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Reconstitution of immune responses against Kaposi sarcoma-associated herpesvirus

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Among HIV-infected people, Kaposi sarcoma (KS) continues to be the most common malignancy diagnosed in sub-Saharan Africa and among men who have sex with men (MSM). This is a direct result of two factors: the high prevalence of KS-associated herpesvirus [KSHV, also known as human herpesvirus 8 (HHV-8)] and the powerful effect of HIV-related immune perturbation to transform asymptomatic KSHV infection to malignant KS. Even though the risk is reduced by approximately 90% when HIV replication is controlled with combination antiretroviral therapy (cART),[1] AIDS KS cases continue to appear. The paper by Sullivan and colleagues in this issue of *AIDS* helps to clarify the impact of cART on the regulation of KSHV and, ultimately, on the risk of AIDS KS.[2] They report that 272 MSM who received cART for 24 months, including 22 who had KS at baseline, experienced a substantial decline in the prevalence of KSHV viremia and substantial increases in the prevalence and levels of anti-KSHV antibodies.

Because KSHV is the primary cause of KS,[3] understanding its lifecycle, pathogenic mechanisms, and immunologic control is central to preventing KS. Like all herpes viruses, the KSHV lifecycle has two distinct phases, both of which probably contribute to the development of KS. In the lytic phase, the majority of KSHV's 84 genes are expressed in a tightly regulated cascade to produce virions that disseminate the infection to susceptible people and to susceptible cells in vivo.[4] Lytic expression may be required to infect endothelial cells that are precursors of the malignant KS spindle cells. [5,6] In the latent phase, KSHV is maintained as a nuclear episome that requires only a few genes for replication and distribution to daughter cells during mitosis.[7] Spindle cells of KS lesions consistently and strongly express the latency-associated nuclear antigen (LANA). In addition, the expression of lytic genes in a few cells in each lesion may propagate both the infection and the malignancy.

How the host controls KSHV, and the dysfunction that results in KS, remain undefined. Detection of KSHV genome in peripheral blood mononuclear cells (PBMC) is highly predictive of the subsequent development of AIDS KS [8–9] and is also associated with advanced stage and likelihood of progression of AIDS KS and non-AIDS KS.[10–12] Thus, correlates of KSHV viremia provide some insight. Pellet and colleagues noted that cART-

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related clearance of KSHV viremia predicted a faster time to response of AIDS KS, with a median time to response of 251 days.[12] In the report by Gill et al., AIDS KS responses to cART were a bit faster, but also closely tied to clearance of KSHV viremia.[13] Without considering KS, Bourbouli et al noted that KSHV viremia (both cell-associated and in plasma) fell substantially, often to undetectable, with cART, but only after 12–24 months. [14] In the current study, at cART initiation KSHV genome was detected in serum in 7 (35%) of 22 KS cases and also in 10 (4%) of 250 other MSM. After 24 months on cART, serum viremia had cleared in all of these except one KS case. Of note, however, 7 MSM who were negative for serum viremia at baseline, were positive after 24 months on cART. [2]

Long term use of effective cART may affect KSHV, and directly or indirectly KS, through humoral immunity. KS is associated with higher levels of anti-KSHV antibodies.[9,11,15] In part, this merely reflects the high burden of KSHV antigens among patients who have established KS. In addition, antibody titers probably increase over time due to ongoing, low level expression of KSHV antigens.[16,17] Without KS, antibody levels against conventional latent (LANA) and lytic (predominantly K8.1) antigens tend to be correlated, but there also are substantial differences in levels among individuals. Importantly, the possibility that serologic responses could reduce KS risk was suggested by one study that observed significantly reduced levels of KSHV neutralizing antibody levels among MSM with AIDS KS,[18] and another that observed an inverse association between anti-KSHV titer and likelihood to develop a new KS lesions within three months.[11] Sullivan and colleagues now report increases in seroprevalence and levels of both anti-LANA and anti-lytic antibodies over the course of 24 months of cART.[2] These results partially conflict with a much smaller study that observed cART-related increases in anti-lytic (K8.1) but not anti-LANA antibodies.[14] In either case, the data are insufficient to determine whether the seroconversions during cART are due to incident KSHV infection or to recovery of humoral response against an earlier, “occult” KSHV infection.

With established KS or with untreated HIV infection, T-cell responses against KSHV are seldom detected. [14,19–21] In contrast, one-quarter of HIV-negative MSM may demonstrate T-cell proliferation against disrupted whole KSHV virions.[21] Of interest, the prevalence and strength of responses to KSHV peptides increase with cART-induced immune reconstitution.[14,19,22–24] Despite these encouraging reports, the effects of cART-generated T-cell responses on KSHV viremia and KS lesions have been inconsistent and required many months to discern.

Understanding the immunologic control of KSHV and the process that results in KS continues to be hampered by the limited tools that are available. Assays to detect and quantify serum antibodies against a wider array of KSHV antigens may prove helpful. [25,26] In the meantime, we are left with impressions based on limited data. Use of cART clearly reduces the onset of KS and, over a period of many months to years, improves or clears KS lesions in the majority of patients. Over the same months to years, cART also has positive, but poorly defined, effects against KSHV. This latter impression is primarily based on studies of KSHV viremia, but companion studies of the effect of cART on KSHV shedding in saliva are needed.[11,27]

As we reduce KS-related morbidity and mortality by administration of cART, we must be cognizant that long term control of AIDS KS, as well as control of non-AIDS KS, will depend on drugs, or ideally vaccines, targeted to critical steps in the life cycle of KSHV. This virus has many ways to evade, suppress, and even subvert immune responses,[6,28–31] presenting major challenges that we must accept.

References

1. Clifford G, Polesel J, Rickenbach M, 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; 97:425–432. [PubMed: 15770006]
2. Sullivan S, Hirsch HH, Franceschi S, Steffen I, Boffiel-Amari E, Mueller NJ, et al. Kaposi sarcoma herpes virus antibody response and viraemia following highly active antiretroviral therapy in the Swiss HIV Cohort Study. *AIDS.* 2010 In press.
3. Moore PS, Chang Y. Kaposi's sarcoma (KS), KS-associated herpesvirus, and the criteria for causality in the age of molecular biology. *Am J Epidemiol.* 1998; 147:217–221. [PubMed: 9482495]
4. Miller G, Heston L, Grogan E, Gradoville L, Rigsby M, Sun R, Shedd D, Kushnaryov VM, Grossberg S, Chang Y. Selective switch between latency and lytic replication of Kaposi's sarcoma-associated herpesvirus and Epstein-Barr virus in dually infected body cavity lymphoma cells. *J Virol.* 1997; 71:314–324. [PubMed: 8985352]
5. Ganem D. KSHV and the pathogenesis of Kaposi sarcoma: listening to human biology and medicine. *J Clin Invest.* 2010; 120:939–949. [PubMed: 20364091]
6. Schulz T. The pleiotropic effects of Kaposi's sarcoma herpesvirus. *J Pathol.* 2006; 208:187–198. [PubMed: 16362980]
7. Chen L, Lagunoff M. Establishment and maintenance of Kaposi's sarcoma-associated herpesvirus latency in B cells. *J Virol.* 2005; 79:14383–14391. [PubMed: 16254372]
8. Whitby D, Howard MR, Tenant-Flowers M, Brink NS, Copas A, Boshoff C, et al. Detection of Kaposi sarcoma associated herpesvirus in peripheral blood of HIV-infected individuals and progression to Kaposi's sarcoma. *Lancet.* 1995; 346:799–802. [PubMed: 7674745]
9. Engels E, Whitby D, Goebel PB, Stossel A, Waters D, Pintus A, et al. Detection and quantification of Kaposi's sarcoma-associated herpesvirus to predict AIDS-associated Kaposi's sarcoma. *AIDS.* 2003; 17:1847–1851. [PubMed: 12891072]
10. Campbell TB, Borok M, Gwanzura L, MaWhinney S, White IE, Ndemera B, et al. Relationship of human herpesvirus 8 peripheral blood virus load and Kaposi's sarcoma clinical stage. *AIDS.* 2000; 14:2109–2116. [PubMed: 11061651]
11. Cannon M, Dollard S, Black J, Edlin B, Hannah C, Hogan S, et al. Risk factors for Kaposi's sarcoma in men seropositive for both human herpesvirus 8 and human immunodeficiency virus. *AIDS.* 2003; 17:215–222. [PubMed: 12545082]
12. Pellet C, Chevret S, Blum L, Gauvill C, Hurault M, Blanchard G, et al. Virologic and immunologic parameters that predict clinical response of AIDS-associated Kaposi's sarcoma to highly active antiretroviral therapy. *J Invest Dermatol.* 2001; 117:858–863. [PubMed: 11676823]
13. Gill J, Bourboulia D, Wilkinson J, Hayes P, Cope A, Marcelin AG, et al. Prospective study of the effects of antiretroviral therapy on Kaposi sarcoma--associated herpesvirus infection in patients with and without Kaposi sarcoma. *J AIDS.* 2002; 31:384–390.
14. Bourboulia D, Aldam D, Lagos D, Allen E, Williams I, Cornforth D, et al. Short- and long-term effects of highly active antiretroviral therapy on Kaposi sarcoma-associated herpesvirus immune responses and viraemia. *AIDS.* 2004; 18:485–493. [PubMed: 15090801]
15. Brown E, Whitby D, Vitale F, Marshall V, Mbisa G, Gamache C, et al. Virologic, hematologic, and immunologic risk factors for classic Kaposi sarcoma. *Cancer.* 2006; 107:2282–2290. [PubMed: 16998933]
16. Biggar R, Engels E, Whitby D, Kedes D, Goedert J. Antibody reactivity to latent and lytic antigens to human herpesvirus-8 in longitudinally followed homosexual men. *J Infect Dis.* 2003; 187:12–18. [PubMed: 12508141]
17. Lane AS, Dollard S, Jaffe H, Offermann M, Spira T, Gunthel C, et al. Repeated measures study of human herpesvirus 8 (HHV-8) DNA and antibodies in men seropositive for both HHV-8 and HIV. *AIDS.* 2004; 18:1819–1826. [PubMed: 15316343]
18. Kimball L, Casper C, Koelle D, Morrow R, Corey L, Vieira J. Reduced levels of neutralizing antibodies to Kaposi sarcoma-associated herpesvirus in persons with a history of Kaposi sarcoma. *J Infect Dis.* 2004; 189:2016–2022. [PubMed: 15143468]

19. Guihot A, Dupin N, Marcelin AG, Gorin I, Bedin AS, Bossi P, et al. Low T cell responses to human herpesvirus 8 in patients with AIDS-related and classic Kaposi sarcoma. *J Infect Dis.* 2006; 194:1078–1088. [PubMed: 16991082]
20. Barozzi P, Bonini C, Potenza L, Masetti M, Cappelli G, Gruarin P, et al. Changes in the immune responses against human herpesvirus-8 in the disease course of posttransplant Kaposi sarcoma. *Transplantation.* 2008; 86:738–744. [PubMed: 18791457]
21. Strickler HD, Goedert JJ, Bethke FR, Trubey CM, O'Brien TR, Palefsky J, et al. Human herpesvirus 8 cellular immune responses in homosexual men. *J Infect Dis.* 1999; 180:1682–1685. [PubMed: 10515832]
22. Wilkinson J, Cope A, Gill J, Bourboulia D, Hayes P, Imami N, et al. Identification of Kaposi's sarcoma-associated herpesvirus (KSHV)-specific cytotoxic T-lymphocyte epitopes and evaluation of reconstitution of KSHV-specific responses in human immunodeficiency virus type 1-Infected patients receiving highly active antiretroviral therapy. *J Virol.* 2002; 76:2634–2640. [PubMed: 11861829]
23. Bihl F, Mosam A, Henry L, Chisholm J, Dollard S, Gumbi P, et al. Kaposi's sarcoma-associated herpesvirus-specific immune reconstitution and antiviral effect of combined HAART/chemotherapy in HIV clade C-infected individuals with Kaposi's sarcoma. *AIDS.* 2007; 21:1245–1252. [PubMed: 17545700]
24. Bihl F, Berger C, Chisholm J, Henry L, Bertisch B, Trojan A, et al. Cellular immune responses and disease control in acute AIDS-associated Kaposi's sarcoma. *AIDS.* 2009; 23:1918–1922. [PubMed: 19609199]
25. Burbelo P, Leahy H, Groot S, Bishop L, Miley W, Iadarola M, et al. Four-antigen mixture containing v-cyclin for serological screening of human herpesvirus 8 infection. *Clin Vaccine Immunol.* 2009; 16:621–627. [PubMed: 19261774]
26. Burbelo P, Issa AT, Ching KH, Wyvill KM, Little RF, Iadarola MJ, et al. Distinct Profiles of Antibodies to Kaposi Sarcoma-Associated Herpesvirus Antigens in Patients with Kaposi Sarcoma, Multicentric Castleman Disease, and Primary Effusion Lymphoma. *J Infect Dis.* 2010 In press.
27. Laney AS, Cannon M, Jaffe H, Offermann M, Ou CY, Radford K, et al. Human herpesvirus 8 presence and viral load are associated with the progression of AIDS-associated Kaposi's sarcoma. *AIDS.* 2007; 21:1541–1545. [PubMed: 17630548]
28. Areste C, Blackburn D. Modulation of the immune system by Kaposi's sarcoma-associated herpesvirus. *Trends Microbiol.* 2009; 17:119–129. [PubMed: 19230674]
29. West J, Damania B. Kaposi's sarcoma-associated herpesvirus and innate immunity. *Future Virol.* 2010; 5:185–196. [PubMed: 20414330]
30. Liang C, Lee JS, Jung J. Immune evasion in Kaposi's sarcoma-associated herpes virus associated oncogenesis. *Semin Cancer Biol.* 2008; 18:423–436. [PubMed: 18948197]
31. Moore PS, Chang Y. Kaposi's sarcoma-associated herpesvirus immunoevasion and tumorigenesis: two sides of the same coin? *Ann Rev Microbiol.* 2003; 57:609–639. [PubMed: 14527293]