Acquired Immunodeficiency Syndrome-Related Kaposi's Sarcoma Regression After Highly Active Antiretroviral Therapy: Biologic Correlates of Clinical Outcome

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Background: **Kaposi's sarcoma (KS) is the most common cancer seen in subjects with acquired immunodeficiency syndrome (AIDS). KS etiology and pathogenesis are still ill defined, and no definite improvement in survival has been obtained with current chemotherapeutic regimens. This open prospective study was aimed at evaluating the clinical response of AIDS-related KS to highly active antiretroviral therapy (HAART), a combination of protease and reverse transcriptase inhibitors, as well as the relationship between clinical response, human immunodeficiency virus type 1 (HIV-1) burden, and antibody titer against human herpesvirus 8 (HHV8) proteins.** ***Patients and Methods:*** **Fourteen KS patients were studied; 12 were in the poor-risk group. At given intervals, the patients underwent clinical examination, and their $CD4^+$ cell counts, plasma HIV-1 RNA levels, and antibody titers to lytic-phase ORF65 and latent-phase HHV8 proteins were determined.** ***Results:*** **When last seen, the overall clinical response rate was 86% (median follow-up, 22 months); 10 complete and two partial responses were achieved, and two patients showed disease progression. All patients with complete or partial response showed a consistent decrease in HIV-1 RNA levels, with a corresponding increase in $CD4^+$ cell counts; HIV-1 RNA levels in the two progressors remained persistently high, despite a change in HAART. HHV8 ORF65 antibody titers were generally higher in patients with extensive skin or mucosal/visceral involvement versus patients with limited disease; no differences in latent-phase HHV8 antibody titers were observed in relation to tumor burden.** ***Conclusion:*** **The findings indicate that antiretroviral therapy with protease inhibitors is effective for AIDS-related KS; the clinical response was correlated with a decrease in plasma HIV-1 RNA levels and an increase in $CD4^+$ lymphocytes, whereas antibody levels to the lytic-phase HHV8 protein were influenced by the extent of tumor involvement. [J Natl Cancer Inst Monogr 2000;28: 44–9]**

The initial suggestion by Thomas *(1)* that an adaptive immune system evolved in vertebrate organisms with the principal aim of preserving cell type uniformity by eliminating spontaneously arising tumor cells was further elaborated by Burnet *(2)* who advanced his theory of immune surveillance. Although this innovative idea triggered many studies on tumor immunology, it also met with much skepticism and eluded many expectations of a major therapeutic breakthrough. Nevertheless, circumstantial evidence indicates that primary or acquired immunodeficiencies greatly increase the risk of tumor development and, particularly, those tumors etiologically linked with a given virus infection *(3).*

Kaposi's sarcoma (KS) is a good example of a tumor whose incidence is remarkably higher in immunocompromised hosts *(4,5).* Following its original description in 1872, KS was long regarded as a rare dermatologic condition appearing in patients of Mediterranean and eastern European origin ("classic" KS) as well as in endemic foci in sub-Saharan African areas ("endemic" KS). That KS was also associated with immunodeficiencies was noticed with the advent of therapeutically induced immunosuppression in organ and marrow transplant recipients ("iatrogenic" KS). Its incidence was dramatically augmented, however, by the onset of the acquired immunodeficiency syndrome (AIDS) epidemic in the early 1980s, and the epidemic KS variant became an AIDS-defining condition, since it was the most common malignancy in people infected by the human immunodeficiency virus type 1 (HIV-1).

Unlike classic KS, but similar to the iatrogenic variant, AIDS-related KS tends to progress rapidly and shows a wide spectrum of lesions, ranging from multiple skin patches and nodules to mucosal and visceral involvement *(6).* At the microscope, spindle cells separated by slits containing red blood cells are the hallmark of KS lesions; mitotic activity is moderate and a diploid profile is usually seen on flow cytometry analysis. The spindle cell phenotype recalls vascular endothelial cells, likely of lymph vessel origin, that may derive from vasoformative mesenchyme. KS tissue also contains admixed lymphocytes, hemosiderin-laden macrophages, and other inflammatory cells *(4).*

The etiology and pathogenesis of AIDS-related KS are still ill defined. On the basis of the natural history and histopathologic findings, it was advanced that, besides determining immunodeficiency, HIV-1 might be involved through its transactivator Tat protein, which is released by infected cells and taken up by nearby cells *(7),* and whose angiogenetic properties are well established *(8).* Moreover, HIV-1 infection might produce an increase in inflammatory cytokines, such as interleukin 1, interleukin 6, oncostatin M, and interferon gamma, which together with other angiogenic growth factors would, in turn, promote the growth of hyperplastic/neoplastic KS cells *(9).*

A novel herpesvirus, termed "KS-associated herpesvirus" or

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See "Notes" following "References."

"human herpesvirus 8" (HHV8), has also been linked to KS *(10,11)*. HHV8 has been detected in the spindle cells, endothelial cells, and monocytes of almost all KS lesions and in about 50% of the peripheral blood mononuclear cells of KS patients *(12)*. Moreover, although almost 100% of the KS subjects studied had antibodies against HHV8, the HHV8 seroprevalence in the general population of the United States and Europe varies from 1% to 25%, depending on the geographic area and the methodology employed *(13)*. The finding that HIV-1 Tat protein exerts a positive effect on HHV8 replication suggests an interplay between HIV-1 and HHV8 *(14)*.

To define a chemotherapeutic strategy for AIDS-related KS, several studies have been conducted. Treatments with cytotoxic drugs, either as a single-agent or in combination, were found to have variable response rates and to increase the frequency of opportunistic infections with no substantial improvement in survival *(15,16)*. The addition of antiretroviral zidovudine treatment to combination chemotherapy did not increase the response rates *(17)*. However, the course of HIV-1 infection has been greatly modified by highly active antiretroviral therapy (HAART), a combination treatment that makes use of reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs). HAART brings about a substantial and sustained decrease in peripheral blood HIV-1 RNA levels, as well as an increase in $CD4^+$ T cells, and significantly delays the development of AIDS-associated opportunistic infections and death *(18)*. Preliminary findings suggested that PIs might also determine a reduction in KS lesions *(19–23)*, and complete remission was recently reported in patients during HAART *(24)*.

This study, which extends a previous report *(25)*, was aimed at evaluating the clinical impact of HAART on AIDS-related KS lesions, as well as the relationship between the clinical response, HIV-1 viral load, and antibody titer against lytic and latent HHV8 proteins.

Patients and Methods

Patients

From October 1996 to October 1998, all HIV-1-seropositive patients with stable or progressive biopsy-proven KS and measurable disease and who were attending the Department of Infectious Diseases of the General Hospital of Padova were enrolled in an open prospective study. At study entry, the patients underwent a physical examination that included the measurement of all cutaneous and mucosal lesions as well as the compilation of a standard body diagram; patients with a clinical suspect of visceral KS underwent gastrointestinal/bronchial endoscopy and chest tomography. The patients' disease was clinically staged according to the AIDS Clinical Trial Group (ACTG) criteria based on tumor extent (T), severity of immunosuppression (I), and other systemic HIV-1-associated diseases (S) *(26,27)*. Performance status was determined according to the criteria of the Eastern Cooperative Oncology Group.

Study Treatment

The HAART regimen consisted of a triple-drug combination, including two RTIs and one PI, according to current guidelines *(28–30)*. During the study, a switch from one HAART regimen to another was allowed because of intolerance or failure to reduce viral load. The drugs used in the different combinations were administered daily at the following doses: RTIs—600 mg zidovudine, 300 mg lamivudine, 2.15 mg zalcitabine, 400 mg didanosine, and 80 mg stavudine; PIs—2400 mg indinavir, 1200 mg ritonavir, 1800 mg saquinavir, and 2250 mg nelfinavir.

Outcome End Points

During the study, a complete physical examination was done every month; tumor measurements, blood cell counts, and $CD4^+$ lymphocyte counts were also recorded. If endoscopic and radiographic findings at study entry were abnormal, these examinations were repeated. Clinical responses were evaluated with the use of the ACTG criteria *(26)*: A complete response (CR) was defined as the absence of new lesions and of any detectable residual disease, including tumor-associated lymphoedema, persisting for at least 4 weeks; for visceral KS, normal endoscopic and radiographic findings were considered a CR. A partial response (PR) was defined as the absence of new lesions and a 50% or greater decrease in the number of all pre-existing lesions, or complete flattening of 50% or more of the lesions, or a 50% or greater decrease in lesion size, determined by calculating the products of two perpendicular dimensions, for at least 4 weeks. Progressive disease (PD) was defined as the development of new lesions or an increase of 25% or more in the size of pre-existing lesions. Any response not meeting the criteria for CR, PR, or PD was considered stable disease.

Quantitative HIV-1 RNA Assay

EDTA peripheral blood samples were centrifuged at 800*g* for 30 minutes at 20 °C over a Ficoll–Hypaque (Pharmacia, Uppsala, Sweden) density gradient. Plasma was recovered from the upper phase and centrifuged at 1000*g* for 10 minutes at 20 °C to ensure a cell-free specimen; 200 μL was employed for HIV-1 RNA determination, and the remainder was aliquoted and stored at −80 °C. HIV-1 RNA was determined with the use of a quantitative reverse transcription–polymerase chain reaction assay (Amplicor Monitor; Roche Diagnostic System, Branchburg, NJ), whose lower limit of detection is 200 HIV-1 RNA copies/mL.

Analysis of HHV8 Antibodies

Plasma samples were analyzed for antibodies to a latency-associated nuclear antigen (LANA) and a capsid-related protein encoded by ORF65, as previously described *(31,32)*. LANA antibodies were evaluated by an indirect immunofluorescence assay on paraformaldehyde-fixed BCP-1 cells; plasma samples were initially analyzed at a dilution of 1 : 100 and subsequently at serial twofold dilutions. ORF65 antibodies were tested by the enzyme-linked immunosorbent assay (ELISA) at an initial plasma dilution of 1 : 100 and then at serial twofold dilutions; the cutoff value was the average of 10 HHV8-seronegative Italian blood donors plus 5 standard deviations. Purified recombinant dehydrofolate reductase (DHFR), the fusion partner of recombinant ORF65 protein, was employed as the control antigen; plasma samples showing reactivity to this DHRF portion were considered nonspecific by ELISA. Antibody titers were calculated as the reciprocal of the highest plasma dilution giving positive results.

Statistical Analysis

Immunologic and virologic data were analyzed by the nonparametric Mann–Whitney and Wilcoxon tests. Specimens in which the HIV-1 RNA load was below the lower detection limit of the assay were assigned a value of 100 copies/mL to include

the data in the statistical analyses. Statistical analyses were performed with the use of SAS software (SAS Institute, Cary, NC). All *P* values are two-sided.

Results

Patient Characteristics at Baseline

Fourteen male patients (median age 41 years; range 28–57 years) were enrolled in this study; nine had a history of previous opportunistic infection, and KS was the AIDS-defining illness in the other five (PM, CL, AO, MA, and FM; Table 1). The median interval between KS diagnosis and study entry was 8.5 months (range, 1–47 months). At study entry, none of the patients had been treated previously with PIs. Five patients (CA, AO, ZC, MA, and FM; Table 1) had never received any antiretroviral therapy; the other nine had been previously treated with RTIs, and four of these patients (PM, SL, CL, and MS) had also received systemic KS chemotherapy (10 mg/m^2 bleomycin and 6 mg/m^2 vinblastine on days 1 and 15 every 2 weeks). After six bleomycin/vinblastine cycles, patients CL and MS were treated with bleomycin (intravenous infusion of 10 mg/m^2 every 2 weeks) and liposomal daunorubicin (40 mg/m^2 every 2 weeks), respectively. Patient PM concluded his chemotherapy 3 months prior to study entry and, at the time of enrollment, had progressive disease based on the appearance of new nodular and mucosal lesions; patients MS, CL, and SL were still under treatment at study entry.

Twelve patients were in the poor-risk group, as defined by any evidence of the following: visceral disease, tumor-associated edema, and CD4$^+$ cell count of fewer than 150 cells/μL *(27).* Of the two patients with visceral disease, one patient (CL) had large lesions in the main left bronchial wall visualized by bronchoscopy, and the other patient (SL) had multiple pulmonary interstitial infiltrates confirmed by chest tomography. One patient (AR; Table 1) fell into the $T_0I_0S_0$ group; this patient had stable KS following a partial remission obtained during treatment with a dual RTI therapy 3 months prior to study entry.

At baseline, the median CD4$^+$ cell count was 58 cells/μL (range, 2–443 cells/μL), and the median plasma HIV-1 RNA level was 75 500 copies/mL (range, 2500–1 870 000 copies/mL). No statistically significant differences were observed between patients with cutaneous or limited mucosal involvement (T_0) and patients with more extensive disease (T_1) regarding both CD4 cell number (T_0 median = 75 cells/μL and range = 11–443 cells/μL versus T_1 median = 21 cells/μL and range = 2–214 cells/μL; P = .38, Mann–Whitney test) and HIV-1 RNA copies/mL (T_0 median = 144 000 copies/mL and range = 2500–1 870 000 copies/mL versus T_1 median = 72 000 copies/mL and range = 23 000–315 000; P = .90, Mann–Whitney test).

Clinical and Biologic Responses

Three patients (MS, CL, and SL) concluded their previous chemotherapies at 9, 5, and 10 months, respectively, following study entry. The initial HAART regimen was changed during the study in four patients (PM, CL, MS, and AR) because of the lack of a satisfactory virologic response and in one patient (CG) because of intolerance.

The median follow-up at last examination was 22 months (range, 8–31 months). When last seen, the overall clinical response rate was 86% (12 of 14), with 10 CRs and two PRs. The median time to CR was 6 months (range, 2–23 months); four patients with limited cutaneous lesions (MA, CW, FM, and AR) achieved a CR in a median time of 3 months (range, 2–5 months), whereas six patients with more extensive disease obtained a CR following a PR in a median time of 13 months (range, 5–23 months). All patients who achieved a CR were still in this clinical condition when last seen (Table 2).

Two patients (AO and SLu) who achieved a PR at 2 months and at 1 month, respectively, were still in this clinical condition at last examination (Table 2). Patient PM obtained a PR 6 months after HAART initiation but showed PD at 15 months. Patient MS showed PD at 9 months, despite concomitant KS chemotherapy; he was then started on paclitaxel (30 mg/m^2 every week) and after 2 months achieved a PR, which was followed 5 months later by PD (Table 2).

At PR, CD4$^+$ cell counts were higher than baseline values (median = 36 cells/μL and range = 2–214 cells/μL versus median = 105 cells/μL and range = 27–350 cells/μL; P = .11,

Table 1. Characteristics of patients at baseline

Patient code	Age, y	PS*	KS staging†	Months‡	Kaposi's sarcoma (KS) lesions				CD4 cells/μL	Human immunodeficiency virus type 1 RNA copies/mL
					Visceral	Lymphoedema	Mucosal	Patch§		
PM	30	1	$T_1I_1S_1$	19			+	++	2	79 000
MS	45	2	$T_1I_1S_1$	47		+	+	++	4	148 000
CL	43	1	$T_1I_1S_1$	9	+		+	+++	98	67 000
SL	33	1	$T_1I_1S_1$	16	+		+	++	21	72 000
CR	47	2	$T_1I_1S_1$	8		+		+	4	315 000
CA	49	1	$T_1I_0S_1$	1		+		++	214	23 000
AO	40	2	$T_1I_0S_1$	12		+		++	212	63 000
SLu	28	1	$T_0I_1S_1$	8			+		40	37 000
ZC	33	1	$T_0I_1S_1$	3			+		32	144 000
CG	43	1	$T_0I_1S_1$	10				++	98	162 000
MA	38	1	$T_0I_1S_1$	6				+	75	1 870 000
CW	57	1	$T_0I_1S_1$	1				+	11	220 000
FM	36	1	$T_0I_0S_1$	5				+	443	2500
AR	42	0	$T_0I_0S_0$	36				+	206	29 000

*PS = performance status, determined according to Eastern Cooperative Oncology Group criteria.

†Clinical staging according to the AIDS Clinical Trial Group criteria based on tumor extent (T), severity of immunosuppression (I), and other systemic HIV-1-associated diseases (S).

‡Time from the date of KS diagnosis.

§+ = fewer than 10 patches; ++ = 10–30 patches; +++ = more than 30 patches.

Table 2. Clinical and biologic response to therapy*

Patient code	Clinical and biologic response									At last examination		
	Partial response (PR)			Complete response (CR)			Progressive disease (PD)					
	Months	CD4 cells/μL	HIV-1 RNA copies/mL	Months	CD4 cells/μL	HIV-1 RNA copies/mL	Months	CD4 cells/μL	HIV-1 RNA copies/mL	Response (months)	CD4 cells/μL	HIV-1 RNA copies/mL
PM	6	106	228 000				15	23	634 000	PD (31)	6	660 000
MS	11	27	124 000				16	51	227 000	PD (20)	81	124 000
CL	5	292	31 000	13	423	<200				CR (31)	400	<200
SL	6	101	<200	23	448	<200				CR (31)	600	<200
CR	8	119	376 000	14	234	<200				CR (17)	290	<200
CA	3	142	<200	16	247	<200				CR (24)	300	<200
AO	2	350	1000							PR (8)	520	1400
SLu	1	34	5300							PR (20)	110	7800
ZC	1	87	<200	5	148	<200				CR (27)	620	<200
CG	2	104	2300	7	196	<200				CR (21)	230	<200
MA				3	287	240				CR (10)	350	14 500
CW				2	51	<200				CR (25)	220	<200
FM				5	430	<200				CR (8)	460	<200
AR				3	276	6500				CR (30)	290	29 500

*HIV-1 = human immunodeficiency virus type 1.

Wilcoxon test), and HIV-1 RNA levels had decreased in most of the patients (median = 75 000 copies/mL and range = 23 000–315 000 versus median = 3800 copies/mL and range = 100–376 000 copies/mL; $P = .15$, Wilcoxon test), but the differences were not statistically significant. Furthermore, no statistically significant differences in the number of $CD4^+$ cells and HIV-1 RNA levels ($P = .33$ and $P = .59$, respectively, Mann–Whitley test) were observed between patients who subsequently achieved a CR and those with a PR or PD.

At the time of CR, $CD4^+$ cell counts were statistically significantly higher than baseline values (median = 262 cells/μL and range = 51–448 cells/μL versus median = 87 cells/μL and range = 4–443 cells/μL; $P = .006$, Wilcoxon test), and the HIV-1 RNA load had dropped to undetectable levels in eight of 10 subjects (median = 100 copies/mL and range = 100–6500 copies/mL versus baseline median = 108 000 copies/mL and range = 2500–1 870 000 copies/mL; $P = .004$, Wilcoxon test).

At last examination, an additional upsurge in the number of $CD4^+$ cells was observed in almost all subjects who achieved a CR or a PR; plasma HIV-1 RNA levels were undetectable in eight subjects with a CR and relatively low in two others with a CR as well as in the two patients with a PR. However, the two patients with PD had persistently high plasma HIV-1 RNA levels and CD4 cell counts below 100/μL despite a change in HAART regimen (Table 2).

Antibodies against HHV8 lytic-phase ORF65 protein and LANA were determined before HAART and at different time points during follow-up. At baseline, the patients with advanced KS showed high titers of ORF65 antibodies; during HAART, small variations with no apparent relationship to the course of disease were observed (Fig. 1, panel A). All patients with T_0 disease except two (CG and AR) showed lower ORF65 antibody titers at baseline and throughout follow-up (Fig. 1, panel B). Of interest, patient CG had extensive cutaneous involvement at study entry (Table 1); he obtained a CR, and, when last seen, his titer was considerably reduced.

LANA antibodies were detected in all patients at baseline (titer range, 200–64 000), with no difference between patients with KS in stages T_0 or T_1; small variations were observed at different time points, i.e., at the PR, CR, PD, and at last examination (data not shown).

Discussion

The clinical response rate to systemic chemotherapy for AIDS-related KS is usually low and short-lived *(15,16);* despite the use of biologic response modifiers or differentiation agents, such as interferon alfa or retinoic acid derivatives, alone or in combination with standard chemotherapy, no substantial change has emerged *(33).* More recent trials *(34–37)* have employed antiangiogenic compounds or human chorionic gonadotropin preparations in the treatment schedule; although these approaches are interesting, they need further evaluation.

In reference to HIV-1 infection, the introduction of multidrug antiretroviral regimens, based on a combination of RTIs and PIs, has greatly improved the clinical outcome, as demonstrated by a substantial decline in AIDS incidence and mortality *(18).* These potent antiretroviral agents induce a clearance of HIV-1 from the plasma and other biologic fluids, even if complete eradication is precluded by the persistence of latently infected cells. Moreover, immune responses to a variety of infectious pathogens are also restored in individuals who show an optimal virologic response to HAART, as evidenced by *in vitro* study findings *(38)* and the remarkable decrease in opportunistic infections *(18).*

HAART also appears to influence the clinical course of AIDS-related KS; partial or complete regressions were reported in KS patients *(19–24),* and our present findings are in line with these observations. In our group of 14 KS patients treated with HAART, 10 CRs and two PRs were achieved and maintained up to the last examination. We observed a substantial decrease in the plasma HIV-1 RNA load associated with a rise in the $CD4^+$ cell count in all 12 patients with clinical remission as well as consistently high levels of viremia with low $CD4^+$ cell counts in the two patients with progressive KS. Thus, a good correlation between efficacy of HAART and KS clinical response was evident. It is worth mentioning that eight of the 10 patients with a CR were never administered antitumor chemotherapy. It is also noteworthy that the addition of paclitaxel to the treatment schedule of patient MS caused a temporary shift from PD to a PR, even if the contemporaneous change in his HAART combination was not followed by a decrease in the plasma HIV-1 load.

Our findings indicate that the evolution of AIDS-related KS greatly depends on the entity of the HIV-1 burden and the en-

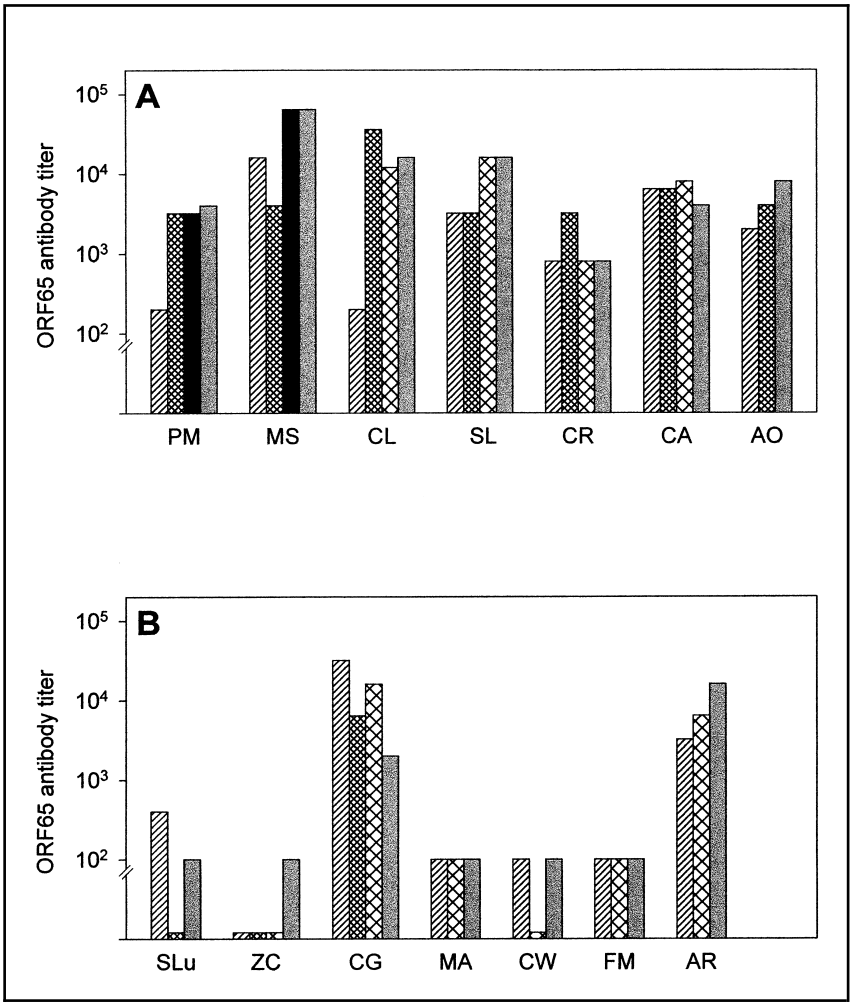

Fig. 1. Antibody titers to ORF65 protein at baseline (▨), partial response (▩), complete response (▩), progressive disease (■), and at last examination (▩ [gray]). Antibody titer was calculated as the reciprocal of the highest plasma dilution giving positive results. **Panel A:** patients with Kaposi's sarcoma (KS) in stage T_1. **Panel B:** patients with KS in stage T_0.

suing degree of immunodeficiency. In addition, previous studies on the angiogenic properties of HIV-1 Tat regulatory protein *(7)* and the activation of the inflammatory cytokine cascade are consistent with the present findings, and they further emphasize the relevant, albeit indirect, role of HIV-1 infection in KS pathogenesis *(9).* However, the possibility that some antiretroviral PIs are also endowed with an intrinsic anti-KS activity cannot be ruled out.

Following the identification of HHV8, an increasing body of evidence has pointed to an etiologic link between this virus and KS development. Like other gamma herpesviruses, i.e., herpesvirus saimiri and Epstein-Barr virus, HHV8 also seems to possess an oncogenic potential; analysis of its genomic sequences revealed a set of genes that are structurally and functionally related to cellular genes known to interfere with cell cycle control or are endowed with growth-promoting and antiapoptotic activity *(39).* Furthermore, two different viral genes, K1 and K12, produced morphologic changes and focus formation indicative of neoplastic transformation when expressed in rodent fibroblasts, and they were tumorigenic *in vivo (40,41).*

We used available first-generation serologic assays to measure plasma antibody titers to lytic (ORF65) and latency-associated nuclear (LANA) antigens in an attempt to discern an antibody trend that might be indicative of HHV8 behavior during KS evolution. The LANA antibody titer showed a variable pattern; ORF65 antibody levels in general seemed to be correlated to baseline tumor extension. However, on the basis of the present data, we cannot draw any conclusions as to whether the ORF65 antibody titers reflect the clinical evolution of KS. We expect that direct evaluation of HHV8 viremia by molecular methods would be more informative in this regard; this approach might also be useful to determine whether HHV8 expression is directly influenced by antiretroviral agents.

In conclusion, our data confirm that the HAART regimen can induce a clinical response in AIDS-related KS and provide evidence that the remission thus obtained is more prolonged than that achieved by conventional antitumor chemotherapy alone.

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NOTES

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