Burden of Kaposi sarcoma according to HIV status: A systematic review and global analysis

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Abstract
In 2020, over 34 000 cases of Kaposi sarcoma (KS) were estimated globally, all attributable to KS herpesvirus (KSHV). Prior to the HIV epidemic, KS already existed in KSHV endemic regions, notably in sub-Saharan Africa (SSA). The HIV epidemic has vastly increased the KS burden. We developed a methodology to provide global estimates of KS burden according to HIV status. A systematic review identified studies reporting HIV prevalence in consecutive KS series. Pooled estimates of HIV prevalence, by country or UN subregion, were used to calculate population-attributable fraction (PAF) and these were applied to IARC’s GLOBOCAN 2020 to estimate burden and incidence of HIV-attributable and non-HIV-attributable KS. We identified 55 eligible studies, reporting HIV prevalence ranging from \( \leq 5\% \) to \( \geq 95\% \). Approximately 80% of KS in SSA was estimated attributable to HIV, vs \( \sim 50\% \) in the rest of the world. By applying PAFs to national GLOBOCAN estimates, an estimated 19 560 KS cases attributable to HIV were diagnosed in SSA in 2020 (\( \sim 80\% \) of the worldwide burden), vs 5064 cases of non-HIV-attributable KS (\( \sim 60\% \) of the worldwide burden). Incidence of HIV-attributable KS was highest in Southern Africa (6.0 cases per 100 000) and Eastern Africa (3.4), which were also the world regions with highest incidence of non-HIV-attributable KS (0.4 and 1.0 cases per 100 000, respectively). This first systematic effort to produce a global picture of KS burden stratified by HIV status highlights the continuing important burden of HIV-attributable KS in SSA, even in the era of combined antiretroviral therapy.

KEYWORDS
HIV, incidence rates, Kaposi sarcoma, population-attributable fraction

What’s new?
Before the HIV/AIDS epidemic, Kaposi sarcoma (KS) was rare in most regions of the world. With HIV’s emergence, however, KS incidence increased dramatically. In this systematic review, approximately three-quarters of KS cases globally were linked to HIV, even in the era of

Abbreviations: ASIR, age-standardized incidence rate; cART, combination antiretroviral therapy; HHV-8 or KSHV, human herpesvirus-8; HIV, human immunodeficiency virus; KS, Kaposi sarcoma; MSM, men who have sex with men; PAF, population-attributable fraction; PLWHIV, people living with HIV; SSA, sub-Saharan Africa; UN subregion, United Nations defined subregion; WHO, World Health Organization.

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1 | INTRODUCTION

An estimated 34,270 Kaposi sarcoma (KS) cases were diagnosed worldwide in 2020 according to the GLOBOCAN 2020 estimates developed by the International Agency for Research on Cancer (IARC). However, the KS burden is disproportionately distributed around the globe, with nearly three-quarters of global KS cases occurring in sub-Saharan Africa (SSA). Geographic variations are known to be driven by the disparate population prevalence of two main infectious risk factors, namely KS herpesvirus (KSHV), the underlying cause of all forms of KS (detected by PCR in >95% of tissue biopsies) and HIV infection, which severely worsens the carcinogenic outcome of KSHV infection.

Before the HIV/AIDS epidemic, KS was rare in most parts of the world and historical variations in incidence are now recognized to broadly reflect geographical differences in population prevalence of KSHV, which is lowest in Asia, the United States and Northern Europe, intermediate in some areas in the Mediterranean basin and highest in regions of equatorial SSA. Various epidemiological forms of KS are recognized to occur in the absence of HIV infection (hereafter referred to collectively as non-HIV-attributable KS): the classic form, originally described in elderly men of Mediterranean/Jewish/Eastern European ancestry and more recently in HIV-negative men who have sex with men (MSM); the endemic form, described in parts of Central and Eastern Africa prior to the HIV epidemic, mostly in men; and the iatrogenic form, arising primarily in immunosuppressed organ transplant recipients. Estimating the incidence of non-HIV-attributable KS has become more difficult since the emergence of the global HIV/AIDS epidemic in the 1980s.

The epidemic form of KS (hereafter referred to as HIV-attributable KS) signaled the emergence of the HIV/AIDS epidemic and is vastly increased among HIV-infected persons with immunodeficiency. KS incidence increased dramatically in the early phase of the HIV/AIDS epidemic, becoming the most commonly diagnosed cancer in many SSA countries. The introduction of combination antiretroviral therapy (cART) subsequently led to a dramatic decline in KS incidence in people living with HIV (PLWHIV) in high-income settings. As an example, relative to the general population, KS rates in PLWHIV in the United States decreased from 2800-fold in the pre-cART era (1991-1995) and to 260-fold in 2009 to 2012. However, decreases have not been uniform by geography and ethnicity, even within the United States. Less marked declines have since been observed in SSA. Despite this decrease, however, KS still accounts for significant morbidity and mortality in patients infected with HIV, and incidence remains high in populations in SSA in the era of cART where access and adherence to cART remain suboptimal.

There has been no recent or global attempt to systematically describe patterns of HIV-attributable (epidemic) vs non-HIV-attributable (classic/endemic/iatrogenic) KS. Thus, as part of the ongoing program to estimate global burden of cancer attributable to infectious agents at the IARC, our aim was to provide the best possible global picture of KS burden stratified by HIV status, in the era of cART. This approach was based on a systematic review of data from KS series of known HIV status in order to estimate population attributable fractions (PAF), followed by the application of these PAFs to the GLOBOCAN estimates of KS burden at a country, world region and global level.

2 | METHODS

2.1 | Identification and selection of relevant studies

We performed a systematic review of four databases (PubMed, Embase, Web of Science and Global Index Medicus) to identify studies reporting the prevalence of HIV infection in consecutively diagnosed series of KS cases. Studies restricted to PLWHIV only were excluded. The details of the search strategy for each of the databases can be found in the Appendix S1 (Table S1). In brief, we used a WHO-validated search for “HIV” and “AIDS,” combined with terms for “Kaposi sarcoma” and standard WHO terms for epidemiological studies. The search was last updated on 2 August 2021. There were no restrictions on language. Studies were screened for inclusion by two independent reviewers (AIK and GMC), with discrepancies resolved by consensus. If several studies used the same dataset, we included only the study with the greatest number of participants, to avoid double inclusion of patients. In order to be eligible, studies had to clearly state the period of KS recruitment (as a sign of representativeness) and to include KS cases from the year 1996 onwards (ie, to exclude studies entirely of the pre-cART era).

2.2 | Estimates of Kaposi sarcoma incidence for the year 2020

Population denominators, number of KS cases and age-standardized incidence rates (ASIR, cases per 100,000 person years) of KS were
extracted for 155 individual countries/territories as described in GLOBOCAN 2020.1

2.3 | Statistical analysis

The prevalence of HIV infection in KS cases ($P_c$) was assumed to equate with PAF, as in previous IARC estimates of the global burden of cancer attributable to infections.16 Indeed, given the very high relative risk (RR) for KS in PLWHIV, even in the cART era,17,18 the classic formula for calculation of PAF from cases tends toward $P_c$:

$$PAF = P_c \frac{(RR - 1)}{RR}$$

Country-specific PAFs were calculated for all countries with eligible studies identified by the systematic review. In the event of multiple relevant studies from the same country, a pooled country-specific PAF was calculated, weighted by study size.

PAFs were calculated for geographical areas according to UN-defined subregions (UN subregion19): four individual UN subregions in SSA, and aggregated UN subregions outside SSA. To calculate subregional and global PAFs, country-specific PAFs from within the given subregion, or the whole world, were pooled, weighted according to GLOBOCAN 2020 KS burden. Countries without relevant data in the systematic review were attributed the subregional PAF.

PAF estimates were applied to number of KS cases, and to the KS ASIRs, as available in GLOBOCAN 2020, to produce numbers of KS cases and ASIRs by HIV attribution status:

$$N_{KS \text{ attributable to HIV}} = PAF \times N_{GLOBOCAN \ 2020 \ KS \ cases}$$

$$ASIR_{KS \text{ attributable to HIV}} = PAF \times ASIR_{GLOBOCAN \ 2020 \ KS}$$

World maps were created to display country-specific ASIRs, divided into five levels.

All statistical analyses were conducted using Stata software (Version 14.2) and world maps drawn using QGIS3 software.

3 | RESULTS

3.1 | Study selection

Overall, 55 studies published between 1996 and 2021 met our inclusion criteria (see flowchart of study selection in Figure 1). Included studies were located in 35 countries, including from UN subregions of Southern Africa (South Africa and Botswana), Eastern Africa (Kenya, Malawi, Mozambique, Rwanda, Tanzania, Uganda, Zambia and Zimbabwe), Western Africa (Côte d’Ivoire, Nigeria and Togo), Central Africa (Cameroon), North America, Australia and New Zealand (USA and Australia), Southern America (Argentina, Brazil and Peru), Northern and

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**FIGURE 1**  Flow chart of the search and Kaposi sarcoma study selection [Color figure can be viewed at wileyonlinelibrary.com]
| UN subregion/Country       | Study                                      | Period     | n/N        | HIV prevalence (%)  | PAF (%) |
|----------------------------|--------------------------------------------|------------|------------|----------------------|---------|
| South Africa               | Stein et al. 2008                          | 1995-2004  | 297/333    | 93.0                 |         |
| South Africa               | Sengupta et al. 2017                       | 2004-2012  | 369/370    | 93.0                 |         |
| Botswana                   | Straugh et al. 2019                        | 2006-2010  | 220/239    | 94.1                 |         |
| Eastern Africa             |                                            |            |            |                      |         |
| Tanzania                   | Chalya et al. 2015                         | 2004-2014  | 122/248    | 78.7                 |         |
| Mozambique                 | Neat et al. 2003                          | 1995-2005  | 74/78      | 78.7                 |         |
| Zimbabwe                   | Chalya et al. 2015                         | 2004-2014  | 122/248    | 78.7                 |         |
| Kenya                      | Derma et al. 2020                         | 2013-2016  | 81/81      | 100.0                |         |
| Western Africa             |                                            |            |            |                      |         |
| Nigeria                    | Jaquet et al. 2015                         | 2011-2012  | 11/22      | 74.9                 |         |
| Malaysia                   | Mohan et al. 2008                          | 2004-2008  | 16/27      | 74.9                 |         |
| Mozambique                 | Neat et al. 2003                          | 1994-1998  | 26/36      | 74.9                 |         |
| Namibia                    | Neat et al. 2003                          | 1994-1998  | 5/3        | 74.9                 |         |
| Southern Africa            | Stein et al. 2008                          | 1995-2005  | 297/333    | 78.7                 |         |
| South Africa               | Sengupta et al. 2017                       | 2004-2012  | 369/370    | 78.7                 |         |
| Botswana                   | Straugh et al. 2019                        | 2006-2010  | 220/239    | 78.7                 |         |
| Central Africa             | Castro et al. 2019                         | 2008-2011  | 680/943    | 72.1                 |         |
| North America, Australia and New Zealand |                    |            |            |                      |         |
| USA                        | Shiel et al. 2011                          | 1996-2007  | 1625/22 053 | 73.7                |         |
| Austria                    | Hong et al. 2002                           | 1993-1999  | 33/44      | 75.0                 |         |
| Southern and Central America, Caribbean |                    |            |            |                      |         |
| Argentina                  | Pérez et al. 2017                          | 2002-2013  | 11/24      | 65.2                 |         |
| Brazil                     | Ramos-da-Silva et al. 2007                 | 1986-2002  | 25/47      | 59.7                 |         |
| Peru                       | Aliaga Ramos et al. 2019                   | 2015-2016  | 12/13      | 92.3                 |         |
| Northern and Western Europe |                                            |            |            |                      |         |
| France                     | Lancon et al. 2014                         | 1997-2009  | 35/37      | 71.5                 |         |
| Morocco                    | Casto et al. 2019                          | 2008-2011  | 680/943    | 72.1                 |         |
| South-Eastern and Eastern Asia |                        |            |            |                      |         |
| Republic of Korea          | Cheong and Kim 2012                        | 1998-2012  | 1/17       | 21.8                 |         |
| China                      | Hsu et al. 2001                            | 1993-1999  | 2/5        | 21.8                 |         |
| Japan                      | Awasawa et al. 2017                        | 1984-2014  | 13/74      | 21.8                 |         |
| South-Central, Western Asia and Northern Africa |                    |            |            |                      |         |
| Turkey                     | Yazici et al. 2018                         | 2005-2017  | 1/91       | 7.7                  |         |
| Tunisia                    | Moridi et al. 2005                         | 1981-2003  | 1/65       | 3.7                  |         |
| Israel                     | Gottstein-Yassky et al. 2003               | 1986-2007  | 4/75       | 3.7                  |         |
| Iran                       | Khatibi et al. 2012                        | 2000-2009  | 2/43       | 3.7                  |         |
Western Europe (Belgium, Finland, France and the United Kingdom), Southern, Central and Eastern Europe (Italy, Portugal, Romania and Spain), Eastern and South-Eastern Asia (Republic of Korea, China and Japan) and South-Central, Western Asia and Northern Africa (Morocco, Turkey, Tunisia, Israel and Iran). There were no eligible studies from the UN subregions of South-Eastern Asia, Central Asia, Central America, the Caribbean or Micronesia/Melanesia/Polynesia. Characteristics of included studies are listed in Table S2.

### 3.2 HIV prevalence in KS (or population-attributable fraction)

HIV prevalence in KS cases was highest (93.0%) in studies from Southern Africa (Figure 2, Table 1), consistently in both South Africa (93.0%) and Botswana (94.1%). In Eastern Africa, HIV prevalence was 76.7% overall, with variation across the represented countries, from 63.4% in Zambia to 100% in Kenya. HIV prevalence was 74.9% in Western Africa (primarily represented by KS cases from Nigeria) and 72.1% in Central Africa (based on one large study of KS from Cameroon). Of note, HIV prevalence in KS in Northern Africa (Tunisia, Morocco) was much lower (3.0%) than the rest of Africa and was combined with estimates for countries from South-Central and Western Asia (Figure 2, Table 1).

In the United States, HIV prevalence in KS cases in the cART era was 73.7% (as estimated by a large HIV and cancer registry linkage study), similar to a KS series in Australia (75.0%), and these studies were used to produce a combined estimate for North America, Australia and New Zealand. HIV prevalence was 65.2% in KS cases in Southern America, predominantly representing KS cases reported from Brazil (Figure 2).

In Europe, HIV prevalence was 71.5% in KS cases from studies in Northern and Western Europe (ranging from 61.0% in a study from France up to 85.7% in a small study from the United Kingdom, but driven predominantly by KS cases reported from France [61.9%] and Belgium [78.2%]), and was 46.7% in Southern, Central and Eastern Europe (ranging from 18.3% in a study from Romania up to 76.9% in a small study from Portugal, but driven predominantly by KS cases from a single large HIV and cancer registry linkage study in Italy [41.9% HIV prevalence]).

With respect to Asia, HIV prevalence was 21.8% in KS cases from Eastern Asia (represented by studies from Korea, China and Japan), and 7.7% in KS cases from South-Central, Western Asia (presented combined with Northern Africa; Figure 2, Table 1), with consistently low prevalence in KS studies from Turkey (5.4%), Iran (3.7%) and Israel (3.7%).

Country-specific PAFs (calculated from national data or subregional averages) are shown in Table S2.

### 3.3 Global and regional burden of KS, by HIV attributable status

In 2020, 71.4% of the global KS burden was estimated to be attributable to HIV, equating to 24 263 HIV-attributable (epidemic) KS cases and 10 007 non-HIV-attributable (classic/endemic/iatrogenic) KS cases (Table 1). In SSA, 79.4% of KS was estimated to be attributable...
to HIV, equating to 19,560 HIV-attributable KS cases and 5,064 non-HIV-attributable KS cases. In the rest of the world, 49.0% of KS was estimated to be attributable to HIV, equating to 4,703 HIV-attributable KS cases and 4,943 non-HIV-attributable KS cases. As reported above, there were considerable variations in PAF between the different (aggregated) subregions (Table 1).

A total of 79.4% of global HIV-attributable KS occurred in SSA alone, with Eastern Africa contributing about half (n = 11,902) of the worldwide burden, followed by Southern Africa (n = 4,385). The global burden of non-HIV-attributable KS burden was split approximately equally between SSA and the rest of the world, with Eastern Africa contributing about one third (n = 3,555) of global burden, followed by South-Central, Western Asia and Northern Africa (n = 1,545) and Southern, Central and Eastern Europe (1,154).

Of note, PAFs were estimated from country-specific data for the 13 countries with the highest KS burden (South Africa, Uganda, Mozambique, Zambia, Malawi, Tanzania, Cameroon, Nigeria, Italy, the United States, Zimbabwe, Kenya and Brazil), and for countries that

(A) HIV-attributable KS

(B) Non-HIV-attributable KS

ASIR (per 100,000 person year)

0 to <0.5

0.5 to <2

2 to <4

4 to <8

≥8

No data

FIGURE 3 Age-standardized incidence rates in 2020 of (A) HIV-attributable (epidemic) Kaposi sarcoma and (B) non-HIV-attributable (classic/endemic/iatrogenic) Kaposi sarcoma. ASIR, age-standardized incidence rate. The designations used and the presentation of the material in this article do not imply the expression of any opinion whatsoever on the part of WHO and the IARC about the legal status of any country, territory, city or area, or of its authorities or concerning the delimitation of its frontiers or boundaries.
collectively contributed 83% of the worldwide KS burden, as estimated in 2020 (see Table S3).

ASIRs of HIV-attributable KS were highest in Southern Africa (6.0 per 100 000 person years), followed by Eastern Africa (3.4), Central Africa (1.5) and Western Africa (0.5) (Table 1). ASIR of HIV-attributable KS was 0.3 per 100 000 person years in Southern and Central America and the Caribbean and ≤0.1 in all other (aggregated) subregions. Country-specific HIV-attributable ASIRs are shown as a map in Figure 3A. ASIRs of HIV-attributable KS were above 8 per 100 000 person years in Uganda, Zambia, Malawi, Eswatini, Mozambique and Namibia, 4 to 8 per 100 000 person years in Cameroon, Burundi, South Africa, Lesotho, Zimbabwe and Botswana, and above 0.5 per 100 000 person years in most countries in SSA. The only countries outside SSA with estimated ASIRs of HIV-attributable KS above 0.5 per 100 000 were Barbados, Peru, the Bahamas and Panama in Southern and Central America, and Portugal in Southern Europe (although, of these countries, only Peru and Portugal had PAFs generated from national data).

ASIRs of non-HIV-attributable KS were highest in Eastern Africa (1.0 per 100 000 person years), followed by Central Africa (0.6), Southern Africa (0.4) and Western Africa (0.2) (Table 1). ASIR of non-HIV-attributable KS was ≤0.1 in all other (aggregated) subregions. Country-specific non-HIV-attributable ASIRs are shown as a map in Figure 3B. ASIRs of non-HIV-attributable KS were above 2 per 100 000 person years in Zambia, Mozambique and Uganda, and above 0.5 for an additional 11 SSA countries. The only countries outside SSA with estimated ASIRs of non-HIV-attributable KS above 0.5 per 100 000 were Italy, Turkey and Israel in the Mediterranean basin.

4 | DISCUSSION

This first systematic effort to produce a global picture of KS burden stratified by HIV status estimated that approximately three-quarters of all KS in 2020 were attributable to HIV, and described the important geographical variation in the incidence of HIV-attributable (ie, epidemic) KS separately from that of non-HIV-attributable.

Variations in PAFs of HIV for KS reflect the interaction between KSHV and HIV infection, and our systematic literature review highlighted dramatic variations in PAFs around the world. PAFs were notably high in SSA, where population-level prevalence of both KSHV and HIV are known to be high.2 However, PAFs were almost equivalently high in KS in some parts of the world where population-based KSHV infection is commonly low (eg, the United States and Australia), but where KSHV infection (and hence KS) clusters in PLWHIV, particularly MSM. At the other extreme, in certain Mediterranean countries, a low PAF of HIV for KS was observed, likely driven by an elevated population prevalence of KSHV combined with a relatively low frequency of HIV. These interactions become clearer, and PAFs more informative, however, when they are combined with the absolute size of the KS burden across different world regions and individual countries. This is an approach we have previously applied to cancers attributable to other infections16 and for cervical cancer attributable to HIV (for which the PAF was much lower than that for KS).20,21

Since the onset of HIV/AIDS epidemic, the independent estimation of classic/endemic KS incidence has become more difficult.22 Our estimates of non-HIV-attributable KS are thus both novel and consistent with historical reports of classic/endemic KS prior to the HIV/AIDS epidemic: non-HIV-attributable KS was highest across parts of SSA,23 and also elevated in certain countries in the Mediterranean basin,24 but rare (<0.5 cases per 100 000) in other parts of the world. Indeed, identification of well-documented hotspots for classic KS in the Mediterranean (eg, Italy and Israel) and endemic KS in SSA (eg, Uganda, Cameroon and Zambia) lends validity to our methodology. Approximately half of all non-HIV-attributable KS cases occurred in SSA. Although our country-specific estimates did not delineate a very specific “KS belt” across equatorial Africa based on latitude,23,25 non-HIV-attributable KS did tend to be higher in Eastern and Middle Africa than in Southern, Western or Northern Africa, despite country-specific data limitations. In these settings, population-level incidence rates of KS can be expected to remain relatively high even after successful prevention of HIV-attributable KS.

Our analysis confirms how the geographical disparity in KS burden has been further exaggerated by the HIV/AIDS epidemic, with more than 80% of global HIV-attributable KS cases in 2020 occurring in SSA alone. HIV-attributable KS incidence was highest in countries across Eastern/Southern Africa, most notably in Zambia, Malawi, Uganda, Mozambique and Zimbabwe. All of these countries had PAF estimates derived from national data identified by the systematic literature review, and certain had GLOBOCAN KS estimates deriving from reports of high KS incidence in the era of cART from population-based cancer registries (Uganda,11 Zimbabwe11 and Mozambique24). Many of these countries are those that also suffer the highest incidence of non-HIV-attributable KS, likely driven by high population prevalence of KSHV infection.25

There are relatively few data on KS incidence trends in SSA, but historical cancer registries in Uganda, Zimbabwe and South Africa have reported large increases in KS incidence in the pre-cART era of the HIV/AIDS with more moderate declines in the cART era.11,12,23 KS incidence in the cART era has not declined as steeply in PLWHIV in SSA as it has in high-income settings8,9,27,28 and KS rates in HIV-positive persons in SSA remain elevated.13 Indeed, since their initiation across SSA, access and adherence to cART programs remain below levels recorded for PLWHIV in high-income countries. For example, in 2016, the proportion of HIV-positive South Africans taking cART was estimated at only 50%.12 cART adherence also remains suboptimal with respect to KS prevention: only 2.5% of HIV-positive KS cases arising in 2009 to 2012 in South Africa had never received cART, yet many were no longer taking cART at the time of their KS diagnosis.29 Hence, KS continues to rank among the most frequent cancers in SSA, even in the cART era. Of note, South Africa was not among the countries with highest HIV-attributable incidence (nor non-HIV-attributable KS), possibly related to a lower population prevalence of KSHV than in Eastern and Central Africa.25 Given its population size, however, South Africa was the country with the single biggest estimated burden of HIV-attributable KS cases, followed by Uganda and Mozambique.
Outside SSA, population-level incidence of HIV-attributable KS is relatively low, with estimated HIV-attributable KS incidence above 0.5 per 100 000 only in Portugal (which has by far the highest incidence of KS and AIDS in Europe), and in a number of countries in Southern America (where KS remains the most frequent malignancy in PLWHIV in the cART era). We used HIV prevalence in KS cases as a proxy for PAF, rather than population prevalence of HIV (as was the case recently for cervical cancer), given the very high RR of KS in KSHV-positive PLWHIV, even in the cART era. Our approach, when combined with national KS estimates from GLOBOCAN 2020, provides a useful estimate of KS by HIV attribution status, but is associated with a number of assumptions and limitations. First, whilst our results are based upon most up to date estimates of KS incidence in 2020, the methods used to develop the GLOBOCAN database are still limited by a lack of population-based cancer registry data in many parts of the world. Although there have been major improvements in cancer registration in many SSA countries, there also remain substantial gaps in the region where the KS burden is the highest. Second, the studies identified by the systematic review included KS cases collected over a wide calendar period, for which we could only partly control for the influence of cART use on KS by excluding studies that recruited solely in the pre-cART era (ie, before 1996). This restriction was the best compromise between obtaining data relevant to PAFs in the cART era and not excluding important country-specific data. Of note, in the United States, the proportion of KS cases diagnosed among PLWHIV (ie, PAF) has been shown to remain relatively stable in the cART era, despite that the risk of KS for PLWHIV has substantially declined.

Given that even experienced clinicians can misdiagnose KS, histological confirmation is highly important to studies of the epidemiology of KS, and was widespread in most of the research studies contributing to PAF estimates. However, histological confirmation is lacking in a majority of KS cases in SSA, and subsequently in the registry data that underpin the GLOBOCAN KS rates (cancer registries have little influence on the availability, or use, of pathology services within their catchment area). Visual diagnosis has been shown to have only 80% positive predictive value for KS and can lead to some false-positive diagnoses, for example, for bacillary angiomatosis. Furthermore, some studies contributing to PAF estimates focused specifically on cutaneous or gastrointestinal KS only. However, we felt that these studies remained informative for PAF estimates, especially in the absence of any other studies from the same country.

Unfortunately, our approach did not allow attributable KS burden to be described separately by sex, nor by age. Indeed, we were not able to extract enough information from published KS series to be confident to further stratify country-specific PAFs by these variables (Table S2). KS has been strongly associated with male sex, although these sex differences are poorly understood. Male/female ratios above three are still found in countries where classic KS is common or where the epidemic form has mainly involved MSM or intravenous drug users (Table S2). However, in studies from SSA, where HIV infection is widespread and predominantly transmitted through heterosexual intercourse, male/female ratio tended to be between 1.5:1 and 2:1. The ratios are consistent with GLOBOCAN 2020 KS estimates from the same countries (Table S2), and with evidence from SSA suggesting that the sex ratio has changed from 20:1 for endemic KS to 2:1 in the era of epidemic KS. This means that application of gender-specific PAFs to gender-specific KS incidence from GLOBOCAN 2020 would not greatly alter the overall KS burden by HIV attribution status, at least not for high burden areas of SSA. Furthermore, whilst it was clear from included studies that the mean age of diagnosis of HIV-positive KS was consistently younger than that of HIV-negative KS, age-stratified prevalence of HIV in KS was not reported, and so we were unable to apply variable PAFs by age at a global level. The only exception was the large linkage study from the United States for which the PAF for HIV was estimated to be 95% for 71 000 KS diagnosed 0 to 59 years and 7% in 12 000 KS diagnosed ≥60 years. Nor were we able to address differences in PAFs between urban and rural areas in high-income countries, as reported in the United States, driven by the concentration of the HIV epidemic predominantly in urban MSM.

Infection-attributable cancer incidence estimates can raise awareness and inform primary and secondary prevention programs at a global, regional and local level. HIV-attributable KS represents the cancer burden that could, in theory, be prevented by avoidance of HIV infection and earlier and wider cART treatment of HIV-infected persons. Conversely, the burden of non-HIV-attributable KS reflects what the global epidemiology of KS would look like in the absence of HIV and could be tackled by, albeit currently ill-defined, lifestyle changes.

Avoidance of KSHV infection would prevent all KS, but specific interventions are hampered by poor understanding of transmission routes. Saliva is the body fluid that most commonly harbors KSHV and transmission in childhood via saliva is considered the principal route of spread in SSA. In high resource countries, the acquisition of KSHV in adults may be related to the use of saliva as a lubricant in sexual practices, especially anal intercourse in MSM. Unfortunately, recommendations to avoid saliva exposure in children or adults are not easy to formulate and there is little prospect of a vaccine against KSHV in the near future. Such a vaccine would of course prevent all KS, but development has been hampered by the virus’s ability to evade the immune system, and the geographic location of most KS in SSA has also limited financial incentives. When building a case for primary KSHV prevention, it should be noted KSHV also causes a number of other malignant and benign diseases: primary effusion lymphoma, KSHV-positive diffuse large B-cell lymphoma, multicentric Castleman disease and KSHV inflammatory cytokine syndrome.

In conclusion, we have shown that over 70% of the current global burden of KS could be prevented by removal of HIV. Given the current lack of an HIV vaccine, reducing HIV transmission, combined with earlier and wider access, as well as improved adherence to cART, could still have a major impact on the still large KS burden, particularly in SSA.

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CONFLICT OF INTEREST
The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of our study derive from several sources. Publicly available sources are: Cancer incidence in five continents volume XI (http://ci5.iarc.fr); and GLOBOCAN 2020 (Global Cancer Observatory https://gco.iarc.fr/today/home). For included studies, please refer to cited published references. Further details and other data that support the findings of our study are available from the corresponding author upon request.

ETHICS STATEMENT
Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

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SUPPORTING INFORMATION

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