did not find an association between development of elevated BP and treatment with PIs or NNRTIs as a class. The impact of NRTIs as a class could not be examined since all patients received NRTIs as part of their HAART regimen. Among PIs, lopinavir/ritonavir was associated with the greatest risk of mainly systolic elevations in BP. Systolic hypertension is an important predictor of cardiovascular disease in the general population [17,19], which raises concern about cardiovascular disease risk among patients receiving lopinavir/ritonavir. We did not find an association of ritonavir with the development of elevated BP in unadjusted analyses or adjusted models suggesting the increased risk associated with lopinavir/ritonavir could be attributed to lopinavir. There were too few patients treated with amprenavir to fully examine its relationship to elevated BP. However, all patients treated with amprenavir developed elevated BP as well as a substantial increase in BMI. The effect of amprenavir appeared to be predominantly on DBP, a well-known cardiovascular risk factor [20]. Although we did not find a significant risk of elevated BP for all patients treated with indinavir, a subset of patients receiving indinavir who did develop an elevated BP had the largest increase in BP among the cohort (> 40 mmHg increase in SBP while on HAART). One possible explanation for these findings is that large elevations in BP among a subset of patients receiving indinavir may represent secondary hypertension via a renal pathway. Taken together, our results suggest that specific PIs affect BP through different mechanisms. Additional studies will be needed to clarify the extent individual PIs impact BP via different mechanisms such as changes in BMI and renal affects.

Zidovudine monotherapy has been reported to be associated with a reduced hypertension risk among women [21]. In our study, patients receiving tenofovir and lamivudine were more likely to develop elevated BP than patients receiving zidovudine and lamivudine. It is not possible to determine whether this was due to a decreased risk among those receiving zidovudine, or increased risk among those receiving tenofovir, or a combination of both effects. Tenofovir has been associated with a decline in renal function [22] that could lead to elevations in BP. Our results suggest that the increase in risk associated with tenofovir was mediated through a change in BMI.

Clinical and demographic characteristics

Previous studies have not found an association between HIV RNA level, or CD4+ cell count, and hypertension [10,11,21]. In our study, lower CD4+ cell count was an independent predictor of developing elevated BP after adjusting for age and other factors, and this effect appeared to be mediated through a change in BMI. Patients with a low CD4+ cell count are more likely to have experienced wasting prior to initiating HAART, which would result in their having a greater change (increase) in BMI after treatment with HAART and yet have a low absolute BMI. This is supported by our finding that patients with a CD4+ cell count < 50 cells/μl had a lower BMI prior to initiating HAART than those with a higher CD4+ cell count. Sex and African-American race are associated with hypertension in the general population [23,24]. Prior studies have found conflicting effects

of demographic characteristics on hypertension among HIV-infected patients [7,10,16]. We found higher SBP among HIV-infected men compared with women before and after initiation of HAART, and a trend toward an increased risk of elevated BP among African-Americans.

Strengths and limitations

The strengths of our study include long-term follow-up, comprehensive clinical data, and precise and accurate antiretroviral treatment data from the UW HIV Cohort captured in the UWHIS. We defined our outcome based on change in BP rather than using an arbitrary cut-off value such as 140/90 mmHg. Studies conducted over the past 20 years, in numerous patient populations, have demonstrated a continuous relationship between elevations in SBP and DBP and cardiovascular disease and death, and that this association is not driven by a particular cut-off value [20]. Our findings are generalizable to similar populations of patients in routine care who represent a broader range of characteristics than patients who enroll in clinical trials. As the cohort continues to be followed, additional information will become available on newer antiretroviral agents.

As with any observational study, there is the concern for unknown or unmeasured confounding factors for which adjustment is not possible. However, potential confounding is minimized in our study by comparing changes over time within individuals rather than examining study patients in relation to control patients. Measurement of BP in the clinical care setting may not be conducted in a uniform manner. We limited the impact of random measurement error by using the average of at least three BP readings before and after HAART treatment. However, the use of average BP does not allow us to assess the length of time on therapy necessary for a patient to develop an elevation in BP. Finally, information regarding other potential risk factors for hypertension such as genetic factors, physical activity, diet, and daily alcohol and tobacco consumption were not available.

Conclusions

A clear understanding of factors contributing to the development of elevated BP among HIV-infected patients is needed to target prevention efforts and help guide research that may lead to improved interventions for hypertension in this population of patients. Additional studies are needed to understand the effect of elevated BP among HIV-infected patients treated with HAART on long-term outcomes such as cardiovascular disease. Further studies are needed to examine the role of intermediate variables such as lipoatrophy and lipohypertrophy on the development of elevated BP among HIV-infected patients. Our findings emphasize the importance of monitoring BP among HIV-infected patients receiving HAART. Clinicians may want to consider the impact of cardiovascular disease risk when making treatment decisions particular among patients with additional cardiovascular disease risks.

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