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## HIV-Related Haematological Malignancies 1

# Epidemiology of haematological malignancies in people living with HIV

*Stephen M Kimani, Matthew S Painschab, Marie-Josèphe Horner, Mazvita Muchengeti, Yuri Fedoriw, Meredith S Shiels, Satish Gopal*

**People living with HIV or AIDS are at increased risk of Hodgkin and non-Hodgkin lymphoma compared with HIV-negative individuals. Data on the risk of multiple myeloma or leukaemia are inconsistent and of low quality but the risk does not seem to be increased. Specific haematological malignancies occur in different contexts of age, CD4 cell count, HIV control, viral co-infections, or chronic inflammation, and the expansion of combination antiretroviral therapy has led to varied demographic and epidemiological shifts among people with HIV. Increased use of combination antiretroviral therapy has substantially reduced the risks of diffuse large B-cell lymphoma, Burkitt lymphoma, and primary CNS lymphoma, and to a lesser extent, Hodgkin lymphoma. There is no effect of combination antiretroviral therapy use on multiple myeloma or leukaemia. Although many cases of HIV are in low-income and middle-income countries, high-quality epidemiological data for haematological malignancies from these regions are scarce. Closing this gap is an essential first step in decreasing mortality from HIV-associated haematological malignancies worldwide. Finally, although multicentric Castleman disease is not a neoplastic condition, it is an emerging precursor to neoplastic high-grade B-cell lymphoproliferation among people with HIV, especially for individuals on long-term combination antiretroviral therapy with well controlled HIV.**

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This is the first in a Series of four papers about HIV-related haematological malignancies

**Division of Hematology and Oncology, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA** (S M Kimani MBChB, M S Painschab MD, Y Fedoriw MD, S Gopal MD)**; University of North Carolina Project-Malawi, Lilongwe, Malawi** (S M Kimani, M S Painschab, Y Fedoriw, S Gopal)**; Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD, USA** (M-J Horner PhD, M S Shiels PhD)**; and National Health Laboratory Service, Johannesburg, South Africa** (M Muchengeti PhD)

Correspondence to: Dr Satish Gopal, Division of Hematology and Oncology, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7305, USA **satish_gopal@med.unc.edu**

## Introduction

In 2018, an estimated 37·9 million people were living with HIV globally, two-thirds of whom were receiving combination antiretroviral therapy (ART).[1] People living with HIV have a high risk of some cancers compared with the general population. A high rate of previously rare malignancies observed among patients with AIDS in the early days of the HIV pandemic led to use of the term AIDS-defining cancers. However, the grouping of AIDS-defining cancers originates from the earliest syndromic case definitions of AIDS, before HIV was discovered, and does not reflect the aetiological understanding of cancer development in people with HIV.[2] Immune dysregulation, co-infection with certain oncogenic viruses, and lifestyle factors, such as tobacco and alcohol use, are thought to be responsible for increased cancer burden in this population.[3–7] The global HIV/AIDS response, including the UNAIDS 90-90-90 worldwide campaign, has led to the expansion of combination ART programmes worldwide.[8] However, marked regional differences persist worldwide with respect to population-level HIV control and exposure to carcinogenic cofactors among people with HIV.[9] As a result, regional differences in the distribution of cancers in this population exist. For example, in high-income countries, despite a declining rate of classical AIDS-defining cancers (eg, Kaposi's sarcoma, aggressive non-Hodgkin lymphoma, and cervical cancer), an ageing population and decreased mortality from infectious diseases have led to a net increase in cancer burden, primarily from an increased incidence of non-AIDS-defining cancers.[10,11] By contrast, AIDS-defining cancers remain the most common cancers for people with HIV in low-income and middle-income countries (LMICs), including in sub-Saharan Africa.[12–15]

In most high-income countries, combination ART became widely available in the mid-1990s.[16] In LMICs, such programmes began about a decade later in 2004.[14,17] This difference is reflected in the temporal trends for regional incidence of HIV-associated malignancies, with changes attributable to the lag in combination ART implementation.[18] Moreover, despite the recommendation to test and treat people with HIV regardless of CD4 count, the proportion of HIV-infected individuals on

### Key messages

- People living with HIV are at increased risk of non-Hodgkin and Hodgkin lymphoma, whereas the risks of multiple myeloma and leukaemia are not increased
- Several HIV-related factors affect the magnitude of this increase, and this magnitude differs between lymphoma subtypes
- Expansion of combination antiretroviral therapy programmes has led to substantial declines in non-Hodgkin lymphoma incidence, and to a lesser degree, the incidence of Hodgkin lymphoma
- In high-income countries, demographic changes among people with HIV, such as ageing and increased life expectancy, might lead to increased burden of Hodgkin lymphoma in this population
- High-quality epidemiological data for haematological malignancies among people with HIV from low-income and middle-income countries are scarce
- Concerted efforts are needed to support linkages of existing regional and national cancer registries to HIV and AIDS databases for the monitoring of HIV-associated malignancies in low-income and middle-income countries



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combination ART varies across countries. As such, broad trends in cancer risks might not apply uniformly to individual countries.

Haematological malignancies are a group of neoplasms derived from myeloid or lymphoid cells. They are broadly classifiable as non-Hodgkin lymphoma, Hodgkin lymphoma, leukaemia, or multiple myeloma.[19,20] Advances in biological understanding and treatment of haematological malignancies among people with HIV in resource-rich settings have resulted in excellent rates of long-term control and cure. Conversely, descriptive studies characterising epidemiological and clinical features in resource-poor settings are scarce. The scarcity of data is primarily a result of the poor infrastructure for cancer registration, diagnosis, and treatment of haematological malignancies, although published data from LMICs have increased.[21–25] In this Series paper, we describe the burden of haematological malignancies in people with HIV, with specific focus on how this burden has evolved with the expansion of combination ART. We will also highlight differences between high-income countries versus LMICs. A detailed discussion of pathobiology, clinical features, management, or prognosis is beyond the scope of this paper.

## Non-Hodgkin lymphoma

Non-Hodgkin lymphoma is a heterogeneous group of nearly 100 unique haematolymphoid malignancies derived from mature B cells, T cells, and natural killer cells.[19,20] This Series paper will use the umbrella term of non-Hodgkin lymphoma unless data on specific subtypes are reported in published literature. Biopsy-proven non-Hodgkin lymphoma of high-grade pathological type (diffuse and undifferentiated) and of B cell or unknown immunological phenotype was among the first recognised haematolymphoid malignancies that disproportionately affected people with HIV. High-grade non-Hodgkin lymphoma was included in the 1985 revised case definition of AIDS as one of three AIDS-defining cancer categories.[2,26] To date, non-Hodgkin lymphoma, particularly aggressive B-cell types, remains the most common haematological malignancy in people with HIV.[4,11,18,27]

Between 2007 and 2017, the global incidence of non-Hodgkin lymphoma increased by an estimated 39%, mostly because of the ageing and growth of the global population rather than changes in age-specific incidence.[28] Consequently, non-Hodgkin lymphoma was the ninth most frequent cancer by incident cases in 2017, accounting for 488 000 people and 250 000 deaths globally, with most cases reported from high-income countries.[28] In the general population, the estimated lifetime risk of non-Hodgkin lymphoma is one in 108 for men and one in 162 for women.[28] Such estimates for the global community of people with HIV are not available. However, HIV infection increases the risk of non-Hodgkin lymphoma, and a study in the USA estimated lifetime risk of about one in 25.[29] Relative to the general population, HIV-infected individuals are diagnosed with non-Hodgkin lymphoma at a younger age, mostly during their fifth decade of life.[30,31] Though HIV is not known to have direct oncogenic properties, several indirect effects of HIV infection on risk of non-Hodgkin lymphoma are implicated. These effects include loss of immune surveillance because of depletion of T lymphocytes, reactivated oncogenic viral infections, such as Epstein-Barr virus and human herpesvirus 8 (also known as Kaposi's sarcoma-associated herpesvirus), HIV-associated immune dysregulation, and chronic antigen stimulation mediated by other viral co-infections, including hepatitis B and hepatitis C viruses.[3,32–36] Exposure to *Plasmodium falciparum* malaria in endemic regions is also linked with increased risk of Burkitt lymphoma.[36,37]

In high-income countries from the early 1980s to the mid-1990s, before combination ART became widely available, the relative risk of non-Hodgkin lymphoma among people with HIV compared with that in the general population was elevated 100–500 times.[38–40] During this pre-combination ART era, the incidence of three subtypes of high-grade B-cell non-Hodgkin lymphoma (diffuse large B-cell lymphoma, Burkitt lymphoma, and primary CNS lymphoma) increased considerably in the USA and were therefore considered as AIDS-defining cancers.[16,40,41] Plasmablastic lymphoma and primary effusion lymphoma, though rare, are subtypes of aggressive, high-grade B-cell non-Hodgkin lymphomas that occur at much higher rates among people with HIV.[42–44] As high-income countries rolled out HIV-treatment programmes in the mid-1990s, several studies linking HIV cohorts or registries to cancer registries showed substantial heterogeneity in the epidemiological characteristics of non-Hodgkin lymphoma subtypes (table 1).

In the USA, from 1996 to 2010, the overall risk of non-Hodgkin lymphoma was 11 times higher for people with HIV than for the general population, occurring at an estimated incidence of 193 per 100 000 person-years.[45] This risk was much greater for high-grade non-Hodgkin lymphoma subtypes, Burkitt lymphoma, and primary CNS lymphoma, than for diffuse large B-cell lymphoma.[39] The incidence of other types of B-cell non-Hodgkin lymphoma is either the same or only slightly increased compared with that in the general population (table 1).[4,45] T-cell non-Hodgkin lymphoma, anaplastic large-cell lymphoma (standardised incidence ratio of 14), extranodal natural killer T-cell lymphoma (standardised incidence ratio of 4), and peripheral T-cell lymphoma (standard incidence ratio of 4) have been diagnosed at increased rates in people with HIV.[45] Studies in France, Germany, Italy, and Sweden report similar increases in overall risk of non-Hodgkin lymphoma at about ten to 20 times that in the general population in the era of combination ART.[31,45,46,49,56]

In North American cohorts of people with HIV, recent immunosuppression and cumulative HIV viraemia were associated with the development of non-Hodgkin lymphoma, with considerable heterogeneity across subtypes.[3,30,57] For instance, among B-cell non-Hodgkin



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lymphoma, primary CNS lymphoma is associated with greater immunosuppression and presents with the lowest CD4 count at diagnosis.[30] By contrast, the risk for Burkitt lymphoma is strongly associated with cumulative HIV viraemia, and is most common in patients who are less immunodeficient.[3,30] Both profound immunosuppression and prolonged viraemia greatly increase the risk of diffuse large B-cell lymphoma.[3] However, this observation does not completely explain why the risk of non-Hodgkin lymphoma remains increased, albeit modestly, among people with HIV with viral suppression and immunological recovery.[31,56] Co-infection with Epstein-Barr virus or human herpesvirus 8 contributes to lymphomagenesis of certain subtypes of high-grade B-cell non-Hodgkin lymphoma.[42,58] Epstein-Barr virus infection is strongly associated with primary CNS lymphoma and plasmablastic lymphoma, and is frequently associated with primary effusion lymphoma.[34,42,58] Human herpesvirus 8 is causally associated with primary effusion lymphoma and evidence of infection is a diagnostic requirement.[59] The association between human herpesvirus 8 infection and plasmablastic lymphoma is not as well defined.[35,59]

In the combination ART era, the epidemiology of HIV-associated non-Hodgkin lymphoma is changing.[30] First, improved access to combination ART is increasing the proportion of patients with high CD4 cell counts and suppressed HIV viraemia.[56] In this context, the incidences of primary CNS lymphoma and diffuse large B-cell lymphoma have decreased,[56,60] whereas the incidence of Burkitt lymphoma has remained largely stable.[45,46] Given the rarity of T-cell non-Hodgkin lymphoma and other high-grade B-cell subtypes, data trends on incidence since the introduction of combination ART have not been clearly described in the published literature. Second, perhaps reflecting trends in the population of people with HIV as a whole, patients are older at the time of diagnosis,[30] although non-Hodgkin lymphoma continues to occur a decade earlier relative to the general population. This finding was shown in a French cohort in which the median age at cancer diagnosis was 41·2 years compared with 52·5 years for the general population, after adjusting for underlying population age differences.[31] Future projections suggest that overall incidence of non-Hodgkin lymphoma will continue to decline in the USA for people with HIV.[61]

In LMICs, the incidence of non-Hodgkin lymphoma for people with HIV is low compared with rates seen in the USA and Europe (table 1). For example, in a record-linkage study done in Uganda, Mbulaiteye and colleagues[52] found an incidence rate of 19 per 100 000 person-years, which is much lower than in the USA (193 per 100 000 person-years) over a similar period.[45] A similar study from 2004 to 2010, estimated an incidence rate of 85 per 100 000 person-years in South Africa.[62] The low incidence of non-Hodgkin lymphoma in these African studies is probably due, in part, to underdiagnosis, a younger age

| | Non-Hodgkin lymphoma* | Hodgkin lymphoma |
|---|---|---|
| **Engels et al (2008),[39] USA, registry-linkage study (n=57 330)** | | |
| 1991–95 | DLBCL: 14·0 (10·0–20·0), BL: 7·1 (0·2–40·0), PCNSL: 490·0 (260·0–840·0) | 2·8 (0·9–6·6) |
| 1996–2002 | DLBCL: 7·9 (5·9–10·0), BL: 17 (8·6–31·0), PCNSL: 170·0 (96·0–280·0) | 6·7 (4·5–9·5) |
| **Gibson et al (2014),[45] USA, registry-linkage study (n=273 705)** | | |
| 1996–2002 | DLBCL: 23·2 (21·6–24·8), BL: 31·9 (26·0–38·8), PCNSL: 56·4 (50·1–63·2) | Not reported |
| 2003–10 | DLBCL: 13·4 (12·3–14·5), BL: 34·9 (29·7–40·7), PCNSL: 37·5 (32–43·6) | Not reported |
| **Hernández-Ramírez et al (2017),[4] USA, registry-linkage study (n=448 258)** | | |
| 1996–99 | DLBCL: 26·7 (23·4–30·4), BL: 28·3 (16·5–45·3), PCNSL: 872·0 (715·0–1054·0) | 9·1 (6·7–12·0) |
| 2000–04 | DLBCL: 13·2 (12·3–14·3), BL: 23·1 (19·1–27·0), 226·0 (194·0–263·0) | 8·6 (7·5–9·7) |
| 2005–08 | DLBCL: 9·8 (9·1–10·5), BL: 22·5 (19·2–26·1), PCNSL: 139·0 (118·0–161·0) | 7·9 (7·1–8·8) |
| 2009–12 | DLBCL: 7·3 (6·8–7·9), BL: 15·9 (13·3–18·8), PCNSL: 59·5 (47·3–74·0) | 6·7 (5·9–7·6) |
| **Franceschi et al (2010),[46] Switzerland, registry-linkage study (n=9429)** | | |
| 1985–96 | 103·0 (88·8–119·0) | 9·2 (3·6–19·0) |
| 1997–2001 | 26·7 (19·9–35·1) | 21·0 (10·8–36·8) |
| 2002–06 | 16·2 (11·1–22·9) | 28·1 (14·9–48·2) |
| **Calabresi et al (2013)[47] and Gotti et al (2013),[48] Italy, registry-linkage studies (n=5090; n=5085)** | | |
| 1999–2009 | 21·1 (1·7–25·7) | 21·8 (15·3–31·0) |
| **Vogel et al (2011),[49] Germany, registry-linkage study (n=1476)** | | |
| 1996–2008 | 35·0 (23·3–49·2)† | 38·7 (16·5–70·2)† |
| **Hleyhel et al (2013)[31] and Hleyhel et al (2014),[50] France, registry-linkage study (n=98 556; n=84 504)** | | |
| 1992–96 | 116·7 (109·9–123·9) | Not reported |
| 1997–2000 | 33·6 (30·8–36·6) | 33·5 (28·5–39·1) |
| 2001–04 | 15·4 (13·9–17·1) | 21·6 (18·2–25·5) |
| 2005–09 | 9·1 (8·3–10·1) | 26·5 (23·2–30·1) |
| **Godbole et al (2016),[51] India, registry-linkage study (n=32 575)** | | |
| 1996–2008 | 10·6 (5·9–17·5) | 7·7 (2·1–19·7) |
| **Mbulaiteye et al (2006),[52] Uganda, registry-linkage study (n=12 607)** | | |
| 1988–2002 | 6·7 (1·8–17·0)‡ | 8·8 (1·0–32·0)‡ |
| **Zhang et al (2011),[53] China, registry-linkage study (n=3554)** | | |
| 2004–08 | 34·5 (11·7–89·9) | Not reported |
| **Stein et al (2008),[54] South Africa, case-control study (n=377)§** | | |
| 1995–04 | 5·9 (4·3–8·1)¶ | 1·6 (1·0–2·7)¶ |
| **Dhokotera et al (2019),[33] South Africa, registry-linkage study (n=95 279)** | | |
| 2004–14 | 2·89 (2·7–3·1)¶ | 1·43 (1·3–1·6)¶ |
| **Mpunga et al (2018),[55] Rwanda, case-control study (n=341)‖** | | |
| 2012–16 | 2·5 (1·4–4·6)¶ | 5·2 (2·3–11·6)¶ |

Data are the standardised incidence ratio (95% CI), unless otherwise stated. Studies were included if HIV and cancer ascertainment was complete and they reported estimates (standardised incidence ratio or odds ratio) by lymphoma category (either non-Hodgkin lymphoma or Hodgkin lymphoma). DLBCL=diffuse large-B-cell lymphoma. BL=Burkitt lymphoma. PCNSL=primary CNS lymphoma. *Estimates for other types of non-Hodgkin lymphoma are not included in these studies. †Estimates for non-Hodgkin lymphoma and Hodgkin lymphoma were available for men only; the standardised incidence ratio for non-Hodgkin lymphoma among women was 18·2 (95% CI 1·7–52·1). ‡Uganda estimates are standardised incidence ratios for the immediate period (4–27 months) after HIV registration. §Non-Hodgkin lymphoma cases (n=223); Hodgkin lymphoma cases (n=154). ¶Adjusted odds ratio estimates. ‖Non-Hodgkin lymphoma cases (n=265); Hodgkin lymphoma cases (n=76).

***Table 1:*** **A summary of standardised incidence ratios for lymphoma subtypes in people living with HIV**



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distribution in LMICs, and increased competing mortality from opportunistic infections. In contrast to these smaller studies, analysis of cohorts from the International Epidemiologic Databases to Evaluate AIDS and Collaboration of Observational HIV Epidemiological Research in Europe showed that the overall incidence of non-Hodgkin lymphoma across five continents was equal.[18]

Nevertheless, the risk of non-Hodgkin lymphoma among people with HIV in LMICs is still increased compared with that in individuals who are HIV negative. For example, in India from 1996 to 2008, Godbole and colleagues[51] found an 11 times increase in non-Hodgkin lymphoma for people with HIV. This finding is consistent with studies in Europe and the USA during the era of combination ART.[31,45–47] Because combination ART roll-out in India occurred at a later timepoint compared with high-income countries, this estimate is unlikely to capture temporal trends from widespread use of combination ART fully. A strong association between non-Hodgkin lymphoma and HIV has also been shown in other LMICs in Africa, Asia, the Caribbean, central America, and South America.[13,15,17,53,55,63–66] As with high-income countries, data from LMICs show substantial heterogeneity in the association between HIV and non-Hodgkin lymphoma subtypes. For example, a record-linkage study in South Africa found that people with HIV were at a greater risk of high-grade non-Hodgkin lymphoma (adjusted odds ratio of 2·89, 95% CI 2·71–3·08) than patients who were HIV negative, with the risk of Burkitt lymphoma being much higher than for other subtypes (7·83, 6·38–9·62).[13] The risk of follicular lymphoma, a low-grade B-cell non-Hodgkin lymphoma, was lower for patients infected with HIV (0·73, 0·55–0·98).[13] In Rwanda, Mpunga and colleagues[55] showed that HIV infection was strongly associated with B-cell non-Hodgkin lymphoma, particularly diffuse large B-cell lymphoma. In contrast to a population-based registry-linkage study in the USA,[45] there was no clear association with T-cell non-Hodgkin lymphoma in this hospital-based case-control study. As in high-income countries, patients from South Africa with diffuse large B-cell lymphoma had lower CD4 counts at presentation (median CD4 count of 109 cells per µL) than those with Burkitt lymphoma (median CD4 count of 176 cells per µL).[67,68] Median CD4 counts at the time of non-Hodgkin lymphoma diagnosis in other African studies have mostly been consistent with data from high-income countries.[21–23,69–73]

Because of the absence of robust longitudinal data on cancer risk and HIV in most LMICs, discerning the effect of combination ART on temporal trends in the incidence of high-grade non-Hodgkin lymphoma associated with HIV is challenging. With an ecological study design, Mutyaba and colleagues[14] found that increasing combination ART coverage was associated with an increase in the incidence of non-Hodgkin lymphoma by 6% in Uganda. Similarly, in South Africa, there was an increase in the proportion of HIV-associated non-Hodgkin lymphoma after the widespread adoption of combination ART into the public health sector in 2004.[67,68,74] In one study, plasmablastic lymphoma, which is uncommon in high-income countries, accounted for approximately 20% of non-Hodgkin lymphomas diagnosed in the combination ART era.[74] Given the high seroprevalence of HIV and human herpesvirus 8 throughout sub-Saharan Africa, primary effusion lymphoma, which is another rare, aggressive B-cell non-Hodgkin lymphoma, is likely to occur with appreciable frequency in the region. Primary effusion lymphoma might be under-represented in sub-Saharan Africa as it poses particular diagnostic challenges compared with other subtypes because of its presentation as body cavity effusions rather than solid tumour masses.[75] Based on a small set of studies, the spectrum of cancer diagnoses among people with HIV in Asia is similar.[64,65] In India, a key difference is low prevalence of human herpesvirus 8 lymphomas and higher burden among men than women, which reflects characteristics of the overall HIV-infected population.[65]

## Hodgkin lymphoma

Hodgkin lymphoma is a B-cell neoplasm with two primary subtypes, classical Hodgkin lymphoma and nodular lymphocyte-predominant Hodgkin lymphoma, which differ in their morphology, immunophenotype, and clinical course.[20] Classical Hodgkin lymphoma is the most common in people with HIV and is further categorised into four distinct histological subtypes (lymphocyte-rich, mixed cellularity, lymphocyte-depleted, and nodular sclerosis), which have different Epstein-Barr virus associations, morphology, and clinical characteristics.[19,20] As Hodgkin lymphoma categorisation in the updated InterLymph hierarchical classification of lymphoid neoplasms for epidemiological research is not yet widely adopted across key cancer surveillance and registration databases, we have included all level 3 and level 4 InterLymph categories in this Series paper. We have also provided additional subtype information when reported in the original references.

Globally, the estimated lifetime risk of Hodgkin lymphoma is one in 655 for men and one in 1122 for women.[28] The global incidence of Hodgkin lymphoma increased by 15% between 2007 and 2017, mostly because of global population growth and ageing.[28] The incidence of Hodgkin lymphoma has a bimodal distribution, with peaks at ages 20–39 years and over 60 years of age.[76] Between 2007 and 2017, global age-specific incidence rates declined, particularly in LMICs. In 2017, there were 101 000 incident cases of Hodgkin lymphoma and 33 000 deaths, with most cases occurring in high-income countries.[76]

The relative risk of Hodgkin lymphoma among people with HIV in high-income countries is five to 26 times the general population, with an estimated rate of approximately 50 incident cases per 100 000 person-years.[4,47,48,77–80] In contrast to non-Hodgkin lymphoma, for which incidence has considerably decreased with the expansion of combination ART programmes worldwide, the risk



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of Hodgkin lymphoma has slightly increased following the introduction of combination ART, and has subsequently remained stable or slightly decreased (2004–20).[50,61,80] Studies on the effect of HIV-mediated immunodeficiency on the risk of Hodgkin lymphoma have yielded conflicting results. In a Swiss cohort study, there was no evidence of increased Hodgkin lymphoma incidence following combination ART initiation, and there was no association with CD4 cell count.[81] By contrast, data from the US HIV/AIDS Cancer Match study showed that the incidence of Hodgkin lymphoma increased from 30 per 100 000 person-years between 1980 and 1995 (pre-combination ART era) to 49 per 100 000 person-years between 1996 and 2002 (early combination ART era).[79] Standardised incidence ratios for Hodgkin lymphoma followed a similar trend, increasing from about eight times in the pre-combination ART era to 13 times in the early combination ART era.[79] In this study, incidence also differed by CD4 count, peaking at 73 per 100 000 person-years in those patients with moderate immunosuppression (225–249 CD4 cells per µL) and decreasing to 27 per 100 000 person-years in patients with profound immunosuppression (<25 CD4 cells per µL).[79] Though the mechanisms of this association are not entirely clear, it is perhaps a result of complex interactions within the tumour microenvironment between Epstein-Barr virus, non-neoplastic T-lymphocytes, and the neoplastic Reed-Sternberg cells.[82]

HIV-associated Hodgkin lymphoma frequently presents with high-risk features, such as mixed cellularity histological subtype, Epstein-Barr virus co-infection of tumour cells, advanced stage disease, and high International Prognostic Score.[83] The high frequency of mixed cellularity subtype is best explained by Biggar and colleagues.[79] They showed that the incidence of each Hodgkin lymphoma subtype decreased with declining CD4 counts, but as other subtypes decreased more quickly, an increase in the proportion of mixed cellularity Hodgkin lymphoma was seen. Furthermore, Epstein-Barr virus co-infection occurs in 80–100% of HIV-associated Hodgkin lymphoma and is strongly associated with the mixed cellularity subtype.[77] Compared with the general population, Hodgkin lymphoma is diagnosed at a later age in HIV-infected persons (median age at diagnosis of 41·6 years *vs* 37·5 years).[50] HIV-associated Hodgkin lymphoma is also characterised by progressive loss of CD4 cells during sustained HIV suppression on combination ART. A cancer diagnosis may only follow later, sometimes by up to 1 year, possibly because of Hodgkin lymphoma-associated lymphopenia.[80] Overall survival is similar for Hodgkin lymphoma in people with and without HIV in the context of contemporary clinical trials. However, the mortality rate for HIV-associated Hodgkin lymphoma is increased in national data from the USA outside of clinical trials. This observation perhaps reflects the continued challenges in providing multidisciplinary management for Hodgkin lymphoma among people with HIV.[77] Detailed descriptions of HIV-associated Hodgkin lymphoma from LMICs are less common. One hospital-based observational study from Malawi found that 33% of cases were diagnosed in people with HIV, many of which were associated with Epstein-Barr virus co-infection.[23]

As with studies in Europe and the USA, there is heterogeneity in the relationship between HIV infection and histological subtypes of Hodgkin lymphoma in LMICs, though the pattern is variable across individual countries. Consistent with findings from high-income countries, in Rwanda mixed cellularity and lymphocyte-depleted subtypes were strongly associated with HIV infection (odds ratio of 12 [95% CI 2·7–53·2] and 20 [95% CI 2·3–175·0], respectively), whereas all patients with nodular sclerosis were HIV negative.[55] This study had a small sample size (n=76), of which ten patients were HIV positive, but is (to our knowledge) the only study from sub-Saharan Africa that reports interpretable measures of association between HIV infection and histological subtypes of Hodgkin lymphoma. In other African studies, the most prevalent subtypes in people with HIV were nodular sclerosis and mixed cellularity.[23,24,69] However, none of these studies reported estimates that quantify the association between HIV and Hodgkin lymphoma subtypes.

There are no robust estimates of the effect of combination ART on incidence of Hodgkin lymphoma in LMICs. After roll-out of nationwide combination ART programmes in South Africa, a retrospective study noted an increase in the number of new Hodgkin lymphoma cases in both HIV-infected and uninfected individuals from 2005 to 2011, with a subsequent decline in incidence after 2011.[69] One in four incident cases were HIV-associated, though HIV testing was incomplete. In one region in Uganda, there was no change in the incidence of Hodgkin lymphoma following increased combination ART coverage.[14] Further studies are needed to understand the link between ART and Hodgkin lymphoma.

## Multiple myeloma and other plasma cell disorders

Plasma cell disorders are a heterogeneous group of disorders that range from non-malignant paraproteinaemia to malignant proliferation of clonal plasma cells.[20] Several hospital-based studies have reported high rates of non-malignant paraproteinaemias among people with HIV, including monoclonal gammopathy of undetermined significance, oligoclonal banding, and polyclonal hypergammaglobulinaemia. In these studies, serum protein electrophoresis showed that 4–26% of individuals with HIV had monoclonal gammopathy of undetermined significance, and up to 10% had polyclonal hypergammaglobulinaemia.[84–88] These estimates, however, are confounded by selection bias because not all patients with HIV enrolled had serum protein electrophoresis tests. Additionally, these cross-sectional, single-centre studies did not include HIV-uninfected populations as controls. Therefore, the actual prevalence



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| | Multiple myeloma | Leukaemia |
|---|---|---|
| **Patel et al (2008),[78] USA, cohort study (not linked; n=54 780)** | | |
| 1992–2003 | 1·4 (0·6–2·9) | 2·5 (1·6–3·8) |
| **Hernandez-Ramirez et al (2017),[4] USA, registry-linkage study (n=448 253)** | | |
| 1996–2012 | 0·9 (0·8–1·0) | 1·2 (1·0–1·7) |
| **Newnham et al (2005),[93] England, registry-linkage study (n=26 080)** | | |
| 1985–2001 | 2·7 (1·0–5·9) | 2·5 (1·5–3·9) |
| **Franceschi et al (2010),[46] Switzerland, registry-linkage study (n=9429)** | | |
| 1985–96 | 14·8 (2·8–43·9) | 2·4 (0·2–8·8) |
| 1997–2001 | 3·2 (0·0–18·2) | 1·1 (0·0–6·5) |
| 2002–06 | 5·1 (0·5–18·9) | 1·1 (0·0–6·5) |
| **Grulich et al (2002),[94] Australia, registry-linkage study (n=13 067)** | | |
| 1985–98 | 4·2 (1·3–9·7) | 3·4 (1·8–5·8) |
| **Mbulaiteye et al (2006),[52] Uganda, registry-linkage study (n=12 607)** | | |
| 1988–2002 | 8·5 (0·1–47·0)* | 15 (0·2–80·0)* |
| **Dhokotera et al (2019),[33] South Africa, registry-linkage study (n=95 279)** | | |
| 2004–14 | 0·8 (0·5–0·7)† | 0·3 (0·3–0·4)† |
| **Mpunga et al (2018),[55] Rwanda, case-control study (n=83)‡** | | |
| 2012–16 | Not reported | 0·6 (0·1–2·1)§ |
| **Zhu et al (2019),[17] China, cohort (not linked; n=399 451)** | | |
| 2008–11 | 1·1 (0·3–2·7) | 2·9 (2·2–3·8) |
| **Godbole et al (2016),[51] India, registry-linkage study (n=32 575)** | | |
| 1996–2008 | Not reported | 8·1 (3·7–15·3) |

Data are the standardised incidence ratio (95% CI), unless otherwise stated. Studies were included if they reported estimates (standardised incidence ratio or odds ratio) by category (either multiple myeloma or leukaemia). Where leukaemia subtypes were provided, we summarised ratios for myeloid leukaemia only. *Standardised incidence ratios might be high because the matching algorithm was of low specificity. †Inverse probability-weighted estimates of the odds ratio to account for missing HIV status data. ‡Leukaemia cases (n=83). §Adjusted odds ratio estimates.

***Table 2:*** **A summary of standardised incidence ratios for multiple myeloma and leukaemia in people living with HIV**

or incidence of these paraproteinaemias among people with HIV is unknown.

As with the general population, both transient and persistent monoclonal gammopathy (the presence of monoclonal protein in the blood) occur in the HIV-infected population.[86,88] Transient monoclonal gammopathy was shown in a single-centre prospective cohort of 341 patients with asymptomatic HIV.[88] Monoclonal protein was detected in 11 patients, in seven (63%) of whom the monoclonal protein had disappeared after a mean follow-up of 50 months.[88] No patients developed overt plasma cell neoplasm or non-Hodgkin lymphoma.[88] People with HIV who develop monoclonal gammopathy tend to be younger than those with monoclonal gammopathy in the general population, with a median age of 42 years,[87,89] which could reflect age differences between HIV-positive and HIV-negative populations in the USA. A similar observation was made in South Africa.[87,89] Whether the prevalence or incidence of persistent monoclonal protein is dependent on combination ART status is not clear, but some studies have identified a decrease in monoclonal protein following response to combination ART.[84,86,90]

Little is known about underlying molecular drivers of these paraproteinaemias but chronic antigenic stimulation of B cells by HIV and other viral antigens, as well as immune dysfunction via selective loss of T cells, have been implicated.[85,91] The importance of higher paraproteinaemia incidence in people with HIV, or change in monoclonal protein concentrations with HIV treatment, with respect to subsequent risk of multiple myeloma, is unknown. Prospective studies with long-term follow-up are needed to define the natural history of these paraproteinaemias better in people with HIV in both high-income countries and LMICs.

Multiple myeloma can occur at any time during HIV infection, including as a presenting feature of HIV or following decades of chronic HIV infection. Myeloma was previously reported to occur at an increased frequency in people with HIV compared with the general population (standardised incidence ratio of 2·6, 95% CI 1·5–4·5).[6] For example, in high-income countries, two meta-analyses showed higher myeloma incidence among people with HIV than in people without HIV.[6,92] However, more recent studies have questioned this increase in incidence.[4] Studies from LMICs show no differences in incidence rates between people with HIV and HIV-uninfected individuals (table 2). Suboptimal case identification or classification is probable, especially in LMICs. Additionally, revisions of diagnostic criteria and changes in the sensitivity of various assays for laboratory identification of paraproteins over time might affect the classification of multiple myeloma. HIV does not directly infect B cells or mature plasma cells; hence, direct effects of HIV infection on pathogenesis are unknown.[95] Patients with multiple myeloma tend to have higher CD4 counts at baseline (median 212 cells per μL, range 65–625) than patients with HIV-related lymphoma (median of <150 cells per μL).[96,97]

Differences in myeloma presentation between people with HIV and the general population have been described. For instance, multiple myeloma seems to occur at slightly younger ages among people with HIV (52 years *vs* 56 years), even after adjustment for differing population age distributions.[98] Additionally, people with HIV have fewer osteolytic lesions, higher proportion of monoclonal protein IgG (compared with other immunoglobins), lower neutrophil counts, and less renal impairment than HIV-uninfected populations.[96] Some of these clinical differences might be due, in part, to the younger age of the HIV-infected population rather than to differences in multiple myeloma pathobiology.

## Leukaemia

Among people with HIV, women and those with AIDS might have a higher incidence of leukaemia.[4,6] A few studies from high-income countries suggest that acute myeloid leukaemia might occur at increased frequency in



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the setting of HIV, but the absence of detailed leukaemia subclassifications (acute *vs* chronic and myeloid *vs* lymphoid) remains an important limitation for many large epidemiological studies.[99] HIV infection does not affect the risk of leukaemia in African studies,[54,100] although these studies are limited by the design of case-control studies and were done in the pre-combination ART era. Concurrent chronic myeloid leukaemia and HIV infection has been described.[101] In general, in the combination ART era, the risk of leukaemia is not substantially higher in people with HIV than in those without (table 2).

## Multicentric Castleman disease

Though multicentric Castleman disease is not a neoplasm, special mention is warranted as it could be an important cause of morbidity and mortality among people with HIV.[102] Multicentric Castleman disease is a life-threatening, polyclonal lymphoproliferative disorder characterised by systemic inflammation and lymphadenopathy.[103] HIV infection is an important risk factor for multicentric Castleman disease, and in the context of HIV, this disease is causally associated with human herpesvirus 8 infection, which represents a crucial biological difference from idiopathic multicentric Castleman disease.[35,104] Human herpesvirus 8 is considered to be the causative agent of multicentric Castleman disease in most people with HIV and in many patients who are HIV negative.[105,106] Viral proteins, including a viral homologue of IL-6, are strongly associated with the cytokine storm that characterises the clinical presentation of multicentric Castleman disease.[107] People with HIV with multicentric Castleman disease have up to 15 times increased risk of non-Hodgkin lymphoma related to human herpesvirus 8 infection.[35] Multicentric Castleman disease can often be controlled with rituximab treatment, but when rituximab is not available, morbidity and mortality are extremely high.[59,104]

Unlike other lymphoproliferative disorders, multicentric Castleman disease is a rare condition, particularly in high-income countries where seroprevalence of human herpesvirus 8 is less than 10%.[108] Before 2007, only 72 cases had been published.[109] More recently, prospective reports were published in 2011 and 2018, including in the UK (n=61) and France (n=169).[103,104] In both studies, it took more than 20 years to accumulate these cases. Though multicentric Castleman disease is very rare in high-income countries, there is reason to believe that incidence is under-reported in sub-Saharan Africa, which has the highest seroprevalence of human herpesvirus 8 in the world (>40% in most countries).[108] The prevalence of HIV is high in sub-Saharan Africa, ranging from 3–20%.[1] Given the strong link between human herpesvirus 8 and HIV, and the high prevalence of these viruses in sub-Saharan Africa, multicentric Castleman disease is probably underdiagnosed, particularly given that diagnosis requires pathology and immunohistochemistry capabilities that are scarce in the region.

A retrospective study of tissue biopsies done at a tertiary referral hospital in South Africa noted an increase in the incidence of HIV-associated multicentric Castleman disease over an 11-year period in the era of combination ART (2007–17).[102] Multicentric Castleman disease is associated with older age, higher CD4 count, and a longer time on combination ART than Kaposi's sarcoma, non-Hodgkin lymphoma, or Hodgkin lymphoma.[97,103,104,109] Moreover, unlike Kaposi's sarcoma, multicentric Castleman disease is typically not controlled or improved with combination ART alone.[110] Given the observed associations of multicentric Castleman disease with long periods of exposure to combination ART, disease incidence might increase with improved public sector access to combination ART, highlighting the need for better diagnostic and treatment capacity as the global HIV epidemic continues to evolve.

## Challenges for studies on cancer epidemiology in LMICs

LMICs are home to most people with HIV globally, with more than two-thirds of the world's total in sub-Saharan Africa.[1] However, cancer registration in LMICs has limited geographical and population coverage.[28,111] For instance, despite having 70% of the global burden of HIV, only 1% of the population in sub-Saharan Africa is captured in high-quality, population-based cancer registries.[111] Where such cancer registries are available, underascertainment remains a major challenge.[62] This issue is perhaps best shown by a Nigerian registry-linkage study whose conclusion that there was no increase in risk of non-Hodgkin lymphoma among people living with HIV compared to the general population was heavily confounded by incomplete cancer ascertainment and poor record matching given the few unique individual identifiers.[112] Moreover, there are often no standardised protocols to ensure that existing registries use harmonised processes for cancer identification and recording, and HIV status is often not collected by African cancer registries.[15,113] Consequently, high-quality epidemiological studies of HIV-associated haematological malignancies in LMICs are scarce. When available, these studies are often restricted by small sample sizes. For example, despite a national seroprevalence of 4·4% in 2005, only 2·3% of patients diagnosed with lymphoma within a 15-year period in a Nigerian centre were HIV positive.[114] Because most of these studies use data from HIV treatment centres, population-level estimates of association between HIV and cancer, such as standardised incidence ratios, might be inaccurate. Notably, cancer registration has now become compulsory in South Africa,[115] which could lead to improved data in the near future. Similar measures should be adopted in other LMICs.

Despite these challenges, incidence trends for HIV-associated malignancies in LMICs are anticipated to follow similar patterns to those observed in high-income countries. However, there will probably be important differences in LMICs, where the high prevalence of



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oncogenic viruses and other infectious co-factors might increase the risk of specific haematological malignancies. Elucidating these epidemiological trends as combination ART scale-up continues will require continued improvements in cancer registration and diagnostic infrastructure. The need for improvements is particularly true for haematological malignancies, for which diagnosis is often dependent on the availability of tissue microscopy and advanced ancillary capabilities, including immunohistochemistry, flow cytometry, or molecular diagnostic tools. Without these capabilities, lymphoma might often be clinically misdiagnosed as tuberculosis because of overlapping symptoms and greater provider familiarity with tuberculosis.[116,117] Improved infrastructure for cancer diagnosis and registration are therefore essential to understand the epidemiology of haematological malignancies in LMICs.

## Conclusions and future directions

Since the identification of specific non-Hodgkin lymphoma subtypes as AIDS-defining cancers, even before HIV was identified as the causal agent of AIDS, high-quality epidemiological studies have identified elevated risks for many cancer types among people with HIV. In the last three decades, the expansion of combination ART programmes in high-income and LMICs have been associated with declines in the incidences of many cancer types. The epidemiology of haematological malignancies in people with HIV is heterogeneous and changing, with less immunosuppression and greater HIV control at diagnosis in the era of combination ART. However, the risk of non-Hodgkin lymphoma and Hodgkin lymphoma is elevated among the HIV-infected population compared with the general population, and the risk for multicentric Castleman disease might even be increasing in the combination ART era. By contrast, the risk of leukaemia or multiple myeloma does not appear to be increased among people with HIV. Scale-up of combination ART access through the 90-90-90 worldwide campaign holds tremendous promise for further reducing the global burden of those haematological malignancies that are strongly associated with immunosuppression. Although demographic changes, such as ageing and increased longevity, are shifting the cancer burden, particularly in high-income countries. In LMICs, high-quality data for cancer incidence and burden among people with HIV is scarce and remains an important challenge because of suboptimal population-based cancer registration and diagnostic infrastructure. Region-specific, population-level epidemiological studies are urgently needed to better inform future cancer burden projections and national cancer control plans. This strategy calls for concerted efforts to support linkages of existing regional and national cancer registries to HIV and AIDS databases for the monitoring of HIV-associated malignancies in LMICs. Ongoing investments in research and clinical care programmes are beginning to address these gaps and might lead to high-value cancer prevention and screening efforts that are coupled to global HIV treatment scale-up. Taken together, these investments could lead to substantial gains in quantity and quality of life among people living with HIV worldwide.

### Search strategy and selection criteria

To identify articles relating to the epidemiology of haematological malignancies, we searched PubMed, Embase, and Global Health biomedical research databases with the search terms "HIV", "AIDS", "hematologic malignancy", "epidemiology", "prevalence", "incidence", "leukemia", "lymphoma", and "myeloma". We also reviewed references from relevant articles to extract studies that might have been missed by the above search terms. Non-English articles were included where an English translation of the abstract was available. The final reference list was generated on the basis of the relevance and originality of the Series paper. We selected studies linking population-based cancer registries with HIV and AIDS registries to report standardised incidence ratios. When these data were not available, we report odds ratios for case-control studies. This paper reports published estimates and does not provide a formal meta-analysis.

#### Contributors

SMK contributed to the conception and design of the Series paper and did the primary literature review. SMK and MSP wrote the manuscript. MJH, MSS, YF, and SG critically revised the manuscript for important intellectual content. All authors gave final approval for submission and further revisions.

#### Declaration of interests

SG reports grants from the National Institutes of Health (NIH) during the conduct of the work. All other authors declare no competing interests.

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