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Title: Changing incidence and risk factors for Kaposi sarcoma by time since starting antiretroviral therapy: Collaborative analysis of 21 European cohort studies

Running title: KS risk in HIV-infected adults on cART

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40 words summary: Early after starting combination antiretroviral therapy low CD4 cell count is the dominant risk factor for developing Kaposi sarcoma. In contrast, detectable HIV-1 RNA viral load becomes an increasingly important risk factor several years after treatment start, independently of immunodeficiency.

Abstract

Background. Kaposi sarcoma (KS) remains a frequent cancer in HIV-positive patients initiating combination antiretroviral therapy (cART). We examined incidence rates and risk factors for developing KS in different periods since starting cART in patients from European observational HIV-cohorts.

Methods. We included HIV-positive adults starting cART after 01/01/1996. We analyzed incidence rates and risk factors for developing KS up to 90, 180 days and one, two, five, and eight years after cART start and fitted univariable and multivariable Cox regression models.

Results. We included 109,461 patients from 21 prospective clinical cohorts in Europe with 916 incident KS cases. The incidence rate per 100,000 person-years was highest six months after starting cART (953, 95% CI 866-1,048) and declined to 82 (95% CI 68-100) after five to eight years. Using multivariable analyses adjusted for exposure group, origin, age, type of first-line regimen and calendar year, low current CD4 cell counts increased the risk of developing KS throughout all observation periods after starting cART. Lack of viral control was not associated with the hazard of developing KS in the first year after cART initiation, but was over time since starting cART increasingly positively associated ($p<0.001$ for interaction).

***Conclusion*.** In patients who started cART both incidence and risk factors for KS change with time since starting cART. Whereas early after starting cART low CD4 cell count is the dominant risk factor, detectable HIV-1 RNA viral load becomes an increasingly important risk factor in patients who started cART several years ago, independently of immunodeficiency.

INTRODUCTION

Kaposi sarcoma (KS) remains a frequent cancer in HIV-positive patients, including in patients who are receiving combination antiretroviral therapy (cART) [1–4]. Higher detection rates of KS and KS becoming evident in the context of the immune reconstitution inflammatory syndrome (IRIS) may contribute to the increased KS risk shortly after cART initiation [5]. Few studies have examined the incidence rate of KS in HIV-positive patients who have started cART some years ago. A recent analysis of a large US cohort of HIV-positive patients found that the incidence of KS was very high in the first 6 months after cART initiation (1,342/100,000 person-years (pys)) but decreased substantially thereafter and stabilized at a rate of around 164/100,000 pys more than six months after starting cART [3].

Infection with human herpresvirus-8 (HHV-8) is a necessary cause of KS [6]. HHV-8 seroprevalence is high among men having sex with men (MSM) and in the general population of some regions of sub-Saharan Africa, including Southern Africa and East Africa [6]. Likewise, high rates of KS incidence among patients having started cART several years ago, have been found among MSM in Europe [2] and in Africa [7–9]. Immunodeficiency, as indicated by low CD4 cell counts, and failure to suppress HIV replication have also been identified as risk factors for developing KS in HIV-positive individuals on cART [2,5,10]. However, it is unclear at present whether these risk factors influence KS development similarly soon after starting cART and many years after starting cART. In particular, the determinants of KS among patients who started cART several years ago have not been well defined.

The aim of the present study was to gain a better understanding of the factors that drive the incidence of KS among patients initiating cART. We analyzed data from a large collaboration of European HIV cohort studies, the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord [11,12] to examine KS incidence rates and risk factors for KS in different time periods after the start of cART, from 30-90 days to 5-8 years after starting cART.

MATERIALS & METHODS

COHERE in EuroCoord

The COHERE in EuroCoord is a collaboration of 40 cohorts of HIV-infected patients across Europe, led by two data centers in Bordeaux and Copenhagen [13]. Twenty-nine cohorts provided data for the current project. Patients are followed-up every 3-6 months. Participating cohorts collect and transfer standardized data using the HIV Cohorts Data Exchange Protocol [14]. Data collected include socio-demographic factors, CD4-cell counts, HIV-1 RNA viral load measurements, antiretroviral drugs, AIDS-defining events and deaths. The dataset for this analysis was merged on 04/06/2014 and included 29 cohorts with 306,482 patients. Cohorts adhere to local ethical requirements for observational research [13].

Inclusion Criteria and Definitions

We included HIV-positive adults aged ≥16 years who enrolled and started cART after 01/01/1996, when cART became widely available in most parts of Europe. Combination antiretroviral therapy was defined as a regimen of at least three drugs from any class, including nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI). We excluded patients with previous ART exposure to mono- or dual therapy. Patients with ≤30 days follow-up and prevalent KS cases diagnosed before or during the first 30 days after cART start were excluded from the analyses. We also excluded patients with missing information for gender, country or region of birth, date of birth; and cohorts with <100 eligible patients.

We defined baseline CD4 cell count as the measurement closest to the start of cART with a time window of -90/+30 days. Baseline HIV-1 RNA viral load was the measurement closest to start cART with a time window of -90/+7 days. Suppression of HIV-1 replication was defined as HIV-1 RNA ≤500 copies/mL. Late presenters were defined as CD4 cell count <350 cells/µl or CDC stage C at enrolment [15]. First-line regimens were classified as NNRTI-based, boosted PI-based, unboosted PI-based, or

other. Sex and exposure groups were defined as MSM, heterosexual men, and heterosexual women. Origin, i.e. country or region of birth, was categorized as European, African or other.

Statistical Analysis

Observation started 30 days after initiating cART. We used an intention-to-continue-treatment approach ignoring subsequent treatment changes and interruptions. We split observation time in six periods: 30-90 days, 91-180 days, 181 days-12 months, 1-2 years, 2-5 years and 5-8 years. The same patient could contribute time to several periods. Observation ended at the earliest of KS diagnosis, last follow-up visit, death or eight years after cART start. We calculated KS incidence rates by dividing the number of patients developing KS by the number of pys at risk and Poisson 95% confidence intervals (CI). We fitted Cox models separately for each of the six periods, including exposure group, origin, first-line regimen, calendar year of enrolment (four categories) and the time-updated (current) variables CD4 cell count (six categories), HIV-1 RNA (four categories) and age (four categories) into the models. We used the likelihood ratio test to test whether HRs changed across time periods (test for interaction between period and risk factor).

In additional analyses we included baseline CD4 cell count or late presentation in the model, included square-root transformed CD4 cell counts and log-transformed HIV-1 RNA viral loads as continuous variables, and excluded the first six months after starting cART or patients enrolled into cohort before 2000. All analyses were done in Stata Version 13 (Stata Corporation, College Station, Texas, USA). Results are presented as medians with interquartile ranges (IQR), incidence rates per 100,000 pys, crude and adjusted hazard ratios (HRs), with 95% CI.

RESULTS

Study Population

A total of 109,461 patients from 21 cohorts from 10 European countries (Austria, Belgium, Denmark, Germany, France, Italy, Spain, Greece, The Netherlands, Switzerland) or the EuroSIDA study [16] were eligible for the current analyses. Supplemental Figure S1 shows the number of included and

excluded patients. The main reasons for excluding patients were enrolment before 1996 (52,717; 27%), patients not starting cART (63,708; 32%), and patients not ART naïve at cART start (34,644; 18%). A total of 9,347 KS cases were excluded. Of these 3,872 (41%) cases were diagnosed before 1996. Of the cases diagnosed after 1996 3,414 (62%) were diagnosed within ≤30 days after cART initiation. Included and excluded patients were similar with respect to gender, age and CD4 cell counts at enrolment (data on file). Included patients had higher HIV-1 RNA viral loads at enrolment compared to excluded patients (median 75,000 copies/mL in included compared to 19,407 copies/mL in excluded patients). Patients who enrolled before 2000 were more likely to have missing HIV-1 RNA measurements and thus to be excluded from the multivariable analysis compared to patients who enrolled later.

The baseline characteristics of the 109,461 included patients are shown in Table 1: 40,972 (37%) patients were MSM; 29,845 (27%) were women. The majority of patients (84,514; 77%) were of European origin; 16,330 (15%) were of African origin. Median age was 37.3 years (IQR 31.2-44.7 years). The median CD4 cell count was 250 cells/µl (IQR 122-370 cells/µl), 15,652 (14%) patients were in CDC stage C. Median follow-up since starting cART was 4.6 years (IQR 2.0-8.7 years), total observation time 501,800 pys.

A total of 916 patients developed KS after starting cART. Median time from starting cART to KS diagnosis was 223 days (IQR 77-987 days). KS patients were more likely to be male, MSM and enrolled during the early years of the cART era (1996-2000) than patients remaining free from KS (Table 1). Among 318 heterosexual men and women developing KS, 66% (211) were men and 34% (107) were women; 38% (124) were of African origin. Patients developing KS were often late presenters and started cART in a more advanced clinical stage than those not developing KS. Of the 916 KS patients 705 had CD4 cell counts below 350, 106 between 350-500 and 105 above 500 cells/µl at KS diagnosis. Patients with >350 cells/µl at KS diagnosis were more likely to be MSM, to have higher age and higher CD4 cell counts at enrolment than patients with CD4 cell count <350 cells/µl at KS diagnosis. Median viral load at KS diagnosis was 358 copies/mL (IQR 0-27,750 copies/mL). Median

CD4 cell count was 243 cells/µl (IQR 107-409 cells/µl) and 450 cells/µl (IQR 280-596 cells/µl) in those developing KS 30-90 days and 5-8 years, respectively, after starting cART. Four hundred and eighteen (46%) KS cases were diagnosed during the first six months after starting cART; these patients had low baseline CD4 cell counts (median 85 cells/µl, IQR 27-230 cells/µl) and were often late presenters (340; 81%).

Incidence Rates

The overall KS incidence rate was 183/100,000 pys (95% CI 171-195). It was 1,472/100,000 pys in the period 30-90 days after starting cART, declined to 582/100,000 in period 91-180 days, to 247/100,000 in period 181 days-1 year and to 120/100,000 in period 1-2 years after starting cART (Figure 1, panel A). The rate was similar in the subsequent two periods: about 82-85/100,000 pys beyond 2 years of starting cART. Panels B to F of Figure 1 show the incidence rate stratified by current CD4 cell count and HIV-1 RNA viral load, origin, exposure group and current age. For incidence rates per risk group and time period see supplement Table S1. In all periods after starting cART incidence rates were highest in patients with current CD4 cell counts <50 cells/µL, in patients with non-suppressed HIV-1 RNA viral replication, and in MSM. More than two years after starting cART, KS incidence in MSM was about 149-160/100,000 pys. The lowest rates were observed 5-8 years after starting cART in women (23/100,000 pys), in patients with suppressed viral load (41/100,000) and in patients with CD4 cell counts >500 cells/µL (36/100,000 pys).

Risk Factors by Period

A total of 100,022 (91.4%) patients had complete data and were included in the multivariable analyses. The HRs from the multivariable Cox models by period after starting cART are shown in Table 2 and supplement Figure S2; results from univariable analyses are shown in supplement Table S2 and Table S3. The risk of KS was increased in MSM, in patients of African origin, and in patients with low current CD4 cell counts. The association was strongest for MSM (HR 5.87 comparing MSM with heterosexual men in period 30-90 days) and for current CD4 cell count (HR 7.37 comparing <50 cells/µL with 350-499 cells/µL in period 30-90 days). There was little evidence for a difference in HRs

across the six periods for exposure group, origin, calendar year of enrolment, first-line cART regimen or current CD4 cell count, with p values from tests of interaction between 0.12 and 0.93 (Table 2). The situation was different for current HIV-1 RNA viral load: there was no evidence of an association in the periods early after starting cART but an increasingly strong association emerged in the later periods (p<0.001). The HR comparing ≥100,000 copies/mL with ≤500 copies/mL was 3.08 (95% CI 1.56-6.09) in period 1-2 years after starting cART and 9.72 (95% CI 5.34-17.7) 5-8 years after starting cART. In the overall multivariable analysis not stratified by time period (supplement Table S4) patients aged >50 years had a higher KS risk compared to patients aged ≤30 years. There was some evidence for an interaction between current age and time since starting cART (p=0.07). However, this finding was not robust in additional analyses (data on file). The baseline CD4 cell count (supplement Table S5) and late presentation (supplement Table S6) were associated with the risk of KS in the early periods after starting cART but not thereafter. Results were similar when including square-root transformed current CD4 cell counts and log-transformed HIV-RNA viral loads as continuous variables rather than categories of current CD4 count and HIV-1 RNA viral load (data on file). Tests for interaction for current CD4 and current HIV RNA were similar when we excluded the first 6 months after starting cART (p=0.413 and 0.004, respectively) and when we excluded patients enrolled before 2000 (p=0.49 and <0.001, respectively).

DISCUSSION

In this collaborative analysis we found that the incidence rate of KS was around 1,500/100,000 pys in the first weeks after starting cART but declined thereafter to plateau at about 82-85/100,000 pys after two years since starting cART. In MSM the KS incidence rate was about 149-160/100,000 pys, even two years after starting cART. This is higher than the age-standardized incidence of the most frequent cancers in the general population (breast cancer 80/100,00 pys, prostate cancer 70/100,00 pys [17]). Other patient groups with high KS incidence rates were migrants from sub-Saharan Africa, late presenters and patients with low CD4 cell counts. The lowest KS incidence rates were seen in heterosexual women who started cART several years ago. The strength of associations with KS in the

different periods tended to be similar for most risk factors with the exception of HIV-1 viral load. Viral load was not associated with KS up to one year after starting cART, but emerged as an increasingly important risk factor thereafter.

Our analysis was based on a large European cohort collaboration including >100,000 patients and >500,000 pys of follow-up with longitudinal CD4 and HIV-1 RNA measurements and detailed information on origin, sexual orientation and drug regimens. This is one of few studies in patients who have started cART five years or longer ago [2,3] and to our best knowledge the first study to thoroughly examine changes in the importance of different risk factors over time since cART initiation, using time-updated values where appropriate. Our study has several limitations. Data on HHV-8 serostatus, KS stage, or KS-related IRIS were not available. For example, we could not assess whether the increased risk of KS during the first 6 months after cART initiation was related to IRIS [5]. The risk of unmasking IRIS is increased in patients with low CD4 cell nadir at cART initiation [18] and previous studies have shown that timely initiation of cART at high CD4 cell counts may reduce the risk of developing unmasking IRIS-KS [18–20].

The most striking finding of our study is the emergence of HIV-1 RNA as an increasingly strong risk factor for KS in patients who had started cART several years ago. In this multivariable analysis the association between current HIV-1 RNA viral load and KS was independent of other risk factors, including immunodeficiency, and a dose-response relation was evident, with the highest risk of KS in those with viral loads $\geq$100,000 copies/mL. It therefore appears that early after starting cART the incidence of KS is largely driven by immunodeficiency whereas later on replicating HIV-1 and immunodeficiency independently contribute to the risk of KS. This might be explained by synergistic interactions between HIV and HHV-8 [21]. The HIV-1 Tat protein facilitates HHV-8 replication, which in turn may lead to an increased risk of KS [22,23]. Likewise, HHV-8 has been shown to activate HIV replication [24]. Our results indicate that consistent long-term suppression of HIV-1 RNA replication prevents such interactions and thus reduces the risk of KS. These findings suggest that monitoring viral load to detect treatment failures in a timely fashion might be important.

The KS incidence rates from this study are generally similar to estimates of previous studies [1–3] from Europe and the US (see supplement Table S7). Our study confirms that MSM have a higher risk of developing KS compared to heterosexual men [10,25–27], probably due to the higher seroprevalence of HHV-8 infection, whereas women are at lower risk of developing KS compared to men [10,27,7]. This and other studies have shown that Europeans have lower KS incidence rates compared to migrants from sub-Saharan Africa [10,28], which may again be explained by the higher HHV-8 seroprevalence in patients with African origins [6]. Previous studies have suggested that the risk of developing KS increases with age in patients who are not receiving cART [28] but not in patients who have started cART [2,3,28]. Our overall analysis not stratified by time period suggested an increased KS risk in patients aged > 50 years compared to patients aged ≤ 30 years. However, we did not observe a dose-response relationship and there was no robust evidence for an interaction with time since starting cART. In contrast to a recent study [29], our study did not show that boosted PI-based first-line regimens were associated with a lower risk of developing KS compared to NNRTI-based regimens. We cannot exclude that confounding by indication may have influenced our findings. Moreover, we examined the initial first-line regimen only and adopted an intention-to-continue-treatment approach, which ignored subsequent treatment changes and therefore limited our ability to detect associations of KS with different cART regimens. We found that low current CD4 cell counts increased the risk of developing KS in each period after starting cART, whereas baseline CD4 cell count or late presentation predicted KS in the first months after cART initiation only. This finding is in line with a previous study which showed that low baseline CD4 cell counts were associated with an increased risk of developing KS in the first 6 months after starting cART but not thereafter [3].

The risk of developing KS is particularly high in late presenters and patients with low current CD4 cell counts shortly after cART initiation. This observation might be explained by an increased vigilance of patients and physicians for signs of disease but also by unmasking IRIS–associated KS [20]. KS incidence and its associated risk factors in patients having started cART several years ago is not

completely understood. Our study confirms that low current CD4 cell count increases the risk of KS throughout all time periods after starting cART.

In conclusion, this collaborative analysis of European HIV cohort studies shows that in patients starting cART both incidence and risk factors for KS change with treatment duration. Whereas early after starting cART immunodeficiency is the dominant risk factor, detectable HIV-1 RNA viral load becomes an increasingly important risk factor in patients who started cART several years ago, independently of immunodeficiency. Further research is needed on the interaction between HIV-1 and HHV-8 replication and the risk of KS, and the potential impact of cART on HHV-8 viremia.

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