Hot News

Welcome to "Hot News", a section of AIDS Reviews written by the editors and invited experts which focuses on recently reported information believed to be of both impact and higher interest to the readership.

AIDS-related Lymphomas – Potentially Curable in the HAART Era

At the beginning of the HIV pandemic, most complications in AIDS patients were due to infectious agents. Following the introduction of highly active antiretroviral therapy (HAART) in 1996, survival dramatically improved and neoplastic diseases become a more frequent diagnose in HIV-positive individuals, being currently recognized in more than 40% of patients at some point of their life.

Following Kaposi's sarcoma, non-Hodgkin's lymphomas (NHL) are the most frequent malignancies in HIV-infected patients. Their incidence is 200 to 650-fold greater in the HIV setting than in the general population. Most are of B-cell origin and often present with high-grade, pathologic type and stage IV with B symptoms.

At the 13th CROI (Denver 2006), the Spanish GESIDA group presented updated data from the national register of AIDS-associated systemic lymphomas (poster 829). The main results are summarized in tables 1 and 2. Interestingly, the prognosis of NHL and the response to therapy is currently mainly dependent of tumor factors rather than influenced by HIV variables. Overall, T-cell lymphomas and Burkitt's lymphomas show the worst prognosis. Moreover, patients with an international prognosis index (IPI) ≥ 3 show a worse outcome, independent of the cell type. The IPI is a parameter directly related with survival of lymphomas and evaluates the percentage of patients that reach complete response and median disease-free survival (Table 3).

HIV-infected patients with NHL and good prognostic indicators must be treated in the same way

Table 1. Main characteristics of patients with AIDS-related NHL treated with HAART at the GESIDA register (n = 210)

Male gender	159 (75%)
Mean age (years)	39 (36-45)
IV drug users	113 (53%)
Prior AIDS diagnosis	78 (37%)
Mean CD4+ T-cells/mm^3	160 (72-263)
Pathology:	
– Diffuse large B-cell	153 (73%)
– Burkitt's and Burkitt's-like	40 (19%)
– T lymphoma	8 (4%)
Bone marrow/CNS involvement	56 (27%)/16(7%)
Ann Arbor stage IV	108 (51%)

Table 2. Therapeutic response in patients with AIDS-related NHL treated with HAART

Complete response (CR)	119/184 (64.7%)
Relapse	19 of 119 patients who achieved CR relapsed
Survival	– Overall (all patients) • median: 51 months • 5-year s urvival: 46% – Disease-free survival (patients with CR) • median not reached • 5-year survival: 81%
Condition of patients in March 2005	– Dead: 106 (50.5%) • NHL-related causes: 71 (33.8%) • AIDS-related causes: 8 (3.8%) • others: 27 (12.9%) – Alive: 91 (43.3%) – Lost to follow-up: 13 (6.25%)

Table 3. IPI in patients with AIDS-related NHL

Risk group	Complete response (%)	Disease-free survival (months)
Low: 0-1	100	> 60
Low/intermediate: 2	88	19
Intermediate/high: 3	50	17
High: 4-5	32	6.8

Variables considered are the following: elevated LDH, more than 65 years-old, Ann Arbor stages III-IV, B symptoms, and ECOG > 2.
(ECOG): 0 = normal activity; 1 = symptoms but with normal activity; 2 = exhausted < 50%; 3 = exhausted > 50%; 4 = exhausted 100%

Table 4. Main characteristics and outcome of AIDS-related HL before and after the introduction of HAART

	HAART (–) n = 21	HAART (+) n = 83	TOTAL n = 104
Male gender	20 (95%)	74 (78%)	94 (90%)
IV drug users	17 (81%)	48 (58%)	55 (62%)
Prior AIDS diagnosis	6 (27%)	30 (36%)	36 (35%)
CD4+ T-cells/mm^3	194 (87-302)	160 (96-306)	163 (87-306)
Ann Arbor stage IV	11 (52%)	40 (48%)	51 (49%)
B symptoms	18 (85%)	60 (72%)	78 (75%)
Bone marrow involvement	8 (38%)	32 (39%)	32 (39%)

as other subjects, using six cycles of CHOP (cyclophosphamide 750 mg/m^2 IV, Adriamycin® 150 mg/m^2 IV, vincristine 1.4 mg/m^2, and prednisone 100 mg IV/oral days 1-5), along with intrathecal chemotherapy (12 mg methotrexate + 30 mg cytarabine + 20 mg hydrocortisone), in an attempt to prevent CNS relapses. In addition, the use of rituximab (375 mg/m^2) associated with each cycle of CHOP is mandatory in diffuse, large, B-cell NHL CD20+, which are the most frequent lymphomas in AIDS patients. However, the results are controversial so far and rituximab must not be used in patients with CD4+ counts < 50 cells/mm^3, since fatalities due to infections are increased compared to patients only treated with CHOP. Prophylactic therapy for PCP must be implemented in all cases, irrespective of the CD4 count during the time chemotherapy is being administered.

Although Hodgkin's lymphoma (HL) is not considered an AIDS-defining condition, its incidence is significantly increased in patients with HIV infection. The incidence of HL is similar across all different risk groups (homosexual men, heterosexuals, and IV drug users). Overall, the risk for developing HL is eight to tenfold higher in HIV-positive subjects than in the general population. Patients with AIDS-related HL have different clinical and pathological features than individuals without HIV infection, including:

a) More frequent presentation (90% of cases) at advanced disease stages (Ann Arbor III and IV), while B symptoms are observed in more than 80% of cases. In contrast, these findings are seen in less than half of HL in HIV-negative patients.
b) Extranodal involvement is very frequent, and nearly all patients show bone marrow invasion. On the other hand, mediastinal involvement appears in less than 25% of patients, while it is seen more in HIV-negative patients with HL.
c) Mixed cellularity and lymphocyte depletion are the predominant pathologic variants.
d) Nearly all HL-associated AIDS patients have integrated Epstein-Barr virus, a finding recognized in only 25-57% of HL patients without HIV infection.

Treatment of HL has not changed in recent years, and standard multi-agent chemotherapy with six cycles of the well-established ABVD regimen (Adriamycin, bleomycin, vinblastine and dacarbazine) provides the best balance of effectiveness and minimal toxicity. In the general population, HL can be cured in at least 80% of patients. In HIV-infected individuals undergoing HAART, the prognosis seems to be quite similar. In another report from the Spanish GESIDA register at the last CROI (poster Q-109), the authors examined survival, therapeutic response, and prognostic factors in a large number of patients with AIDS-related HL before and after the introduction of HAART. The results are summarized in tables 4 and 5. Complete response was significantly higher in patients receiving HAART and in those with a

Table 5. Therapeutic response in AIDS-related HL before and after the introduction of HAART

Complete response (CR)	All patients: 85/98 (86.7%) – HAART (–): 14/20 (70%) – HAART (+): 71/78 (91%); p = 0.023
Relapse	11 of 85 (16%) patients with CR relapsed after a median of 14 months – HAART (–): 5/14 (37%) – HAART (+): 6/71 (8.5%)
Survival	All patients: median 110 months – HAART (–): 39 months – HAART (+): median not reached; p = 0.0089

baseline CD4 count ≥ 1000 cells/mm^3 at the time of initial diagnosis. As expected, the achievement of complete response was the only factor associated with overall survival.

In summary, since the introduction of HAART, the prognosis of AIDS-related lymphomas has improved dramatically. Factors linked to the neoplasm rather than HIV variables are the main predictors of outcome. Thus, treatment of lymphomas in HIV-infected patients on HAART should follow the same rules as in HIV-negative patients.

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Discovery of the Receptor for HHV-8, the Agent of Kaposi's Sarcoma

A critical human cell surface molecule involved in infection by human herpes virus type 8 (HHV-8), the etiologic agent of Kaposi's sarcoma (KS) and certain rare lymphomas, such as multicentric Castleman's disease and primary effusive lymphomas, has been recently discovered by researchers at the NIH (Kaleeba, et al. Science 2006;311:1921-4). The protein xCT is a major gateway that HHV-8 uses to enter human cells. Besides, it may also play a role in the development of KS as well as the other syndromes associated with the virus. The natural function of xCT in the body is to transport molecules necessary for protecting against stress into cells. When cells are stressed, they express more xCT on their surfaces. Of note, this sort of stress can be caused by HHV-8 itself, suggesting that the virus may facilitate its own infectivity and dissemination in the body by inducing a physiologic state that results in increased numbers of its own cell receptor (Fig. 1).

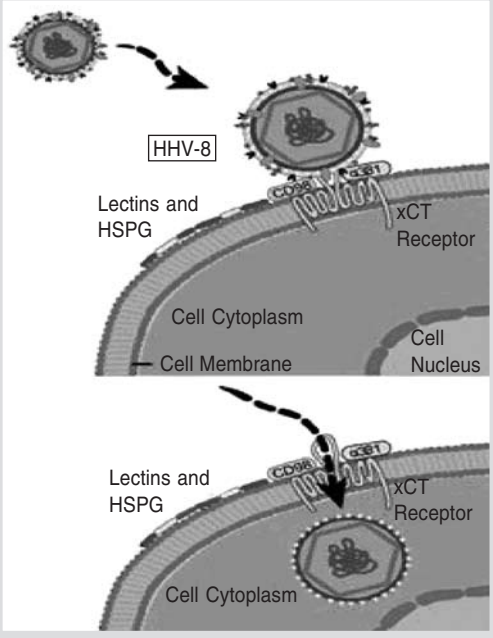

Figure 1. *Entry of HHV-8 into the cells. HSPG, heparan-sulphate proteoglycans.*

Although KS is currently less common in HIV-infected individuals than in earlier times of the AIDS pandemic, it is still the most common cancer associated with HIV infection. Prior to the HIV era, KS was an obscure disease. First identified as a multi-pigmented skin disease by a Hungarian doctor named Moritz Kaposi in 1872, it was considered to be quite rare and usually found in particular populations such as older Italian men, transplant patients, and young men in certain parts of sub-Saharan Africa. But then, at the dawn of the AIDS pandemic in the early 1980s, the small, purplish KS skin lesions began appearing on the bodies and mucosae of young American and European homosexual men, in whom they disseminated rapidly.

The discovery of the receptor for HHV-8 may lead to new approaches for treating HHV-8-associated illnesses. Moreover, it should be assessed whether levels of xCT determine disease severity, and studies made as to whether the expression of xCT on cells varies among different groups, hopefully contributing to explain why homosexual men are more at risk for KS than other risk groups.

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Outbreaks of Acute Hepatitis C Among HIV+ Homosexual Men in Europe

Outbreaks of hepatitis C among homosexual men have recently been reported in several large European cities (Berlin, London, Paris, Amsterdam). This observation is striking since HCV was not believed to be efficiently transmitted by sexual contact, as is well established for HBV or HIV. At the last CROI, held in Denver in February 2006, British investigators (Danta, et al. abstract 86) described the main characteristics of a series of 111 cases of acute hepatitis C among HIV-infected individuals in London. All occurred in male homosexuals, and HCV genotype-1 accounted for 88% of cases. Phyloge-

netic analyses of HCV sequences derived from these individuals identified multiple clusters. One involved 43 cases infected by the same HCV genotype-1a virus. In order to investigate which factors were associated with the acquisition of acute hepatitis C, the authors did a case-control study. Not surprisingly, cases had more sexual partners than controls (median number of 30 ***vs.*** 10) in the preceding 12 months. Unprotected, receptive and insertive anal intercourse, fisting, and sexual activity under the influence of drugs such as ketamine and ecstasy (generally taken nasally or orally) were all independently associated with the acquisition of acute hepatitis C. The authors concluded that better education and prevention programs are urgently needed for male homosexuals.

In another presentation at CROI, Dutch authors reported a similar outbreak of acute hepatitis C among male homosexuals in Amsterdam (Coutinho, et al. abstract 87). HCV antibodies among 1836 male homosexuals (both HIV-positive and HIV-negative) belonging to the Amsterdam cohort (followed during 1985-2003) were found in 26 cases (prevalence 1.3%). Since 2000, the authors have identified 29 cases of acute hepatitis C, highlighting the increased incidence in recent years. Of note, all but one case were documented among HIV-positive men. Two large clusters were identified, one involving 14 cases infected with HCV genotype-4 and another involving seven cases of transmission of HCV genotype-1a. Of note, these clades did not show a close similarity with HCV isolates circulating among intravenous drug users in Amsterdam, suggesting that the jump from drug users to male homosexuals has not been the cause of the recent epidemic. Because most of these cases of acute hepatitis C presented along with ulcerative sexually transmitted diseases (STD), it is possible that male homosexuals coming from regions with high HCV endemicity could have been the source of the recent spread among male homosexuals in Amsterdam. As in other studies, the Dutch authors found that rectal mucosa disruption during some sexual activities, HIV coinfection, and concomitant STD were significantly associated with the acquisition of acute hepatitis C in male homosexuals.

Up to one third of HIV-negative individuals with acute HCV infection may show spontaneous viral clearance within the first 12 weeks following initial exposure. Younger age, female sex and symptomatic acute infection have all been associated with a higher chance of spontaneous HCV recovery. Conversely, patients with HIV enter into chronic HCV infection more frequently. Therefore, early therapeutic intervention in acute HCV infection is particularly indicated in patients with HIV disease, although treatment should not be instituted before 12 weeks of estimated initial exposure, in order to discard spontaneous HCV clearance and because this delay does not seem to influence the therapeutic outcome.

Treatment of acute hepatitis C in HIV-positive patients seems to provide a lower rate of cure than in those HIV-negative, where it is almost universal using 24 weeks of treatment (Kamal, et al. Hepatology 2006;43:923-31). Since the antiviral activity of interferon may be mediated through the cytokine network, immunologic abnormalities in the HIV setting could determine the lower response seen in these patients. In a recent report, French authors (Dominguez, et al. AIDS 2006;20:1157-61) studied prospectively the efficacy and tolerability of pegylated interferon alpha and ribavirin in HIV-infected patients with acute hepatitis C. Treatment was offered to subjects with detectable HCV-RNA 12 weeks after diagnosis. Only one subject with HCV genotype-3 (out of 25 patients with acute hepatitis C) experienced spontaneous HCV clearance. Of the remaining 24 patients, only 10 out of 14 (71%) who began HCV therapy and had 24 weeks post-treatment follow-up, achieved sustained virologic response. This rate is substantially higher than in chronic hepatitis C seen in HIV-infected patients, but lower than in HIV-negative individuals with acute hepatitis C.

Patients with acute hepatitis C due to HCV genotypes-2 and 3 respond better than with genotypes-1 or 4 in both HIV-negative and HIV-positive individuals. Moreover, high ALT levels during the acute episode and rapid viral clearance (undetectable HCV load at week) predict better chances of SVR. Patient's age, CD4 count, HIV or HCV load and having symptomatic infection do not seem to influence treatment response. At this time it seems worth recommending the combination of pegylated interferon and ribavirin in HIV-positive subjects, in order to maximally ensure the attainment of HCV clearance. Following what is advised in HIV-negative persons, six months of therapy is the recommended duration of treatment of acute hepatitis C in HIV-positive individuals, irrespectively of the HCV genotype.

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