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Impact of Antiretroviral Therapy on the Incidence of Kaposi's Sarcoma in Resource-rich and Resource-limited Settings

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Abstract

Purpose of the review—Given the recent availability of antiretroviral therapy (ART) in resource-limited settings and the significant burden exacted by Kaposi's sarcoma (KS) in these areas, we reviewed data regarding the impact of ART on KS incidence. We summarized the sizeable literature in resource-rich settings as well emerging data from resource-limited regions. Importantly, we delineated ways impact can be defined, including a) individual patient-level effectiveness; b) population-level effectiveness; c) change in population-level incidence; and d) residual risk of KS.

Recent findings—In resource-rich settings, there are now ample data demonstrating beneficial individual patient-level and population-level effects of ART on KS incidence. There is, however, considerable variability between studies and important methodologic shortcomings. Data from resource-limited settings are much more limited; while they preliminarily indicate individual patient-level effectiveness, they do not yet provide insight on population-level effects.

Summary—ART has had a substantial impact on KS incidence in resource-rich settings, but more attention is needed on validly quantifying this effect in order to determine whether additional interventions are needed. Emerging data from resource-limited regions also suggests beneficial impact of ART on KS incidence, but — given the scope of KS in these settings — more data are needed to understand the breadth and magnitude of the effect.

Keywords

Kaposi's sarcoma; HIV/AIDS; incidence; antiretroviral therapy; resource-limited settings

The advent of HIV/AIDS in 1981 transformed Kaposi's sarcoma (KS) from a medical oddity to an epidemic [1]. In resource-rich settings, the cumulative lifetime incidence of KS among HIV-infected homosexual men reached nearly 40% [2]. In many resource-limited settings, particularly sub-Saharan Africa, the extent of the HIV epidemic resulted in KS becoming the most common malignancy not just among HIV-infected individuals but among all adults [3]. Yet, just as abruptly as AIDS impacted KS, the advent of potent antiretroviral therapy (ART) has transformed HIV disease. In resource-rich areas where ART is routinely available, the lifespan of HIV-infected individuals has nearly normalized [4]. ART has come more slowly to resource-limited settings, but by the end of 2010 over 5

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million patients in sub-Saharan Africa alone had initiated ART [5] with overall reduction in mortality comparable to resource-rich settings [6].

While the general impact of ART on morbidity and mortality has been well documented, this review will summarize the specific influence of ART on KS incidence. We shall summarize the abundant data from resource-rich settings and examine emerging data from resource-limited settings. Importantly, we will clarify what is referred to as the "impact", "influence" or "effect" of ART on KS occurrence. We believe that patients and practitioners may be interested in as many as five questions:

- Question 1. *What is the individual patient-level efficacy of ART on KS incidence?* This is akin to the question which would be addressed in a randomized trial of ART versus no ART in select HIV-infected patients with optimal adherence. It asks: what is the best effect on KS incidence that could be expected among ART users? While interesting, such a trial has never been conducted because it is now unethical, and the question has never been addressed with observational data. Hence, we will not summarize literature for this question.
- Question 2. *What is the individual patient-level effectiveness of ART use on KS incidence?* This is akin to the question in a randomized trial of ART versus no ART in "real world" clinical practice, which allows for variable ART adherence and other circumstances. Such a randomized trial also cannot be ethically performed today, but several observational studies have attempted to estimate this effect.
- Question 3. *What is the population-level effectiveness of ART on KS incidence?* This is what would be addressed in a randomized trial of "real world" communities of HIV-infected individuals comparing availability of ART in a community versus no availability. This question incorporates the answer to question 2 above (individual patient-level effectiveness), but it extends upon it by encompassing the act of starting therapy. In other words, population-level effectiveness is a function of starting ART, adhering to ART, and the inherent efficacy of ART.
- Question 4. *How has KS incidence among HIV-infected persons changed since the availability of ART?* While the randomized trial that addresses this question can be stated — what is the effect on KS incidence if one is randomized to live in the pre-ART era (up to 1996) versus the era when ART is available (after 1996) — it has no basis in reality. Yet, the question is relevant from a public health and population perspective in that it asks how KS incidence has changed among all HIV-infected individuals since ART has become available. While question 3 asks specifically whether ART *per se* is responsible for a change in KS incidence among the HIV-infected population (independent of other factors), question 4 simply asks whether KS incidence has changed since ART became available regardless of why.
- Question 5. *What is the residual risk of KS given ART?* This asks whether ART among HIV-infected patients, either in terms of use at the individual patient-level or availability at the population-level, reduces KS incidence to that seen in HIV-uninfected individuals. It addresses the ultimate goal of ART in HIV-infected patients as it relates to KS, which is to preclude any excess risk.

In reviewing the impact of ART on KS incidence, we focused on the last four questions, namely individual patient-level effectiveness, population-level effectiveness, change in KS incidence in the ART era, and residual risk.

Methods

We reviewed published literature from 1996 to 2012, searching Medline and the Web of Science, which described the impact of ART on KS incidence in either resource-rich or resource-limited settings. Search terms included: Kaposi's sarcoma, HIV malignancy, neoplasm, incidence, epidemiology, antiretroviral therapy, and highly active antiretroviral therapy.

Resource-Rich Settings

We discuss the impact of ART on KS incidence in terms of individual patient-level and population-level effectiveness.

Individual patient-level effectiveness—With variable findings (Table 1), nine studies [7–12••,13–15••] across three continents have evaluated individual patient-level effectiveness of ART on KS incidence (Question 2). The lowest KS incidence among ART users was 109 per 100,000 person-years [8] while the highest incidence was 700 per 100,000 person-years [13]. Of special interest is the absolute KS incidence among ART users who have achieved a CD4+ T-cell count of ≥350 cells/μl. This is important because the majority of ART users will spend the rest of their lives in this immunological state, and some notable case series have suggested that KS may continue to be common in this range [19, 20]. Unfortunately, few reports provide formal estimates of KS incidence among such patients. Among individuals with a CD4 count of ≥350 cells/μl, Francheschi et al. [9] and Lodi et al. [12••] reported incidences of 118 and 368 per 100,000 person-years, respectively. A lower incidence (89 per 100,000 person-years) was reported among ART users with CD4 count ≥500 cells/μl [12••].

After adjustment (in some studies) for various confounding factors, the KS incidences among ART users represented declines between 19% and 93% compared to non-ART users (Table 1). Studies from Europe had a range between 61 % and 93% [7–12••,13], a 57% decline was observed in a multi-country study in Europe, Australia and Canada [12••], while a 19 to 39% reduction was seen in the U.S. [14, 15••]. The substantial variability between studies could have several explanations. First, the populations differed. For instance, Mocroft et al. [13] performed their work between 1994 and 1998, a period when ART users were heavily treatment-experienced and likely enriched for those unable to achieve full virologic suppression on combination ART regimens compared to patients who started ART in later years. This could in part explain the smaller 61% reduction in KS incidence that was found compared to other European estimates. Second, although rarely reported, ART impact also depends on compliance. For example, there was a 7-fold increase in KS risk in the CD4 count-guided episodic ART arm of the SMART trial [21]. Third, the magnitude of losses to follow-up was also rarely reported, leaving open the possibility of selection bias. While some studies [8–11] were less susceptible, the potential for differential losses to follow-up between ART users and non-users is uninterpretable in others [7, 12••, 13]. Fourth, with few exceptions [8], the mode of KS diagnosis was not reported. While biopsy was surely performed in many instances, we also know that clinical diagnosis alone was common in some areas. The non-specificity of clinical diagnosis will typically attenuate the apparent effect of ART.

As all available studies are observational, confounding could be another reason for variability. While some studies reported adjusted estimates [7, 11, 14, 15••], others were either unadjusted [8, 9, 12••, 13], or adjustment was not reported [10, 14]. Notably, only two studies controlled for CD4 count [11, 14], which would be expected to be a strong confounder. Yet, CD4 count in this context is also a time-dependent mediator of the effect of ART, which if adjusted for conventionally could attenuate the effect of ART. To manage

confounding of this type, advanced approaches known as marginal structural models have emerged in the past decade [22]. Because none of the studies used these advanced techniques, we may qualitatively know the individual patient-level effectiveness of ART on KS incidence but are yet to have an unbiased quantitative estimate.

In the one study that estimated residual KS risk (Question 5) at the individual patient-level, ART users had a 25.3-fold higher rate of KS compared to the general population [8] (Table 2). This report, however, used contemporaneous rates of KS from the general population, which, because virtually all KS in the general population today is derived from HIV-infected patients, tends to underestimate the parameter of interest (a comparison of ART-treated/HIV-infected persons to HIV-uninfected persons) [27]. On the contrary, any comparison (in most Resource-rich settings) of HIV-infected persons to the general population (irrespective of era) that does not consider differences in the underlying prevalence of infection with Kaposi's sarcoma-associated herpesvirus (KSHV) will overestimate the residual risk of KS in the HIV-infected group.

Population-level effects—Population-level impact of ART on KS incidence has been evaluated by nine studies, all of which used regional/national cancer registries to ascertain incidence (Tables 3 and 4). In these studies, calendar time was the predictor variable, with pre-ART era (before 1996) compared to ART era (after 1996). Whether or not authors adjusted for one or more factors dictated the question they could address. Estimating population-level effectiveness of ART on KS incidence (Question 3) requires adjustment for whatever factors differ across calendar time. Population-level effectiveness was estimated by 5 studies [15••, 25••, 26, 28, 29•], which found reductions between 33% and 95% in KS incidence in the ART era (Table 3). Given that estimating the change in KS incidence since ART became available (Question 4) is simply a crude comparison of incidences over time, it requires no adjustment. For this question, 5 studies [23, 24, 29•, 31, 32•] provided estimates, ranging from 27% to 88% reductions in KS incidence (Table 4).

Similar to individual patient-level effectiveness, the variability in the population-level estimates may also have several explanations. First, the nature of the HIV-infected populations differed across studies. Specifically, some studies included all HIV-infected individuals [25, 31], while others examined only those with AIDS [15••, 23, 24, 26••, 28, 29•, 32•]. Furthermore, there were differences in the reference calendar periods for the pre-ART era. While some studies used a period beginning in the early 1980s [23, 25, 29], others used the period 1990–1995 [26••, 28]. Second, there again may be differences in KS ascertainment. Even though cancer registries were used to ascertain KS, most studies insufficiently described the registries' processes. Differences across studies in the fraction of clinical KS diagnoses, which are prone to non-specificity, could contribute to the differences in the derived inferences. Finally, in the studies addressing population-level effectiveness of ART, in which differences across eras have to be addressed, there was disparity in how this was handled. For example, one study adjusted for ART use over and above calendar period, which because it is on the causal pathway would be expected to attenuate effects [15••]. Notably, no study accounted for CD4 count. Therefore, we again conclude that while we know the qualitative population-level effectiveness of ART on KS incidence, we do not have an accurate quantitative estimate.

Residual KS risk in the ART era was assessed in three populations [23–25••, 26••] (Table 2), with standardized incidence ratios ranging from 22.9 [25••] to 3640 [24]. Differences in composition of the general population comparator groups across studies likely explain this wide range. Specifically, the highest estimates used a general population group from the late 1970's that predated the HIV epidemic [24, 26••], and the lowest used the contemporary general population [25••]. As mentioned earlier, because almost all KS that occurs in

contemporary resource-rich general populations (outside of the Mediterranean) is derived from HIV-infected persons, underestimation of the true residual risk among HIV-infected persons will result if this contemporaneous comparison group is used [27].

Non-population-based cohorts—A number of non-population-based cohorts [14, 33–35•, 36–42•], typically clinic-derived, also compared incidence of KS in both the pre-ART and ART eras (Table 5). However, when viewed from the perspective of the questions we initially outlined, these studies are not directly estimating any parameter of clinical or epidemiologic relevance (which is unfortunate because many of these studies have the best measurements). In a clinic-based cohort, the population-level effectiveness of ART will be overestimated. This is because the patients analyzed in the ART era are systematically enriched for those in care and are devoid of patients not on ART. Likewise, these studies are not validly estimating individual patient-level effectiveness because ART use *per se* was not the predictor variable. Indeed, many patients in these studies in the ART era were not actually using ART, thus leading to likely underestimation of the individual patient-level effectiveness of ART. It is therefore in the realm of individual patient-level effectiveness of ART that these non-population-based cohort studies have their greatest contribution. Given that most are estimating >70% reduction in KS incidence, we can infer that the true value is likely in this range.

Resource-limited settings

Despite having the vast majority of the worldwide HIV/AIDS and KS burden, resource-limited settings have yielded substantially less data regarding the impact of ART on KS. It is nonetheless useful to consider the data in terms of individual patient-level and population-level effectiveness.

Individual patient-level effectiveness—In the one published study on this question, KS incidence among ART users in Uganda was 340 cases per 100,000 person-years [16••] (Table 1). This study did not have a comparator group of non-ART users, but it can, in theory, be compared to historical work in the country. In 1988–2002 (a period with minimal ART availability), Mbulaiteye et al. reported a KS incidence of 380 per 100,000 person-years among HIV-infected patients in Kampala [43]. This would seem to indicate no effectiveness of ART, but differences in KS ascertainment between studies likely preclude any valid comparison. The recent work was in the context of a clinical trial where patients were being prospectively examined. In contrast, the older work originated in a clinic population where KS diagnoses may have been easily missed, and, furthermore, to be counted by the study, a KS diagnosis had to be captured in a local cancer registry and matched back to the patient's clinic record. This likely resulted in substantial underestimation of KS incidence in the pre-ART report, a limitation noted by the authors [43].

More recent data, presented to date in abstract form only, promises to better estimate individual patient-level effectiveness. In the East Africa Consortium of the International Epidemiologic Databases to Evaluate AIDS (IeDEA) Project [44], 98,024 HIV-infected adults at 26 HIV clinics in Uganda and Kenya were followed for incident KS [18]. A unique feature of the work was that histological diagnosis was made available at the participating sites and accounted for approximately 50% of KS diagnoses. In Uganda, KS incidence was 1876 per 100,000 person-years in non-ART users and 201 in ART users, translating to a 78% reduction in KS incidence [18]. In Kenya, KS incidence was 596 per 100,000 person-years in non-ART users and 270 users in ART users, translating to a 50% reduction [18]. Another abstract, from Southern Africa IeDEA, covering 10 clinic-based cohorts with 184,592 patients, reported an incidence of 624 per 100,000 person-years among non-ART

users and 174 per 100,000 person years in ART users, translating to a 72% reduction [17]. What accounts for the clinically important differences in ART effectiveness in Kenya versus Uganda (or South Africa) remains unclear given the unpublished nature of the work. Of note, in neither of these analyses was the role of CD4 count as a time-dependent confounder/mediator appropriately managed, again leaving us without a valid quantitative estimate of ART effect.

Population-level effects—In the one published report of the population-level effectiveness of ART on KS incidence in resource-limited settings, Msyamboza et al. estimated an *increase* in KS in 2007–2010 in Malawi compared to earlier periods (Table 3) [30•]. However, with the majority of KS diagnoses being clinical (only 18% histopathologic), this study highlights the challenges of using registries to estimate population-level effects in resource-limited settings. These challenges also include issues with completeness [45] and unknown HIV status among the cases [46]. As such, we view the findings from these nominally population-based studies as generally uninterpretable, and we therefore have no evaluable population-level data as it relates to KS.

Conclusions

There is now ample evidence to indicate substantial effectiveness of ART on KS incidence at the individual patient-level and population-level in resource-rich settings. Although in preliminary form, there is now emerging evidence to also suggest that the individual patient-level effectiveness of ART on KS incidence in resource-limited settings is comparable to that of resource-rich settings. Yet, considering the public health magnitude of KS in resource-limited settings, particularly in sub-Saharan Africa, much more data from diverse settings are needed to confirm the individual patient-level effectiveness observed in the initial studies, determine population-level effectiveness, and establish residual risk of KS given ART use. From a methodological perspective, while we can safely qualitatively conclude that ART works in preventing KS, the actual magnitude of the effect has never been properly estimated due to the improper handling of time-dependent confounding/mediation. Not knowing the actual magnitude of the ART effect is more than just academic in that it will inform whether additional interventions (e.g., anti-KSHV agents) are needed in combination with ART in order to more fully reduce KS incidence. This is critical since evaluating additional interventions will be very expensive. Finally, to understand the face of HIV-associated KS in the future, we need additional specific estimates of the incidence of KS in ART-treated patients who have achieved CD4 counts >350 cells/μl as well as an understanding why patients continue to develop KS at this stage of HIV disease.

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References

Papers of particular interest, published within the annual period of review, have been highlighted as

• of special intrest

•• of outstanding interest

1. Hymes KB, Cheung T, Greene JB, Prose NS, Marcus A, Ballard H, et al. Kaposi's sarcoma in homosexual men-a report of eight cases. Lancet. 1981; 2(8247):598–600. [PubMed: 6116083]
2. Hoover DR, Black C, Jacobson LP, Martinez-Maza O, Seminara D, Saah A, et al. Epidemiologic analysis of Kaposi's sarcoma as an early and later AIDS outcome in homosexual men. Am J Epidemiol. 1993; 138(4):266–78. [PubMed: 8356967]
3. Wabinga HR, Parkin DM, Wabwire-Mangen F, Mugerwa JW. Cancer in Kampala, Uganda, in 1989–91: changes in incidence in the era of AIDS. Int J Cancer. 1993 Apr 22; 54(1):26–36. [PubMed: 8478145]
4. Zwahlen M, Harris R, May M, Hogg R, Costagliola D, de Wolf F, et al. Mortality of HIV-infected patients starting potent antiretroviral therapy: comparison with the general population in nine industrialized countries. Int J Epidemiol. 2009 Dec; 38(6):1624–33. [PubMed: 19820106]
5. GLOBAL REPORT: UNAIDS Report On The Global AIDS Epidemic 2010. Geneva: Joint United Nations Programme on HIV/AIDS (UNAIDS); 2010 Nov.
6. Fairall LR, Bachmann MO, Louwagie GM, van Vuuren C, Chikobvu P, Steyn D, et al. Effectiveness of antiretroviral treatment in a South African program: a cohort study. Arch Intern Med. 2008 Jan 14; 168(1):86–93. [PubMed: 18195200]
7. Carrieri MP, Pradier C, Piselli P, Piche M, Rosenthal E, Heudier P, et al. Reduced incidence of Kaposi's sarcoma and of systemic non-hodgkin's lymphoma in HIV-infected individuals treated with highly active antiretroviral therapy. Int J Cancer. 2003 Jan 1; 103(1):142–4. [PubMed: 12455069]
8. Clifford GM, Polesel J, Rickenbach M, Dal Maso L, Keiser O, Kofler A, et al. Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. J Natl Cancer Inst. 2005 Mar 16; 97(6):425–32. [PubMed: 15770006]
9. Franceschi S, Maso LD, Rickenbach M, Polesel J, Hirschel B, Cavassini M, et al. Kaposi sarcoma incidence in the Swiss HIV Cohort Study before and after highly active antiretroviral therapy. Br J Cancer. 2008 Sep 2; 99(5):800–4. [PubMed: 18665172]
10. Ledergerber B, Egger M, Erard V, Weber R, Hirschel B, Furrer H, et al. AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy: the Swiss HIV Cohort Study. JAMA. 1999 Dec 15; 282(23):2220–6. [PubMed: 10605973]
11. Ledergerber B, Telenti A, Egger M. Risk of HIV related Kaposi's sarcoma and non-Hodgkin's lymphoma with potent antiretroviral therapy: prospective cohort study. Swiss HIV Cohort Study. BMJ. 1999 Jul 3; 319(7201):23–4. [PubMed: 10390454]
12••. Lodi S, Guiguet M, Costagliola D, Fisher M, de Luca A, Porter K. Kaposi sarcoma incidence and survival among HIV-infected homosexual men after HIV seroconversion. J Natl Cancer Inst. 2010 Jun 2; 102(11):784–92. Estimates recent individual patient-level effectiveness of ART on KS risk using known HIV seroconvertors in the CASCADE collaboration. By limiting analysis to homosexual men, authors largely precluded potential confounding by underlying infection with Kaposi's sarcoma-associated herpesvirus (KSHV). Important delineation of KS incidence amongst ART users who reached high levels of CD4+ T cell counts (350–499 and >500 cells/μl) is provided. [PubMed: 20442214]
13. Mocroft A, Katlama C, Johnson AM, Pradier C, Antunes F, Mulcahy F, et al. AIDS across Europe, 1994–98: the EuroSIDA study. Lancet. 2000 Jul 22; 356(9226):291–6. [PubMed: 11071184]
14. Patel P, Hanson DL, Sullivan PS, Novak RM, Moorman AC, Tong TC, et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992–2003. Ann Intern Med. 2008 May 20; 148(10):728–36. [PubMed: 18490686]
15••. Pipkin S, Scheer S, Okeigwe I, Schwarcz S, Harris DH, Hessol NA. The effect of HAART and calendar period on Kaposi's sarcoma and non-Hodgkin lymphoma: results of a match between an AIDS and cancer registry. AIDS. 2011 Feb 20; 25(4):463–71. Provides cogent distinction between individual patient-level and population-level impact of ART. However, adjustment for ART use when estimating population-level impact of ART may have substantially attenuated the population-level effectiveness estimate. [PubMed: 21139489]
16••. Asiimwe F, Moore D, Were W, Nakityo R, Campbell J, Barasa A, et al. Clinical outcomes of HIV-infected patients with Kaposi's sarcoma receiving nonnucleoside reverse transcriptase inhibitor-based antiretroviral therapy in Uganda. HIV Med. 2012 Mar; 13(3):166–71. Using a well-characterized cohort from within a randomized controlled trial in Uganda, with the majority

of KS cases histologically proven, this study offers the first published individual patient-level estimate of KS incidence among ART users in sub-Saharan Africa. [PubMed: 22112164]

17. Bohlius, J.; Valeri, F.; Maskew, M.; Prozesky, H.; Chimbetete, C.; Lumano-Mulenga, P., et al. Incidence of Kaposi Sarcoma in HIV-Infected Patients-AProspective Multi-Cohort Study From Southern Africa. 13th International Conference on Malignancies in AIDS and Other Acquired Immunodeficiencies (ICMAOI); November 7–8, 2011; Bethesda, Maryland. 2011.
18. Martin, J.; Wenger, M.; Busakhala, N.; Buziba, N.; Bwana, M.; Muyindike, W., et al. Prospective evaluation of the impact of potent antiretroviral therapy on the incidence of Kaposi's Sarcoma in East Africa: Finidings from the International Epidemiological Databases to Evaluate AIDS (IeDEA) Consortium. 13th International Conference on Malignancies in AIDS and Other Acquired Immunodeficiencies (ICMAOI); November 7–8, 2011; Bethesda, Maryland. 2011.
19. Maurer T, Ponte M, Leslie K. HIV-associated Kaposi's sarcoma with a high CD4 count and a low viral load. N Engl J Med. 2007 Sep 27; 357(13):1352–3. [PubMed: 17898112]
20. Chan J, Kravcik S, Angel JB. Development of Kaposi's sarcoma despite sustained suppression of HIV plasma viremia. J Acquir Immune Defic Syndr. 1999 Oct 1; 22(2):209–10. [PubMed: 10843538]
21. Silverberg MJ, Neuhaus J, Bower M, Gey D, Hatzakis A, Henry K, et al. Risk of cancers during interrupted antiretroviral therapy in the SMART study. AIDS. 2007 Sep 12; 21(14):1957–63. [PubMed: 17721103]
22. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology. 2000 Sep; 11(5):550–60. [PubMed: 10955408]
23. Dal Maso L, Polesel J, Serraino D, Lise M, Piselli P, Falcini F, et al. Pattern of cancer risk in persons with AIDS in Italy in the HAART era. Br J Cancer. 2009 Mar 10; 100(5):840–7. [PubMed: 19223894]
24. Engels EA, Pfeiffer RM, Goedert JJ, Virgo P, McNeel TS, Scoppa SM, et al. Trends in cancer risk among people with AIDS in the United States 1980–2002. Aids. 2006 Aug 1; 20(12):1645–54. [PubMed: 16868446]

25••. Franceschi S, Lise M, Clifford GM, Rickenbach M, Levi F, Maspoli M, et al. Changing patterns of cancer incidence in the early- and late-HAART periods: the Swiss HIV Cohort Study. Br J Cancer. 2010 Jul 27; 103(3):416–22. Provides recent estimate of the population-level effectiveness of ART on KS incidence in Switzerland. Only report that used a nationally representative population of all HIV-infected persons (as opposed to just AIDS patients) to match against the national cancer registry. [PubMed: 20588274]

26••. Simard EP, Pfeiffer RM, Engels EA. Spectrum of cancer risk late after AIDS onset in the United States. Arch Intern Med. 2010 Aug 9; 170(15):1337–45. Not only presents recent estimates for population-level effectiveness of ART but also provides KS residual risk estimates using a general population comparison group that predated the HIV epidemic. Use of this historical comparator group provides a less biased estimate for residual KS risk than using a contemporary comparator. [PubMed: 20696958]

27. Chaturvedi AK, Mbulaiteye SM, Engels EA. Underestimation of relative risks by standardized incidence ratios for AIDS-related cancers. Ann Epidemiol. 2008 Mar; 18(3):230–4. [PubMed: 18083545]
28. Biggar RJ, Chaturvedi AK, Goedert JJ, Engels EA. AIDS-related cancer and severity of immunosuppression in persons with AIDS. J Natl Cancer Inst. 2007 Jun 20; 99(12):962–72. [PubMed: 17565153]

29•. Polesel J, Franceschi S, Suligoi B, Crocetti E, Falcini F, Guzzinati S, et al. Cancer incidence in people with AIDS in Italy. Int J Cancer. 2010 Sep 1; 127(6):1437–45. Large study, covering nearly one-third of Italy, presenting recent estimates of both the population-level effectiveness of ART on KS incidence as well as the unadjusted change in KS incidence since the availability of ART. [PubMed: 20049835]

30•. Msyamboza KP, Dzamalala C, Mdokwe C, Kamiza S, Lemerani M, Dzowela T, et al. Burden of cancer in Malawi; common types, incidence and trends: National population-based cancer registry. BMC Res Notes. 2012 Mar 16.5(1):149. This study uses a population based cancer registry in Malawi and gives a realistic appraisal of the limitations of registries in resource-limited settings. [PubMed: 22424105]

31. Grulich AE, Li Y, McDonald AM, Correll PK, Law MG, Kaldor JM. Decreasing rates of Kaposi's sarcoma and non-Hodgkin's lymphoma in the era of potent combination anti-retroviral therapy. AIDS. 2001 Mar 30; 15(5):629–33. [PubMed: 11317001]

32•. Simard EP, Pfeiffer RM, Engels EA. Cumulative incidence of cancer among individuals with acquired immunodeficiency syndrome in the United States. Cancer. 2011 Mar 1; 117(5):1089–96. Sophisticated analysis of the change in KS incidence since the availability of ART, portraying incidence in an easy to interpret cumulative incidence format and accounting for competing events. [PubMed: 20960504]

33. Bedimo R, Chen RY, Accortt NA, Raper JL, Linn C, Allison JJ, et al. Trends in AIDS-defining and non-AIDS-defining malignancies among HIV-infected patients: 1989–2002. Clin Infect Dis. 2004 Nov 1; 39(9):1380–4. [PubMed: 15494916]

34. Brodt HR, Kamps BS, Gute P, Knupp B, Staszewski S, Helm EB. Changing incidence of AIDS-defining illnesses in the era of antiretroviral combination therapy. AIDS. 1997 Nov 15; 11(14): 1731–8. [PubMed: 9386808]

35•. Crum-Cianflone NF, Hullsiek KH, Ganesan A, Weintrob A, Okulicz JF, Agan BK. Is Kaposi's sarcoma occurring at higher CD4 cell counts over the course of the HIV epidemic? AIDS. 2010 Nov 27; 24(18):2881–3. Evaluation of KS incidence in the U.S. Military HIV Natural History Study. Although they documented a decrease in the incidence of KS since ART has become available, authors found an increasing percentage of KS cases are occurring at CD4+ T cell counts >350 cells/μl. [PubMed: 20827160]

36. Gingues S, Gill MJ. The impact of highly active antiretroviral therapy on the incidence and outcomes of AIDS-defining cancers in Southern Alberta. HIV Med. 2006 Sep; 7(6):369–77. [PubMed: 16903981]

37. Hessol NA, Seaberg EC, Preston-Martin S, Massad LS, Sacks HS, Silver S, et al. Cancer risk among participants in the women's interagency HIV study. J Acquir Immune Defic Syndr. 2004 Aug 1; 36(4):978–85. [PubMed: 15220706]

38. Highly active antiretroviral therapy and incidence of cancer in human immunodeficiency virus-infected adults. J Natl Cancer Inst. 2000 Nov 15; 92(22):1823–30. [PubMed: 11078759]

39. Jones JL, Hanson DL, Dworkin MS, Jaffe HW. Incidence and trends in Kaposi's sarcoma in the era of effective antiretroviral therapy. J Acquir Immune Defic Syndr. 2000 Jul 1; 24(3):270–4. [PubMed: 10969352]

40. Long JL, Engels EA, Moore RD, Gebo KA. Incidence and outcomes of malignancy in the HAART era in an urban cohort of HIV-infected individuals. AIDS. 2008 Feb 19; 22(4):489–96. [PubMed: 18301061]

41. Portsmouth S, Stebbing J, Gill J, Mandalia S, Bower M, Nelson M, et al. A comparison of regimens based on non-nucleoside reverse transcriptase inhibitors or protease inhibitors in preventing Kaposi's sarcoma. AIDS. 2003 Jul 25; 17(11):F17–22. [PubMed: 12853764]

42•. Seaberg EC, Wiley D, Martinez-Maza O, Chmiel JS, Kingsley L, Tang Y, et al. Cancer incidence in the multicenter AIDS Cohort Study before and during the HAART era: 1984 to 2007. Cancer. 2010 Dec 1; 116(23):5507–16. Evaluation of KS incidence in the U.S. Military HIV Natural History Study. Although they documented a decrease in the incidence of KS since ART has become available, authors found an increasing percentage of KS cases are occurring at CD4+ T cell counts >350 cells/μl. [PubMed: 20672354]

43. Mbulaiteye SM, Katabira ET, Wabinga H, Parkin DM, Virgo P, Ochai R, et al. Spectrum of cancers among HIV-infected persons in Africa: the Uganda AIDS-Cancer Registry Match Study. Int J Cancer. 2006 Feb 15; 118(4):985–90. [PubMed: 16106415]

44. International Epidemiologic Databases to Evaluate AIDS. 2011. [cited 2011 14/09/2011]; Available from: http://iedea.org/whoweare

45. Somdyala NI, Bradshaw D, Gelderblom WC, Parkin DM. Cancer incidence in a rural population of South Africa, 1998–2002. Int J Cancer. 2010 Nov 15; 127(10):2420–9. [PubMed: 20162610]

46. Parkin DM, Nambooze S, Wabwire-Mangen F, Wabinga HR. Changing cancer incidence in Kampala, Uganda, 1991–2006. Int J Cancer. 2010 Mar 1; 126(5):1187–95. [PubMed: 19688826]

Key points

- There are abundant data from resource-rich settings indicating the beneficial effect of ART on preventing Kaposi's sarcoma (KS) both among ART users and within the entire HIV-infected population.
- Methodological shortcomings of published studies in resource-rich settings, however, preclude our understanding of the actual magnitude of ART impact on KS incidence and hence whether there are need for additional interventions besides ART to reduce incidence.
- Emerging data from resource-limited countries preliminarily suggest a beneficial impact of ART on KS incidence comparable to that seen in resource-rich settings, but — considering the magnitude of KS in resource-limited settings — much more data are needed to confirm the individual patient-level effectiveness, determine population-level effectiveness, and establish residual risk of KS given ART use.
- In both resource-rich and resource-limited settings, more precise specific estimates of the incidence of KS in ART-treated patients who have achieved CD4 counts >350 cells/μl are needed.

Table 1

Studies estimating individual patient-level effectiveness of antiretroviral therapy (ART) on the incidence of Kaposi's sarcoma (KS) in resource-rich and resource-limited settings.

Authors	Year Published	Cohort	Country	Incidence of KS per 100,000 person-years		% Reduction in KS Incidence[a]
				Non-ART Users	ART Users	
Resource-rich						
Carrieri et al. [7]	2002	DMI-2	France	640	122	78%
Clifford et al. [8]	2005	SHCS	Switzerland	1229	109	91%
Francheschi et al. [9]	2008	SHCS	Switzerland	1500	130	88%
Ledergerber et al. [10]	1999	SHCS	Switzerland	2020	140	93%
Ledergerber et al. [11]	1999	SHCS	Switzerland	na	na	92%
Lodi et al. [12••]	2010	CASCADE	Many [b]	822	358	57%
Mocroft et al. [13]	2000	EuroSIDA	Many [c]	1800	700	61%
Patel et al. [14]	2008	ASD & HOPS	USA	na	na	39%
Pipkin et al. [15••]	2011	SFAR	USA	na	na	19%
Resource-limited						
Asiimwe et al. [16••]	2012	HBAC	Uganda	na	340	na
Bohilius et al. [17]	2011	IeDEA-S. Africa	Many [d]	624	174	72%
Martin et al. [18]	2011	IeDEA-East Africa	Kenya	596	270	50%
			Uganda	1876	201	78%

[a] Percent reduction in KS incidence in users of ART vs. non-users. Estimates are adjusted for a variety of factors, according to individual study

[b] Europe, Australia and Canada

[c] Europe, Israel and Argentina

[d] Botswana, Mozambique, South Africa, Zambia, Zimbabwe

ASD: Adult/Adolescent Spectrum of Disease project; **CASCADE**: Concerted Action of Seroconversion to AIDS and Death in Europe; **DMI-2:** Longitudinal database of HIV-infected individuals followed at Nice University Hospital, France; **EuroSIDA**: Collection of European cohort studies (includes Israel and Argentina); **HBAC**: Home Based AIDS Care program; **HOPS**: HIV Outpatients' Study; **na:** Not available; **IeDEA**: International Epidemiological Databases to Evaluate AIDS; **SFAR**: San Francisco AIDS Registry; **SHCS**: Swiss HIV Cohort Study

Table 2

Studies estimating residual Kaposi's sarcoma (KS) risk comparing either HIV/AIDS patients in antiretroviral therapy (ART) era or ART users (the HIV-infected index group) with the general population.

Authors	Year Published	Country	HIV-infected Index Group	Source of General Population	Standardized Incidence Ratio (SIR)[a]
Clifford et al. [8]	2005	Switzerland	ART users	Contemporary	25.3
Dal Maso et al. [23]	2009	Italy	AIDS Patients	Contemporary	572
Engels et al. [24]	2006	USA	AIDS Patients	Pre-HIV	3640
Francheschi et al. [25••]	2010	Switzerland	HIV-infected Patients	Contemporary	22.9
Simard et al. [26••]	2010	USA	AIDS Patients	Pre-HIV	1584

[a]Ratio of observed number of KS cases in the HIV-infected index group compared to expected number of KS cases as derived from rates in the general population, standardized for age, race, sex and calendar time.

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Table 3

Studies estimating population-level effectiveness of antiretroviral therapy (ART) on the incidence of Kaposi's sarcoma (KS).

Authors	Year Published	Population-based Data Source	Country	Incidence of KS per 100,000 person-years		% Reduction in KS Incidence [a]
				Pre-ART Era	ART Era	
Resource-rich						
Biggar et al. [28]	2007	HIV Cancer Match Study	USA	1839	334.6	78%
Francheschi et al. [25••]	2010	SHCS	Switzerland	1375[b]	66.9[b]	95%
Pipkin et al. [15••]	2011	SFAR-CCR	USA	na	na	33%
Polesel et al. [29•]	2010	CARL	Italy	2131[b]	250[b]	88%
Simard et al. [26••]	2010	HIV Cancer Match Study	USA	1282	190	80%
Resource-limited						
Msyamboza et al. [30•]	2012	Malawi Cancer Registry	Malawi	10.9/5.1[c]	25.3/11.9[c]	[d]

[a] Percent reduction in KS incidence, which is attributed to antiretroviral therapy, among HIV-infected individuals observed in the era when ART is available compared to the era when it was not. Estimates are adjusted for a variety of factors, according to individual study.

[b] Rates are age-and sex-standardized.

[c] Age-standardized rates in men/women. Pre-ART era defined as 1999–2002 and ART era as 2007–2010.

[d] Rates represented a 2.3-fold increase in both men and women.

na: Not available; **CARL:** Cancer and AIDS Registries Linkage Study; **SFAR-CCR:** San Francisco AIDS Registry & California Cancer Registry Linkage

Table 4

Studies estimating population-based change in the incidence of Kaposi's sarcoma (KS) since availability of antiretroviral therapy (ART).

Authors	Year Published	Population-based Data Source	Country	Incidence of KS per 100,000 person-years		% Reduction in KS Incidence [a]
				Pre-ART Era	ART Era	
Dal Maso et al. [23]	2009	IAR-ICR	Italy	895	653	27%
Engels et al. [24]	2006	HIV Cancer Match Study	USA	na	na	84%
Grulich et al. [31]	2001	HIV & Cancer Registries	Australia	460	190	59%
Polesel et al. [29•]	2010	CARL	Italy	1859	216	88%
Simard et al. [32•]	2011	HIV Cancer Match Study	USA	14.3%[b]	1.8%[b]	87%[c]

[a]Percent reduction in crude KS incidence among HIV-infected individuals observed in the era when ART is available compared to the era when it was not. There is no adjustment for any other factors.

[b]Denotes 5 year cumulative incidence of Kaposi's sarcoma; incidence rate was not reported.

[c]Denotes 5 year cumulative incidence ratio; incidence rate ratio was not reported.

na: Not Available; **CARL:** Cancer and AIDS Registries Linkage Study; **IAR-ICR:** Italian AIDS Registry & Italian Cancer Registry; **SHCS**: Swiss HIV Cohort Study

Table 5

Clinic-based cohort studies estimating change in the incidence of Kaposi's sarcoma (KS) since availability of antiretroviral therapy (ART).

Authors	Year Published	Cohort	Country	Incidence of KS per 100,000 person-years		% Reduction in KS Incidence [a]
				Pre-ART Era	ART Era	
Bedimo et al. [33]	2004	SHALOM	USA	2782	541	81%
Brodt et al. [34]	1997	Frankfurt AIDS	Germany	17500	4400	75%
Crum-Cianflone et al. [35•]	2010	US Military Natural History	USA	650	180	72%
Gingues et al. [36]	2006	Southern Alberta Clinic	Canada	3200	400	88%
Hessol et al. [37]	2004	WIHS	USA	160.5	36.9	77%
Int'l Collaboration [b] [38]	2000	Many [c]	Many [d]	1520	490	68%
Jones et al. [39]	2000	ASD	USA	4100	700	50%
Long et al. [40]	2008	John's Hopkins AIDS Clinic	USA	500	100	80%
Patel et al. [14]	2008	ASD & HOPS	USA	2500	250	90%
Portsmouth et al. [41]	2003	Chelsea & Westminster	UK	3000	3	66%
Seaberg et al. [42•]	2010	MACS	USA	2515	327	87%

[a] Percent reduction in KS incidence among HIV-infected individuals observed in the era when ART is available compared to the era when it was not. Estimates are adjusted for various factors, according to individual study.

[b] International Collaboration on HIV & Cancer

[c] 23 cohorts: Amsterdam, Aquitaine, ASD, CASCADE, DMI-2, HERS, HOPS, MACS, MHCS, RHIHP, and SFCCC.

[d] Europe, Australia, Canada, and USA

ASD: Adult/Adolescent Spectrum of Disease Project; **CASCADE**: Concerted Action of Seroconversion to AIDS and Death in Europe; **DMI-2**: Longitudinal database of HIV-infected individuals followed at Nice University Hospital, France; **HERS**: HIV Epidemiology Research Study; **HOPS**: HIV Outpatients' Study; **MACS:** Multicenter AIDS Cohort Study; **MHCS**: Multicenter Hemophilia Cohort Study; **RHIHP:** Registry of HIV-Infected Hemophilia Patients; **SFCCC**: San Francisco City Clinic Cohort; **SHALOM**: Studies of HIV/AIDS Longitudinal Outcome Metrics cohort; **SHCS:** Swiss HIV Cohort Study; **WIHS**: Women's Interagency HIV Study.