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Frequency of fungal pathogens in autopsy studies of people who died with HIV in Africa: a scoping review

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Abstract

Background: Fungal infections are common in HIV-infected individuals and significantly contribute to mortality. However, a substantial number of cases are undiagnosed before death.

Objective: To determine the frequency of fungal pathogens in autopsy studies of people who died with HIV in Africa.

Methods: We conducted a scoping review of autopsy studies conducted in Africa.

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Author contributions

FB conceptualized the study. FB, WK, LA, and BM conducted literature search and extracted the data. FB, WK, LA, BM, BO, ISRS, NvR, CM, DWD, and DHH contributed to drafting of the manuscript and all authors approved of the final manuscript.

Transparency declaration

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Data sources: PubMed, Scopus, Web of Science, Embase, Google Scholar, and African Journal Online.

Study eligibility criteria: The review encompasses studies published from inception to September 2023, and no language restrictions were imposed during the search process. We included studies that reported histopathological or microbiological evidence for the diagnosis of fungal infections and other pathogens.

Data synthesis: Data were summarized using descriptive statistics and no meta-analysis was performed.

Results: We examined 30 articles reporting studies conducted between 1991 and 2019, encompassing a total of 13 066 HIV-infected decedents across ten African countries. In five studies, the autopsy type was not specified. Among those studies with specified autopsy types, 20 involved complete diagnostic autopsies, whereas 5 were categorized as partial or minimally invasive autopsies. There were 2333 pathogens identified, with 946 (40.5%) being mycobacteria, 856 (36.7%) fungal, 231 (3.8%) viral, 208 (8.9%) parasitic, and 92 (3.9%) bacterial. Of the 856 fungal pathogens identified, 654 (28.0%) were *Cryptococcus* species, 167 (7.2%) *Pneumocystis jirovecii*, 16 (0.69%) *Histoplasma* species, 15 (0.64%) *Aspergillus* species, and 4 (0.17%) *Candida* species. Other major non-fungal pathogens identified were cytomegalovirus 172 (7.37%) and *Toxoplasma gondii* 173 (7.42%).

Conclusions: Invasive fungal infections occur in over one-third of people who succumb to HIV in Africa. In addition to cryptococcosis and *Pneumocystis jirovecii* pneumonia, integrating other priority fungal pathogen detection and management strategies into the broader framework of HIV care in Africa is recommended. This involves increasing awareness regarding the impact of fungal infections in advanced HIV disease and strengthening diagnostic and treatment capacity.

Keywords

Advanced HIV disease; Africa; AIDS; Autopsy; Fungal pathogens; Opportunistic infections

Introduction

The burden of HIV remains substantial, with an estimated 39 million people living with HIV worldwide at the end of 2022, and approximately 82% of all people living with HIV are in Africa and Asia and the Pacific [1]. Although the advent of antiretroviral therapy (ART) has significantly improved the life expectancy and quality of life for many individuals with HIV [2,3], the interplay between HIV infection and other infectious diseases such as tuberculosis (TB) and fungal diseases such as cryptococcosis remains a critical factor influencing clinical outcomes [2,4,5].

In Africa, HIV-related mortality remains high, particularly among ART-naïve people living with HIV and those in their 1st year of ART, with 5%–30% of deaths occurring among hospitalized patients [6–9]. Although the leading causes of HIV-related deaths, such as TB, *Pneumocystis jirovecii* pneumonia (PCP), and cryptococcosis, are well recognized, there is growing evidence to suggest that other fungal infections such as histoplasmosis, aspergillosis, emerymycosis, and other HIV-related mycoses may be underrecognized

and significant contributors to mortality among individuals with advanced HIV disease, especially in Africa where diagnostics for fungal infections are not widely available [10–12].

Pathological autopsies are the reference standard to establish causes of death and provide a unique window into the pathophysiology of fatal outcomes in individuals with HIV [13,14]. An early literature review by Cox et al. [13] identified nine complete and 11 partial or minimally invasive autopsy series. This review, which included 593 HIV-positive adults and 177 HIV-positive children, found that infectious diseases were the main causes of death in Africa, with TB being the most frequent. TB was present in 21%–54% of HIV-positive adults and was considered the cause of death in 32%–45%. However, this review included studies conducted on both HIV-infected and HIV-uninfected decedents and was published over 10 years ago. A more recent systematic review involving autopsied patients with HIV in Africa focused on only TB and non-tuberculosis mycobacterial (NTM) infections [15].

With more autopsy studies recently published [7,16–28], we conducted this scoping review aimed at synthesizing existing evidence from autopsy studies conducted in Africa to discern the role of fungal infections in contributing to mortality in individuals living with HIV. Therefore, the overall objective of this study was to assess and quantify the prevalence of infectious pathogens in autopsy studies conducted on individuals who died with HIV in Africa, with the goal of determining the proportion of fungal pathogens among all identified pathogens.

Methods

Study design

We conducted a scoping review of literature adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines [29] that ensured transparent and comprehensive reporting.

Research question

The research question for this study was designed in accordance with the Population, Exposure, and Outcome framework.

Population (P): Children and adults who died with HIV in Africa.

Exposure (E): Autopsy studies.

Outcome (O): Proportion of fungal pathogens among all pathogens identified.

The final scoping review question was then formulated as ‘What is the proportion of fungal pathogens among all pathogens identified in autopsy studies of individuals who died with HIV in Africa?’

Search strategy

With the help of a qualified medical librarian (BM), a systematic literature search was conducted using the following electronic databases: PubMed, Scopus, Embase, Web of

Science, and African Journal Online. The search strategy was tailored to emphasize autopsy studies and encompassed keywords and medical subject headings related to 'HIV' OR 'AIDS', 'autopsy' OR 'post-mortem', 'infectious diseases' or individual aetiology such as hepatitis B virus, hepatitis C virus, cytomegalovirus (CMV), TB, etc., 'fungi' OR individual pathogen or disease such as '*Pneumocystis jirovecii*' OR 'Pneumocystosis' OR 'PCP', '*Aspergillus*' OR 'Aspergillosis' OR 'Aspergill*', etc., AND 'Africa'. Boolean operators were used to refine the search and ensure inclusivity. No language restriction was applied.

Inclusion and exclusion criteria

We included autopsy studies conducted in Africa, involving individuals (both children and adults) diagnosed with HIV, reporting histopathological or microbiological confirmed infectious pathogens. We included both single case reports and large autopsy series. Verbal autopsies and studies not indicating how pathogens were identified or not reporting absolute number of pathogens identified were excluded.

Selection process

Two independent reviewers (WK and LA) conducted the initial screening of titles and abstracts, focusing on autopsy-related studies. Full-text assessment was performed for selected articles. Discrepancies in inclusion/exclusion decisions were resolved through discussion or consultation with a third reviewer (FB).

Data extraction

A standardized data extraction form was developed by FB, and pilot tested by WK and FB. Extracted data encompassed study characteristics, autopsy methodologies (full or minimally invasive), associated pathogen identified, and specific details on fungal contributions to mortality. Data extraction was independently conducted by two reviewers (WK and LA) and any discrepancies were discussed with and resolved by FB.

Data analysis

We conducted a narrative synthesis using Microsoft Excel summarizing key information on autopsy studies, infectious diseases, and the specific contribution of fungi to mortality as frequencies and percentages. No meta-analysis was conducted.

Ethical considerations

Because the review involves the analysis of publicly available, previously published studies, ethical approval is not applicable.

Results

Selection of sources of evidence

Of the 884 citations retrieved, 344 duplicate records were removed. We excluded 473 articles that were not within the scope and accessed 66 full texts for review. We excluded 26 full texts for reasons such as no infectious pathogens reported ($n = 20$), autopsy performed

in non-HIV population only ($n = 14$), and study not conducted in Africa ($n = 2$). We included 30 unique articles in the final review (Fig. 1).

Demographics

We included 30 articles reporting studies conducted between 1991 and 2019, involving a total of 13 066 HIV-infected decedents from ten countries across Africa: South Africa (8 studies), followed by Kenya and Mozambique (4 studies each), Uganda (4 studies), Ghana (2 studies), Tanzania (3 studies), Cote d'Ivoire (2 studies), and Nigeria, Zambia, and Zimbabwe each represented by a single study (Table 1) [30–48].

Study designs and autopsy types

Of the 30 studies included, 25 were prospective case series, four were case reports, and one was a retrospective chart review. In five studies, the autopsy type was not specified. Among those specified, 20 involved complete diagnostic autopsies, whereas 5 were categorized as partial or minimally invasive autopsies.

Pathogens

There were 2333 pathogens identified: 946 (40.5%) mycobacteria, 856 (36.7%) fungal, 231 (3.8%) viral, 208 (8.9%) parasitic, and 92 (3.9%) bacterial (Fig. 2, Table 2).

Fungal pathogens

Of the 856 fungal pathogens identified, 654 (28.0%) were *Cryptococcus* spp, 167 (7.16%) *Pneumocystis jirovecii*, 16 (0.69%) *Histoplasma* species, 15 (0.64%) *Aspergillus* spp, and 4 (0.17%) *Candida* spp.

Mycobacterial

Of the 946 *Mycobacteria* identified, 929 (39.8%) were because of *M. tuberculosis* complex and 17 (0.73%) were identified as NTM.

Viral pathogens

Of the 231 viral infections identified, cytomegalovirus was the most prevalent, constituting 172 cases (7.37%). Varicella-zoster virus accounted for 15 cases (0.64%), whereas herpes simplex virus, human papillomavirus, respiratory syncytial virus, influenza A, measles virus, adenovirus, hepatitis B virus, SARS-CoV-2, and human herpesvirus eight each contributed to less than 1% of the cases.

Parasites

Of 208 parasitic infections, *Toxoplasma gondii* was identified in the majority, 173 cases (7.42%). *Cryptosporidium* species constituted 17 cases (0.73%), *Strongyloides stercoralis* contributed to 11 cases (0.47%), and *Plasmodium falciparum* was identified in seven cases (0.3%).

Bacteria

Of the 92 bacterial infections identified, *Nocardia* species accounted for 23 cases (0.99%), *Klebsiella pneumoniae* contributed to 22 cases (0.94%), *Streptococcus pneumoniae* accounted for 12 cases (0.51%), and unspecified bacteria were identified in 11 cases (0.47%). Other bacterial species, including *Enterobacter* spp., *Acinetobacter* spp., *Salmonella* spp., *Clostridia* spp., *Staphylococcus aureus*, *Escherichia coli*, *Haemophilus influenzae*, *Pseudomonas* spp., *Mycoplasma hominis*, *Streptococcus dysgalactiae*, and *Proteus mirabilis*, each contributed to less than 0.2% of the cases (Table 1).

Discussion

The AIDS epidemic, a global public health challenge for more than four decades, has resulted in approximately 40 million deaths [1,49,50]. In this review of autopsy studies involving 13 066 HIV-infected decedents, with over 2300 pathogens identified, 40.5% were mycobacterial and 36.7% were fungal. Our findings align with existing clinical epidemiological data, indicating that infectious diseases such as TB and cryptococcal meningitis continue to be leading causes of death among people with HIV globally [7,51–53]. Studies from Africa have shown that pulmonary infections account for two-thirds of pathology and central nervous system infections for approximately 20% in autopsy series [13].

Fungal infections, PCP in particular, were commonly identified in the AIDS epidemic in the early 1980s [49,54]. Before the introduction of ART, between 58% and 81% of patients with AIDS were observed to contract fungal infections at some time, and 10%–20% of them died as a direct consequence of such infections [55]. Despite widespread ART use, fungal diseases still occur in high frequency among people with advanced HIV disease, particularly in resource-limited settings where retention to care remains a challenge and almost one-third of patients enter care with advanced HIV disease [56,57]. Establishment of reflex screening for cryptococcosis and other opportunistic fungal diseases has been shown to improve diagnostic yield, early initiation of pre-emptive and targeted treatment, and improved clinical outcomes in Guatemala [58].

Cryptococcal meningitis is the leading cause of meningitis among adults living with HIV in Africa, along with toxoplasmosis and TB meningitis, they present the greatest cause of neurological morbidity and mortality [59–61]. We found cryptococcosis in 28% of all autopsied HIV individuals included in this study. An estimated 152 000 cases of cryptococcal meningitis, resulting in 112 000 cryptococcal-related deaths, accounted for 19% of AIDS-related mortality in 2020 with over 70% of these cases and substantial associated mortality occurring in Africa [5]. The introduction of cryptococcal antigen tests has simplified the screening and diagnosis of cryptococcal meningitis in resource-limited settings [62]. Therefore, most cases of cryptococcal meningitis are now diagnosed antemortem.

In this review, we found a low occurrence of histoplasmosis (0.64%), aspergillosis (0.17%), and candidiasis (0.2%). One of the earliest studies reviewed from Cote d'Ivoire found histoplasmosis in 11 cases, compared with 21 cases of cryptococcosis [16]. This

speaks to under-diagnosis of histoplasmosis. Histoplasmosis in Africa has recently been highlighted by Oladele et al. [63] and Ocansey et al. [64]. However, some recent studies particularly from the West African region of Africa have shown increased report of histoplasmosis cases after advocacy, small pilot studies, and increased awareness among clinicians [65,66]. The most sensitive means of diagnosis disseminated histoplasmosis using antigen or PCR detection is not available in Africa [12]. Importantly, we have recently argued that histoplasmosis significantly overlaps with the TB-HIV syndemic in Africa owing to remarkable similarities in clinical presentation and co-infection [67]. Furthermore, a study from Calabar in Nigeria showed that approximately 13% of patients with presumptive pulmonary TB had histoplasmosis [68]. Despite a high level of prior subclinical histoplasmosis from studies utilizing histoplasmin skin tests in Africa [69,70], studies investigating active disease have yielded prevalence from as low as <1% to as high as 13% [68,71,72].

Aspergillosis has been well described to occur in advanced HIV disease [73]. A recent review of 853 cases of aspergillosis in people living with HIV from 16 countries (none from Africa) showed a very high mortality rate (707, 83%) with an average time from diagnosis to death of just over 2 months [74]. In this study, 21% of recorded cases of aspergillosis were diagnosed through post-mortem diagnosis. Bilateral pulmonary shadows, especially with cavitation, should alert clinicians to this diagnostic possibility. A multi-moded approach to the diagnosis of invasive aspergillosis involves a combination of respiratory fungal culture, serum, and bronchoalveolar lavage antigen detection and serum *Aspergillus* antibody is required to identify most cases. Chronic pulmonary aspergillosis did not figure in any of the studies reviewed.

TB is highly endemic in Africa and contributes to significant morbidity and mortality among both HIV-infected and HIV-uninfected people in this region [75]. We found that approximately 40% of patients with HIV who had autopsies performed had mycobacterial infection. Our findings are in line with a recent systematic review that found a prevalence of NTM infection and TB at autopsy to range from 1.3% to 27.3% and 11.8% to 48.7%, respectively [15]. PCP and acute bacterial infections, particularly TB, remain the leading respiratory causes of morbidity and mortality among people with advanced HIV disease [76,77]. In addition to early detection of drug resistance, the introduction of GeneXpert, a sensitive and rapid molecular assay, has revolutionized TB care in resource-limited settings and has significantly reduced the proportion of clinically diagnosed TB [75,78].

This review is not without limitations. First, there were limited demographic data that could be extracted from the selected papers, such as age, sex of decedents, HIV variables such as nadir CD4 count, ART status, and clinically diagnosed causes of death. Second, several studies reported bacterial infections without describing the specific pathogens and hence might have led to underreporting of bacterial and other pathogens. Third, we were unable to perform a meta-analysis given heterogeneity of the various study designs. Furthermore, small case series and case reports do not require formal assessment of quality of studies and thus this was not performed for the rest of the other studies. Also, the role of specific pathogens as contributors to HIV-associated mortality was not clearly elucidated in the autopsy studies. Finally, another major limitation of this study is that autopsies

were probably performed for specific reasons such pharmacokinetic studies, evaluation of diagnostics, and others and may not necessarily represent all patients who died.

Nevertheless, we conducted extensive literature review of several databases to extract all available literature on the topic and strictly adhered to the PRISMA-ScR guidelines to ensure robustness of the review process. The findings from this scoping review highlight the contribution of fungal diseases and other co-infections to inform clinical investigations and clinical care on possible differential diagnoses and target therapy among hospitalized patients with HIV in Africa.

Conclusions

Our autopsy-based review in Africa revealed fungal pathogens, notably *Cryptococcus* species and *Pneumocystis jirovecii*, as possible contributors to mortality in advanced HIV disease. Therefore, integrating fungal pathogen detection into HIV care frameworks is crucial for clinical management. The high burden highlights the need for targeted interventions, including timely diagnosis and antifungal therapy. The study emphasizes diagnostic advancements and awareness to reduce mortality.

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Data availability

All relevant data are within the article and its supporting information files. Data are available upon reasonable request from the first author.

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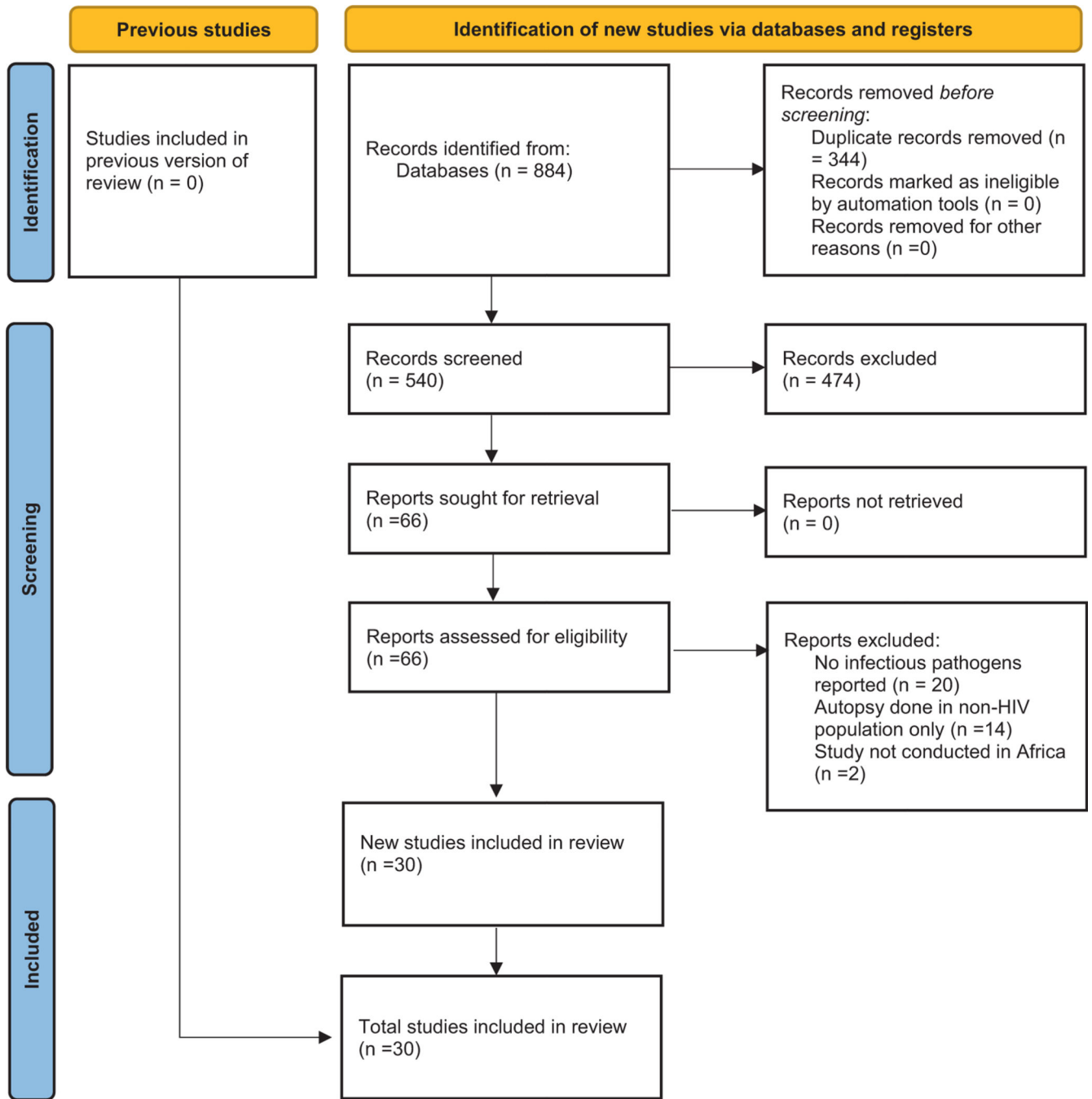


Fig. 1.
PRISMA flow diagram.

N=2333

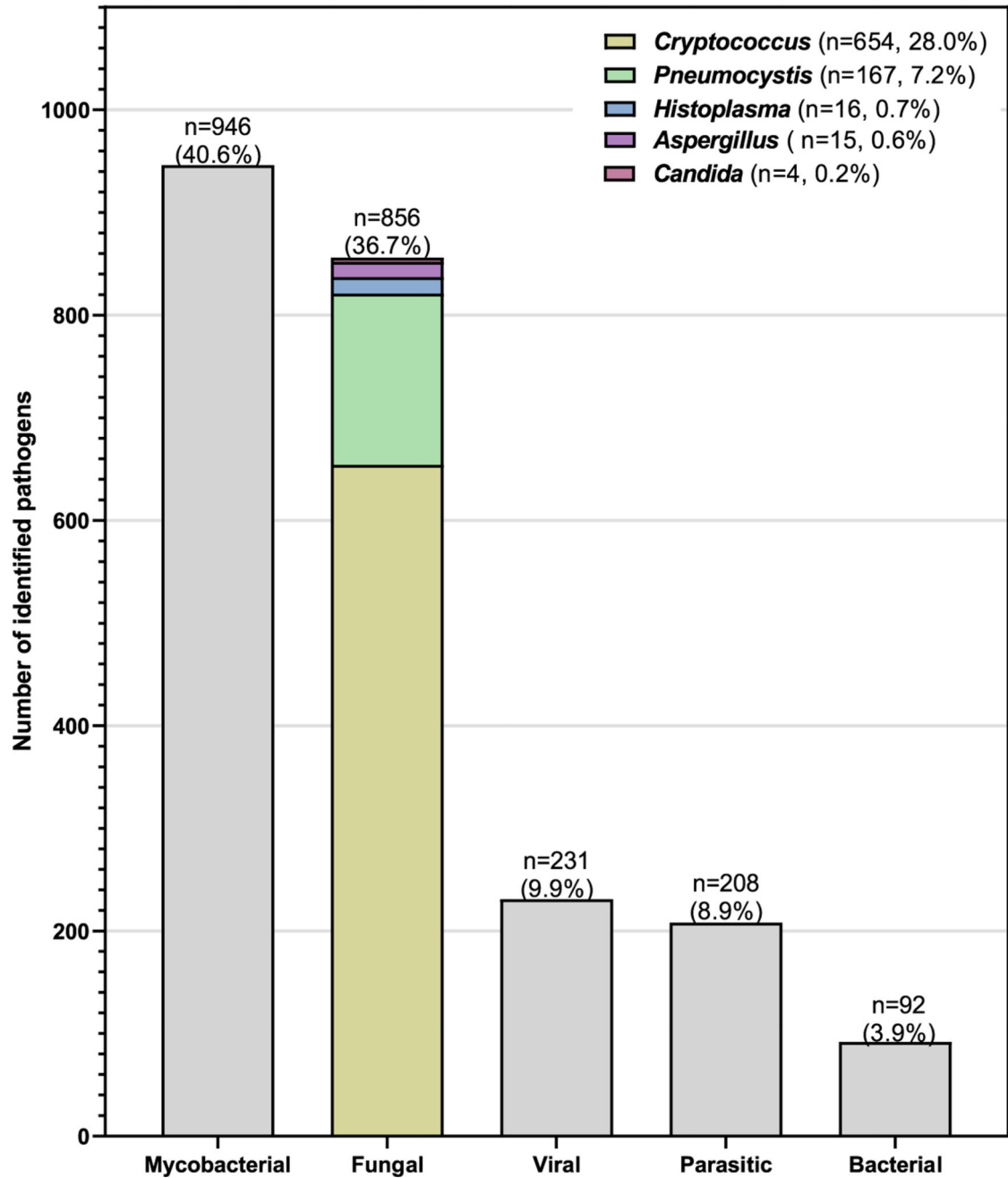


Fig. 2. Distribution of pathogens identified following autopsy, highlighting the relative contribution of fungal pathogens.

Table 1

Characteristics and summary of the studies included

S/n	Author/year	Country	Study period	Design	Number of autopsies on people who died with HIV	Autopsy type	Fungal	Non-fungal
N1	Onyang'o et al., 2022 [28]	Kenya	2018–2019	Prospective	176	Complete	–	<i>K. pneumoniae</i> (n = 16), adenovirus (n = 3), CMV (n = 3), <i>S. pneumoniae</i> (n = 4)
2	Letang et al., 2021 [30]	Mozambique	2013–2015	Prospective	164	Partial	<i>Cryptococcus</i> spp (n = 12), <i>P. jirovecii</i> (n = 3)	<i>M. tuberculosis</i> (n = 25), <i>T. gondii</i> (n = 15), <i>P. falciparum</i> (n = 3)
3	Njuguna et al., 2021 [27]	Kenya	2014–2015	Prospective	64	Complete	<i>P. jirovecii</i> (n = 7)	RSV (n = 7), Influenza A virus (n = 5), <i>S. pneumoniae</i> (n = 5)
4	Khaba et al., 2020 [31]	South Africa	NS	Case report	1	Complete	–	SARS-CoV-2 (n = 1)
5	Hurtado et al., 2019 [32]	Mozambique	2013–2015	Prospective	284	Complete	<i>C. gattii</i> (n = 5), <i>C. neoformans</i> var. <i>grubii</i> (n = 10), <i>Cryptococcus</i> spp (n = 2), <i>Histoplasma</i> spp (n = 1), <i>Candida</i> spp (n = 2)	<i>T. gondii</i> (n = 1), <i>M. tuberculosis</i> (n = 2), <i>S. pneumoniae</i> (n = 1), CMV (n = 1)
6	Wake et al., 2019 [24]	South Africa	2015–2017	Prospective	201	Partial	<i>Cryptococcus</i> spp (n = 67), <i>Histoplasma</i> spp (n = 3)	–
7	Raphael et al., 2018 [33]	Nigeria	NS	Prospective	754	NS	<i>Cryptococcus</i> spp (n = 1), <i>P. jirovecii</i> (n = 1)	<i>M. tuberculosis</i> (n = 8)
8	Castillo et al., 2017 [34]	Mozambique	2013–2015	Prospective	57	Complete	<i>Cryptococcus</i> spp (n = 4)	<i>M. tuberculosis</i> (n = 5), <i>P. falciparum</i> (n = 4)
9	Castillo et al., 2015 [18]	Mozambique	2013	Prospective	30	Partial	(<i>P. jirovecii</i> (n = 2), <i>Cryptococcus</i> spp (n = 2)	HBV (n = 2), HHV 8 (n = 1), <i>T. gondii</i> (n = 2), <i>Acinetobacter baumannii</i> (n = 1), <i>S. pneumoniae</i> (n = 1), CMV (n = 1), <i>M. tuberculosis</i> (n = 3), <i>M. hominis</i> (n = 1), <i>Enterococcus faecalis</i> (n = 1), <i>Streptococcus dysgalactiae</i> (n = 1)
10	Larney et al., 2015 [7]	Ghana	2007	Retrospective	135	Complete	<i>Cryptococcus</i> spp (n = 4)	<i>M. tuberculosis</i> (n = 69), <i>T. gondii</i> (n = 26)
11	Akakpo et al., 2014 [35]	Ghana	2014	Case Report	1	Complete	<i>Cryptococcus</i> spp (n = 1)	0
12	Cox et al., 2014 [36]	Uganda	2013	Prospective	191	Complete	<i>Cryptococcus</i> spp (n = 13), <i>P. jirovecii</i> (n = 3), <i>Aspergillus niger</i> (n = 2), <i>C. albicans</i> (n = 1)	<i>M. tuberculosis</i> (n = 42)
13	Kilale et al., 2013 [21]	Tanzania	NS	Prospective	74	NS	–	<i>M. tuberculosis</i> (24)
14	Wong et al., 2012 [37]	South Africa	2009	Prospective	39	Partial	<i>Cryptococcus</i> spp (n = 4), <i>C. albicans</i> (n = 1)	<i>M. tuberculosis</i> (n = 17), HBV (n = 1), <i>K. pneumoniae</i> (n = 3), <i>A. baumannii</i> (n = 1), <i>Enterobacter cloacae</i> (n = 1), <i>E. coli</i> (n = 2),

CMV, cytomegalovirus; HBV, hepatitis B virus; HHV, human herpes virus; HPV, human papilloma virus; HSV-herpes simplex virus; NTM, non-tuberculosis mycobacterial; RSV, respiratory syncytial virus; VZV, varicella-zoster

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Table 2

Proportion of pathogens identified from autopsy samples

Pathogen group	Frequency	%/group	%/total
Mycobacteria			
<i>Mycobacterium tuberculosis</i> complex	929	98.2	39.8
Non-tuberculous mycobacteria	17	1.8	0.73
	946		40.6
Fungi			
<i>Cryptococcus</i> spp	654	76.4	28.0
<i>Pneumocystis jirovecii</i>	167	19.5	7.16
<i>Histoplasma</i> spp	16	1.9	0.69
<i>Aspergillus</i> spp	15	1.8	0.64
<i>Candida</i> spp	4	0.5	0.17
	856		36.7
Viruses			
Cytomegalovirus	172	74.5	7.37
Varicella-zoster virus	15	6.5	0.64
Herpes simplex virus	10	4.3	0.43
Human papillomavirus	8	3.5	0.34
Respiratory syncytial virus	8	3.5	0.34
Influenza A virus	5	2.2	0.21
Measles	5	2.2	0.21
Adenovirus	3	1.3	0.13
Hepatitis B virus	3	1.3	0.13
Severe acute respiratory syndrome coronavirus 2	1	0.4	0.04
Human herpesvirus 8	1	0.4	0.04
	231		9.9
Parasites			
<i>Toxoplasma gondii</i>	173	83	7.42
<i>Cryptosporidium</i> spp	17	8	0.73
<i>Strongyloides stercoralis</i>	11	5	0.47

Pathogen group	Frequency	%/group	%/total
<i>Plasmodium falciparum</i>	7	3	0.30
Bacteria	208		8.9
<i>Nocardia spp</i>	23	25	0.99
<i>Klebsiella pneumoniae</i>	22	24	0.94
<i>Streptococcus pneumoniae</i>	12	13	0.51
Unspecified	11	12	0.47
<i>Enterobacter spp</i>	4	4	0.17
<i>Acinetobacter spp</i>	4	4	0.17
<i>Salmonella spp</i>	3	3	0.13
<i>Clostridia spp</i>	3	3	0.13
<i>Staphylococcus aureus</i>	3	3	0.13
<i>Escherichia coli</i>	2	2	0.09
<i>Haemophilus influenzae</i>	1	1	0.04
<i>Pseudomonas spp</i>	1	1	0.04
<i>Mycoplasma hominis</i>	1	1	0.04
<i>Streptococcus dysgalactiae</i>	1	1	0.04
<i>Proteus mirabilis</i>	1	1	0.04
Grand total	92		3.9
	2333		100%