



## SYSTEMATIC REVIEW

# AIDS-defining causes of death from autopsy findings for HIV-positive individuals in sub-Saharan Africa in the pre- and post-ART era: A systematic review and meta-analyses [version 1; peer review: 2 approved with reservations]

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## Abstract

**Background:** The lack of representative data on causes of death in sub-Saharan Africa (SSA) hampers our understanding of the regional burden of HIV and impact of interventions. In spite of the roll-out of antiretroviral therapy (ART) programs, HIV-infected individuals are still dying from complications of AIDS in SSA. We reviewed autopsy findings in SSA to observe whether the prevalence of 14 AIDS-defining illnesses changed from the pre-ART era to the post-ART era.

**Methods:** We conducted a systematic review of autopsy findings in SSA using Medline, CINAHL, Evidence Based Medicine, EMBASE, Scopus, Web of Science, and abstracts from the Conference on Retroviruses and Opportunistic Infections, for literature published between January 1, 1990 and September 30, 2018. We focused on 14 AIDS-defining illnesses as causes of death.

**Results:** In total, 33 studies were identified, including 9 from South Africa, 4 from the Ivory Coast, and the rest from eastern regions of sub-Saharan Africa. Of these, 18 studies were included in the meta-analyses for each of the AIDS-defining illnesses for adults. A 'mixed group' of studies that included adults and children was used for separate meta-analyses. Most opportunistic infections (OIs) showed a

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decrease in prevalence, with the notable exception of tuberculosis (TB), which showed a 13% increase in adult deaths and a 5% increase in mixed population group deaths. Kaposi's sarcoma and non-Hodgkin's lymphoma both showed a notable increase in prevalence, and liver disease showed a 10% increase in prevalence in the adult group.

**Conclusions:** Even though ART has reduced the contribution of OIs to causes of death for people infected with HIV in SSA, targeted and strategic efforts are needed in order to strengthen existing prevention, diagnosis, and treatment of TB. More research is required to understand the complex role ARTs have on liver and kidney diseases.

### Keywords

HIV, AIDS-defining illnesses, mortality, ART, sub-Saharan Africa, tuberculosis, systematic review, meta-analysis

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## Introduction

The last decade has seen tremendous changes in the landscape of HIV treatment, care, and mortality. In 2017, UNAIDS reported a 51% global reduction in deaths due to HIV since the height of the epidemic in 2004<sup>1</sup>. Increasing HIV testing and counseling, expanding antiretroviral therapy (ART) programs, and improving quality metrics (e.g. CD4 count measurement) as per guidelines have contributed to significant survival gains, particularly in low- and middle-income countries (LMICs).

The overall incidence of AIDS and death related to HIV infection has decreased worldwide. In 2017, 21.7 million HIV-infected people were accessing ART, which increased from 8 million in 2010<sup>1</sup>. High-income countries have shown that causes of death (COD) in HIV-infected individuals have changed, with non-AIDS-defining cancers, cardiovascular diseases (CVD), and liver diseases becoming the leading causes of mortality. A detailed understanding of COD and their associated risk factors is vital for optimal management of HIV-related diseases and comorbidities. However, in low-resource settings, COD are not well described or reported. Even though ART programs have expanded rapidly, and ART has a high efficacy, mortality remains high in the first few months of ART initiation, particularly in LMICs<sup>2-5</sup>. Treatment failures (e.g. secondary to drug resistance) may also facilitate the development of opportunistic infections (OIs) at any time while taking ART. As a result, AIDS-defining illnesses such as OIs or malignancies have remained a major cause of morbidity and mortality in HIV-infected individuals in low-resource settings, even in the era of wide-scale ART rollout<sup>6</sup>. There is a dearth of information on the impact of ART on mortality outside of controlled study settings. Therefore, measurement of treatment effectiveness in the population needs improvement, in particular regarding which factors contribute to HIV deaths worldwide and what the primary causes of these deaths are<sup>2,7</sup>.

## Rationale and objectives

COD data in many LMICs are obtained from clinical studies or verbal autopsies. Evidence has shown that there is discordance between clinical diagnoses and postmortem diagnoses, with many missed OIs in clinical diagnoses<sup>6</sup>. Postmortem causes of death studies are therefore integral to establishing the correct diagnoses. This study is one of the first systematic reviews of autopsy findings in the pre- and post-ART eras in sub-Saharan Africa (SSA) focusing on specific AIDS-defining illnesses as a cause of death and synthesized quantitatively with meta-analyses. In this study, we review autopsy findings in SSA to observe whether the prevalence of 14 AIDS-defining illnesses changed from the pre-ART era to the post-ART era.

## Methods

### Protocol and registration

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (*Extended data*, Supplementary Table 1)<sup>8,9</sup>.

### Study eligibility criteria

**Participants and comparators.** Participants were HIV-positive deceased individuals in SSA in the post-ART era who had a complete, partial, or minimally invasive autopsy performed to determine their COD. Comparators were HIV-positive deceased individuals in SSA in the pre-ART era who had a complete, partial, or minimally invasive autopsy done to determine the COD<sup>6</sup>. Study populations were categorized into three age groups: adult (15 years or older), child (under 15 years), or unknown (unspecified or mixed age groups).

**Interventions.** Definitions for complete, partial, and minimally invasive autopsies were taken from Cox *et al.*<sup>6</sup>. A complete autopsy refers to a macro- and microscopic assessment of all thoracic and abdominal organs and the brain. Partial autopsies are defined as the micro- or macro-sampling and examination of a singular organ or multiple organs. Minimally invasive autopsies included guided or unguided percutaneous needle autopsies, as well as investigations using endoscopic or laparoscopic techniques.

**Context/setting.** The deceased were from any sub-Saharan African country where the death had occurred in a hospital or community setting.

**Outcomes.** The outcomes were the prevalences of 14 AIDS-defining illnesses in adults and mixed adult and child cases divided into three categories, namely:

- Infections (tuberculosis, *Pneumocystis pneumonia* [PCP/PJP], other pneumonia, cryptococcal meningitis, other meningitis, toxoplasmosis, cytomegalovirus, and liver infection [hepatitis B, hepatitis C, pyogenic abscess])
- Cancers (Kaposi's sarcoma, non-Hodgkin's lymphoma, other/unspecified cancers); and
- Others including CVD/cerebrovascular disease, kidney disease, and liver disease.

**Report characteristics.** Peer-reviewed studies and gray literature were deemed eligible for inclusion if they: 1) were published between January 1, 1990 and September 30, 2018 inclusive; 2) had full text available in English or French; 3) were conducted within sub-Saharan Africa; 4) were original studies reporting results of complete, partial, or minimally invasive autopsies; 5) listed the year(s) in which the autopsies were conducted; and 6) reported autopsy findings for a minimum of 8 HIV-positive cases.

Original studies reporting verbal autopsy results or only clinical causes of death (without postmortem autopsy findings) were excluded. Sub-studies reporting selected results from a previously published large-scale autopsy study were also excluded. If two or more studies utilized an identical group of participants with overlapping or similar study periods, the study that reported the most complete and clearly articulated pathogen and disease prevalence was retained. Studies that recruited

subjects with a particular diagnosis were excluded, if they only presented pathology findings related to that specific disease category. Refer to [Figure 1](#) for the process.

### Search strategy

The search strategy was developed by an information specialist at St. Michael's Hospital Health Sciences Library located in Toronto, Canada, and was run on the following electronic databases: Medline, CINAHL, Evidence Based Medicine, EMBASE, Scopus, and the Web of Science. Search terms for the electronic databases are outlined in *Extended data*, Supplementary Table 2<sup>9</sup>. This search yielded 1,346 relevant articles up to and including December 31, 2016. In October 2018, the search was updated to include the International AIDS Society conferences, and to extend the review time period up to and including September 30, 2018. All available abstracts from the Conference on Retroviruses and Opportunistic Infections (CROI) were also reviewed for inclusion eligibility.

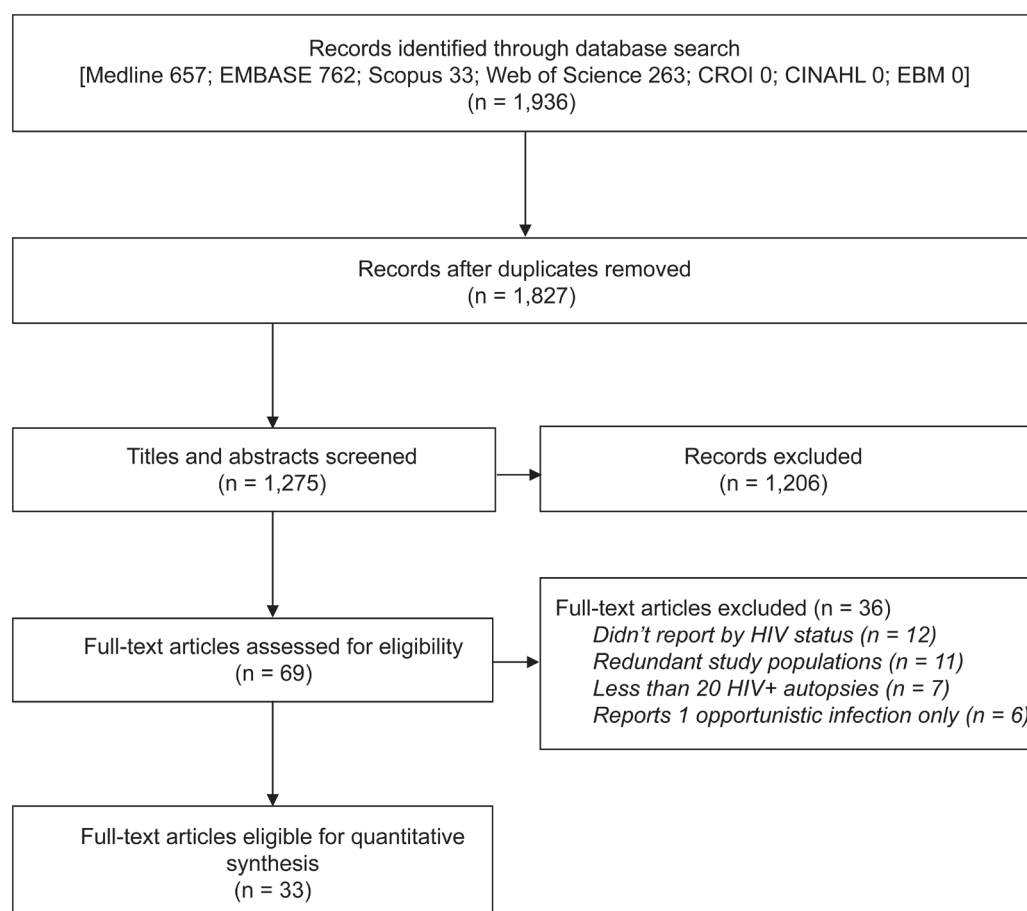
The titles and abstracts of all articles found were screened by two reviewers for duplicates or relevance. Both reviewers independently conducted the full-text screening and data extraction; if an agreement could not be reached, a third reviewer adjudicated.

### Data collection process and data items

A data extraction sheet was developed and piloted by the study authors extracting the following information from the included studies: country, years of data collection, the number of HIV-positive patients, the number of patients that received ART, age category of HIV-positive patients, type of autopsy conducted (complete, partial, or minimally invasive), and the autopsy-determined pathogens and diseases listed as outcomes above<sup>10,11</sup>.

If multiple pathogens or diseases were reported within each of these 14 AIDS-defining illnesses in the original study, the counts were not aggregated; instead, the pathogen or disease with the highest prevalence was recorded in that category unless otherwise specified above, in order to prevent over-reporting the number of patients with that specific pathogen or disease. For example, if a more potent pathogen or disease was reported, it was recorded as the cause of death even if there were other infectious pathogens or diseases. The most potent pathogen or disease was determined to be the disease most likely causing the death<sup>12</sup>.

If pathogens and diseases were not reported by ART status in the source study, the study was categorized as occurring within the pre- or post-ART era by reviewing the number of



**Figure 1.** PRISMA flow diagram.

individuals who received ART in each study or using World Bank ART country coverage estimates<sup>13</sup>. If the number of study subjects who received ART was one or more, the study was classified as taking place within the post-ART era. If the ART status of none of the study subjects were reported, and the World Bank ART coverage estimate was lower than 30% during the year(s) of study data collection, the study was considered to be pre-ART.

### Risk of bias in individual studies

Each full-text study and conference abstract was evaluated for reporting quality according to items listed in the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) statement for reporting observational studies<sup>14,15</sup>. The items on the STROBE checklist include study participant numbers, bias, variables, and analysis. One full point was given for full completion of each item, a half-point was given for partial completion, and zero points were given for poorly explained items or items that were not addressed. Some items were found to be not applicable for all studies, and were marked as such.

### Summary measures and synthesis of results

To measure whether there is a difference in the prevalence of AIDS-defining illnesses in autopsy samples pre- and post-ART, a random effects meta-analysis of single proportions with binomial exact 95% confidence intervals was conducted for each AIDS-defining illness by age group<sup>16,17</sup>. The Freeman-Tukey double arcsine transformation was used to stabilize the proportions. Heterogeneity was quantified using the  $I^2$  statistic for each of the groups of studies<sup>18,19</sup>. All analyses were conducted in Stata version 14.2 using the metaprop command<sup>16,20</sup>. For AIDS-defining illnesses with data from two or more studies in each of the pre- and post-ART eras, forest plots were generated to display the prevalence of 14 AIDS-defining illnesses given as the cause of death at autopsy. Study prevalence estimates were separated by age category (adult and mixed) and stratified by pre- and post-ART eras.

### Risk of bias across studies

Two funnel plots, one for adult and mixed studies and one for adult studies only, were generated to assess risk of publication bias in each age group.

## Results

### Study selection

Figure 1 describes the stepwise process of study selection. A total of 1936 records were found in the original search. Two independent reviewers removed the duplicates, resulting in 1827 studies retained. Titles and abstracts were screened, resulting in 69 articles and conference abstracts. A review of the full-text articles and conference abstracts resulted in 33 articles included in the quantitative synthesis (Figure 1), including 30 articles<sup>7,12,21–48</sup> and 3 conference abstracts<sup>49–51</sup>. Other articles and abstracts were excluded because insufficient autopsies in HIV-positive individuals were performed, the autopsies were not reported by HIV status, or reporting on outcomes was duplicated for the same study population.

### Study characteristics

Refer to *Extended data*, Supplementary Table 3<sup>9</sup> for study characteristics of the 33 included publications. There were 16 cross-sectional, 12 prospective cohort, 4 retrospective cohort, and 1 mixed study design. The majority of the studies were conducted in South Africa (9 studies) and the Ivory Coast (4 studies), with the remainder in eastern SSA. Years of study data collection ranged from 1989 to 2014. Of the studies, 28 were hospital-based and the rest were community-based, of which two were conducted in pathology departments and two others in treatment centers at mines in South Africa. Sample sizes ranged from 20 to 3725.

Study participants were individuals who died either in a hospital or community setting and were then transferred to hospital for an autopsy. All participants were HIV-positive and from SSA. Interventions in the studies were complete, partial, or minimally invasive autopsies, with additional interventions including radiology, ELISA, and Western blot HIV testing. Study outcomes were COD prevalence of the 14 AIDS-defining illnesses mentioned above.

The 2014 study by Field *et al.* was the only article that reported autopsy results by HIV-positive patients receiving ART versus those not on ART, and is reported in our analyses in both pre- and post-ART eras<sup>36</sup>. All other included articles and abstracts were classified as pre- or post-ART according to study criteria.

### Risk of bias within studies

The 30 full-text studies generally had high reporting quality with respect to the STROBE guidelines for observational studies (*Extended data*, Supplementary Table 4a)<sup>9,14</sup>. Introduction sections, including background and objectives, and Results sections were generally complete across all included studies. Due to the nature of most autopsy studies, 24/30 included studies did not report on “outcome data” and so were graded “not applicable” for this item, instead reporting on main results. The Methods and Discussion sections contained much more variability. In particular, definitions were frequently not explicit or were missing for study design (16/30 studies) and included variables (13/30 studies). In the Discussion section, key results and interpretation were complete for 29/30 studies. However, limitations and generalizability of the studies were less well addressed, with 17/30 studies lacking explicit reference to one or both of these areas. In total, 19 of the 30 studies declared a funding source.

Of the three conference abstracts, two had high levels of reporting according to the corresponding STROBE checklist (Supplementary Table 4b)<sup>9,15</sup>. For all three abstracts, study titles and authors were always provided, and results sections, including participant count, main results, and conclusions, were complete. The methods sections of the abstracts were more variable with regards to reporting items, as was clear definition of study objectives.

### Results of individual studies

Refer to the *Extended data*, Supplementary material Table 5<sup>9</sup> for outcome data of the individual studies.

## Synthesis of results

Meta-analyses were conducted for the adult and mixed age categories for all 14 AIDS-defining illnesses, and selected results are presented here as prevalence estimates with 95% confidence intervals. Nineteen studies conducted autopsies on HIV-positive adults<sup>12,21–36,49</sup> and 9 on HIV-positive children<sup>37–45</sup>. A ‘mixed group’ refers to six studies that did not report results by age<sup>7,46–48,50,51</sup>. Only 1 of the 9 eligible child studies was conducted in the post-ART era. As a result, no meta-analysis could be conducted for this age category.

**Table 1** shows the estimated overall prevalence of AIDS-defining illnesses when examining the meta-analyses for all deaths according to categories. **Figure 2–Figure 7** report on the studies and trends per AIDS-defining illness as reported by 18 studies (pre-ART: 13 studies; post-ART: 6 studies; pre- and post-ART: 1 study).

**Infectious diseases.** The estimated overall prevalence of TB as a cause of death in adults during the pre-ART era was 27.9% (95% CI 19.9–36.5%), and rose to 40.8% (95% CI 29.6–52.4%)

**Table 1. Estimated overall prevalence of AIDS-defining illnesses as reported by autopsy studies conducted in sub-Saharan Africa from 1990 to 2016 on HIV-positive adults and mixed population groups in the pre- versus post-antiretroviral therapy (ART) era.**

AIDS-defining illnesses	Adult % overall prevalence (95% CI)		Mixed (adult and children) overall % prevalence (95% CI)	
	Pre-ART	Post-ART	Pre-ART	Post-ART
<b>Infectious diseases</b>				
Tuberculosis	27.9 (19.9, 36.5)	40.8 (29.6, 52.4)	24.1 (11.5, 39.3)	29.5 (19.8, 40.2)
<i>Pneumocystis</i> pneumonia (PCP/PJP)	8.7 (5.7, 12.1)	2.5 (0.9, 4.7)	*8.9 (3.6, 17.4)	*2.5 (0.0, 7.7)
Other pneumonia	24.2 (19.9, 28.8)	21.4 (11.2, 33.7)	*16.3 (6.3, 29.4)	6.5 (1.8, 13.4)
Cryptococcal meningitis	6.8 (3.1, 11.5)	5.8 (0.7, 14.2)	7.6 (2.8, 14.1)	9.3 (3.5, 17.0)
Other meningitis	13.8 (5.5, 25.0)	5.2 (1.7, 10.3)	-	-
Toxoplasmosis	*3.2 (0.4, 8.0)	*11.0 (4.9, 20.5)	-	-
Cytomegalovirus	5.9 (1.8, 11.8)	2.9 (0.9, 5.7)	-	-
Liver infection†	13.8 (0.6, 38.0)	7.7 (1.4, 17.6)	-	-
<b>Cancers</b>				
Kaposi's sarcoma	2.9 (1.0–5.5)	4.6 (2.3, 7.5)	*5.2 (1.1, 11.3)	*8.6 (1.8, 23.1)
Non-Hodgkin's lymphoma	2.4 (1.2, 3.8)	3.8 (0.6, 8.9)	-	-
Other/unspecified cancers	2.1 (1.1, 3.4)	3.9 (1.8, 6.5)	-	-
<b>Other</b>				
Cardiovascular/cerebrovascular diseases	4.9 (1.9, 8.9)	5.0 (2.7, 7.9)	*6.2 (3.7, 9.4)	*6.0 (1.4, 12.7)
Kidney disease	14.7 (2.3, 34.5)	5.8 (0.9, 13.6)	-	-
Liver disease‡	9.1 (1.8, 20.6)	19.4 (12.3, 27.7)	-	-

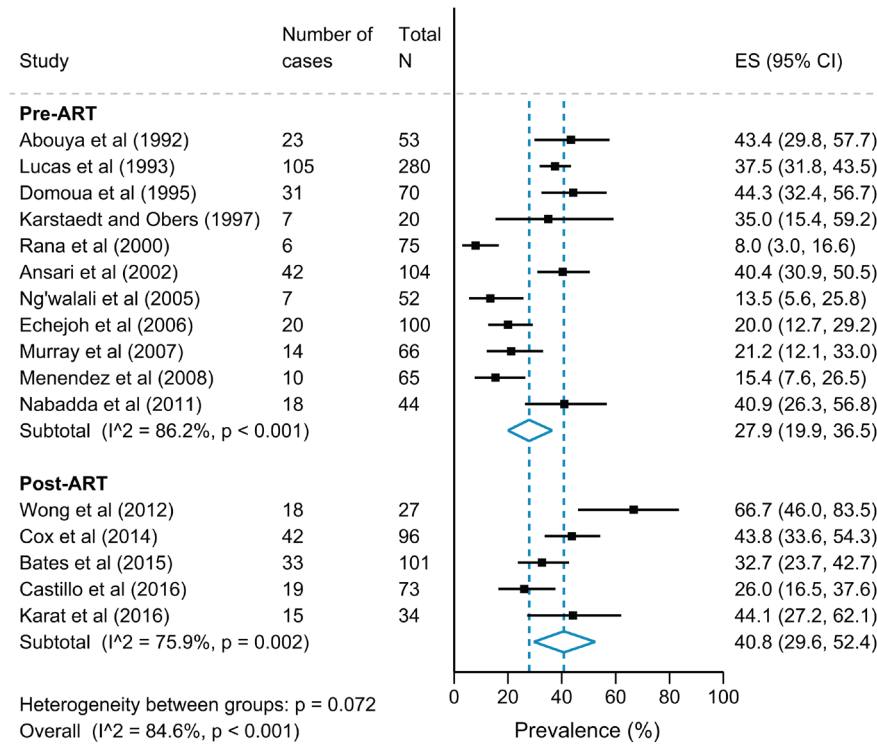
Note: Rows with missing data indicate causes of death for which only one or no studies reported on either disease prevalence or pre- or post-ART, resulting in insufficient data with which to conduct a meta-analysis.

\* These values must be interpreted with caution due to low study numbers.

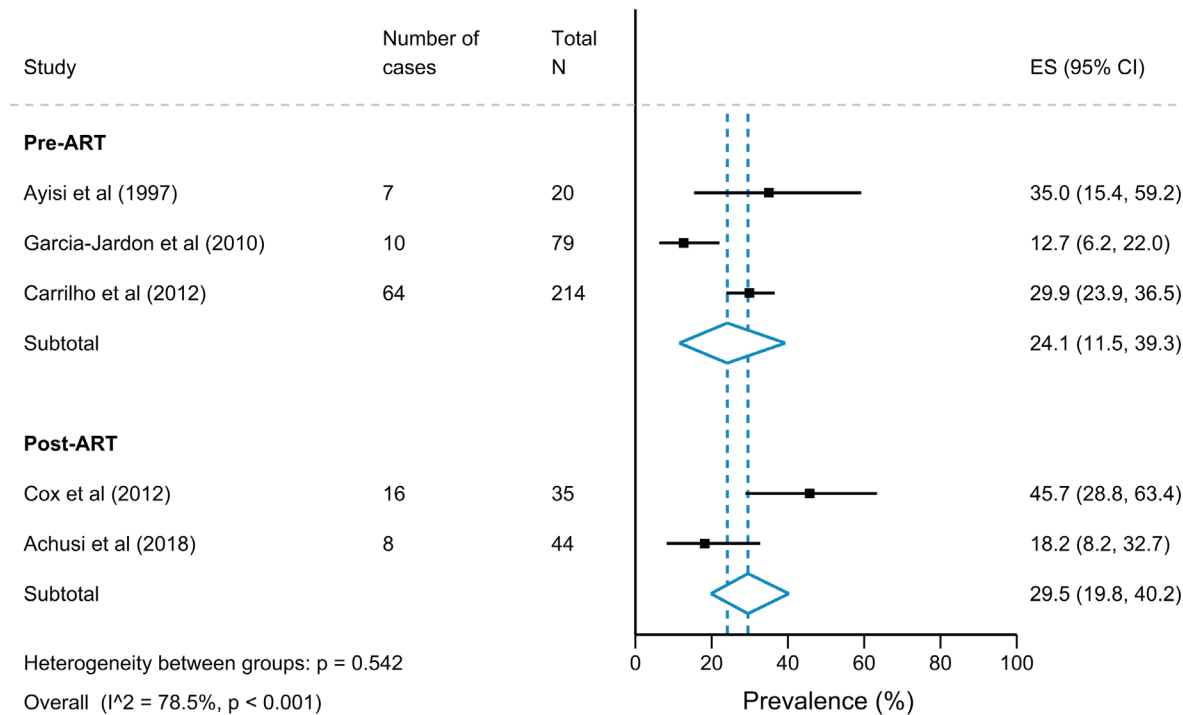
† Liver infection includes hepatitis B, hepatitis C, and pyogenic abscess.

‡ Liver disease includes cirrhosis, steatosis, hepatocellular cancer, and portal triaditis.

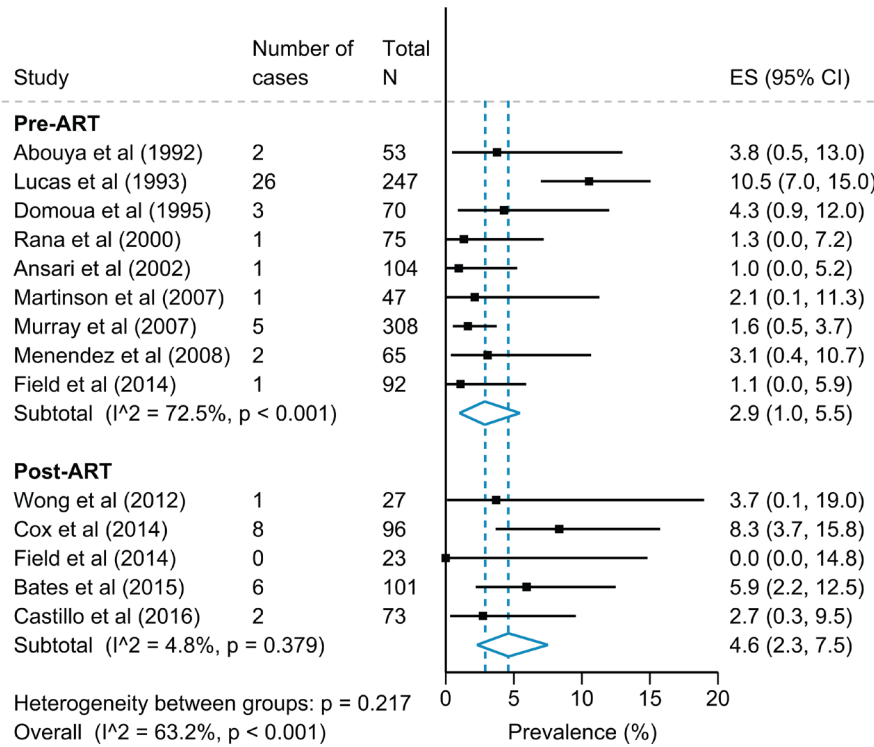




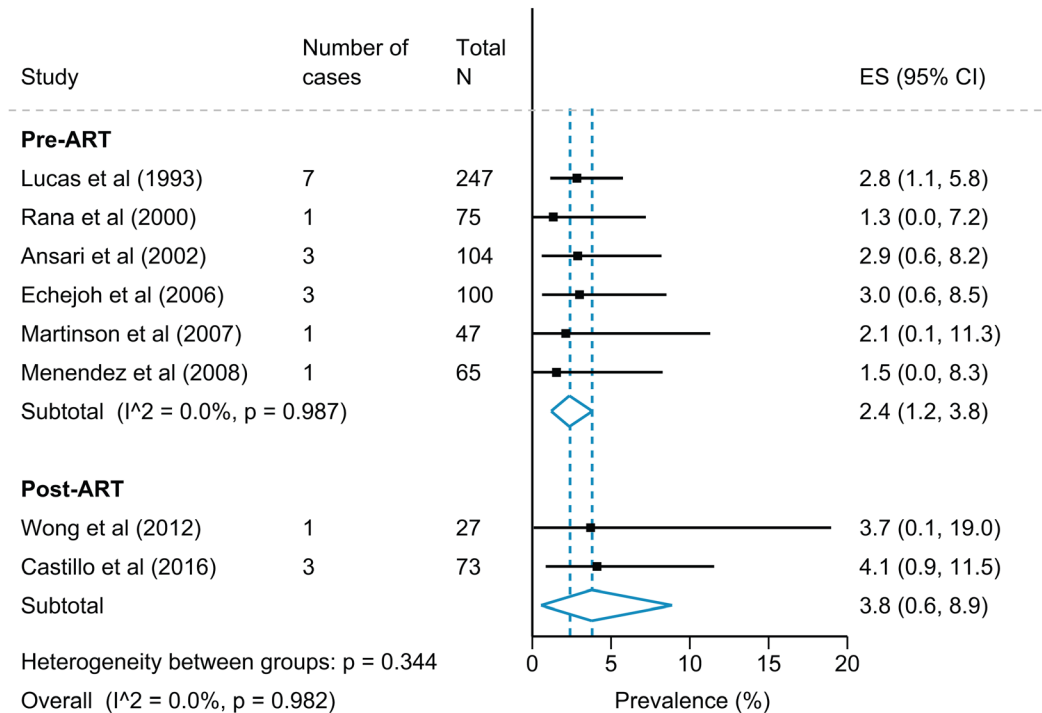
**Figure 2. Prevalence of tuberculosis among HIV-positive adult autopsy patients in pre- and post- antiretroviral therapy (ART) eras.**



**Figure 3. Prevalence of tuberculosis among HIV-positive autopsy mixed population patients in pre- and post- antiretroviral therapy (ART) eras.** Note: No heterogeneity effect measures or p-values are presented at the subtotal level due to sample requirements.

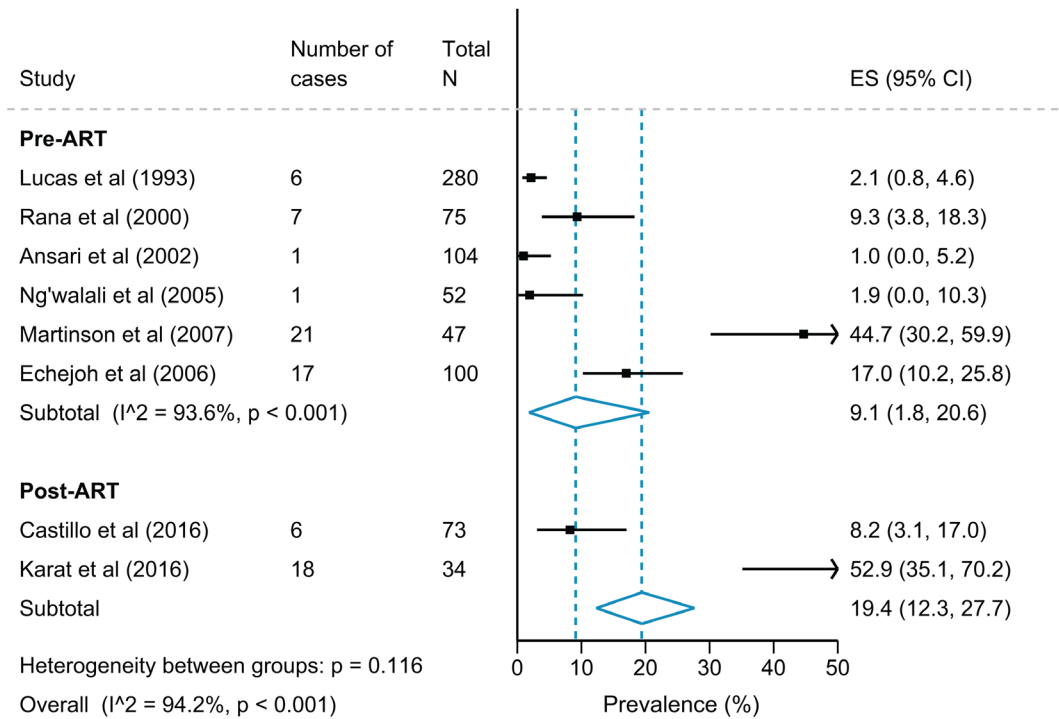


**Figure 4. Prevalence of Kaposi's sarcoma among HIV-positive adult autopsy patients in pre- and post- antiretroviral therapy (ART) eras.**

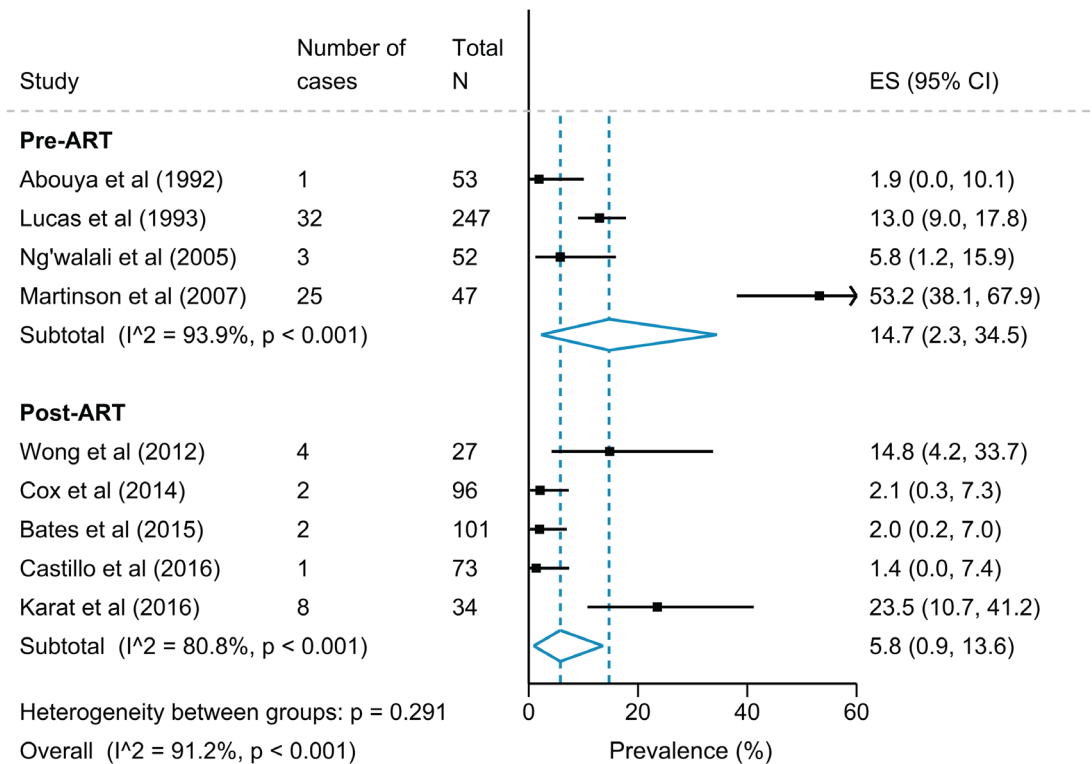


**Figure 5. Prevalence of non-Hodgkin's lymphoma among HIV-positive adult autopsy patients in pre- and post- antiretroviral therapy (ART) eras.** Note: No heterogeneity effect measures or p-values are presented at the subtotal level for the post-ART studies due to sample requirements.





**Figure 6. Prevalence of liver disease among HIV-positive adult autopsy patients in pre- and post-antiretroviral therapy (ART) eras.** Note: No heterogeneity effect measures or p-values are presented at the subtotal level for the post-ART studies due to sample requirements.



**Figure 7. Prevalence of kidney diseases among HIV-positive adult autopsy patients in pre- and post- antiretroviral therapy (ART) eras.**

in the post-ART era (Figure 2). The overall TB prevalence in pre-ART mixed groups was approximately 24.1% (95% CI 11.5-39.3%), and also increased in the post-ART era to 29.5% (95% CI 19.8-40.2%; Figure 3).

The overall prevalence of *Pneumocystis* pneumonia as a cause of death during the pre-ART era in adults was 8.7% (95% CI 5.7-12.1%), while the overall prevalence in the post-ART era decreased to 2.5% (95% CI 0.9-4.7%; Extended data, Supplementary Figure 1)<sup>9</sup>. In adults, the overall prevalence of other causes of pneumonia as a cause of death in the pre-ART era was 24.2% (95% CI 19.2-28.8%), while the overall prevalence in the post-ART era was lower at 21.4% (95% CI 11.2-33.7%; Extended data, Supplementary Figure 2)<sup>9</sup>. For the mixed population group, the overall prevalence of other causes of pneumonia as a cause of death in the pre-ART era was 16.3% (95% CI 6.3-29.4%), while the overall prevalence in the post-ART era was lower, at 6.5% (95% CI 1.8-13.4%; Extended data, Supplementary Figure 3)<sup>9</sup>.

In adults, the observed overall prevalence of cryptococcal meningitis as a cause of death was 6.8% (95% CI 3.1-11.5%) pre-ART, and 5.8% (95% CI 0.7-14.2%) post-ART (Extended data, Supplementary Figure 4)<sup>9</sup>. In the mixed group, overall prevalence of cryptococcal meningitis in the pre-ART era was 7.6% (95% CI 2.8-14.1%), and increased to 9.3% (95% CI 3.5-17.0%; Extended data, Supplementary Figure 5)<sup>9</sup>. The overall prevalence of other meningitis in adults reported in the pre- and post-ART era were 13.8% (95% CI 5.5-25.0%) and 5.2% (95% CI 1.7-10.3%), respectively (Extended data, Supplementary Figure 6)<sup>9</sup>.

The overall cytomegalovirus prevalence in pre-ART adults was 5.9% (95% CI 1.8-11.8%), while the estimated overall prevalence in the post-ART era for adults was 2.9%, (95% CI 0.9-5.7%; Extended data, Supplementary Figure 7)<sup>9</sup>.

Liver infection in adult deaths decreased from 13.8% (95% CI 0.6-38.0%) pre-ART to 7.7% (95% CI 1.4-17.6%) post-ART (Extended data, Supplementary Figure 8)<sup>9</sup>. These included HIV co-infections with hepatitis B and/or C, as well as pyogenic abscess.

**Cancers.** There was minimal increase in estimated difference in overall prevalence for Kaposi's sarcoma in adults, with pre-ART value 2.9% (95% CI 1.0-5.5%) and post-ART value 4.6% (95% CI 2.3-7.5%) observed (Figure 4).

For non-Hodgkin's lymphoma, the overall prevalence in adult deaths in pre-ART was 2.4% (95% CI 1.2-3.8%), and 3.8% (95% CI 0.6-8.9%) in the post-ART era (Figure 5). For other/unspecified cancers in adult studies, the overall prevalence for pre-ART era was 2.1% (95% CI 1.1-3.4%), and the post-ART era was 3.9% (95% CI 1.8-6.5%; Extended data, Supplementary Figure 9)<sup>9</sup>.

**Other diseases.** The overall prevalence of CVD/cerebrovascular diseases in adults in the pre-ART era was 4.9% (95% CI

1.9-8.9%), and 5.0% (95% CI 2.7-7.9%) in the post-ART era (Extended data, Supplementary Figure 10)<sup>9</sup>; prevalence of CVD/cerebrovascular diseases was similarly stable in the mixed population from the pre- to post-ART time period (Extended data, Supplementary Figure 11)<sup>9</sup>. Liver disease in adult deaths increased from 9.1% (95% CI 1.8-20.6%) in the pre-ART era to 19.4% (95% CI 12.3-27.7%) in the post-ART era (Figure 6). These included cirrhosis, steatosis, hepatocellular cancer, and portal thrombosis. For kidney disease, the overall prevalence reported in adults for the pre-ART era was 14.7% (95% CI 2.3-34.5%), and 5.8% (95% CI 0.9-13.6%) in the post-ART era (Figure 7).

### Risk of bias across studies

Two funnel plots explore publication bias in the studies for the adult (Extended data, Supplementary Figure 12)<sup>9</sup> and mixed population groups (Extended data, Supplementary Figure 13)<sup>9</sup> reporting AIDS-defining causes of death of HIV-infected individuals. There seems to be no apparent publication bias, i.e. that small studies are only published if they show a significant effect. This makes sense as most of these studies did not explicitly target the effects of ART (pre vs post) themselves.

## Discussion

### Summary of evidence

To our knowledge, this is the first systematic literature review and meta-analysis of AIDS-defining illnesses as diagnosed by autopsy studies in the pre- and post-ART eras in HIV-infected adults and children in SSA. The dearth of autopsy studies in SSA available in the post-ART era makes it challenging to assess differences in the prevalence of AIDS-defining illnesses pre- and post-ART, especially in children.

There was a reduction in most OIs post-ART with the notable exception of TB, which showed a 13% increase in prevalence in adults and a 5% increase in the mixed population group (consisting of adults and children). A systematic review by Gupta *et al.* showed that, in resource-limited settings, TB prevalence decreased by more than 10% in HIV-infected children but increased in HIV-infected adults post-ART<sup>52</sup>. This could account for why the increase in the mixed population is not as high as in the adult population for our review. Studies included in our review contained insufficient data for a child population meta-analysis to confirm this. Another review by Low *et al.* showed a reduction in all other OIs in the first 12 months of ART, except for TB<sup>53</sup>. While ART improves overall outcomes in patients with HIV and TB co-infection, the mortality rate during the first two months of TB treatment is not reduced by ART<sup>13,54</sup>, and may be driven by other explanations such as delayed initiation of treatment in very advanced cases, or immune reconstitution inflammatory syndrome (IRIS). In the study by Wong *et al.*, TB was the leading cause of death regardless of ART status and was particularly high in subjects dying in the first 3 months of ART<sup>32</sup>. Gupta *et al.* also conducted additional meta-regression analyses that indicated a positive association between prevalence of TB at autopsy and national population TB prevalence<sup>52</sup>. This would be relevant for eight of the studies included in this review which used data from

South Africa, where TB prevalence rates are among the highest in the world<sup>55</sup>.

Evolving TB diagnostics may also contribute to the increase in TB prevalence in the adult population. During the pre-ART era, TB diagnostics largely relied on sputum samples being tested for the presence of acid-fast bacilli, a procedure with typically very low sensitivity, especially in the context of HIV co-infection<sup>56–59</sup>. More recently, nucleic acid amplification TB diagnostic modalities such as the Xpert MTB/RIF assay were rolled out in many SSA settings during the post-ART era and resulted in significantly higher sensitivity compared to sputum smear microscopy<sup>60</sup>. The increase in TB in adults may additionally be linked to accelerated decreases in mortality from other causes of death. As autopsy studies by definition are limited to deceased individuals, changes in specific causes of death are always relative to other causes of death.

The World Health Organization (WHO) has recommended TB/HIV collaborative activities in high HIV prevalence settings to combat death from TB. Integrated TB/HIV centers and programs promote testing for TB in HIV-positive patients who are on ART. However, there are challenges integrating HIV and TB programs, which may be culminating in poor patient outcomes in those with co-infection<sup>61</sup>.

The study by Low *et al.* also showed significant decreases in oral candidiasis, PCP, and toxoplasmosis post-ART<sup>53</sup>. We did not look at oral candidiasis, and our toxoplasmosis study numbers were negligible. However, the PCP findings of the study by Low *et al.* were consistent with the decrease in prevalence indicated by our analysis. Even in the pre-ART era, the WHO recommended cotrimoxazole (CTX) prophylaxis for people infected with HIV to prevent OIs. CTX, a combination of two antimicrobial drugs, is active against a range of bacterial, fungal, and parasitic infections that reduces morbidity and mortality in people living with HIV. CTX prophylaxis and increase in coverage could have contributed to this decrease.

Prevalence of all cancers in the study, including non-Hodgkin's lymphoma and Kaposi's sarcoma, increased modestly from the pre-ART era to the post-ART era. Kaposi's sarcoma remains the second most frequent tumor in HIV-infected people globally and has become the most common cancer in SSA<sup>62</sup>. It has also been reported as occurring in patients with well-controlled HIV infection and CD4+ T cell count >200 cells/μl, and patients with Kaposi's sarcoma on ART typically have a less aggressive presentation when compared to those not receiving ART. In a 2012 review, Semeere *et al.* looked at the impact of ART on Kaposi's sarcoma, and found only one population-level study report in an LMIC, which estimated an increase in prevalence from 2007 to 2010 in Malawi compared to earlier periods<sup>63</sup>. However, individual patient-level effectiveness of ART on Kaposi's sarcoma incidence in LMIC is comparable to high-income countries. Conclusions of this study were that more studies are required in order to produce evidence in LMICs. Non-Hodgkin's lymphoma incidence tends to be less affected by the use of ART, which could account for the observed increase in our review<sup>64</sup>.

In high-income countries where ART has been available for longer, availability of ART markedly improved survival of people living with HIV<sup>65</sup>. However, there is a consequent increased risk of developing non-communicable diseases (NCDs), with common causes of death including liver disease, CVD, and non-AIDS malignancies<sup>66–68</sup>. This risk increases with age and can be related to HIV and use of ART<sup>69</sup>. It has been estimated that liver disease accounts for 13–18% of all-cause mortality in people infected with HIV in the post-ART era<sup>68</sup>. The observed increase in liver disease in our review is consistent with this finding. Liver disease is also an independent risk factor for CVD. Our findings in this review were that CVD/cerebrovascular diseases showed negligible change in prevalence. This is inconsistent with findings of post-ART populations in high-income countries where CVD including heart failure in HIV-infected people is one of the leading causes of death, and is predicted to increase globally in the next 15 years<sup>70,71</sup>. In most LMICs, NCDs are managed episodically, which results in patients being at risk for long-term complications and death<sup>69</sup>. In high-income countries where NCD patients have access to appropriate long-term care and treatment, there is a reduction in morbidity and mortality<sup>72</sup>. As a result, improved NCD data in ageing HIV-infected individuals receiving ART is needed to inform cost-effective solutions for health systems in LMICs to create diagnostic and treatment processes inclusive of both HIV and NCDs.

In our study, we found a notable decrease in kidney disease incidence (almost three times lower) in the post-ART era. The reason for this could possibly be because most deaths in the included studies were hospital-based and there could have been other underlying causes of death. It is known that the risk of acute and chronic kidney disease remains higher in people infected with HIV when compared to the general population<sup>73</sup>. Acute kidney disease is associated with an increased risk of heart failure, CVD, and end-stage renal disease, which ultimately leads to mortality. However, widespread highly effective ART has attenuated HIV-associated nephropathy as a form of chronic kidney disease (CKD), characterizing CKD in people infected with HIV as being related to diabetes or hypertension<sup>73</sup>. Also worth mentioning is that partial autopsies and minimally invasive tissue samples do not always sample kidney tissue. As usage of these two techniques increases in the absence of complete autopsies, mortality due to kidney diseases may be diagnosed less frequently. More research is warranted to further explore the relationship between HIV infection and kidney disease in the post-ART era.

It is worth noting that, over the last decade, academic journals have begun to improve reporting quality of studies by requesting checklists such as STROBE along with new submissions. Many of the studies included in this review predate reporting quality guidelines like the STROBE checklist that are frequently used today. It is therefore unsurprising that many of the more recent studies included in this review have higher reporting quality by current standards than do the studies from the 1990s or early 2000s. This is especially clear for particular STROBE checklist items, such as indication of study design in the study title, as well as declaration of funding source.

## Limitations

Our review has several important limitations. Even though we believe our literature search to be comprehensive, it is always possible relevant studies were not identified. The high heterogeneity values in the meta-analyses are also a limitation. As with other meta-analyses of observational studies, this could be attributable to the original studies being too heterogeneous and may not have been suitable to combine. We could have conducted a sensitivity analysis for each meta-analysis in order to explore the source for heterogeneity; however, this was not a plausible alternative due to the small number of studies. Autopsies in these countries are not routinely performed, resulting in an important selection bias towards those cases with an unclear diagnosis that warranted an autopsy.

An important caveat when comparing disease prevalence between the pre- and post-ART eras is that better diagnostic methods have arisen over time. This could account for a better diagnosis pre-mortem in the post-ART era, therefore reducing the need for an autopsy to understand the cause of death. Therefore, the decrease in the causes of certain OI may be due to a true decrease in their incidence, but could also be significantly decreased because of improved screening tools for OIs. The findings could also reflect selection bias of autopsies done in non-OI deaths, and not a true change. This bias can go in both directions, so the increase of TB diagnosis may also be due to the fact that these cases had been better diagnosed pre-mortem. Another limitation is that the ART-era labeling per study may not necessarily reflect the reality of the study country.

## Conclusions

With the expansion of ART rollout and the introduction of more effective and tolerable ART regimens, ongoing, innovative, and accurate methods and tools to monitor causes of death are required in SSA. Some OIs like TB still require targeted and strengthened efforts to screen, prevent, diagnose, and treat in HIV-positive individuals. More knowledge is also needed on prevention, screening, and management of non-AIDS-related NCDs like liver and kidney diseases in HIV-infected people in SSA. In view of the paucity of high-quality, eligible studies identified in this review, further autopsy studies ascertaining the causes of death in HIV-infected individuals need to be conducted.

## Data availability

### Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

## Extended data

Open Science Framework: AIDS-defining causes of death from autopsy findings for HIV-positive individuals in sub-Saharan Africa in the pre- and post-ART era: A systematic review and meta-analyses.

<https://doi.org/10.17605/OSF.IO/3UR5F9>.

This project contains the following extended data:

- Figures\_S1\_S13.pdf (Supplementary Figures 1–13).
- Table\_S1.pdf (PRISMA checklist).
- Table\_S2.pdf (Search terms for electronic database search).
- Table\_S3.pdf (Study characteristics of the 33 included publications).
- Table\_S4.pdf (Table 4a: Reporting quality assessment for 30 included full-text articles; Table 4b. Reporting quality assessment for 3 included conference abstracts).
- Table\_S5.pdf (Results of 33 included studies, by age group, ART era, and AIDS-defining illness).

## Reporting guidelines

Open Science Framework: PRISMA checklist for “AIDS-defining causes of death from autopsy findings for HIV-positive individuals in sub-Saharan Africa in the pre- and post-ART era: A systematic review and meta-analyses. <https://doi.org/10.17605/OSF.IO/3UR5F9>.

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](#) (CC-BY 4.0).

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Thank for you for the opportunity to review this paper. This a well-written review on an important topic. I have some comments and questions, mostly around the analysis.

## Methods:

- 1. Use of the term "AIDS-defining":** At least five of the outcomes listed are not strictly 'AIDS-defining' and it could be argued that some should not even be described as 'HIV-associated'. The consideration of these diseases as AIDS-defining risks undermining one of the main points of the authors, which I believe is that the prevalence of most *true* AIDS-defining conditions decreases substantially after starting ART. I had wondered why there was no figure presented for 'overall prevalence of AIDS-defining conditions pre- and post- ART', but presumably because of the blurry distinction between the two types of condition this would have shown no difference? It would make the results of the analysis considerably clearer to consider these conditions separately, or at the least to make it clear that 'kidney disease' and others are not technically AIDS-defining conditions.
- 2. Prevalence vs. cause of death:** The terms 'prevalence' and 'cause of death' seem to be used somewhat interchangeably - as the authors know, they are rather different, and the outcome reported has major implications for how the results of the review are interpreted. In relation to this, I found the description of the process for classifying outcomes a little confusing (second and third paragraphs under 'data collection process...'). The use of 'potency' as a measure for which was the 'more important' disease is problematic - the impact on clinical outcome of one pathogen or disease varies considerably by individual and depends on a number of other interrelated factors; these kinds of judgements (most often to determine cause of death) are generally made through a standardised process - the paper by Castillo *et al.* cited by the authors describes a review of MIA data by three specialists - was this process replicated during this review?

This comes back to the issue of describing prevalence vs. cause of death - if aiming to describe the prevalence of various disease then it is surely important to record the presence of multiple organisms/diseases in one individual – I would suggest not doing this risks under-reporting the prevalence of particular diseases, rather than over-reporting, as is stated in the manuscript. If reporting on causes of death, however, then it would be more usual to settle on the most important/potent disease; aggregating counts of pathogens in this case would indeed lead to over-reporting.

I hope I have not misunderstood – apologies if so. I would ask that the authors be more clear about the outcomes they are reporting on and be consistent with the language used in the title and throughout the manuscript (including avoiding, for example, discussing disease ‘incidence’ in the context of autopsy – penultimate paragraph, page 11).

3. **Classification of pre-/post-ART:** The classification of studies as occurring in either the pre- or post-ART era seems convenient, but I am concerned that this in fact makes it more difficult to elicit the effects of ART on the outcomes under consideration. A single person receiving ART being enough for a study to be considered to have occurred in the ‘post-ART’ era seems to me to be overly reductive, inconsistent with the ‘30% national coverage’ used as an alternative criterion, and risks underestimating the effects of ART. The authors acknowledge this in the limitations, saying that the labels may not reflect the reality in the country at the time - I would go further and say that they may not reflect the reality even within that study. When considering the occurrence of OIs or other HIV-associated disease in individuals, it is surely that individual’s exposure to ART that is most important, regardless of how many people in the community or country happen to be receiving treatment. Though, as the authors point out, most included studies did not report results by ART status, almost every study will have at least reported the number of individuals who received ART prior to death/autopsy. Would it be possible for the authors to use ‘ART coverage within the study’ as a continuous, rather than a binary, variable and conduct meta-regression, plotting it against ‘disease prevalence’? At the very least, I would ask the authors to acknowledge, more explicitly, the limitations of their classification system and its potential impacts on their main findings. I would also strongly suggest that Table S3 is moved from the online supplement to the main manuscript, with columns added for ‘number of autopsies’, and ‘number of decedents on ART’, to show more clearly how decisions were made about classification as pre-/post-ART and to allow readers to interpret better the results of the analysis.
4. **Use of STROBE to assess quality:** Although STROBE is a useful checklist, it is not designed to assess the quality of studies, only to assess the completeness of how they were reported (see da Costa *et al.*, 2011<sup>1</sup>). The absence of a true assessment of quality in this case also hampers the interpretation – the authors discuss the potential for selection bias in the limitations (page 12), but have not made an objective assessment of bias in the studies included (which, I would suggest, should have been a standard part of the review process), and are therefore restricted to hypothesising. I appreciate that it is a lot of extra work, but some assessment of study quality is critical to interpretation of the results, and I would suggest that the authors reassess each study using a standardised tool, appropriate to the

study type.

5. As the authors acknowledge briefly in the penultimate paragraph on page 11, complete autopsy is considerably better than MIA and partial autopsy at detecting non-communicable diseases and most cancers. The autopsy approach and laboratory methods used by a study would likely have had a large effect on that study's ability to detect a particular outcome, but this has not been considered when comparing estimates from different studies. It may not be possible to factor this into the analysis, but I would ask that the authors address this in more detail in the discussion and/or limitations.

**Results:**

1. As suggested above, please consider moving Table S3 to the main manuscript and adding at least two additional columns.
2. It would also have been nice to see a comparison of prevalence of all/any AIDS-defining illnesses in pre- and post-ART studies, though this is perhaps made difficult by the classification issues discussed above. Might this be possible, either in the form of a table or forest plot?

**Discussion:**

1. Paragraph 2: the reference to the SR by Low *et al.* is of course relevant, but please could the authors make it clear that this is a review of living individuals, not of people who have died, as this has considerable impact on how the findings are interpreted. Similarly, it would be ideal if the review by Gupta *et al.* could be described at the top of the paragraph as a review 'of autopsy studies' or something similar.
2. Apologies if I am missing something, but the argument on page 11 about better diagnostics increasing the prevalence of TB does not entirely make sense to me. Undoubtedly the roll-out of Xpert, etc., will have increased the proportion of people with active TB that are detected by health services, but I cannot see how it will have increased the actual prevalence of TB disease in the populations where they are used – if anything, prevalence in those communities should decrease, as a result of earlier detection and treatment, leading to less transmission. If the authors had meant the methods used to detect TB *at autopsy*, that would perhaps make more sense, and would speak to the point raised above regarding differentiation of studies by the autopsy methods used. Again, apologies if I have misunderstood.
3. Please see comments above regarding potential additions to the limitations section.

**Minor points:**

1. Regarding the study by our group (Karat *et al.*, 2016), please note that it was not a hospital-based study; though many individuals did die in hospital, all were recruited from primary care clinics and autopsies were conducted in private mortuaries in the community. Autopsy findings and ART status for each decedent are available in the second supplementary table and in the publicly-available dataset (<http://datacompass.lshtm.ac.uk/243/>).

## References

1. da Costa B, Cevallos M, Altman D, Rutjes A, et al.: Uses and misuses of the STROBE statement: bibliographic study. *BMJ Open*. 2011; **1** (1). [Publisher Full Text](#)

**Are the rationale for, and objectives of, the Systematic Review clearly stated?**

Yes

**Are sufficient details of the methods and analysis provided to allow replication by others?**

Partly

**Is the statistical analysis and its interpretation appropriate?**

Partly

**Are the conclusions drawn adequately supported by the results presented in the review?**

Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** TB epidemiology, mortality studies, systematic reviews

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

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**Frank Post**

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Peer and colleagues have summarized autopsy studies from sub-Saharan Africa and compared causes of death in the pre-ART and ART era. There are a modest number of studies with a modest number of patients (around 850 and 350) that could be included in the meta-analysis. The authors report some differences in the prevalence of specific causes of death, notably TB, which may reflect the increasingly widespread use of ART in the latter era.

While these observations are of interest, there are a number of limitations, most notably the difference in regions where the pre-ART vs. ART era autopsies were performed (56% vs. 0% in West Africa). There is substantial regional variability in co-morbid conditions across SSA, particularly for TB, hepatitis B and HIVAN. The reported comparison is as much one between regions as pre-ART vs. ART era. Given the sample size and the complete lack of West-African data in the ART era, I

don't think this can be addressed but this major limitation should be acknowledged in the abstract and discussion.

I suspect that a large number of deaths in the ART era occurred in people who did not have the benefit from fully suppressive ART (no ART, non-adherence to ART, or late presentation). It would have been more informative if the causes of death in the ART era could have been analysed by immuno-virological status. I suspect these data were not available, but perhaps the authors can discuss this issue?

I wondered if the separation of liver deaths into liver infection and liver disease is artificial and, as mere HBV or HCV co-infection does not constitute an AIDS diagnosis, whether these two categories are best combined?

**Are the rationale for, and objectives of, the Systematic Review clearly stated?**

Yes

**Are sufficient details of the methods and analysis provided to allow replication by others?**

Yes

**Is the statistical analysis and its interpretation appropriate?**

Partly

**Are the conclusions drawn adequately supported by the results presented in the review?**

Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** HIV Medicine

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**