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Burden, Determinants, and Pharmacological Management of Hypertension in HIV-Positive Patients and Populations: A Systematic Narrative Review

Kim Anh Nguyen[1,2], Nasheeta Peer[1,2], Edward J. Mills[3] and Andre Pascal Kengne[1,2]

[1]Non-Communicable Diseases Research Unit, South African Medical Research Council, Cape Town, South Africa; [2]Department of Medicine, University of Cape Town, Cape Town, South Africa; [3]Faculty of Health Sciences, University of Ottawa, Ottawa, Canada

Abstract

Hypertension among HIV-positive populations has emerged as a new threat to the health and well being of people living with HIV, particularly among those receiving antiretroviral therapy. We reviewed the global evidence on the burden of disease (including prevalence and incidence), determinants of hypertension among HIV-positive populations, and the pharmacological management of hypertension in HIV-positive patients.

We systematically searched PubMed-MEDLINE and EMBASE from January 2000 through February 2015 for relevant studies and traced their citations through the ISI Web of Science. We also searched the websites of the World Health Organisation, the International Society of Hypertension, and the International AIDS Society and constructed a narrative data synthesis.

Hypertension is common in HIV-positive populations, with prevalence estimates ranging from 4.7 to 54.4% in high-income countries, and from 8.7 to 45.9% in low- and middle-income countries. The role of HIV-specific factors including disease severity, duration of disease, and treatments on the presence of hypertension in HIV-positive patients is reported, but patterns remain unclear. The clinical management of hypertension in HIV-positive patients is similar to those with hypertension in the general population; however, additional considerations should be given to potential drug interactions between antihypertensive agents and antiretroviral drugs to inform the clinician's selection of these therapies.

Hypertension is common in HIV-positive populations and remains an important comorbidity affecting mortality outcomes. Further research examining the development of hypertension and its associated care in HIV-positive patients is required to optimize management of the dual conditions. **(AIDS Rev. 2015;17:83-95)**

Corresponding author: Andre Pascal Kengne, andre.kengne@mrc.ac.za

Key words

HIV. Hypertension. Comorbidity. Prevalence. Risk factors.

Correspondence to:
Andre Pascal Kengne
South African Medical Research Council
PO Box 19070
Tygerberg, 7505 Cape Town, South Africa
E-mail: andre.kengne@mrc.ac.za

Introduction

The increasing global availability of antiretroviral therapy (ART) has gradually changed the landscape of the HIV pandemic. With increasing uptake of ART, HIV-associated morbidity and mortality have substantially declined and estimates of life expectancy among HIV-positive populations now approache those of the general population[1]. With more HIV-positive patients than ever now on ART and a global commitment of resolute action to mobilize resources, an AIDS-free generation is for the first time within reach[2].

However, as HIV-positive patients are now living longer and healthier lives than before, new epidemics of non-infectious comorbidities have emerged as a serious public health concern[3,4]. Hypertension, defined as having chronically high blood pressure (BP), is a leading cause of death worldwide, responsible for 13-14% of all global mortality[5]. Hypertension is a major risk factor for cardiovascular disease (CVD), including ischemic heart disease, stroke, heart failure, and is significantly associated with CVD-attributable morbidity and mortality[6]. Of all comorbidities in HIV-positive populations, hypertension and CVD have emerged as among the most important contributors of non-AIDS related mortality[7].

Causative factors of the development of these conditions in HIV-positive populations may be similar to uninfected populations. However, CVD in HIV-positive populations may also be the result of opportunistic infections in the presence of advanced immunosuppression, be a consequence of HIV-induced immune activation or derived from ART-associated dyslipidemia and insulin resistance[8].

In low- and middle-income countries, where the majority of HIV-positive populations reside, less is known about the epidemiology and risk factors for hypertension. This can be attributed to the evolution of dedicated HIV clinical management programs in developing regions, where care for HIV is often provided in isolation from other general healthcare services[9]. Furthermore, the additional costs and time associated with operating a CVD screening program in an already resource-limited environment may contribute to the relative lack of data compared to higher-income settings[10].

We aimed to review the data on the burden of disease (including prevalence and incidence) and determinants of hypertension among HIV-positive populations, as well as the pharmacological management of hypertension among HIV-positive patients.

Evidence base

We searched MEDLINE via PubMed for papers presenting on the burden, determinants, and clinical management of hypertension in HIV-positive patients. The search was restricted to January 2000 to February 2015, and used a combination of MeSH terms and keywords related to hypertension, HIV infection, determinants, diagnosis, treatment, and control. The identified articles were screened (title, abstract, and full text as appropriate) and the most relevant were included in the current review. We also examined publications from the World Health Organisation, the International Society of Hypertension, and the International AIDS Society.

We then organized our results into a priori identified themes: burden of hypertension in HIV-positive populations, determinants of hypertension in HIV-populations, and pharmacological management of hypertension in HIV-positive patients. Each study identified in our search strategy was then tabulated according to theme and findings were synthesized to construct a narrative review.

We identified 41 studies that reported on the prevalence of hypertension in HIV-positive populations (Table 1 A) and 14 studies that reported a comparative prevalence between HIV-positive and -negative populations (Table 1 B). We identified four studies that reported on incidence or time-trend in the prevalence of hypertension in HIV-positive populations (Table 2), 21 that reported on the determinants of hypertension in HIV-positive populations (Table 3), 13 that reported on the pharmacological management of HIV among hypertensive and HIV-positive populations (Table 4), and eight studies and sub-studies that reported on the awareness, treatment, and control of hypertension among hypertensive and HIV-positive populations (Appendix Table 1).

Burden of hypertension in HIV-positive populations

Prevalence of hypertension

Hypertension is a prevalent comorbidity among HIV-positive adults worldwide. Using the World Bank method of designating low- middle- and high-income countries, we found a prevalence of hypertension among HIV-positive populations of 4.7-54.4% in high-income countries and 8.7-45.9% in low- and middle-income countries (Table 1 A and 1 B). The

Table 1 A. Studies identifying prevalence of hypertension among HIV-positive populations

Study	Country	Design	Study setting	Sample size; % men	Mean age	Diagnosis	Prevalence (%)
Americas							
Chu, et al. (2011)[13]	USA	Cross-sectional	Clinic-based	854; 57%	44	SBP (and/or DBP) ≥ 140 (90) mmHg or known HTN	26
Medina-Torne, et al. (2012)[15]	USA	Cross-sectional	Clinic-based	707; 92%	41	SBP (and/or DBP) ≥ 140 (90) mmHg or known HTN	31
Balderson, et al. (2013)[11]	USA	Cross-sectional	Clinic-based	452; 72%	55.8	Participant self-report	46
Buchacz, et al. (2013)[12]	USA	Cohort	Clinic-based	3,166; 79%	47	–	54.4
Krauskopf (2013)[14]	USA	Cohort	Hospital-based	2,390; 80%	43	Participant self-report	22
Myerson, et al. (2014)[57]	USA	Cross-sectional	Hospital-based	4,278; 75%	46	SBP (and/or DBP) ≥ 140 (90) mmHg or known HTN	43
Míguez-Burbano, et al. (2014)[47]	USA	Cohort	Clinic-based	400; 72.5%	42	SBP (and/or DBP) ≥ 140 (90) mmHg or known HTN	38
Sherer, et al. (2014)[64]	USA	Cross-sectional survey	Clinical, community based		–	Patient self-report	32
Silva. et al. (2009)[65]	Brazil	Cohort	Outpatient clinic	319	39.5	–	18
De Arruda, et al. (2010)[44]	Brazil	Cohort	Hospital-based	958	≥ 18	SBP/DBP ≥ 140/90 mmHg	25.6
Sherer, et al. (2014)[64]	Brazil	Cross-sectional survey	Clinical, community based		–	Patient self-report	15
Cahn, et al. (2010)[66]	7 Latin American countries	Cohort	–	4,010	41.9	SBP/DBP ≥ 130/85 mmHg	31.5
Europe							
Flexor, et al. (2013)[67]	France	Cohort	Hospital-based	149; 77%	65.4	–	36
Glass, et al. (2006)[68]	Switzerland	Cohort	Outpatient clinics	8,033; 69%	40	SBP (and/or DBP) ≥ 140 (90) mmHg or known HTN	26.1
Nüesch, et al. (2013)[61]	Switzerland	Cohort	Clinic-based	10,361	–	–	25
Jung, et al. (2004)[45]	Germany	Cohort	Outpatient clinic	214; 90%	42	SBP (and/or DBP) ≥ 140 (90) mmHg or known HTN	29
Reinsch, et al. (2012)[69]	Germany	Cross-sectional	Clinic-based	803	44.2		21.4
Manner, et al. (2012)[38]	Norway	Cohort	Outpatient hospital	434; 72%	43	SBP (and/or DBP) ≥ 140 (90) mmHg or known HTN	34.8 ~ general population
Palacios, et al. (2006)[50]	Spain	Cohort	Clinic-based	95; 82%	40	SBP (and/or DBP) ≥ 140 (90) mmHg	26
Mothe et al (2009)[55]	Spain	Cross-sectional	Outpatient hospital	179; 76%	≥ 70	–	36
Mehta, et al. (2004)[70]	Spain	Retrospective	Hospital-based	464	–	SBP/DBP ≥ 130/85 mmHg	38.5
Bernardino, et al. (2011)[46]	Spain	Cross-sectional	Hospital-based	310; 76.8%	42	SBP (and/or DBP) ≥ 140 (90) mmHg or known HTN	20.6
Masiá, et al. (2012)[71]	Spain	Prospective	Hospital-based	1,019; 76%	40	–	9.4

(Continue)

Table 1 A. Studies identifying prevalence of hypertension among HIV-positive populations (continued)

Study	Country	Design	Study setting	Sample size; % men	Mean age	Diagnosis	Prevalence (%)
Europe							
Janiszewski, et al. (2011)[72]	Italy	Cross-sectional	Clinic-based	2,322; 63.7%	–	–	35
Fabbiani, et al. (2013)[73]	Italy	Cross-sectional	Clinic-based	245; 75.5%	46	SBP (and/or DBP) ≥ 140 (90) mmHg or known HTN	15.1
De Socio, et al. (2014)[54]	Italy	Cross-sectional	Multi-center, clinic-based	1,182; 71%	47	SBP (and/or DBP) ≥ 140 (90) mmHg or known HTN	29.3 ~ general population
Sherer, et al. (2014)[64]	Europe	Cross-sectional survey	Clinical, community based		–	Patient self-report	14
Asia							
Hejazi, et al. (2013)[48]	Malaysia	Cross-sectional	Clinic-based	340; 79%	–	SBP/DBP ≥ 130/85 mmHg	45.6
Wu. et al, (2014)[74]	Taiwan	Cross-sectional	Hospital-based	920; 92%	≥ 40	SBP (and/or DBP) ≥ 140 (90) mmHg or known HTN	17.6
Oceania							
Broom, et al. (2012)[56]	Australia	Cross-sectional	Clinic-based	180; 89%	–	SBP (and/or DBP) ≥ 140 (90) mmHg or known HTN	16
Chan, et al. (2013)[75]	Australia	Cross-sectional, audit	Clinic-based,	733; 93%	–	SBP (and/or DBP) ≥ 140 (90) mmHg	28
Sherer, et al. (2014)[64]	Australia & Korea	Cross-sectional survey	Clinical, community based		–	Patient self-report	15
Africa							
Mateen, et al. (2012)[23]	Uganda	Cohort	Outpatient clinic	5,563; 33.1%	34	SBP (and/or DBP) ≥ 140 (90) mmHg	24.8
Denue, et al. (2012)[18]	Nigeria	Cohort	Clinic-based	227; 51%	40	SBP (and/or DBP) ≥ 140 (90) mmHg	31.7
Manuthu, et al. (2008)[22]	Kenya	Cross-sectional	Outpatient hospital	295; 42%	–	–	13.4
Bloomfield, et al. (2013)[17]	Kenya	Retrospective	Clinic-based	12,194; 35.2%	43	SBP (and/or DBP) ≥ 140 (90) mmHg	8.7
Zannou, et al. (2009)[25]	Benin	Prospective cohort	Clinic-based	88; 40%	38	SBP/DBP ≥ 130/85 mmHg	42.6
Botha, et al. (2014)[76]	South Africa	Prospective cohort	Clinic-based	(ART-naive) 71; 34%	43	SBP (and/or DBP) ≥ 140 (90) mmHg or known HTN	40.9
				(on ART) 66; 26%	44		31.8
Julius, et al. (2011)[20]	South Africa	Cross-sectional	Clinic-based	304; 22%	18-45	SBP/DBP ≥ 140/90 mmHg	19.1
Malaza, et al. (2012)[21]	South Africa	Survey	Population-based	2,513/ 14,918	≥ 15	SBP (and/or DBP) ≥ 140 (90) mmHg	19.5/27.9
Sherer, et al. (2014)[64]	Cote d'Ivoire & South Africa	Cross-sectional survey	Clinical, community based		–	Patient self-report	8
Diouf, et al. (2012)[19]	Senegal	Cross-sectional	Hospital-based	242; 42%	46	SBP (and/or DBP) ≥ 140 (90) mmHg or known HTN	28.1

(Continue)

Table 1 A. Studies identifying prevalence of hypertension among HIV-positive populations (continued)

Study	Country	Design	Study setting	Sample size; % men	Mean age	Diagnosis	Prevalence (%)
Africa							
Berhane, et al. (2012)[16]	Ethiopia	Cross-sectional	Hospital-based	313; 34.8%	≥ 18	SBP (and/or DBP) ≥ 140 (90) mmHg or known HTN	16
Muronya, et al. (2011)[24]	Malawi	Cross-sectional	Hospital-based	174; 39%	41	SBP (and/or DBP) ≥ 140 (90) mmHg or known HTN	45.9
Kagaruki, et al. (2014)[77]	Tanzania	Cross-sectional	Clinical-based	671; 29.5%	38.7	SBP (and/or DBP) ≥ 140 (90) mmHg or known HTN	26.2
Global							
Sherer, et al. (2014)[64]	Global	Cross-sectional survey	Clinical, community based	2,035; 63%	–	Patient self-report	15

SBP: systolic blood pressure; DBP: diastolic blood pressure; HTN: hypertension. Table 1 B. Studies comparing the prevalence of hypertension among HIV-positive populations

Table 1 B. Studies identifying prevalence of hypertension among HIV-positive populations

Study	Country	Method	Study setting	Sample size (HIV+/HIV–)	Age average	Prevalence % (HIV+/HIV–)
Khalsa, et al. (2007)[33]	USA	Prospective cohort	Hospital-based	2,057/569 100% female	–	26/28
Triant, et al. (2007)[30]	USA	Cohort	Hospital-based	3,851/1044589	–	21.2/15.9
Önen, et al. (2010)[29]	USA	Prospective cross-sectional	Clinic-based	122/122 (83%)	55.8	54/38
Gazzaruso, et al. (2003)[28]	Italy	Case-control	Hospital-based	287/287	41	34/11
Saves, et al. (2003)[8]	France	Cross-sectional	Clinic-based	274/1,038 (81%/51%)	35-44	4.7/9.1*
Jerico, et al. (2005)[34]	Spain	Prospective cross-sectional	Hospital-Based	710/802 (72%/69%)	42	13.1/13.5
Coloma Conde, et al. (2008)[27]	Spain	Retrospective case-control	Hospital-based	740/740 (75%)	41.8	25/15
Calvo-Sánchez, et al. (2013)[78]	Spain	Case-control	Hospital-based	230/339	–	9.1/38.8
Bergersen, et al. (2003)[35]	Norway	Cross-sectional	Hospital-based	283/438 (80%/81%)	40	19/24
Baekken, et al. (2008)[36]	Norway	Cohort	Clinic-based	542/24 968	–	36.1/37.7
Ngatchou, et al. (2013)[79]	Cameroon	Cross-sectional	Clinic-based	108/96 (26%/28%)	39/41	41/44
Kendall, et al. (2014)[80]	Canada	Case-control	Clinic-based	14,005/71,410 (80.5%/48.8%)	45/47	19.3/20.3
Peck, et al. (2014)[32]	Tanzania	Cross-sectional	Clinic-based	ART-naive/HIV(–) 151/153 (41%/39%)	37/38	5.3/16.3
				On ART/HIV(–) 150/153 (23%/39%)	40/38	28.7/16.3
Ogunmola, et al. (2014)[31]	Nigeria	Cross-sectional	Hospital-based	ART-naive/HIV(–) 120/153 (43%/43%)	37/36	19/13.7
				On ART/HIV(–) 130/153 (33%/43%)	39/36	12.3/13.7

*Hypertension, systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 95 mmHg.

Table 2. Studies identifying incidence of hypertension among HIV-positive populations

Study	Country	Method	Study setting	Sample size; male %	Age average	Incidence (1000 person-years)
Thiébaut, et al. (2005)[37]	21 nations, USA, Europe, Australia	Cohort	Clinic-based	17,170; 76%	38.9	72
Manner, et al. (2012)[38]	Norway	Cohort	Outpatient hospital	434; 72%	43	29.8
Krauskopf, et al. (2013)[14]	USA	Cohort	Hospital-based	2,390; 80%	43	64.1

prevalence was highest in the USA (21.2-54.4%)[11-15] and the lowest in Africa (8.7-45.9%)[16-25]. This range in hypertension prevalence may partially be attributed to differences in study methodology, including study design (cross-sectional vs. cohort), methods of data collection (telephone vs. in-person, self-report vs. clinician-measured), study setting (clinic/hospital vs. community), sample sizes, population characteristics (age, ethnicity and sex) and the definition of the outcome variable hypertension (e.g. BP ≥ 140/90 mmHg; systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or known hypertension; BP ≥ 130/85 mmHg) (Table 1). There is also concern that, in addition to differences in screening definitions and small sample sizes, under-detection of hypertension in African regions is likely due to low clinical suspicion and limited access to resources[26].

Studies that have determined the prevalence of hypertension in both HIV-positive and HIV-negative populations are presented in table 1 B. Six studies reported a higher prevalence of hypertension in HIV-positive populations compared to HIV-negative populations[27-32]. Of the three studies including patients from the USA, two reported higher hypertension prevalence in the HIV-positive patients compared to the HIV-negative patients[29,30], while a third found no statistically significant difference[33]. Of 16 studies and substudies reviewed in this thematic section that compared their findings to the general population[15,17-21,23,24,28,34-36], seven reported a higher prevalence of hypertension in HIV-positive populations compared with the general population; three studies reported a similar hypertension prevalence to the general population, and in two studies, prevalence among the HIV-positive population was lower.

Incidence and time-trend in the prevalence of hypertension

The incidence of hypertension in the HIV-positive population has been examined in only three studies[14,37,38] (Table 3). These studies were all conducted at healthcare facilities rather than in the community. One study by Thiébaut, et al. was a multi-country cohort study with over 17,000 participants[37], while the others were conducted in Norway[38] and the USA[14]. The incidence of hypertension in these studies was 72/1000 person-years[37], 29.8/1000 person-years[38], and 64.1/1000 person-years[14], respectively. These studies did not report an incidence estimate for hypertension among a comparative HIV-negative population. The Data collection on Adverse events of Anti-HIV Drugs (D:A:D) study at different follow-up time-points was 11% in 2001, 23% in 2006, and 32% in 2011[4]. During this time period, correlation of hypertension including age and diabetes prevalence increased while body mass index remained stable. The duration on ART and proportion of patients on such therapies, as well as median CD4 count and proportion of patients achieving viral loads < 400 copies per ml, increased[4].

Determinants of hypertension in HIV-infected individuals

Many of the factors associated with the development of hypertension in HIV-positive populations can be characterized as similar to those found in HIV-negative populations, including family history, older age, excess body fat, physical inactivity, excessive alcohol consumption, and a salt-rich diet among others[39]. However, the unique role of HIV infection and its clinical management with ART is of interest to this this review. Table 3

Table 3. Studies identifying factors associated with hypertension among HIV-positive populations

Study	Country	Study design (duration in years)	Sample size; % men	Mean age (years)	Association				
					HIV duration	CD4 count	Viral load	ART	ART duration
Americas									
Khalsa, et al. (2007)[33]	USA	Cohort (5)	2,059 women	–	–	No	No	No	No
Crane, et al. (2006)[49]	USA	Cohort (7)	444; 84%	35	–	(≥ 200 cells/μl Negative	No	Yes	No
Seaberg, et al. (2005)[51]	USA	Cohort (20)	5,578 men	32.6	No	–	–	–	ART ≥ 2 yrs Positive
Medina-Torne, et al. (2012)[15]	USA	Cross-sectional	707; 92% male	41	(≥ 10 yrs) Positive	No	Negative	No	No
Krauskopf, et al. (2013)[14]	USA	Cross-sectional	2,390	43	(≥ 6 yrs) Positive	Positive	No	No	–
	USA	Prospective cohort	2,390	43	No	No	No	No	–
Factor, et al. (2013)[43]	USA	Cohort (3)	329 men	54.4	–	No	–	Negative	–
	USA	Cohort (3)	330 women	43.4	–	Positive	–	No	–
Míguez-Burbano, et al. (2014)[47]	USA	Cohort (not provided)	400	42	No	No	No	No	No
de Arruda, et al. (2010)[44]	Brazil	Case-control	958	–	–	No	–	No	No
Europe									
Palacios, et al. (2006)[50]	Spain	Cohort (1)	95	40	–	Negative	–	–	Positive
Coloma Conde, et al. (2008)[27]	Spain	Retrospective	740; 75% male	41.8	No	No	No	–	No
Bernardino, et al. (2011)[46]	Spain	Cross-sectional	310; 76.8% male	42	(≥ 10 yrs) No	No	No	Positive	No
Baekken, et al. (2008)[36]	Norway	Cohort	542	–	No	–	–	–	HAART ≥ 5 yrs Positive
Manner, et al. (2012)[38]	Norway	Cohort (3)	434	43	(≥ 10 yrs) Positive	No	No	No	No
Jung, et al. (2004)[45]	Germany	Cohort (1)	214	42	(7 yrs) No	No	No	No	No
Asia									
Hejazi, et al. (2013)[48]	Malaysia	Cross-sectional	340	–	(≥ 10 yrs) No	No	No	No	No
Africa									
Diouf, et al. (2012)[19]	Senegal	Cross-sectional	242	46	–	No	No	–	No
Denue, et al. (2012)[18]	Nigeria	Cohort (2)	227	40	No	No	–	–	HAART ≥ 2 yrs Positive
Ogunmol, et al. (2014)[31]	Nigeria	Cross-sectional	403	–	–	No	–	No	No
Bloomfield, et al. (2013)[17]	Kenya	Retrospective (3)	12,194; 35.2%	–	–	Positive in women	–	–	No
Peck, et al. (2014)[32]	Tanzania	Cross-sectional	454	–	–	(> 500) Positive	–	Positive	No
Dillon, et al. (2013)[81]	14 countries	Meta-analysis of 52 cross-sectional studies	29,755	–	–	–	–	Positive	–

Table 4. Studies identifying pharmacological management of HIV among hypertensive and HIV-positive populations

Reference	Country	Design	FUP (yrs)	Protease inhibitors										NNRTIs			NRTIs									
				PIs	Nelfinavir	Lopinavir	Indinavir	Atazanavir	Saquinavir	Amprenavir	Ritonavir	Lopinavir/Ritonavir	Non-PIs	NNRTIs	Efavirenz	Nevirapine	NRTIs	Lamivudine	Zidovudine	Stavudine	Tenofovir	Didanosine	Abacavir	Zalcitabine	Emtricitabine	Tenofovir/Lamivudine
Chow, et al. (2003)[52]	USA	Retrospective cohort	6	(+)										(+)			na									
Thiebaut, et al. (2005)[37]	Multi-country	Prospective cohort	4	na										(–)			na									
Palacios, et al. (2006)[50]	Spain	Prospective cohort	1	(+)										(+)												
Crane, et al. (2006)[49]	USA	Prospective cohort	7	na	(–)		(–)	(–)				(+)		na	(–)				(–)		(+)					(+)
Khalsa, et al. 2008[33]	USA	Prospective cohort	6.5	na									na	na			na									
Grandominico, et al. (2008)[82]	USA	Prospective cohort	0.5	na									(–)													
De Arruda, et al. (2010)[44]	Brazil	Case-control study		na										na			na									
Medina-Torne, et al. (2012)[15]	USA	Cross-sectional		na		na								na	na		na	na	na		na	na	na		na	
Wilson, et al. (2009)[53]	UK	Cross-sectional		na										(+)			na									
Diouf, et al. (2012)[19]	Senegal	Cross-sectional										(–)								na						
Krauskopf, et al. (2013)[14]	USA	Prospective cohort	6.5	na										na												
Hejazi, et al. (2013)[48]	Malaysia	Cross-sectional		na															na	na						
Peck, et al. (2014)[32]	Tanzania	Cross-sectional		(+)											na	na			na	na	na					

PI: protease inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; FUP: follow-up period; na: no association; (+): increased blood pressure; (-): reduced blood pressure.

displays studies that report clinical correlates of hypertension among HIV-positive patients. We discuss the role of the severity and duration of HIV infection, as well as the role of ART on the development of hypertension.

Severity of HIV infection and hypertension

Severe HIV infection is typically characterized by a low CD4 count, indicating immune system suppression and a poor lymphocytic response, or with a high viral load[40]. Lymphocyte proliferation may play a role in the maintenance of BP levels[41] since inhibition of enzyme production required for the growth of T-cells with the drug mycophenolate mofetil results in a significant drop in BP levels[42]. The role of T-cells in regulating BP among HIV-positive patients remains under investigation. Four studies reported a positive association between increasing CD4 count and rising BP levels and/or incident hypertension in HIV-infected participants[14,17,32,43] (Table 3). However, 13 studies failed to show a relationship between BP levels and CD4 count[14,15,18,19,27,31,33,38,43-48], while two studies reported inverse associations between CD4 count and BP levels[49,50]. There appears to be no reported relationship between HIV plasma viral load and the development of hypertension[14,19,27,33,38,45-49].

Duration of HIV infection and hypertension

We identified 12 studies in 11 published manuscripts[14,15,18,27,36,38,45-48,51] that examined the relationship between the duration of HIV infection and the presence of hypertension (Table 3). Of these, two studies (one cross-sectional and one cohort) reported significant positive associations between duration of HIV infection and development or presence of hypertension[15,38], while seven studies found no association[18,27,36,45-48,51]. In a single published manuscript, Krasukopf, et al. reported a significant positive association between HIV infection and the presence of hypertension in a cross-sectional study, but no association in the follow-up cohort[14]. These associations, in patients with more than 10 years of HIV infection, appear to be present independent of HAART use and patient age, suggesting that a shorter exposure period may not be sufficient to demonstrate the HIV effects on hypertension.

Antiretroviral therapy and hypertension

Five cohort studies of between one and five years of follow-up time demonstrated that ART independently predicted hypertension[18,33,36,50,51] (Table 3). However, a handful of studies using cross-sectional and retrospective designs reported no effect[15,17,19,27,48]. These methodological differences may partly explain the discrepancy in the association between the length of ART utilization and elevated BP in HIV-positive patients.

In addition to the duration of ART, the class of antiretroviral drugs used may play a role in the development of hypertension (Table 4). Some studies highlight the role of protease inhibitors (PI)[32,50,52], nucleoside reverse transcriptase inhibitors (NRTI)[49], and non-nucleoside reverse transcriptase inhibitors (NNRTI)[50,53]. Other studies found no association between class of antiretroviral drug and the development of hypertension[14,15,33,37,44,48]. Prospective cohort studies of adequate duration that control for confounding factors, such as age, baseline BP, and adherence to ART, among other influences, are required to determine the effects of the various antiretroviral drugs on the development of hypertension.

Awareness, treatment, and control of hypertension in HIV-positive patients

Awareness, treatment, and control rates were less reported across studies. Where reported, awareness rate was 12% in ART-naive and 25.6% in ART-treated HIV-positive patients in Tanzania[32], while it was 64.9% among HIV-positive patients in Italy[54]. Compared with HIV-negative hypertension patients in Tanzania, the awareness rate was twofold higher in ART-treated HIV-positive patients (12 vs. 25.6%)[32]. Treatment rate was zero percent among ART-naive and 16.3% among ART-treated HIV-positive patients in Tanzania[55], and ranged from 42% in Australia[56] to 75% in the USA[57] across five studies from high-income countries.

The principles of clinically managing hypertension in HIV-positive patients are similar to those of the general population, where the presence of comorbidities, such as heart failure, ischemic heart disease, diabetes, and chronic renal disease, dictate the class of anti-hypertensive agent prescribed[58]. However, in HIV-positive patients with hypertension, an additional consideration of the effect of possible drug interactions between antihypertensive agents and antiretroviral drugs must inform the clinician's selection of both therapies[59].

Pharmacokinetic interactions between antiretroviral drugs and antihypertensive agents are more likely with NNRTIs or PIs (Appendix). Among available antihypertensive medications, calcium channel blockers (CCB)

are reported to interact with PIs and NNRTIs; their concentration levels increased with some antiretroviral drugs, but decreased with others[60]. Plasma concentrations of certain beta-blockers may be prolonged with some PIs, while the use of diuretics with indinavir may increase the development of kidney stones through volume depletion. Peyriere, et al.[59] suggest that the antihypertensive treatment of choice in HIV-positive patients on ART may be renin-angiotensin system (RAS) inhibitors, such as angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB), and in combination with CCBs or low-dose diuretics.

The hypertension control rates among HIV-positive patients ranged from zero percent among ART-naive patients in Tanzania[32] to 89.8% in the USA[13]. There appears to be no clear difference between control of hypertension through clinical management between HIV-positive and HIV-negative patients[13,32,38,56,57,61]. A lower prevalence of hypertension control in HIV-positive patients compared to HIV-negative patients was reported in Norway (20 vs. 26%)[38], and Australia (25.0 vs. 39.7%)[56], while better control of hypertension was reported in HIV-positive patients compared to the HIV-negative patients in the USA (89.8 vs. 30.0%)[13]. Despite regular and routine access to healthcare, the low rates of hypertensive control in HIV-positive patients highlights the possible one-dimensional focus of HIV care. Enhanced simultaneous surveillance of hypertension and HIV, particularly in low- and middle-income countries, would generate the empirical data needed to better understand the dual burden of disease and identify places to target coordinated care[62].

Conclusion

This review indicates that hypertension is prevalent in HIV-positive populations. Similar to the general population, risk factors that contribute to the development of hypertension include genetic and lifestyle factors; however, the unique role of HIV and its disease management may also play a substantial role. Prospective cohort studies of sufficient duration comparing HIV-positive and HIV-negative cohorts are needed to determine the impact of HIV-attributable factors on the development of hypertension. Potential interactions between antihypertensive drugs and antiretroviral agents, especially PIs and NNRTIs, need to guide the selection of both therapies in HIV-positive patients with hypertension. Many HIV-infected patients with hypertension, similar to the general population, receive suboptimal hypertension care despite being at higher risk than their HIV-uninfected counterparts for CVD complications[63]. A focus on vulnerable populations by strengthening social protections and improving access to healthcare services as well as integrating public health activities for both HIV and CVD should extend beyond healthcare services to prevention and health promotion activities.

Conflict of interest

The authors declare no conflict of interest

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Appendix 1 Table 1. Studies identifying the awareness, treatment and control of hypertension among HIV-infected individuals

Study	Country	Study design	Sample size; male %	Age average (years)	Hypertensive management		
					Awareness (%)	Treated (%)	Controlled (%)
Chu, et al. (2011)[13]	USA	Cross-sectional	854; 57%	44	Not provided	Not provided	89.8
Myerson, et al. (2014)[57]	USA	Cross-sectional	4,278; 29%	46	Not provided	75	57
Míguez-Burbano, et al. (2014)[47]	USA	Cohort	400; 72.5%	42	Not provided	45	Not provided
Manner, et al. (2012)[38]	Norway	Cohort	434; 72%	43	Not provided	49	22
De Socio, et al. (2014)[54]	Italy	Cross-sectional	1,182; 71%	47	64.9	52.9	33
Broom, et al. (2012)[56]	Australia	Cross-sectional	180; 89%	–	Not provided	42	25
Peck, et al. (2014)[32]	Tanzania	Cross-sectional, comparative	ART-naive/ HIV(-) 151/153; (41%/39%)	37/38	~ 12	0	0
			On ART/ HIV(–) 150/153; (23%/39%)	40/38	25.6/12.0	16.3/0	2.3/0

Appendix Table 2. Drug-drug interactions between antiretroviral and anti-hypertensive drugs. Adapted from www.hiv-druginteractions.org[60]

Anti-hypertensive drugs	ATV/r	DRV/r	FPV/r	IDV/r	LPV/r	SQV/r	EFV	ETV	NVP	RPV	MVC	DTG	EVG/c	TDF
Angiotensin Antagonists														
Irbesartan	↓	↓	↓	↓	↓	↓	↑	↑	↔	↔	↔	↔	↓	↔
Losartan	↓[a]	↓[a]	↓[a]	↓[a]	↓[a]	↓[a]	↑[b]	↑[b]	↔	↔	↔	↔	↓[a]	↔
B-blockers														
Bisoprolol	↑[d]	↑	↑	↑	↑[d]	↑[d]	↔	↔	↔	↔	↔	↔	↑	↔
Carvedilol	↑↓[d]	↑↓	↑↓	↑↓	↑↓[d]	↑↓[d]	↑↓	↑↓	↔	↔	↔	↔	↑	↔
Metoprolol	↑[d]	↑	↑	↑	↑[d]	↑[d]	↔	↔	↔	↔	↔	↔	↑	↔
Propanolol	↑[d]	↑	↑	↑	↑[d]	↑[d]	↔	↔	↔	↔	↔	↔	↑	↔
Calcium channel Antagonists														
Amlodipine	↑[c]	↑	↑	↑	↑	↑[c]	↓	↓	↓	↔	↔	↔	↑	↔
Diltiazem	↑[c]	↑	↑	↑	↑	↑[c]	↓	↓⇑	↓	⇑	⇑	⇑	↑	↔
Felodipine	↑[c]	↑	↑	↑	↑	↑[c]	↓	↓	↓	↔	↔	↔	↑	↔
Lacidipine	↑[c]	↑	↑	↑	↑	↑[c]	↓	↓	↓	↔	↔	↔	↑	↔
Lercanidipine	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔
Nicardipine	↑[c]	↑	↑	↑	↑	↑[c]	↓	↓⇑	↓	⇑	⇑	⇑	↑	↔
Nifedipine	↑[c]	↑	↑	↑	↑	↑[c]	↓	↓	↓	↔	↔	↔	↑	↔
Nisoldipine	↑[c]	↑	↑	↑	↑	↑[c]	↓	↓	↓	↔	↔	↔	↑	↔
Verapamil	↑[c]	↑	↑	↑	↑	↑[c]	↑	↑⇑	↑	⇑	⇑	⇑	↑	↔
Diuretics														
Benzoflumethiazide	?	?	?	?	?	?	↔	↔	↔	↔	↔	↔	?	↔
Furosemide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	⇑
Indapamide	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔
Torasemide	↓	↓	↓	↓	↓	↓	↑	↑	↔	↔	↔	↔	↓	↔
Others														
Doxazosin	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔

Color legend

These drugs should not be co-administered.

Potential interaction, which may require a dose adjustment or close monitoring.

Potential interaction but weak intensity predicted. No prior dose titrate is recommended.

No clinically significant interaction expected.

↑: potential increased exposure of the anti-hypertensive drug; ↓: potential decreased exposure of the anti-hypertensive drug; ↔: no significant effect; ⇑: potential increase exposure of the antiretroviral drug; a: concentrations of parent drug decreased but concentrations of metabolite increased; b: concentrations of parent drug increased but concentrations of metabolite decreased; c: ECG monitoring recommended; d: risk of PR interval prolongation.

Note: Although some drug interactions require a dose adjustment based on the drug metabolic pathway, clinical experience with a particular anti-hypertensive and antiretroviral drugs may indicate that dose adjustments are not a prior requirement.

ATV: atazanavir; DRV: darunavir; FPV: fosamprenavir; IDV: indinavir; LPV: lopinavir; SQV: saquinavir; EFV: efavirenz; ETV: etravirine; NVP: nevirapine; RPV: rilpivirine; MVC: maraviroc; DTG: dolutegravir; EVG: elvitegravir; TDF: tenofovir DF.