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Kaposi sarcoma in ART-treated people living with HIV: A wake-up call for research on HHV-8

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Running title

Kaposi sarcoma in the ART era
Introduction.

Kaposi sarcoma (KS) remains the strongest stigma of the AIDS epidemic and a harbinger of severe immunodeficiency. Introduction of antiretroviral therapy (ART) allowed the control of HIV replication and dramatically decreased KS prevalence in people living with HIV (PLWH). However, recent data suggest that KS remains a concern for ART-treated PLWH, despite recovered CD4 T-cell count and undetectable HIV viremia. The risk of KS in this setting has thus been estimated as 35 to 60-fold higher than in the general population [1]. In a French study conducted between 2010 and 2015, KS in virologically-suppressed PLWH represented 11.4% of epidemic KS cases [2]. By constituting both a puzzling clinical observation and a recall for patients of the darkest days of the AIDS epidemic, KS arising or persisting in the context of successful ART raises questions about the physiopathology of this disease. In particular, the contribution of viral replication and specific immune response against human herpes virus-8 (HHV-8), the causing agent of KS, remains unknown.

Reported cases in the literatures.

Since the first report of KS in ART-treated PLWH in 2003, increasing cases of KS in virally suppressed ART-treated PLWH have been reported in the literature (patient characteristics reviewed in Table 1). The three most recent reports arose from France. Two studies identified 21 and 54 cases of KS, respectively, in PLWH with undetectable HIV VL on ART for at least 6 months [3,4] and another study reported 12 cases of KS in PLWH with undetectable VL for at least 12 months [5]. Overall, described patients were mostly middle-aged men (90% male, median age 49 years), with a median HIV infection duration of nine years before KS development (Table 1) and limited cutaneous KS lesions. None of these patients had a previous history of opportunistic infections or multicentric Castleman disease (MCD) or primary effusion lymphoma (PEL), two conditions associated with HHV-8. Notably, two of the French studies as well as our ongoing prospective cohort study in Montréal identified elevation of CD8 T-cell count and lower CD4/CD8 T-cell ratio as factors
associated with KS development [3–6]. Similarly, Caby et al. recently published a large collaborative study evaluating the impact of CD4/CD8 T-cell ratio on KS and non-Hodgkin lymphoma in PLWH from 27 European cohorts [7]. Among 19,133 PLWH with CD4 T-cell counts above 500 cells/mm³, 65 presented with KS including 51 with HIV viral control, and a strong inverse association between CD4/CD8 T-cell ratio and KS development was found.

Physiopathology of KS in ART-treated PLWH: influence of immunosenescence?

Increasing evidences suggest that chronic viral infections with HIV, CMV, or hepatitis B and C viruses induce senescence of the immune system through persistent immune activation. Senescent T-cells lose their inherent properties, ranging from proliferative capacities to interferon-γ production, and exhibit shorter telomere length due to telomerase loss [8,9]. Markers of immunosenescence include a decrease of the CD4/CD8 T-cell ratio, an upregulated expression of immune checkpoint molecules as Programmed cell death 1 (PD-1) and an increased frequency of immunosenescent CD57⁺CD28⁻ T-cells [10,11]. In ART-treated PLWH, low CD4/CD8 T-cell ratio has become a surrogate marker of immune dysregulation and T-cell activation, and has been associated with age-related diseases, non-AIDS comorbidities and even mortality [12,13]. Normalization of CD4/CD8 T-cell ratio is seldom observed after ART introduction, even with optimal CD4 T-cell count recovery and early ART initiation. Chronic CMV or EBV infections, that frequently co-exist with HIV, have been associated with CD8 T-cells expansion and might contribute to this dysregulation [14,15]. Whether a similar impact of HHV-8 coinfection on CD8 T-cells expansion in ART-treated people exists is, however, unknown. Independently of the etiology, increased CD8 T-cell counts and overproduction of CD8 T-cells inflammatory cytokines have been associated with KS development and progression, and with a lack of anti-HHV-8 T-cell response [16,17]. Patients with KS were also found to exhibit decreased HHV-8-specific T-cell responses compared to asymptomatic HHV-8 carriers, independently of age or CD4 T-cell counts [16,18]. Moreover, in skin biopsies of patients with epidemic or endemic KS, CD8 T-cells and macrophages did not colocalize with HHV-8-infected cells indicating that cytotoxic cells are kept at bay from infected cells [19]. Altogether, the exact role
of T-cell response in controlling HHV-8-related diseases constitutes an important gap in knowledge, probably owing to the frequent concurrent immunosuppression of the host.

Other factors involved in this reemergence of KS have been proposed. Long-term viral synergy between HHV-8 and HIV should be further explored, as HIV-1 regulatory Tat and Nef proteins have been reported to enhance HHV-8 infectivity and trigger replication after latency establishment [20]. In addition, the impact of new genetic HHV-8 variants with distinct oncogenic potential, the influence of protease inhibitors regiments or microbiota alterations are also suspected [21–23].

**Clinical management: immunomodulation beyond CD4 T-cell count restoration.**

Regarding clinical management, controlling HIV replication and restoring CD4 T-cell counts through ART initiation, which has long been considered as the primary therapeutic option for KS in PLWH, is obviously irrelevant in long-term ART-treated PLWH. Liposomal anthracyclines or paclitaxel chemotherapies constitute the first line of treatment in these patients, with inherent toxicities [24,25]. Immunomodulating capacities of HHV-8 and the suspected role of immunosenescence would suggest a potential role for immunotherapies and immunomodulating drugs. In this sense, thalidomide-derivate pomalidomide has shown substantial efficacy and is approved for KS since 2020 by the United States Food and Drug Administration (FDA), including in PLWH [26]. Blockade of PD-1 and its ligand PD-L1 also constitutes a promising option, given its success for other cancers and also considering the known upregulation of PD-1 expression following HHV-8 infection in vitro [27,28]. Another potential benefit of PD-1/PD-L1 blockade therapies in the context of HIV-related KS is their potential ability to revert latent HIV infection and decrease HIV reservoir size [29]. A small clinical trial reported remission with these immunotherapies in 6 out of 9 patients with endemic KS [30]. Clinical trials are underway and will shed light on the efficacy of novel therapies in this population.
Concluding remarks.

Altogether, increasing reports bring to light the risk of KS development in well-treated and virologically controlled PLWH. Occurrence of KS in this population is no longer anecdotic and becomes a new challenge, given the large number of aging ART-treated patients worldwide. PLWH with successful virological suppression still harbor immune dysregulation and experience aging-related comorbidities, opening up unchartered new conditions where HHV-8-related comorbidities may develop.

Could this new wave of KS represent its fifth form, where persons may have developed KS even in absence of HIV, likely at an older age? Inflammaging may lead to inadequate control of HHV-8 and early emergence of KS in this setting, and possibly also to other HHV-8-related diseases. Immunomodulating therapies that have revolutionized cancer treatments should offer an alternative to chemotherapy in these cases. Technological improvements in viral detection could also be used to fill the gap of HHV-8-specific assays, still lacking validation in clinical practice. Such re-emergence of KS justifies the implementation of large international cohorts of PLWH, with or without KS, in developed and developing countries, with detailed information on patient characteristics including sexual practice, along with epidemiologic, pathologic, immunologic and virologic assessment. Comparison with non-HIV case of KS will also be needed to identify common or divergent factors associated with tumor development. After 40 years into the HIV epidemic, this reoccurrence of KS that came as a harbinger of AIDS emerges as an unaddressed medical concern paired with social stigma justifying urgent multidisciplinary research. We strongly suspect that KS in ART-treated PLWH constitutes a novel form of the disease that is emerging and needs further investigation.

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Conflict of interest

L.R., S.I., A.C., J.P.R.: No conflicts of interest related to this work.
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Table 1. Clinical characteristics of virally suppressed ART-treated HIV-positive patients at KS onset

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Period</th>
<th>N. of cases</th>
<th>HIV characteristics</th>
<th>% of men</th>
<th>% of MSM</th>
<th>Median age (years)</th>
<th>Median HIV duration (years)</th>
<th>Median ART duration (years)</th>
<th>CD4 count, median</th>
<th>CD4/CD8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Masi.</td>
<td>Italy</td>
<td>2005</td>
<td>10</td>
<td>UD VL, on ART, for at least 3 months</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Manz.</td>
<td>USA</td>
<td>2002</td>
<td>9</td>
<td>VL &lt; 400 copies/ml for at least 2 years, CD4 &gt; 500 cells/μl</td>
<td>NA</td>
<td>NA</td>
<td>21 (range 41, 74)</td>
<td>18 (range 4, 20)</td>
<td>8 (range 1, 19)</td>
<td>140 (range 90, 415)</td>
<td>NA</td>
</tr>
<tr>
<td>Masi.</td>
<td>USA</td>
<td>2002</td>
<td>20</td>
<td>UD VL, CD4 &gt; 500 cells/μl</td>
<td>95</td>
<td>10</td>
<td>43 (range 55, 59)</td>
<td>4.2 (range 9, 10.1)</td>
<td>5 (range 0, 12)</td>
<td>150 (range 10, 773)</td>
<td>NA</td>
</tr>
<tr>
<td>Stebbing</td>
<td>UK</td>
<td>2006</td>
<td>4</td>
<td>UD VL, CD4 &gt; 500 cells/μl</td>
<td>81</td>
<td>NA</td>
<td>42 (QQR 30, 46)</td>
<td>4.5 (QR 11, 22)</td>
<td>NA</td>
<td>NA</td>
<td>449 (QQR 14, 621)</td>
</tr>
<tr>
<td>Polish</td>
<td>France</td>
<td>2014-2017</td>
<td>21</td>
<td>VL &lt; 50 copies/ml, on ART, for at least 6 months</td>
<td>81</td>
<td>NA</td>
<td>54 (QQR 35, 61)</td>
<td>18 (QR 6, 22)</td>
<td>NA</td>
<td>NA</td>
<td>467 (QR 35, 819)</td>
</tr>
<tr>
<td>Poznań</td>
<td>France</td>
<td>2010-2015</td>
<td>21</td>
<td>VL &lt; 50 copies/ml, on ART, for at least 6 months</td>
<td>87.5</td>
<td>18</td>
<td>48 (QQR 39, 54.7)</td>
<td>7.4 (QR 2.8, 10.7)</td>
<td>4.1 (QR 14, 10.5)</td>
<td>NA</td>
<td>541 (QR 0.2, 0.9)</td>
</tr>
<tr>
<td>Poznań</td>
<td>France</td>
<td>2010-2017</td>
<td>12</td>
<td>VL &lt; 50 copies/ml, for at least 12 months, on ART</td>
<td>100</td>
<td>NA</td>
<td>54 (range 58, 60)</td>
<td>8.2 (range 0.4, 5.4)</td>
<td>NA</td>
<td>723 (range 520, 881)</td>
<td>0.65</td>
</tr>
</tbody>
</table>
