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Hypertension in HIV: Management and Treatment

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Abstract

Hypertension is among the leading risk factors for cardiovascular disease and accounts for 6% of adult deaths worldwide. It is estimated that in 2013, hypertension was responsible for at least 45% of deaths due to heart disease and 51% of deaths due to stroke. Accordingly, management of hypertension and its long-term complications in HIV-infected subjects is a significant component of routine care. The choice of an effective anti-hypertensive therapy in HIV-infected patients is important and must be made carefully in order to prevent cardiovascular mortality and morbidity in these patients. **(AIDS Rev. 2017;19:198-211)**

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Key words

Blood pressure. AIDS. Cardiovascular disease. Antihypertensive treatment.

Introduction

The life expectancy of HIV-infected patients in high-income countries is approaching that of the general population[1,2]. Along with improved survival, the practice and complexity of HIV management have changed. As the demographics and life expectancy of those affected evolve, so does our understanding of the disease. As a result of this increase in life expectancy, up to 50% of the HIV population will be over 50 years old by the year 2015[3]. Because the HIV infected are living longer, diseases of the elderly, such as cancer or cardiovascular disease (CVD), now emerge as prominent causes of death in this population[4-10]. Large epidemiologic studies have found that HIV-infected subjects are likely to be at higher risk for premature CVD compared to the general population[11,12]. The prevention and management of risk factors in HIV-infected populations is particularly important given their increased CVD morbidity and mortality. In a meta-analysis, the pooled relative risk for CVD in HIV-infected individuals compared to non-infected individuals was 1.61. Furthermore, the relative risk for CVD was even greater when comparing HIV patients treated with combined antiretroviral therapy (cART) to untreated HIV[13].

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Cardiovascular disease in HIV populations

Different studies seem to evidence an increased cardiovascular risk in the HIV population. The relationship between CVD and HIV seems to be the result of different factors[14]. Premature atherosclerotic CVD among HIV-infected people is well known[15]. Therefore HIV-infected subjects compared with those HIV negative showed about 50% greater occurrence of myocardial infarction[16] or 1.5 times higher in acute coronary syndrome compared to the

uninfected population[17]. The association between vascular disease and HIV shows an increased in prevalence of vascular disease, regardless of the severity of HIV viral load, increased atherogenic lipoprotein, and chronic inflammation[18]. In HIV populations we observe a higher prevalence of traditional cardiovascular risk factors when compared to the uninfected population[19]. In addition, HIV infection itself leads to an early decrease in HDL cholesterol levels along with an increased CVD risk[20]. Another finding is the cardiometabolic effects of cART; investigations have focused on protease inhibitors (PI) and nucleoside reverse transcriptase inhibitors (NRTI). Older PIs have been associated with dyslipidemia[9]. PIs are also known to contribute to endothelial dysfunction and insulin resistance[21]. PIs can lead to atherosclerotic disease due to an upregulation of CD 36-dependent cholesterol ester. First-generation PIs showed that they promote atherosclerotic plaque formation[22]. The NRTIs induce mitochondrial toxicity such as inhibiting DNA polymerase γ or depletion of mitochondrial DNA that may manifest as alterations of organ functions[23,24]. For example, zidovudine causes myocyte mitochondrial damage, which is reversed after discontinuation of the drug[25]. Recent abacavir exposure is associated to CVD[26,27]. Several studies show direct HIV damage to the vascular endothelium. Endothelial dysfunction is a major component of CVD; in fact, it is associated with increased cardiovascular events[28]. Given the biochemical pathways leading to endothelial dysfunction, studies showed different contributors, such as soluble intercellular adhesion molecules, tissue plasminogen activator molecules, adipokine, interleukin (IL)-6, and soluble vascular cell adhesion molecule 1, in this dysfunction cascade[29,30]. Evidence suggests that after adjustment for known cardiovascular risk factors, HIV RNA replication is associated with increased levels of soluble vascular cell adhesion molecule 1, chemokine ligand 2, and decreased levels of IL-10[31]. Moreover, HIV alters the endothelial progenitor cell trafficking by infecting and depleting progenitors belonging to the hematopoietic lineage[32]. Naive patients experience a significant depletion of the hematopoietic progenitor colony forming unit/endothelial cell compartment compared with healthy persons. Similarly, hematopoietic progenitor colony forming unit/endothelial cells in the group of patients receiving cART was significantly higher than in naive patients, although it was lower than in healthy group[33]. Therefore, after HIV infection the vascular endothelium induces an inflammatory response through leucocyte recruitment, cytokine production, and coagulator system derangements[34]. Modifiable cardiovascular risk factors are more prevalent in HIV populations[35].

Hypertension in HIV populations

The incidence of hypertension in HIV-infected patients is growing and is only partly related to the improved survival and the aging effect of the HIV population[36]. Older HIV-infected patients develop more hypertension and other cardiovascular comorbidities than what is expected due to aging in the HIV-uninfected population[37]. Hypertension prevalence in HIV individuals is estimated to range from 19-54%[38]. Moreover, by stratifying for age and hypertension prevalence, in HIV-positive people under 35 years of age, the prevalence of hypertension is around 10%, while in HIV-positive populations ranging in age from 65-75 years, it is over 60%[39]. Some studies have shown that hypertension is more prevalent among HIV-positive groups than among HIV-negative groups[40,41]. Many risk factors for hypertension in the general population have also been associated with hypertension in HIV-infected subjects, such as older age, male gender, African American ethnicity, visceral adiposity, body mass index (BMI) > 30, diabetes, dyslipidemia, chronic kidney disease, and previous CVD[39-42]. Moreover, the association between higher blood pressure (BP) and acute myocardial infarction was stronger for HIV-positive compared to HIV-negative populations[38]. The causes of the high prevalence of hypertension in HIV-positive populations remain unclear and may be related to the HIV-dependent endothelial inflammatory process and to endothelial damage from antiretroviral drugs[5,32,33,43,44]. In the MACS study, the use of antiretroviral drugs for more than two years was associated with hypertension, cART lasting for 2-5 years and for more than five years was associated with odds ratio, for hypertension of 1.51 and 1.7, respectively[45]. In another trial conducted in Norway, the lowest prevalence of hypertension was found in HIV-positive individuals treated with cART for less than two years, observing a continuous increase in the prevalence, from 23% in those treated for less than two years to 44% in those treated with cART for more than five years[46]. This data was confirmed by a meta-analysis that showed how cART exposure was associated with increased systolic and diastolic BP levels[47].

Some studies explored the association between antiretroviral drugs and BP, with conflicting results. There was evidence for use of non-nucleoside reverse transcriptase inhibitors (NNRTI). A study showed lower risk of development of hypertension[48], while showing an increased risk of hypertension[49]. For nucleoside reverse transcriptase inhibitor (NRTI) studies, it found an association between hypertension and tenofovir exposure[46,47,50]. For PIs, several studies showed an association with BP elevation. In particular, treatment with lopinavir/ritonavir showed to be significantly associated with hypertension[50]. Another study reported that indinavir-containing regimes were associated to hypertension[51]. In addition, PIs seem to induce the activation of the renin angiotensin system[52].

Hypertension has been associated with increased risk of CVD and stroke in several studies of HIV individuals. Among the participants affected by hypertension in a Swiss HIV cohort, each 10 mmHg of increase in systolic BP was associated with a hazard ratio for CVD events of 1.18, after adjustment for cardiovascular risk factors and cumulative exposure to PIs or triple-nucleoside regimens[53]. Another relevant study, the Veterans Aging Cohort Study, examined whether HIV-infected people with hypertension had a higher risk of myocardial infarction compared to uninfected subjects. The median follow up was 5.9 years and 860 myocardial infarction events were recorded. Low and high prehypertension and hypertension, regardless of antihypertensive treatment in HIV-positive individuals, were associated with an increased risk of myocardial infarction compared to HIV-negative, untreated, normotensive individuals[54]. Several studies showed that, compared to normotensive HIV populations or hypertensive HIV-negative populations, hypertensive HIV populations had more comorbidities. In fact a BMI > 25 kg/m^2, increased albumin urinary excretion, dyslipidemia, and insulin resistance were all associated with hypertension in the HIV population[8,55,56]. Finally, there are potential pharmacokinetic and metabolic interactions between antihypertensive drugs and cART[57].

Clinical implications

Hypertension is a major, partially modifiable risk factor for the development of major cardiovascular complications[58]. Therefore, lowering BP substantially reduces the risk of developing such complications[59]. In fact, clinical trials conducted in the general population have shown that treatment of hypertension reduces the risk of CVD outcomes, including incident stroke (up to 40%), myocardial infarction (up to 25%) and heart failure (up to 65%)[60,61]. Moreover, BP control among treated hypertensive patients is very low. In a general population study in Italy, BP was controlled in approximately 50% of the hypertensive population, with an awareness of hypertension in approximately 65% of the patients[59]. A recent study in an HIV population in Italy showed that only 33% of hypertensive subjects achieve the recommended BP target. The data was remarkable in that approximately 50% of the population was not treated with anti-hypertensive drugs, despite having hypertension[39]. However, the target for BP lowering is debated. Observational trials have shown a progressive increase in the cardiovascular risk as systolic BP rises above 115 mmHg, but the available evidence from randomized controlled trials in the general population showed benefit only for treatment of systolic BP > 150 mmHg[62]. Furthermore, in a trial that enrolled diabetic hypertensive subjects, the rate of stroke was lower when the systolic BP target was < 120 mmHg. A recent trial (SPRINT) that enrolled 9,361 persons with a systolic BP > 130 mmHg, with increased cardiovascular risk and without diabetes, showed that lowering systolic BP to a target goal of < 120 mmHg resulted in a significantly lower rate of fatal and non-fatal cardiovascular events and death from any cause compared to the standard goal of < 140 mmHg[63]. A recent meta-analysis on the effects of intensive BP lowering on cardiovascular and renal events showed a reduction in major cardiovascular events in the intensive BP lowering group. Furthermore, it is still not yet clear if all patients need intensive antihypertensive treatment[64], in particular patients with HIV-infection or the very elderly.

Management in hypertensive patients

The guidelines for hypertension management in HIV populations were based on those regarding the general population[65]. The initial evaluation of a hypertensive patient should consist of the following steps: confirmation of the diagnosis of hypertension, detection of all the causes of secondary hypertension, and assessment of the cardiovascular risk and the concomitant clinical conditions. This calls for BP measurement, medical history, family history, physical examination, and laboratory tests. Some of the investigations are needed in all patients, while others are only in specific patient groups.

Table 1. Hypertension: Grading and management

Other risk factors, asymptomatic organ damage or disease	Blood pressure (mmHg) High normal SBP 130-139 or DBP 65-69	Blood pressure (mmHg) Grade 1 hypertension SBP 140-159 or DBP 90-99	Blood pressure (mmHg) Grade 2 hypertension SBP 160-179 or DBP 100-109	Blood pressure (mmHg) Grade 3 hypertension SBP ≥ 180 or DBP ≥ 110
No other risk factors	No BP intervention	Lifestyle change for several months Then add BP drugs targeting < 140/90	Lifestyle change for several weeks Then add BP drugs targeting < 140/90	Lifestyle change Immediate BP drugs targeting < 140/90
1-2 risk factors	Lifestyle change No BP intervention	Lifestyle change for several weeks Then add BP drugs targeting < 140/90	Lifestyle change for several weeks Then add BP drugs targeting < 140/90	Lifestyle change Immediate BP drugs targeting < 140/90
≥ 3 risk factors	Lifestyle change No BP intervention	Lifestyle change for several weeks Then add BP drugs targeting < 140/90	Lifestyle change BP drugs targeting < 140/90	Lifestyle change Immediate BP drugs targeting < 140/90
Organ damage, CKD stage 3 or diabetes	Lifestyle change No BP intervention	Lifestyle change BP drugs targeting < 140/90	Lifestyle change BP drugs targeting < 140/90	Lifestyle change Immediate BP drugs targeting < 140/90
Symptomatic CVD, CKD stage ≥ 4 or diabetes with organ damage/risk fators	Lifestyle change No BP intervention	Lifestyle change BP drugs targeting < 140/90	Lifestyle change BP drugs targeting < 140/90	Lifestyle change Immediate BP drugs targeting < 140/90

Modified from EACS Guidelines.

For BP measurement, conventional office BP measurement by the use of a validated device is the gold standard for screening, diagnosis, and management of hypertension. Hypertension is defined as a systolic BP ≥ 140 mmHg and /or diastolic BP ≥ 90 mmHg. The diagnosis of hypertension should be based on at least two BP measurements in the seated position per visit on at least two visits[66]. Estimation of glomerular filtration rate, urinary proteins, microalbuminuria, lipid parameters, and fasting glucose are considered routine tests in all patients with hypertension. Electrocardiography is recommended in all hypertensive patients, but other cardiovascular tests, such as echocardiography or Holter monitoring, should be considered after the evaluation of physical examination, history, and electrocardiogram findings. Decisions on the management of hypertensive patients depend on the initial level of total cardiovascular risk and on BP levels. Cardiovascular risk factors, asymptomatic organ damage, the presence of diabetes, symptomatic CVD, or chronic kidney disease are currently used for stratification. The classification in low, moderate, high, and very high risk refers to 10 years risk of cardiovascular mortality as defined in the 2012 Joint CVD Prevention Guidelines[65,67] (Table 1). Appropriate lifestyle changes are the milestone for the prevention of hypertension and are also important for its treatment. These are the recommendations: salt restriction to 6 g/day; increased consumption of vegetables, fruits, and low fat products; moderation of alcohol < 30 g ethanol/day in men (< 20 g ethanol/day in women); a BMI of < 25 g/m^2; regular aerobic exercise (more than 30 minutes/day, 5-7 days per week); and smoking cessation[65,66].

Initiating antihypertensive therapy

The decision to start a therapy is related to BP levels and cardiovascular risk factors. Antihypertensive drug therapy must be initiated in patients with grade 2 hypertension with multiple risk factors or

grade 3 hypertension with or without risk factors. Antihypertensive drug therapy should be considered in patients with moderate or low risk when BP remains > 140/90 mmHg after several weeks or months of appropriate lifestyle measures. In elderly patients, it is recommended to start antihypertensive treatment when BP is > 160 mmHg. Guidelines do not recommend initiating antihypertensive therapy in the range of high-normal blood pressure and in younger persons with grade 1, isolated, systolic blood pressure. A systolic BP goal of < 140 mmHg is recommended in all hypertensive patients, with the exception of the very elderly patients for whom the goal is < 150 mmHg. A target of < 130 mmHg could be considered in patients with proteinuria. A diastolic BP goal of < 90 mmHg is recommended for every patient, except for those with diabetes for whom values < 85 mmHg are recommended[65,67]. On the other hand, the recent SPRINT trial showed that in patients with high cardiovascular risk, an intensive treatment aiming at a systolic BP of < 120 mmHg resulted in lower rates of fatal and non-fatal major cardiovascular events and death from any cause, compared to a standard treatment with systolic BP target of < 140 mmHg, although there was a significantly higher rate of adverse events in the intensive-treatment group[63]. In the Veterans cohort, HIV-infected pre-hypertensive patients showed an increased risk of myocardial infarction compared to uninfected veterans[54]. This data highlights the need for a more intensive strategy of treatment with new BP targets for some HIV-positive hypertensive patients (Table 1).

Antihypertensive drugs in HIV-infected patients

Several classes of drugs can be used in the treatment of hypertension, with different interactions with cART. The choice of antihypertensive drugs in HIV-infected patients must also take into account several factors related to the metabolic pathways of antiretroviral and antihypertensive drugs, with the potential of pharmacokinetic drug interaction, and the effect of antihypertensive drugs on some biological parameters. Pharmacokinetic interactions between antiretroviral drugs and antihypertensive drugs are more expected with NNRTIs and PIs. For NNRTIs in particular we can mention the inducer effect of nevirapine, efavirenz, and, to a lesser degree, etravirine and rilpivirine, and the inhibitor effect of efavirenz and etravirine on the same cytochrome P 450 isoenzymes. For PIs, the potent inhibitor effect of most drugs are on the class CYP3A4 and, to a lesser extent, of ritonavir, cobicistat, and lopinavir on CYP2D6. Significant interactions are unlikely to occur with raltegravir, dolutegravir, and maraviroc since they do not affect the cytochrome P450 activity. Some interactions can be expected with the integrase inhibitor elvitegravir on CYP3A4, and the co-formulation with cobicistat increases the interaction risk[68].

We have three classes of diuretics (thiazides, potassium-sparing, and loop diuretics) that inhibit sodium reabsorption at different anatomic segments of the tubule. The potential for pharmacokinetic drug interactions between antiretrovirals and the three classes of diuretics is low. Anyway, since loop and thiazide diuretics are excreted by glomerular filtration and tubular secretion, increasing both natriuresis and diuresis, they can interfere with drugs that are primarily eliminated by kidneys such as tenofovir. Diuretics have adverse metabolic effects, such as dyslipidemia, hyperglycemia, and hyperuricemia, and facilitate new-onset diabetes. Consequently, in the general population, thiazide diuretics are not recommended in patients with metabolic syndrome[67]. Considering that metabolic syndrome is a highly prevalent condition within the HIV populations[69], thiazide diuretics are not recommended in monotherapy or at high dose in most of the HIV-infected patients. Thiazides may be used in the prevention of osteoporosis, as they increase bone mineral density by raising renal calcium reabsorption, secondarily to the inhibition of the thiazide-sensitive sodium/chloride co-transporter in the distal tubule[70]. Therefore, thiazide diuretics can be used for patients with stage 1-3 chronic kidney disease, while a loop diuretic can be used in all stages of chronic kidney disease[71]. Among diuretics, the majority of interactions occur with the use of indapamide and torasemide, which are metabolized mainly by CYP450 and CYP2C9, respectively.

Alpha blockers are agents that act as selective blockade of alpha-1 adrenergic receptors. Alpha blockers relax certain muscles and help small blood vessels remain open. These drugs are not recommended as monotherapy for hypertension. Doxazosin and terazosin are metabolized mainly by CYP3A4. Therefore, PIs and pharmacokinetic enhancers increase the levels of these drugs and NNRTIs reduce their plasmatic levels. Prazosin is extensively metabolized, primarily by demethylation

and conjugation, but interaction with PIs and NNRTIs cannot be excluded.

Beta blockers inhibit the action of beta receptors; there are cardio-selective beta blockers, non-selective beta blockers, and beta blockers with effects also on alpha-1 receptors. Clinically significant interactions with NNRTI are not expected, since beta blockers are primarily metabolized by CYP2D6[57]. On the other hand, we expect significant interactions with ritonavir and cobicistat or with boosted PIs, that may increase plasma concentrations of beta blockers, increasing or prolonging their therapeutic effects and adverse reactions. In these circumstances, a beta blocker reduction may be needed[72]. Beta blockers have adverse metabolic effects such as dyslipidemia and hyperglycemia. Consequently, in the general population, they are not recommended in patients with metabolic syndrome[67]. Nebivolol, however, has shown a neutral effect on glucose and lipid metabolism[73] and it should be preferred if beta blockers are necessary.

Calcium channel blockers (CCB) are a heterogeneous group of agents sharing the property of blocking the transmembrane flow of calcium ions through voltage-gated channels. There are two subclasses: dihydropyridines (most used) and non-dihydropyridines. All the CCBs are substrates for CYP3A4. A few studies describe the interactions between CCBs and PIs, with an increase of the area under the curve (AUC) of dihydropyridine and non-dihydropyridine CCBs[74-76]. Indeed, if the coadministration of CCBs and PIs is needed, it should be initiated at low doses, with a careful titration to response, and monitoring adverse effects. In the coadministration with NNRTIs, these may decrease the bioavailability of CCBs, and titration is recommended. CCBs do not show adverse effects on glucose metabolism, lipid metabolism, or renal function. CCBs have some positive effects on vascular diseases such as stroke, arteriopathy of the lower limbs, and Raynaud disease, related to their vasodilator effects[77].

Angiotensin converting enzyme (ACE) inhibitors block the activity of angiotensin enzyme, a potent vasoconstrictor and stimulant for aldosterone secretion. The ACE inhibitors are not involved in any significant interaction with CYP450, and therefore no interaction with cART is expected. The ACE inhibitors demonstrated favorable effects on mortality and glucose homeostasis. In fact, a reduction in the rate of new-onset diabetes has been observed during ACE-inhibitor treatment compared with diuretics or beta blockers[78]. The ACE inhibitors reduce protein excretion and further slow the progression rate of kidney disease[79].

Angiotensin receptors blockers (ARB) inhibit the activity of angiotensin enzyme, a potent vasoconstrictor and stimulant for aldosterone secretion, at the level of angiotensin II receptors. Some interactions between cART and ARBs are expected. Losartan is bio-activated by CYP2C9, and therefore drugs that inhibit CYP2C9, such as etravirine or efavirenz, can reduce the efficacy of losartan by reducing the formation of its active metabolite. Moreover, losartan is also metabolized by CYP3A4, and therefore PIs can increase the levels of losartan[72]. For irbesartan and candesartan, coadministration with PIs, ritonavir, and cobicistat may decrease their plasma concentrations, while coadministration with etravirine or efavirenz may increase their plasma concentrations, although these concentration alterations may be not clinically relevant. Valsartan, eprosartan, and telmisartan are not metabolized by the CYP450 system and therefore have a low potential for interaction. The ARBs demonstrated favorable effects on mortality and glucose homeostasis[8,56,69]. In fact, a reduction in the rate of new-onset diabetes has been observed during ARB treatment compared with diuretics or beta blockers[78]. The ARBs reduce protein excretion and further slow the progression rate of kidney disease[80].

Antihypertensive drug choice

Diuretics, beta blockers, CCB, ACE inhibitors, or ARBs are all suitable for the start and maintenance of antihypertensive treatment, either in monotherapy or in combination therapy. However, some combinations are considered more suitable than other (Fig. 1). Some agents should be chosen as preferential in specific conditions (Table 2):

- Cerebrovascular disease: all agents are recommended after the acute phase.
- Coronary heart disease: all agents are recommended. Beta blockers are recommended in case of recent myocardial infarction, and beta blockers and CCB in patients with angina pectoris.
- Diabetes: ACE inhibitors or ARBs are the preferred agents.
- Heart failure: diuretics, beta blockers, ACE inhibitors, ARBs and mineralocorticoid receptor antagonists are recommended.
- Nephropathy: ACE inhibitors or ARBs are preferred agents in cases of proteinuria or microalbuminuria.

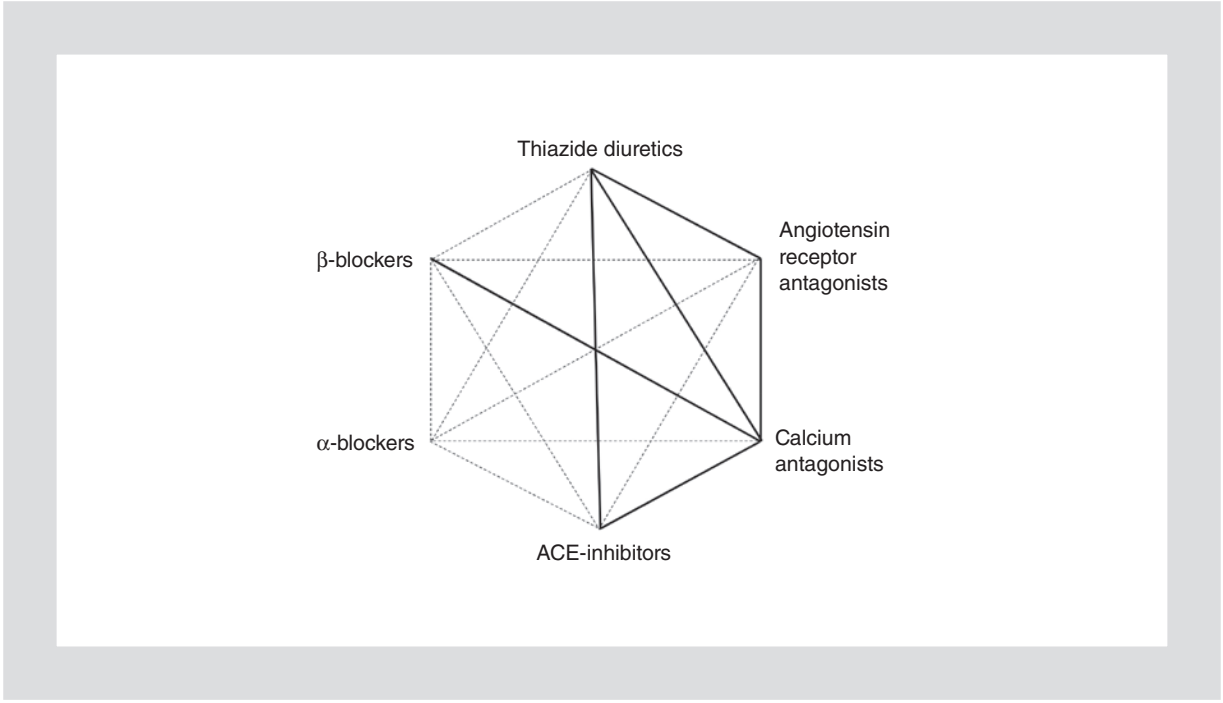

Figure 1. *Antihypertensive combinations. The preferred combinations in the general hypertensive population are represented as thick lines. The frames indicate classes of agents proven to beneficial in controlled intervention trials. ACE: angiotensin converting enzyme.*

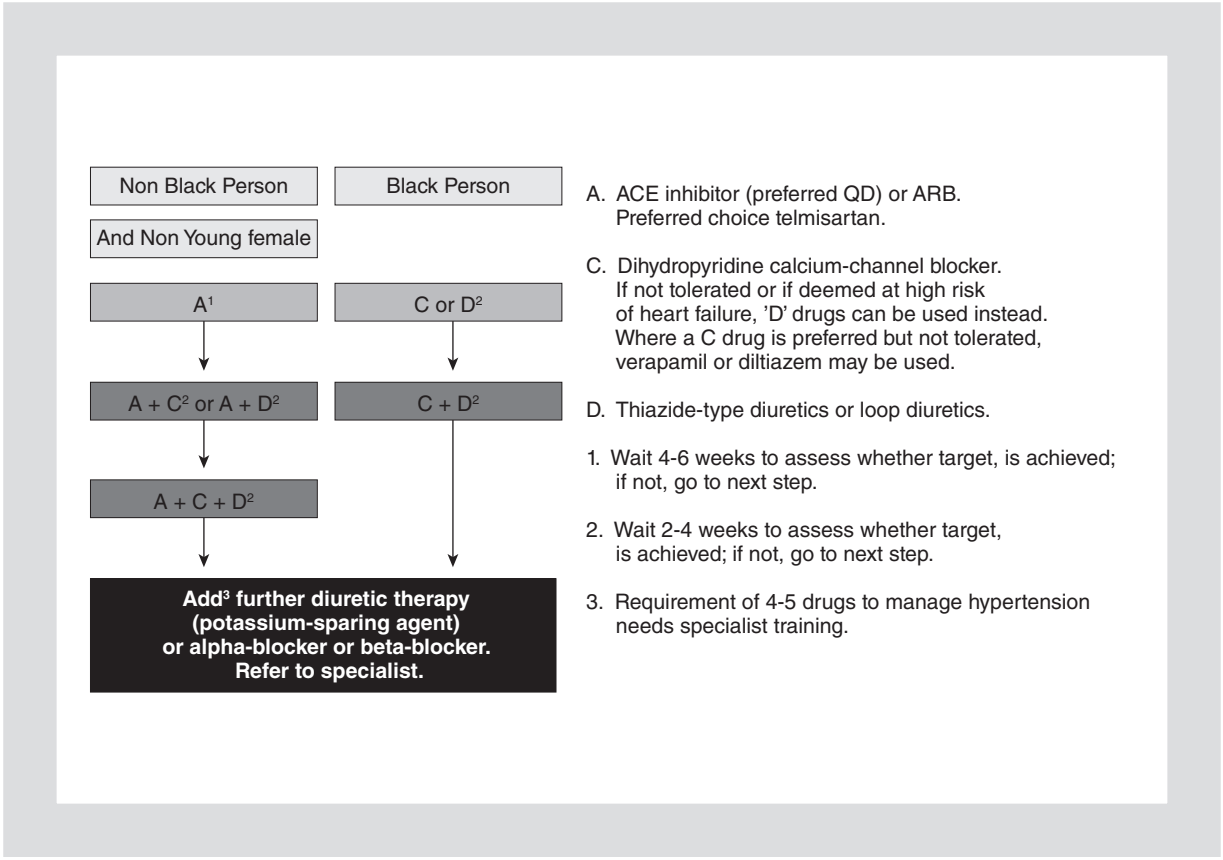

Figure 2. *Hypertension and HIV: Drug choice. ACE: angiotensin converting enzyme.*

Table 2. Antihypertensives: Drug dosing and interactions with antiretrovirals

Drug name	Usual dosage for hypertension	ARV drug interactions	Comments
		Diuretics	
Chlorthalidone	12.5-50 mg/day QD	No predicted effect	– Thiazide diuretics and CCBs may be more effective than other antihypertensives for African American patients. – Monitor electrolytes periodically. Other potential adverse effects include rash, hyperglycemia, sexual dysfunction, and frequent urination. – Thiazide showed cardioprotective effect in ALLHAT study.
Hydrochlorothiazide	12.5-50 mg/day QD	No predicted effect	
Indapamide	1.25-2,5 mg/day QD in the morning	Possible ↑ indapamide with PIs Possible ↓ indapamide with NNRTIs Possible ↑ indapamide with EVG/cobi	
Furosemide	25-50 mg/day QD/BID (max 250 mg)	No predicted effect	
Metolazone	2.5-5 mg/day QD (max 10 mg)	No predicted effect	
Spironolactone	50-100 mg/day QD (max 200 mg)	No predicted effect	
Torasemide		Possible ↓ torasemide with PIs Possible ↑ torasemide with NNRTIs Possible ↓ torasemide with EVG/cobi	
		Alpha blockers	
Doxazosin	2-4 mg/day QD (max 16 mg)	Possible ↑ doxazosin with PIs Possible ↓ doxazosin with NNRTIs Possible ↑ terazosin with EVG/cobi	– Not a first-line agent. – Possible adverse effects include risk of CHF, dizziness, postural hypotension, drowsiness, and syncope. – Recommended administration at bedtime.
Prazosin	Start 1 mg BID or TID; usual dosage 20 mg/day divided BID or TID; (max 40 mg)	Titrated until the required therapeutic effect is reached	
Terazosin	1-5 mg/day QD or divided BID; (max 20 mg)	Possible ↑ terazosin with PIs Possible ↓ terazosin with NNRTIs Possible ↑ terazosin with EVG/cobi	
		Beta blockers	
Atenolol	25-50 mg/day BID (max 100 mg)	Possible ↑ atenolol PIs Possible ↑ atenolol EVG/cobi ATV may ↑ atenolol concentrations; no dosage adjustment appears to be necessary if unboosted Possible QT/PR prolongation with ritonavir or cobi	– Useful for patients with concomitant CAD, CHF, previous MI, or those in need of rate control owing to atrial fibrillation or flutter. – May be associated with increased risk of stroke (particularly in smokers) and insulin resistance. – Use with caution in patients with reactive airway disease. – Potential adverse effects include bradycardia, hypotension, fatigue, and sexual dysfunction. – Cardiac events have been reported with patients on ritonavir and beta blockers.
Metoprolol	50-100 mg/day BID (max 250 mg)	PIs may ↑ metoprolol levels Possible ↑ metoprolol with EVG/cobi Possible QT/PR prolongation with ritonavir or cobi	
Nebivolol	2.5-5 mg/day QD (max 10 mg/day)	PIs may ↑ metoprolol levels Possible ↑ metoprolol with EVG/cobi Possible QT/PR prolongation with ritonavir or cobi	

(Continue)

Table 2. Antihypertensives: Drug dosing and interactions with antiretrovirals *(continued)*

Drug name	Usual dosage for hypertension	ARV drug interactions	Comments
		Mixed alpha-beta blockers	
Carvedilol	6.25-25 mg/day BID	PIs may ↑ carvedilol levels Possible ↑ propranolol with EVG/cobi Possible QT/PR prolongation with ritonavir or cobi	– Useful for patients with known CAD or CHF. – Avoid in patients with decompensated heart failure who are dependent on sympathetic stimulation. – May be associated with increased risk of stroke (particularly in smokers) and insulin resistance. – Use with caution in patients with reactive airway disease. – Potential adverse effects include bradycardia, hypotension, fatigue, and sexual dysfunction.
Labetalol	200-800 mg/day BID	PIs may ↑ labetalol levels Possible ↑ propranolol with EVG/cobi Possible QT/PR prolongation with ritonavir or cobi	
		Calcium channels blockers	
Amlodipine	5-10 mg/day QD	PIs ↑ amlodipine levels EVG/cobi ↑ amlodipine levels NNRTI ↓ amlodipine levels Possible QT/PR prolongation with ritonavir or cobi	– CCB and thiazide diuretics may be more effective than other antihypertensives for African American patients. – If CCB must be used with PIs, reduce initial dosage and titrate up while monitoring for side effects (e.g. hypotension, conduction block, bradycardia, and peripheral edema). – Metabolism of CCBs may be induced by the NNRTIs EFV and NVP, leading to blunted antihypertensive effect. – Avoid in patients with CHF.
Diltiazem	180-240 mg QD (max 360 mg)	PIs ↑ diltiazem levels EVG/cobi ↑ diltiazem levels NNRTI ↓ diltiazem levels (higher diltiazem dose required) Possible QT/PR prolongation with ritonavir or cobi	
Felodipine	5 mg/day QD (max 10 mg)	PIs ↑ felodipine levels EVG/cobi ↑ felodipine levels NNRTI ↓ felodipine levels Possible QT/PR prolongation with ritonavir or cobi	
Lacidipine	2-6 mg/day QD	PIs ↑ lacidipine levels EVG/cobi ↑ lacidipine levels NNRTI ↓ lacidipine levels Possible QT/PR prolongation with ritonavir or cobi	
Lercanidipine	10-20 mg/day QD	PIs ↑ lercanidipine levels EVG/cobi ↑ lercanidipine levels NNRTI ↓ lercanidipine levels Possible QT/PR prolongation with ritonavir or cobi	
Nifedepine	20-30 mg/day QD or BID (max 90 mg)	PIs ↑ nifedepine levels EVG/cobi ↑ nifedepine levels NNRTI ↓ nifedepine levels Possible QT/PR prolongation with ritonavir or cobi	
Verapamil	180-240 mg/day QD (max 480 mg)	PIs ↑ verapamil levels EVG/cobi ↑ verapamil levels NNRTI ↓ verapamil levels Possible PR prolongation with ritonavir or cobi	

(Continue)

Table 2. Antihypertensives: Drug dosing and interactions with antiretrovirals *(continued)*

Drug name	Usual dosage for hypertension	ARV drug interactions	Comments
		ACE inhibitors	
Benazepril	10-40 mg/day QD or BID (max 80 mg)	No predicted effect	– Avoid during pregnancy. – Cardioprotective, renal protective. – Use with caution in patients who are elderly, are fluid depleted, or have renal insufficiency. – Risk of hyperkalemia. – Other potential adverse effects include angioedema, cough (5-10%), renal insufficiency, and sexual dysfunction.
Captopril	25-100 mg/die BID or TID	No predicted effect	
Cilazapril	2.5-5 mg/day QD (max 10 mg)	No predicted effect	
Enalapril	5-20 mg/day BID (max 40 mg)	No predicted effect	
Fosinopril	10-20 mg/day QD or BID (max 40 mg)	No predicted effect	
Lisinopril	5-20 mg/day QD (max 40 mg)	No predicted effect	
Perindopril	4-8 mg/day QD	No predicted effect	
Quinapril	5-40 mg/day QD or BID (max 80 mg)	No predicted effect	
Ramipril	2.5-10 mg/day QD (max 20 mg BID)	No predicted effect	
Trandolapril	0.5-4 mg/die QD	No predicted effect	
Zofenopril	15-30 mg/day QD (max 60 mg/day BID)	No predicted effect	
		Angiotensin II receptor blockers	
Candesartan	8-32 mg/day QD	PIs ↓ candesartan levels (may not be relevant) EVG/cobi ↓ candesartan levels (may not be relevant) EFV and ETR ↑ candesartan levels (may not be relevant)	– Avoid during pregnancy. – Cardioprotective, renal protective. – Use with caution in patients who are elderly, are fluid depleted, or have renal insufficiency. – Risk of hyperkalemia. – Other potential adverse effects include angioedema and renal dysfunction. – Telmisartan is most studied antihypertensive in HIV population. – Telmisartan and partially irbesartan showed PPAR γ activating properties.

(Continue)

Table 2. Antihypertensives: Drug dosing and interactions with antiretrovirals *(continued)*

Drug name	Usual dosage for hypertension	ARV drug interactions	Comments
Eprosartan	600 mg/day QD (max 400 mg BID)	No predicted effect	
Irbesartan	150-300 mg/day QD	PIs ↓ irbesartan levels (may be not be relevant) EVG/cobi ↓ irbesartan levels (may not be relevant) EFV and ETR ↑ irbesartan levels (may not be relevant)	
Losartan	50-100 mg/day QD	PIs ↓ active metabolite may be result ↓ efficacy NNRTI ↑ active metabolite may be result ↑ efficacy	
Olmesartan	10-140 mg/day QD	No predicted effect	
Telmisartan	40-80 mg/day QD	No predicted effect	
Valsartan	40-320 mg/day QD or BID	No predicted effect	

ACE: angiotensin converting enzyme; ARV: antiretroviral; BID: twice a day; cobi: cobicistat; CAD: coronary artery disease; CCB: calcium channel blocker; CHF: congestive heart failure; EFV: efavirenz; ETR: etravirine; EVG: elvitegravir; MI: myocardial infarction; NNRTI: nonnucleoside reverse transcriptase inhibitor; NVP: nevirapine; PI: protease inhibitor; PPAR: peroxisome proliferator-activated receptor; QD: once a day; TID: three times a day.

– Pregnancy: nifedepine is the preferred agent; methyldopa or labetalol should also be considered. ACE inhibitors or ARB should be avoided in women with childbearing potential.

Antihypertensive drugs in the HIV population

The choice of an effective antihypertensive therapy in HIV-infected patients is important and must be made carefully according to metabolic complications and interactions with antiretroviral drugs (Fig. 2). Moreover, both HIV infection and exposure to cART might have an additional role in the development and maintenance of hypertension through metabolic disturbance and endothelial damage. Cardiovascular risk increases with the increase in systolic BP. The Swiss HIV cohort study showed that a 10 mmHg increase in systolic BP was associated with an 18% increased risk of cardiovascular events[53]. Similar data was shown by the Veteran cohort study[54]. Despite these data, both the awareness and treatment of hypertension are insufficient in HIV populations: more than one third of HIV-infected individuals with hypertension are, in fact, unaware of their condition and more than two thirds of HIV-infected with hypertension show non-controlled BP values[39].

Very little data on antihypertensive therapy in HIV populations is available. A great part of data comes from case reports. Those cases showed a severe CCB interaction in the HIV population[74,75,81], no clinical interaction with low-dose lercanidipine and efavirenz[81], an efficacy of direct renin inhibitor[82], and a favorable effect of ARBs in the HIV population[69,81,83].

Very few trials are available in the HIV population[8,56,80,84-86]. The vast majority of these studies used telmisartan, an ARB that has strong peroxisome proliferator-activated receptor γ (PPARγ) activating properties at the plasma concentrations used in the treatment of hypertension[87]. Telmisartan demonstrated to be quickly efficacious and reduce BP after four weeks of administration in HIV-positive cART-treated patients[56]. In addition, telmisartan is the only antihypertensive agent that has a long-term efficacy study in the HIV population[9].

Telmisartan, by its PPARγ-activating properties, showed a very favorable activity on lipid profiles, in particularly in reducing triglycerides and the total cholesterol/HDL ratio[9,56]. In addition, it managed to

improve insulin resistance and glucose metabolism[56,69]. The metabolic effects were associated with a significant reduction in the calculated cardiovascular risk, such as Framingham risk score[56]. A decrease in cystatin C levels was also observed during telmisartan administration[56]. Cystatin C is a low-molecular-weight cysteine protease inhibitor involved in vascular extracellular matrix remodeling and is a novel marker for cardiovascular risk and mortality[5,29,88,89]. Another trial showed an improvement in arterial flow-mediated dilatation, a measurement closely related to CVD[86], in particularly in subjects with PIs and/or abacavir therapy. This data is confirmed by a reduction in endothelin-1, a potent proinflammatory and mitogenic peptide produced by endothelial inflammation[56]. Telmisartan administration also reduces microalbuminuria[8,56,80,83], which is a feature of hypertensive renal damage and is independently correlated with mortality[90]. Proteinuria reduction by telmisartan was shown also in a case report in an African male patient, heavily medicated for hypertension[83]. This data is an important finding since ACE inhibitors, ARBs, and beta blockers may show weaker activity than diuretics and CCBs in the African American population. Similar data was shown in a case with irbesartan and lisinopril[81].

Summary

Hypertension is a major cardiovascular risk factor worldwide, influencing cardiovascular morbidity and mortality also in the HIV populations. One third of the HIV population exhibits hypertension. Accordingly, treatment of hypertension has a pivotal importance in HIV populations to prevent end organ damage and to reduce CVD and mortality. Clinical management of hypertension has shown to be inadequate in a greater part of the HIV population. A few studies have been designed for testing antihypertensive therapy in this population. To date, the most studied drug in the HIV population was telmisartan, which shows a favorable efficacy and tolerability profile. Consequently, this drug could be used as the preferred antihypertensive drug in male, non-African, HIV patients.

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Disclosure of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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