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Hypertension among people living with human immunodeficiency virus in sub-Saharan Africa: a systematic review and meta-analysis

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We performed a systematic review and meta-analysis of hypertension in people living with human immunodeficiency virus (HIV) in sub-Saharan Africa (SSA). We searched the PubMed, Google Scholar, African Index Medicus, and Embase databases to identify studies published from January 1, 2010, to December 31, 2021. We used a random-effects model to estimate the pooled prevalence of hypertension and mean SBP/DBP level on a sex-specific basis. We included 48 studies reporting data on a pooled sample of 193,843 people living with HIV (PLW-HIV) in SSA. The pooled mean SBP/DBP level was 120 (95% CI 113–128)/77 (95%CI 72–82) mmHg, while the overall pooled prevalence of hypertension was 21.9% (95% CI 19.9–23.9%). Further meta-regression analyses suggested that the prevalence of hypertension was 1.33 times greater in males, 1.23 times greater in individuals receiving antiretroviral therapy (ART) and 1.45 times greater in those individuals with a CD4-count ≥ 200. This meta-analysis of the contemporary pattern of BP levels among PLW-HIV in SSA, suggests that around one in five of such individuals also have hypertension. Given the further context of greater access to ART and subsequently greater longevity, study findings support calls to integrate cardiovascular management into routine HIV care.

Given that sub-Saharan Africa (SSA) remains the "epicentre" of the human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDs) epidemic[1], (67% of the estimated 38.4 million people living with HIV [PLW-HIV] worldwide live in SSA)[1], increasing longevity of those affected via inexpensive and effective antiretroviral therapy (ART)[2] remains a priority. However, such therapy has some adverse implications for the future health of those individuals who are treated. For example, while early studies showed that HIV infection is associated with significantly reduced blood pressure (BP) levels[3], some commonly prescribed formulations of ART appear to reverse this phenomenon by increasing BP levels[2]. Given that the risk of future cardiovascular events in early adulthood[4] starts to increase well below the conventional threshold of "hypertension" defined by the World Health Organization (WHO) as a systolic blood pressure (SBP)/diastolic blood pressure (DBP) of ≥ 140 and/or ≥ 90 mmHg[5], understanding the contemporary pattern of BP levels in PLW-HIV is of paramount importance. This is especially true considering that SSA is also the "epicentre" of the global epidemic of hypertension, with an estimated 9.9% and 38% of the adolescent[6] and adult populations[7] reportedly affected, respectively.

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In this context, a previous systematic review and meta-analysis of 150,886 PLW-HIV in SSA revealed a pooled prevalence of hypertension (19.6%, 95% confidence interval [CI], 16.6–22.5%)[5]. This figure is lower than that reported for the wider population (even when considering potential age-differences and fewer cases of obesity)[7]. Despite having lower BP levels overall, PLW-HIV are at increased risk of developing and dying from cardiovascular disease[8]. Moreover, despite the well-characterised effects of some ART on lipid metabolism and increased risk of atherosclerotic events[9] and consistent with the differential pattern of cardiovascular disease in SSA (much of which is driven by hypertension)[10], cases of HIV-related cardiomyopathy[11] and/or pulmonary hypertension appear to be common[12]. Critically, the intersection between HIV and hypertension in SSA is likely to increase due to the combination of greater ART coverage, rising obesity levels and increasing longevity[13].

Hence, we performed a contemporary systematic review of research reports focusing on hypertension in PLW-HIV in SSA. We specifically focused on determining which countries/regions were represented (relative to the distribution of HIV in SSA) and when possible, identified studies reporting actual BP levels. We then performed a meta-analysis considering sex of participants, their ART status and cluster of differentiation 4 (CD4) when possible. These factors were used to derive pooled estimates of the prevalence of hypertension among PLW-HIV in SSA and the mean SBP/DBP levels underpinning these factors. We also performed a series of sub-group and meta-regression analyses to identify the effects of different factors, such as age, sex, ART status, and CD4 count on the incidence of hypertension and BP levels.

Methods

Search strategy and selection criteria

For this systematic review and meta-analysis, two investigators (AC and LW), with the help of an expert librarian, performed a comprehensive search of the PubMed, Google Scholar, African Index Medicus, and Embase databases to identify all relevant articles on hypertension in PLW-HIV in Africa published in English from January 1, 2010, to December 31, 2021 (to generate contemporary data and to reduce heterogeneity between studies). A search strategy based on the combination of relevant terms and the individual names of each of the 49 countries in SSA using their English and official versions (e.g., "Ivory Coast" and "Côte d'Ivoire") was applied. The key search terms included "hypertension", "blood pressure", "systolic hypertension", and "diastolic hypertension" in conjunction with "HIV", "human immunodeficiency virus", "CD4", "cluster of differentiation 4", "ART", and "antiretroviral". The main search strategy used for PubMed (which is adapted for the other databases) is available in the review protocol (supplementary material). The references of all relevant articles were screened to identify additional data sources with input from AOM and DBO.

To be included, primary studies had to be observational studies of PLW-HIV residing in SSA, irrespective of their ethnic, socioeconomic, and educational backgrounds, reporting the prevalence of hypertension or with enough data to compute an estimate. We excluded studies on non-systemic hypertension (intracranial or pulmonary hypertension), studies focused on non-resident Africans, and studies in which participants were selected based on the presence of hypertension (e.g., clinical trials or case–control studies). We also excluded case series with a small sample size (< 100 participants), letters, reviews, commentaries, editorials, and studies without primary data or explicit descriptions of methods. For studies reporting duplicate analyses, we considered the most comprehensive report and the study with the largest sample size.

Two investigators (AC and LW) independently screened the titles and abstracts of articles retrieved from the literature search, and full texts of potentially eligible studies were obtained and further assessed for final inclusion, which was determined by consensus (AC, LW and SS). All duplicates were removed during the study selection process.

Data extraction

Three investigators (AC, LW and SS) independently extracted relevant data from individual studies using a standardised data extraction form. This information included the author's last name, year of publication, recruitment period, area (rural versus urban), country, study design, setting, sample size, mean or median age of participants, age range, proportion of male participants, body mass index, and criteria used to identify hypertension. As noted previously, we used WHO guidelines to define hypertension as BP equal to or greater than 140/90 mmHg. We assigned a United Nations Statistics Division (UNSD) African region (Central Africa, Eastern Africa, Northern Africa, Southern Africa, and Western Africa) for each country studied. Disagreements between authors were resolved through discussion and consensus (among all authors).

Data analysis

As per a previous systematic review/meta-analysis[6], a qualitative synthesis of eligible studies was conducted. We evaluated the methodological quality of the eligible studies using the tool developed by Hoy and colleagues[14]. We assigned each item a score of 1 for yes or 0 for no, and summed scores across items to generate the overall quality score, which ranged from 0 to 10. According to the overall scores, we classified studies as having a low (0–3), moderate (4–6), or high (7–9) risk of bias. Three investigators (AC, LW and SS) independently assessed study quality, with disagreements resolved by consensus.

The overall distribution and origin of eligible study data (both for the size of the cohorts and number of studies) are reported against the estimated regional population distribution of SSA. We further determined the number of reports specifically derived from the 10 countries in SSA that have the highest concentration of PLW-HIV worldwide- Ethiopia, Kenya, Malawi, Mozambique, Nigeria, South Africa, Tanzania, Uganda, Zambia, and Zimbabwe[15].

We used meta-analyses to summarise both the prevalence of hypertension and the reported SBP/DBP. To be included in the prevalence meta-analysis, studies had to define hypertension, include randomly selected

participants with no comorbidities (such as diabetes) other than HIV and hypertension, have a low risk of bias (methodological quality), and describe prospective data collection. We analysed the data using Open Meta for Windows. We determined standard errors (SEs) for study-specific estimates using the point estimate and the appropriate denominators. We pooled the study-specific estimates using a random-effects meta-analysis model to obtain an overall summary estimate of the prevalence across studies. We assessed heterogeneity using the χ^2 test on Cochran's Q statistic and determined heterogeneity by calculating I^2 statistics (with values of 25%, 50%, and 75% representing low, medium, and high heterogeneity, respectively). In addition to the pooled analyses, the data were analysed on a sex-specific basis. A series of subgroup meta-analyses, including sex-specific, ART-specific, and CD4-specific meta-analyses (see *supplementary material*) were also performed. Meta-regression analyses on SBP/DBP levels by age and body mass index were also performed. Leave-one-out analysis was performed to show how each individual study affected the overall estimate of the remaining studies.

This systematic review/meta-analysis was approved and registered in the PROSPERO International Prospective Register of Systematic Reviews (registration number CRD42022297948) (protocol published) and reported according to Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines[16].

Results

We identified 2559 records, and after eliminating duplicates, 2456 records remained (Fig. 1). After screening the titles and abstracts, we found 2389 records to be irrelevant or noneligible and excluded them. The inter-rater agreement for study selection was high ($\kappa = 0.85$). We assessed the full texts of the remaining 67 papers for eligibility, 19 of which were excluded. We therefore included a total of 48 full-text articles in this review—see Supplementary Table T1—for a description of the methods/quality of each study[3,17–63]. Interrater agreements were high for both study inclusion ($\kappa = 0.86$) and data extraction (0.92). Available data from 193,197 PLW-HIV from 46 studies and a subset of 144,645 PLW-HIV from 20 studies, were used to derive pooled estimates of the prevalence of hypertension and mean BP levels. According to similar analyses performed on a sex-specific basis, the prevalence of hypertension was reported in 22 studies including 89,627 people [59,315 (66.2%) participants were female] and specific BP levels were reported in four studies including 15,268 people from four studies [10,276 (67.3%) participants were female].

Table 1 presents the summary statistics of all studies. All the data were extracted from cross-sectional studies. All 48 included studies had a relatively low risk of bias in their methodology and randomly selected participants. Eight studies focused on rural-dwelling individuals, seven focused on urban-dwelling individuals, and the remaining focused on a combination of both. The definition of hypertension was derived from the guidelines of the WHO (SBP/DBP ≥ 140/90 mmHg)[5]. The specific methods used to measure BP were heterogeneous with varying intervals (often not reported) and repeated measurements applied.

All 48 studies sought to identify the independent correlates of hypertension by applying different methodologies, with a particular focus on demographic, anthropometric and socioeconomic correlates. In 16/48 studies, there was a positive correlation between age and hypertension, while four studies reported a negative correlation. Similarly, 19/48 studies reported a greater prevalence of hypertension in females than in males, while 12/48 studies reported the opposite. A positive correlation between body mass index and BP was found in 33/48 studies. Other potential correlates of hypertension included education level (positive/negative correlations—six studies), family history and alcohol use (positive correlations—eight studies), residence in an urban area (higher than rural cohort—five studies) and a higher economic status (positive correlation—four studies).

From a geographic perspective, the data were derived from 12/49 countries distributed across all four UNSD regions of SSA (Supplementary Fig. S1). The top three countries were Uganda (ten studies), South Africa (eight studies), and Ethiopia (six studies). Overall, much of SSA, including many low-income countries, had no contributing data. However, with respect to the ten identified countries in SSA with the highest reported burden of PLW-HIV globally, 9/10 countries were represented (Fig. 2). Two lower-middle-income countries (Uganda and Ethiopia), and one higher-middle-income country (South Africa) accounted for half (24/48) of all included studies. Mozambique, which has the lowest gross domestic product (GDP) per capita among the ten countries, was not represented.

Figure 3 presents the main results of our meta-analysis on the pooled prevalence of hypertension in PLW-HIV in SSA. Among the 193,197 PLW-HIV, the pooled prevalence was estimated to be 21.9% (95% CI 19.9–23.9%; p-value < 0.001). The I^2 statistic was 99.1%, indicating high heterogeneity. Therefore, a sex-specific meta-analysis was performed.

On this basis, findings from 89,627 PLW-HIV revealed a greater percentage of males (odds ratio, 1.33, 95% CI 0.89–1.98; p-value < 0.001) with hypertension (20.4%, 95% CI 18.6%–22.2%; p-value < 0.001) than females (14.5%, 95% CI 12.9%–16.1%; p-value < 0.001)—Supplementary Fig. S2. The I^2 statistic was 98.9%, indicating high heterogeneity.

Figure 4 presents the results of our meta-analysis of actual BP levels when reported. Among 27,155 PLW-HIV, the pooled mean SBP/DBP was 120 (95% CI 113–128; p-value < 0.001)/77 (95% CI 72–82; p-value < 0.001) mmHg. The I^2 statistic was 99.9%, indicating high heterogeneity. Among 15,268 of these 27,155 PLW-HIV with sex-specific data, the pooled SBP/DBP was 118 (95% CI 115–121)/76 (95% CI 74–78) mmHg in males versus 115 (95% CI 112–118)/75 (95% CI 73–77) mmHg in females: the mean difference in SBP and DBP levels between females and males being −2.7 (95% CI −6.9 to 1.4; p-value < 0.001)/−0.4 (95%CI −1.0 to 0.3; p-value < 0.001) mmHg (Supplementary Fig. S3). The I^2 statistics were 98.1% and 69.1% for SBP and DBP, respectively, indicating high and moderate heterogeneity, respectively.

A series of subgroup and sensitivity analyses are presented in Supplementary Figs. S4–S9. The results of the sex-specific, ART-specific, and CD4-specific meta-analyses were not statistically significant. Notably, only one study (Manne-Goehler, 2019) exerted a large influence on the pooled analyses Supplementary Fig. S7. Finally,

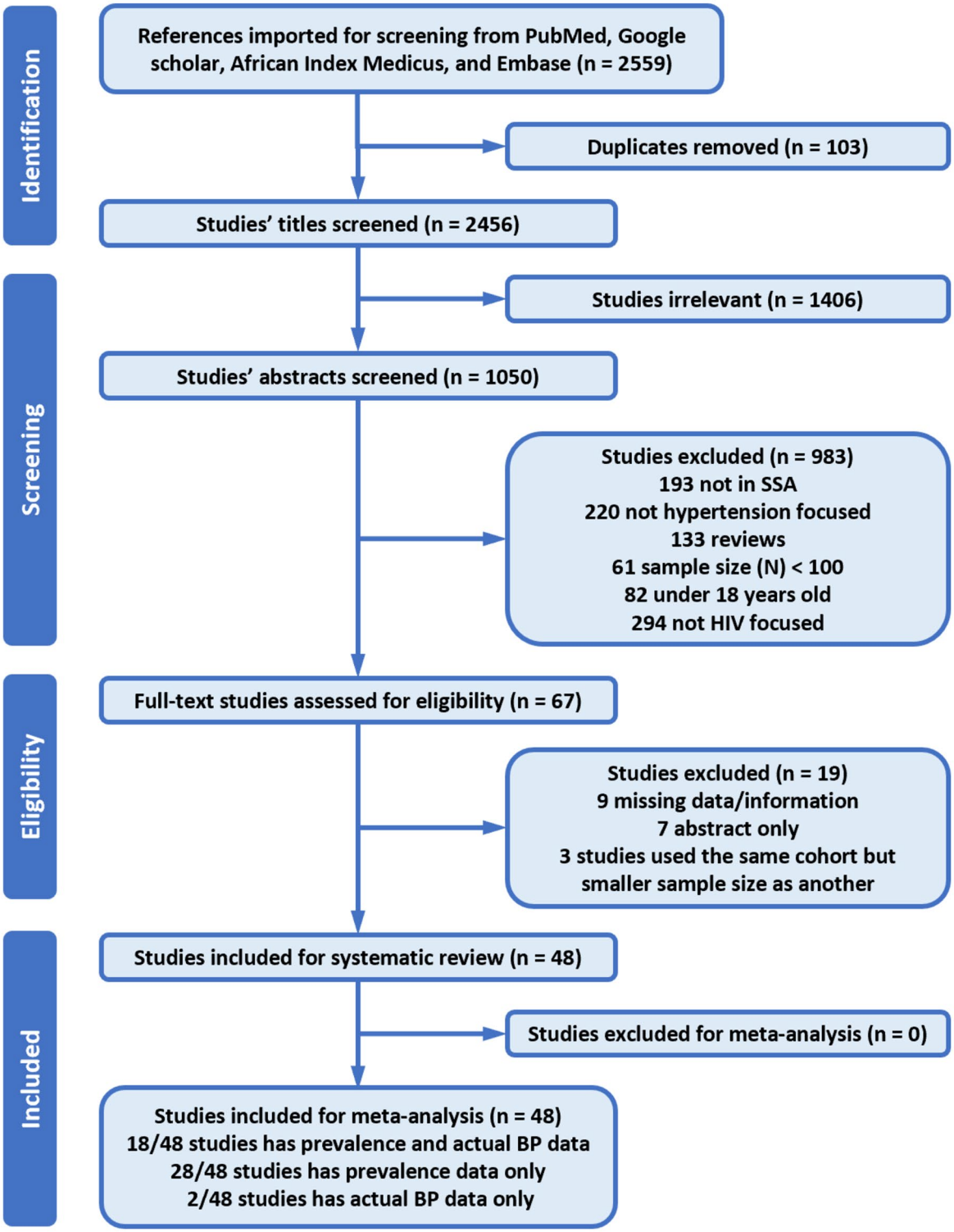


Figure 1. Study selection. This figure shows the study selection process. The process consisted of four stages: identification, screening, eligibility, and inclusion.

as shown in Supplementary Figures S8 and S9, when the data were reported, there was a positive correlation between participant age and body mass index and SBP/DBP levels.

Discussion

To our knowledge, this is the largest and most contemporary systematic review and meta-analysis of studies reporting the pattern of hypertension among PLW-HIV in SSA. This included looking beyond reports of individuals who reach the threshold for "hypertension", but, when possible, the mean BP levels underpinning the

Summary statistics
Number of participants: 193,843
Males: 64,550 (33%); females: 129,293 (67%)
Mean age (SD) of the participants: 41 years (2.58)
Studies included in the systematic review and meta-analysis: (n = 48)
Timing of data collection: all cross-sectional
Risk of bias: 48 studies had a low risk of bias
Selection of participants: all random
Representativeness: all subnational (n = 48)
Study cohort: all community-based cohorts (n = 48)
Year of publication: 2010–2021
Settings: rural (n = 8), urban (n = 7), and both (n = 33)

Table 1. Summary statistics. This table shows the summary statistics and methodological quality of the included studies. A more detailed description of each included study is provided in Supplementary Table S1.

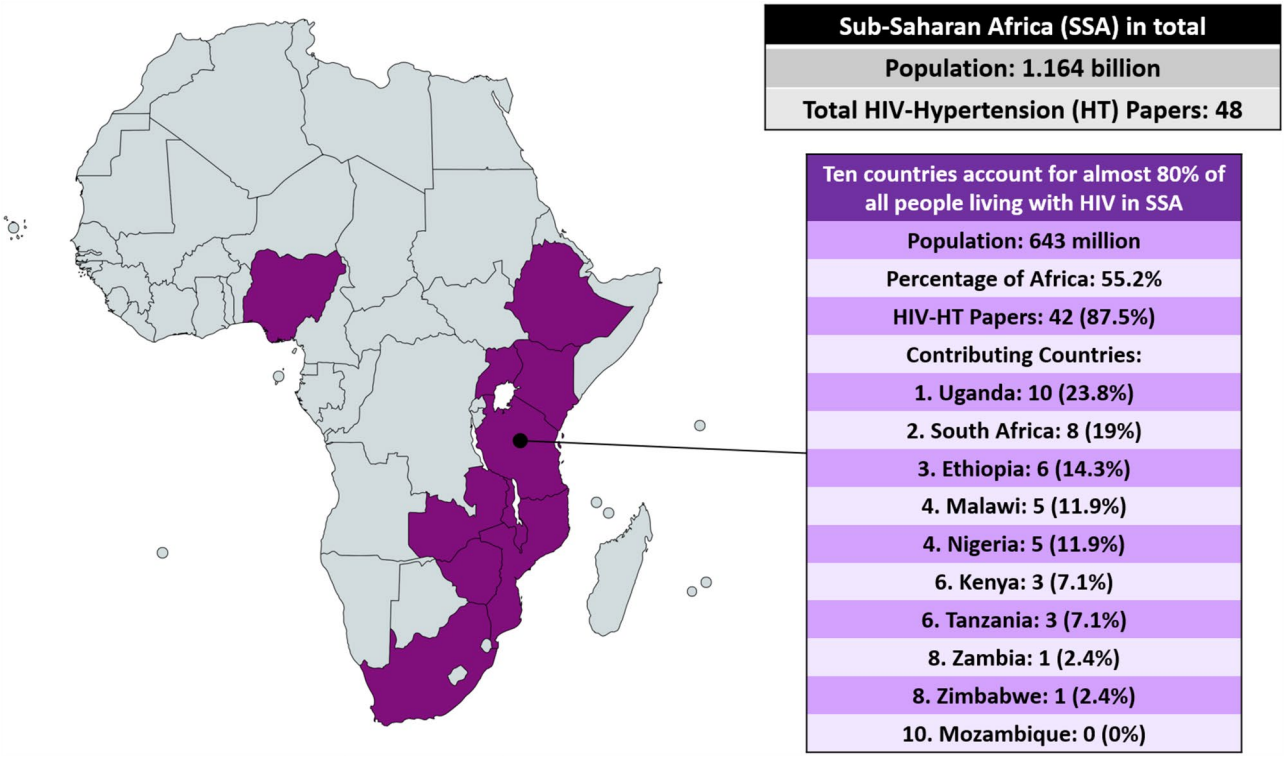


Figure 2. Top 10 sub-Saharan African countries with the highest burden of people living with HIV. This figure presents the number of included studies of the top 10 sub-Saharan African countries with the highest burden of people living with HIV.

co-presence of hypertension on a sex-specific basis. We specifically focused on ten countries in SSA where the epicentres of HIV and hypertension (from SSA to a global perspective) essentially collide. Overall, our specific search revealed 48 studies focusing on the BP pattern among 193,843 PLW-HIV from only 12/49 countries in SSA. However, consistent with the epidemiological distribution of HIV infection, 9/10 countries (except for Mozambique) accounting for 80% of all cases of HIV in SSA[15], were represented. Overall, our findings suggest that approximately one in five PLW-HIV in SSA with no other significant illnesses reported, have hypertension. Overall, the study methodologies varied, with not all studies providing sex-specific data and actual BP levels. Despite consistently reported differences in the pattern of hypertension between African women (more women have hypertension) and men[10], we found that the prevalence of hypertension was 1.33 times greater in males living with HIV than in females living with HIV, but the difference was not statistically significant.

Our finding that 21.9% of PLW-HIV in SSA have hypertension, is at the upper end of the 95%CI estimate of a previous meta-analysis reporting a pooled hypertension prevalence of 19.6% in PLW-HIV in SSA[5]. This figure is also broadly consistent with estimates for SSA (range 6–22%) and global estimates of the prevalence of hypertension in PLW-HIV (24%, accounting for 8.9 million individuals)[64]. Regardless of the exact figure, these estimates (including the estimate from this contemporary analysis) represent the reported prevalence of

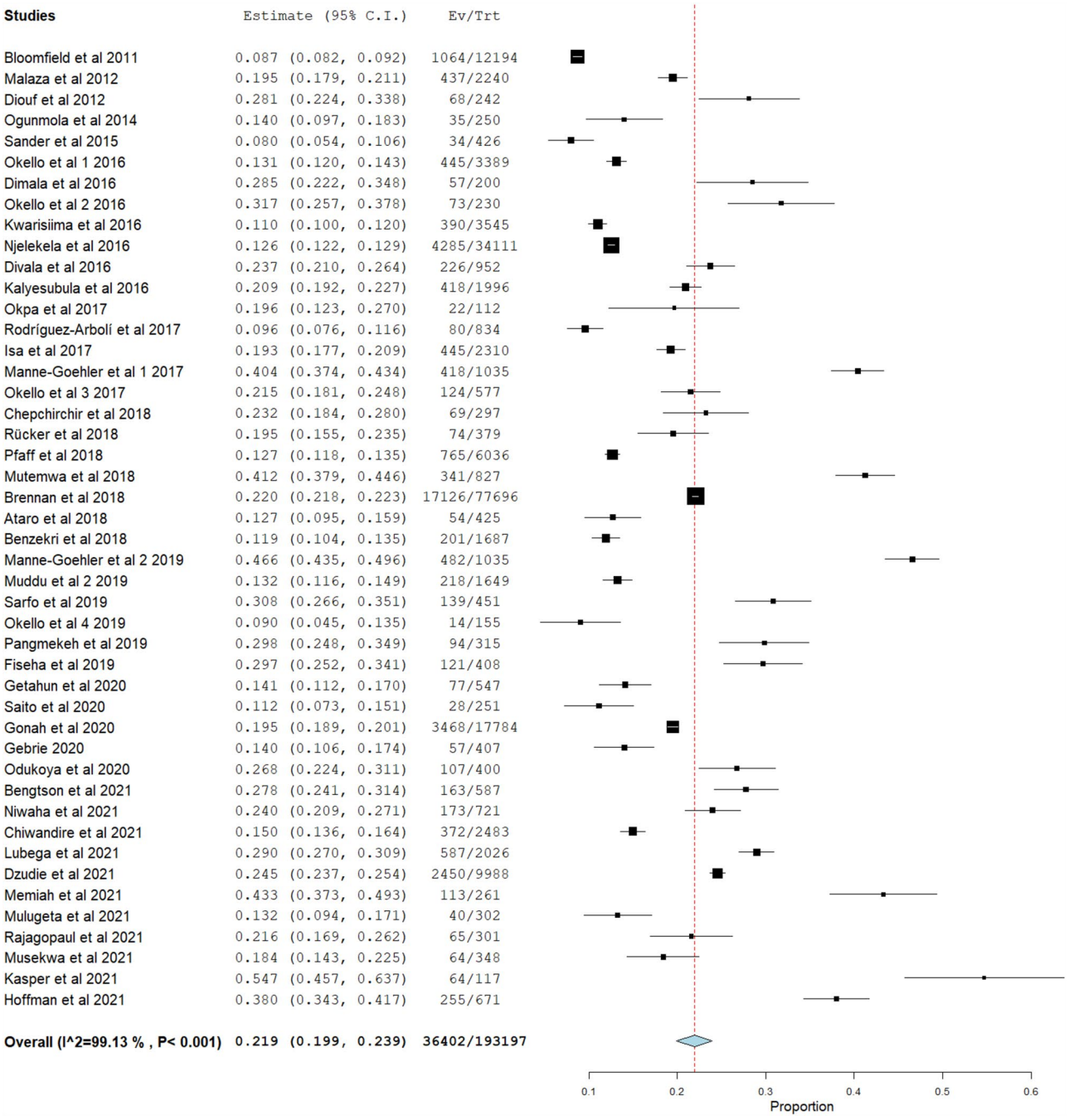
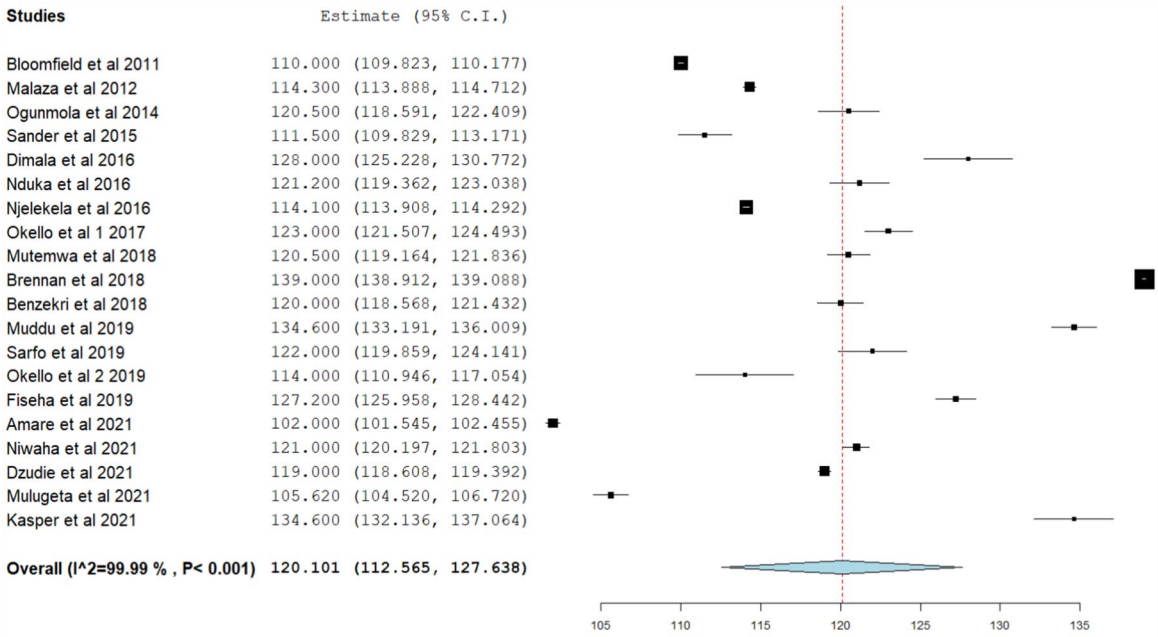


Figure 3. Pooled prevalence of hypertension. This figure presents the main results of our meta-analyses on the pooled prevalence of hypertension.

hypertension within the broader population in SSA[10]. Apart from the relatively young age of PLW-HIV, it has been established that uncontrolled HIV infection is associated with lower BP and body mass index values[3]. In a matched case–control study of 577 PLW-HIV and 538 healthy controls, a difference of −3.3/−1.5 mmHg in BP was observed. Importantly, group differences with respect to body mass index explained only 25% of BP variance in BP[3]. Consistent with a causal pathway, the initiation of ART for HIV infection is associated with increased BP[65]. In one pre- and post-study of 53 PLW-HIV, a BP increase of 10/8 (SBP/DBP) mmHg was observed following the initiation of ART[65]. Numerous mechanisms have been postulated to explain this "opposing" phenomenon; from initial autonomic dysfunction linked to inflammation or a compromised immune system at the time of infection[66] to immune system recovery and weight gain after ART is initiated[65]. Importantly, some older forms of ART cause lipodystrophy, which is also associated with hypertension[64]. Although newer agents have been designed to have fewer adverse effects[67], a meta-analysis of more than 44 000 PLW-HIV revealed that the risk of hypertension was two-fold greater in individuals who received ART than in treatment-naive individuals[68]. In many countries in SSA, PLW-HIV do not have access to newer ART regimens. In fact, many children and adolescents living with HIV in the region still use abacavir (shown to be associated with an increased risk of



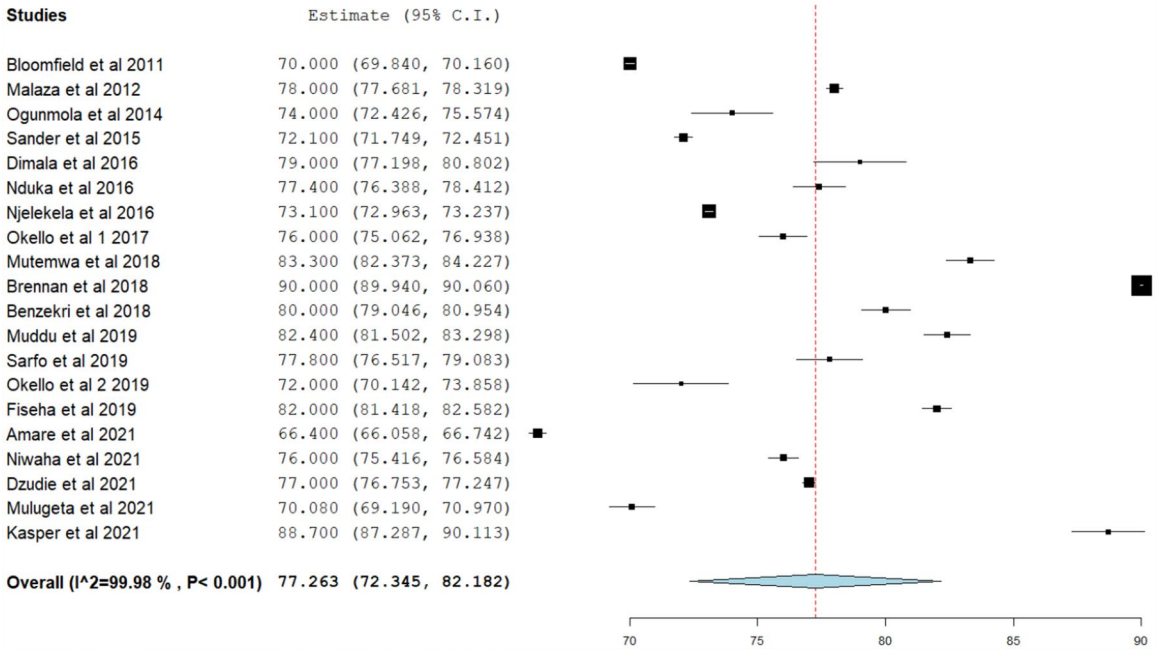


Figure 4. Pooled blood pressure levels. This figure presents the results of our meta-analysis of SBP and DBP levels.

cardiovascular events)[69] as part of their ART regimen. These findings, including our own, reaffirm the potential for long-term ART to increase the risk of developing hypertension[65]. Unfortunately, we were unable to differentiate between individuals receiving newer and older ART regimens, and this remains an important avenue of investigation from a BP perspective[70]. Consistent with our overall findings, the nadir CD4 cell count in PLW-HIV has also been shown to be associated with hypertension due to sustained immune activation, chronic inflammation, endothelial dysfunction, and microbial translocation that occurs when immune recovery is inadequate[71].

Independent of other factors and consistent with studies of the broader population[6] in SSA, we found that older age and a higher body mass index were positively correlated with BP levels.

Overall, our systematic review/meta-analysis included more studies and participants than previously reported studies[5]. Crucially, given the context of opposing factors that might determine if an individual reaches the arbitrary threshold for "hypertension", this is one of the few[72] meta-analyses to report on, and analyse actual BP levels in this vulnerable population. In any population (even in young adults[4]) the risk of a future cardiovascular event increases with increasing BP[4]. This is an important observation given that beyond the broader pattern of cardiovascular events occurring at a younger age in individuals living in SSA[8], multiple observational cohort studies have suggested that PLW-HIV have a 1.5 to twofold increased risk of experiencing acute myocardial infarction due to the accelerated development of coronary heart disease compared to people without HIV[73]. However, contrary to the expected predominance of atherosclerotic events[74], PLW-HIV in SSA appear to develop a more diverse range of cardiovascular conditions, including HIV-related cardiomyopathy[4] and pulmonary hypertension[4]. The lack of identified atherosclerotic events in PLW-HIV in SSA is thought to be due to limitations in diagnostic resources for identification in SSA, and more recent literature has suggested quite a high (and disproportionate) burden of atherosclerotic cardiovascular disease events in the region[75].

Regardless of the underlying causes, it is striking that while SSA is the global epicentre of both HIV and hypertension with an increasingly complex caseload of multimorbid cases due to a confluence of communicable and noncommunicable diseases in the region[8] health services are rarely integrated. Research has shown that people in SSA rate their health and healthcare as the lowest worldwide[76]. The lack of detection and treatment contributes to the high prevalence of hypertension in PLW-HIV in SSA. On this basis that INTE-AFRICA study (a multicountry, cluster-randomised, controlled trial) compared an integrated care approach to a standard vertical care approach delivered separately for people with HIV, diabetes, or hypertension[77]. Overall, this study demonstrated that high-quality standards of care could be provided for each condition without comprising HIV-specific care/management goals. However, despite enhancing patient engagement/retention, achieving BP control (among hypertensive individuals) proved to be problematic[77]. Despite this (i.e., the need to consider how to achieve multiple management/health goals for the same person more carefully), our findings reaffirm that there are tangible costs, resources and opportunities to integrate cardiovascular risk monitoring and disease management into routine HIV care. Accordingly, considering that one in five PLW-HIV in SSA already have hypertension, obesity levels among such patients are increasing, and the BP-elevating effects of ART, we believe that BP surveillance/management should be treated with the same urgency as lipid management among individuals living with HIV in SSA. Unfortunately, in many countries such as Mozambique[4], national guidelines for HIV care do not recommend screening for cardiovascular risk factors and/or established forms of (comorbid) cardiovascular disease. On this basis, we are both awaiting the results of current trials relevant to this issue and discussing how best to develop SSA-wide recommendations for integrated HIV/cardiovascular care.

There are several limitations when considering the veracity of our data and interpreting the clinical and public health implications. This includes considering the location/distribution of source data. From the perspective of SSA overall, only 12/49 countries in SSA were represented, and a more systematic approach to hypertension surveillance and reporting for a wider distribution of countries in SSA remains a priority. Although we excluded studies in which BP/hypertension was not the specific focus of the research or studies in which HIV was not the focus (e.g., studies of people living with diabetes), we acknowledge that such studies are important for improving our understanding of the interaction and consequences of HIV and hypertension. It is also worth noting that heterogeneity in reported BP levels is a consistent feature of data from this region[6]. Detailed explanations can be found in the supplementary material. One such study was performed in Mozambique, where cardiovascular profiling of 264 PLW-HIV (aged 39.3 years, 70.5% female) from an HIV clinic revealed that 20.5% had hypertension[4]; this finding is entirely consistent with the pooled prevalence derived from our meta-analyses of studies from the other "big 10" countries most affected by the HIV epidemic[15]. However, this study, like most of the studies included in our analyses, reported on people visiting HIV clinics. Unfortunately, a significant proportion of less affluent people (estimated to be 15 million or more)[78] cannot visit an HIV clinic and/or afford life-saving ART treatment. Beyond the specific implications of slowing disease progression with appropriate treatment, this has implications for our findings and how the need for optimal BP management is recognised and interventions are implemented among all PLW-HIV. By focusing on the published English literature and full study reports, we may also have missed potentially important data. We would also like to further investigate the type of ART regimen and hypertension, however, based on the current literature and studies, such data are sparse. Therefore, we did not have sufficient data to perform a meta-analysis on this topic.

In conclusion, our meta-analysis of contemporary observation data suggested that approximately one in five PLW-HIV in SSA, including most of the countries in which HIV infection is most prevalent, can be classified as having hypertension according to conventional BP thresholds. However, the distribution of reported mean BP levels within the same cohort, suggests that many more PLW-HIV have BP levels that mean they are at high risk of developing future cardiovascular disease. Such cases are likely to increase due to numerous factors. This includes the wider implementation/coverage of (antiquated) ART and rising obesity levels, both of which are likely to increase BP levels. Given that PLW-HIV are already at risk of developing cardiovascular disease prematurely, these data suggest that BP levels and cardiovascular event rates will inevitably rise among PLW-HIV in SSA. Consequently, our findings support efforts to integrate HIV and cardiovascular care in SSA. This strategy has strong potential to improve health outcomes among the millions of people living in SSA while applying limited resources in a more cost-efficient way.

Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Author contributions
SS and AC conceptualised and designed the study in collaboration with AOM and DBO. AC and LW, with the help of an expert librarian, did a comprehensive search according to the study protocol. AC and LW independently screened the titles and abstracts of articles retrieved from the literature search. Full text screening was independently conducted by AC, LW and SS. AC did the meta-analyses and generated all the forest plots (primary and supplementary outputs) in consultation with SS and YKC. AC, LW and SS generated the flow-chart & Table 1. AC drafted the first draft of the manuscript. AC, YKC and SS had access to and verified all the data. All authors then reviewed, edited, and commented on the interpretation of study data (available to all authors and provided as supplementary material). SS approved submission of the manuscript based on these findings.

Competing interests
The authors declare no competing interests.

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