Immunodeficiency lymphoma

483 EPSTEIN-BARR VIRUS (EBV) DNA MONITORING BY QUANTITATIVE REAL-TIME POLYMERASE CHAIN REACTION IS A USEFUL SURROGATE MARKER OF DISEASE ACTIVITY IN BOTH MONOMORPHIC AND POLYMORPHIC POST TRANSPLANTATION LYMPHOPROLIFERATIVE DISEASE (PTLD)

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Background: PTLD is a rare but aggressive complication of solid organ transplantation. Epstein-Barr virus (EBV) reactivation is predictive for development of PTLD. Monitoring of EBV DNA levels post-transplant allows for early pre-emptive immuno-modulation for high-risk patients (pts), and also assists in diagnosis of PTLD in symptomatic pts. There is however a paucity of data on the utility of EBV DNA levels to follow disease activity once PTLD has been diagnosed.

Aims: To evaluate the role of EBV DNA levels as a surrogate marker of disease activity in PTLD.

Methods: Consecutive patients with newly-diagnosed PTLD at a major transplant centre were prospectively followed with serial EBV viral load monitoring using a quantitative real-time polymerase chain reaction (PCR) targeted at the conserved region of EBNA-1 gene of EBV from whole-blood samples. The tests were paired and correlated with imaging studies done at diagnosis, for assessment of response (by IWG criteria) and upon relapse of disease.

Results: From 2005-2010, a total of 11 pts with newly-diagnosed PTLD post-renal transplantation were included. The mean age of pts was 59 years. Histology was centrally reviewed for consistency according to WHO 2008 classification of PTLD. Of these, 9 pts had monomorphic PTLD (8 with diffuse large B-cell lymphoma [DLCL], 1 peripheral T-cell lymphoma [PTCL], while 2 had CD20 negative polymorphic PTLD. 8 pts with EBV-associated PTLD (based on histological staining for EBER and LMP1) had elevated EBV DNA titers at diagnosis. Among 3 pts with EBV- negative PTLD, 2 pts (DLBCL) had negative EBV DNA titers while 1 (PTCL) had detectable levels at diagnosis. Treatment which included the tapering of immune suppression, rituximab and CHOP chemotherapy was administered at the discretion of the treating physician. At a median follow-up of 8.4 months, 8 of 11 patients had achieved complete remission, and there were 3 relapse/progression events documented by CT or PET imaging. The negative predictive value of a normal EBV DNA titer with CR was 0.89, while the positive predictive value of a reappearance of an elevated EBV titer after achieving a response was 1. A diminution of EBV titers correlated with partial responses at interim staging.

Conclusion: In our patients with a positive EBV DNA at diagnosis, monitoring these levels accurately predicted clinical response for all entities of EBV-associated PTLD. Larger studies are needed to show whether this approach translates into a meaningful clinical standard.

484 AGE-RELATED EBV-ASSOCIATED LYMPHOPROLIFERATIVE DISORDER – A CLINICOPATHOLOGICAL SPECTRUM

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Background: We describe a series of age-related EBV-associated lymphoproliferative disorders (AR-EBVLPD). This spectrum of reactive hyperplasia, indolent "EBV-positive mucocutaneous ulcer" (EBVMCU) and aggressive B-cell lymphoma is underreported.

Patients and Methods: Cases were identified from files of the All Wales Lymphoma Panel and studied by immunocytochemistry, EBER in situ hybridisation and PCR for IgH/TCR clonality.

Results: 14 patients (8 male, 3 female; median age 76y, range 68-82) were classified as: 2 EBVMCUs, 4 polymorphous B-cell lymphomas (Poly-BCL) and 8 diffuse large B-cell lymphomas (DLBCL). EBVMCUs were circumscribed tongue lesions. Poly-BCL and DLBCL presented with lymphadenopathy (7), thyroid (1), stomach (1), bone marrow (1) or brain involvement (1) (stage I-IV (8%-50%)). 75% had B-symptoms. EBVMCUs and Poly-BCL showed Hodgkin-like and PTLD-like histological features, respectively. 37% of DLBCLs were of NOS type and 63% were Hodgkin-like. 79% showed non-germinal centre phenotype. 14% co-expressed CD30 and CD15. EBER was abundant in all cases. 87% (7/8) had clonal IgH rearrangements. 50% (3/6), 17% (1/6) and 33% (2/6) showed polyclonal, clonal and restricted T-cell patterns, respectively. Of 2 EBVMCUs, 1 had a complete response to interferon-α-2b. In the second, the ulcer regressed spontaneously but he died shortly after with clonally unrelated EBV-negative CNS DLBCL. Patients with Poly-BCL and DLBCL received chemotherapy with CVP (3), R-CVP (4), R-GCVP (1), R-CHOP (1), CCEP (1) and high dose methotrexate (1), combined with radiotherapy in 3 cases. 1 patient received supportive care only. 2 (17%) achieved complete remission, 6 (50%) partial remission and 4 (33%) progressed. 6 (50%) died of disease, 1 (8%) died of unrelated causes and 5 (42%) are alive (median follow up 4 months (range 2-14)).

Conclusion: Indolent EBCMCUs may respond to conservative and immunomodulatory treatment. Age-related Poly-BCL and DLBCL are aggressive lymphomas responding poorly to conventional therapy. Restricted and clonal T-cell responses suggest defective T-cell surveillance of EBV due to immunosenescence. Novel approaches including adoptive immunotherapy with EBV-specific allogeneic cytotoxic T-cells should be considered.

485 EBV POSITIVE MUCOCUTANEOUS ULCER – A NOVEL IMMUNOSUPPRESSION ASSOCIATED LYMPHOMA-LIKE ENTITY REQUIRING CONSERVATIVE MANAGEMENT

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Background: We describe a series of Epstein-Barr virus (EBV)-positive mucocutaneous ulcers (EBVMCU) associated with immunosuppression (IS) of different causes. Clinical course is indolent but historically patients have received aggressive treatments for lymphoma. Material and methods: Cases were identified from files of the All Wales Lymphoma Panel and studied by immunocytochemistry, EBER in situ hybridisation and PCR for IgH/TCR clonality.

Results: The study group comprised 8 patients (4 males, 4 females), median age 74 years (range 52- 84). 6 received IS with azathioprine, methotrexate or cyclosporin-A for ulcerative colitis (1), autoimmune hepatitis (1), rheumatoid arthritis (2) or post transplant setting (2). 2 had age-related immunosenescence. Patients presented with sharply circumscribed, solitary and localised ulcers in skin (2), oropharynx (3) and colon (3). 1 had a concomitant lung lesion. The same Hodgkin-like histological features were seen regardless of aetiology or site of presentation. The atypical B-cell blasts showed strong CD30 and EBER positivity in a background of abundant T cells. 43% (3/7) co-expressed CD15 and CD30. PCR revealed 75% (3/4) clonal IgH rearrangements with 25% (1/4) and 75% (3/4) of clonal and restricted T-cell patterns, respectively. 6 patients with iatrogenic IS were treated with reduction of IS, one having had hemicolectomy for suspected lymphoma. 1 patient in addition received chlorambucil. 2 post transplant cases also received rituximab. 5 of 6 iatrogenic cases had a complete treatment response and are alive with no disease (median follow up 8 months (range 3-24)). 1 patient showed regression of ulcer but died of unrelated causes. Of 2 age related cases, 1 had a complete response to interferon-α-2b. In the second, the ulcer regressed spontaneously but he died shortly after with clonally unrelated EBV-negative CNS DLBCL.

Conclusion: EBVMCU is a new clinicopathological entity with Hodgkin-like features and indolent clinical course, responding well to conservative management and reduction of IS in iatrogenic cases. In patients with age-related immunosenescence, immunomodulatory treatment may be beneficial. Restricted and clonal T-cell responses point to abnormal T-cell surveillance of EBV.

486 HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PATIENTS WITH LYMPHOMATOID GRANULOMATOSIS: A SURVEY OF THE LYMPHOMA WORKING PARTY OF THE EUROPEAN GROUP FOR BLOOD AND MARROW TRANSPLANTATION (EBMT)

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Introduction: Lymphomatoid granulomatosis (LG) is a rare, EBV- associated B cell lymphoproliferative disorder. Treatment that includes

corticosteroids, chemotherapy, interferon-alpha and Rituximab only shows moderate results.

Patients and Methods: To describe the results of intensive therapy and stem cell transplantation (SCT) in patients with LG, a retrospective survey was conducted among centers belonging to the EBMT. As LG is not reported as a histological entity to the EBMT database, a questionnaire was sent to the centers identifying 9 patients (8 ASCT, 1 allo-SCT). In addition, we collected follow-up data of a patient with LG, who was subject of a case report (Lemieux et al., Hematology 2002 Vol. 7 (6), pp. 355- 358). The patient cohort finally consisted of 5 males and 5 females with a median age of 41 (range 14 – 52) years. Two patients had localized disease (stage I + II), 8 patients had stage IV disease. The lungs were the most frequently involved extranodal site (8 patients).

Results: Nine patients had received ≥ 2 lines of therapy before SCT including Rituximab in 6 patients, the median time interval from diagnosis to SCT being 10 (range 5 - 52) months. All patients had active disease at the time of SCT: 7 patients had a partial remission, 2 had stable disease and 1 progressive disease (PD). Seven of the 9 ASCT patients were conditioned with the BEAM regimen, 1 patient with thiotepa, melphalan and carboplatin and the remainder with fludarabine, busulfan and cyclophosphamide. A reduced intensity-conditioning regimen (fludarabine and alkylating agent) was used prior to allo-SCT. One ASCT patient died of NRM (S. salivarius, no evidence of LG at autopsy), 1 ASCT patient committed suicide being disease-free 19 months after SCT and 1 patient died of PD 10 days post ASCT. The remaining 7 patients (6 ASCT, 1 allo-SCT) are alive and disease-free with a median follow up of 43 (range 25 – 57) months.

Conclusions: Hematopoietic SCT shows very promising results for patients with relapsed LG.

487 NON HODGKIN LYMPHOMA IN HIV PATIENTS – SINGLE INSTITUTION EXPERIENCE

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Introduction/background: The aim of this study was to evaluate characteristics of patients with HIV related lymphoma (HRL) treated in Clinical Center Serbia, Belgrade.

Material and methods: A retrospective study of 25 patients with HRL treated between January 2000 and December 2010 was conducted.

Results: Diffuse large B cell lymphoma (DLBC) was the most observed histological type (72%) while Burkitt lymphoma was diagnosed in 28% patients ($p<0.05$). The median CD4 lymphocyte count at lymphoma diagnosis was 178 cells per microliter while median LDH level was 581 U/L. Significant differences in CD 4 count and LDH level between histological subtypes of lymphoma was not observed. HAART was applied in 20 patients. Nineteen patients were died during follow up period. Overall survival of whole group of HRL was 5 months (95% CI=0.6–9.4 months). There was not statistical significant difference in survival time between patients with DLBCL and Burkitt lymphoma ($p=0.62$). Also, patients on HART regimen with Burkitt lymphoma had tendency to better survival than patients without antiviral therapy (median survival 7 vs 1 months, $p=0.082$).

Conclusions: Our results show that the reduced OS observed could be explained by poor immune status seen in our population of HIV-positive patients.

488 A FEASIBILITY STUDY OF COMBINATION CHEMOTHERAPY WITH FRACTIONATED CYCLOPHOSPHAMIDE, VINBLASTINE, ORAL ETOPOSIDE AND PREDNISOLONE IN PATIENTS WITH AIDS RELATED LYMPHOMAS (ARL): EARLY YET PROMISING RESULTS

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Aggressive biology, poor treatment tolerance, tumour regrowth make therapy of ARL a tough task. The Cochrane reviews on treatment of ARL remarked on the conspicuous absence of studies from developing world where 95% of HIV infected people live. Till date best results have been with infusional EPOCH therapy based on the premise that cancer cell resistance can be overcome by prolonged low concentration exposure to chemotherapy. However its use in developing world is limited due to need for central catheters, growth factors and risk of infections. To address these issues we tested combination of fractionated cyclophosphamide, vinblastine, etoposide and prednisolone.

Methods: Patients between 18-60 years with de-novo ARL were enrolled from September 2007 to October 2010. Poor performance status, comorbidities, ongoing infections and CNS involvement were not the exclusion criteria. All patients received antiretroviral therapy during chemotherapy. The 3weekly chemotherapy included intravenous bolus of cyclophosphamide 375 mg/m^2 and vinblastine 4 mg/m^2 on day 1 and 8, oral Etoposide 50 mg day 1to14 and Prednisolone 40 mg/m^{2}day 1 to7, with weekly 10 doses of intrathecal methotrexate. Radiation was given to extranodal and bulky disease sites. Response evaluation was done after 4 cycles and at the end of therapy. The decision rule was if >6/19 complete responses are seen it would be considered feasible.

Results: 23 patients (17 males, 6 females) with median age of 38 years (range 21 to 58 years) received proposed therapy. Significant number of patients had poor risk features like PS more than 2 (60%), stage3/4 disease (70%), extranodal sites (60%), bulky disease (65%) low albumin (52%), raised serum LDH (60%). Median CD4 count was 112/uL (range 29-496/uL). Histology was plasmablastic lymphoma (14), diffuse large B-cell (7) and immunoblastic DLBL (2). Median 6 cycles (range 2 to 8) of chemotherapy were given. Radiotherapy was given to 21 patients. Complete responses were 65% after 4 cycles, 82% at the end of chemotherapy, and 91% after radiation. At 13 months follow up median survival has not reached. 1-year PFS and OS is 85% and 81.9% respectively. Treatment was well tolerated with 1 death and 4 episodes of febrile neutropenia requiring hospitalization.

Conclusion: The proposed regimen is feasible and safe.

489 CHARACTERISTICS AND OUTCOMES OF AIDS-RELATED LYMPHOMA (ARL) PATIENTS AFTER INTRODUCTION OF HIGH ACTIVE ANTIRETROVIRAL THERAPY. EXPERIENCE OF TWO INSTITUTIONS

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Background: With the advent of highly active antiretroviral therapy (HAART), the epidemiology of AIDS-related Non Hodgkin's lymphoma (ARL) has changed, and prognosis has improved. Since early 2000's National Institute of Oncology and Radiobiology (INOR) and the Institute of Tropical Medicine ''Pedro Kouri'' (IPK) have collaborated for the treatment of HIV/AIDS-related neoplasm.

Methods: A retrospective study was made to analyze the characteristics and treatment outcomes of ARL patients, diagnosed and treated at the INOR and the IPK after HAART was introduced in the management of HIV/AIDS patients

Results: From January, 2000 to July, 2010, 82 patients were diagnosed and treated from ARL. Median age at diagnosis was 39 years. Most of the patients were diagnosed in stages III-IV (75%), 75% had age adjusted IPI intermediate-high or high and 25 % had performance status 2-3. Diffused large B-cell lymphoma was most common lymphoma subtype (55 %). Most of the patients were treated with chemotherapy using CHOP-like regimens. Median overall survival was 45.6 months. (CI 95% 35-58) and 5 years overall survival was 45%. In the multivariate analysis the only factors significantly associated with decrease in overall survival was CD4 cell under 200/mm^3 ($p< 0.01$) at diagnosis.

Conclusions: Our results did not differ from others previously reported. Introduction of more aggressive chemotherapy regimens like DA-EPOCH could improve outcomes in our patients.

490 TREATMENT OUTCOMES IN LYMPHOMA IN HIV POSITIVE PATIENTS

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Introduction: The advent of anti-retroviral treatment (ARV) has significantly improved treatment outcomes in HIV positive patients with lymphoma treated with conventional chemotherapy with a reduced incidence of infection and with response rates similar to that of non-HIV patients. We present results on a cohort of patients with HIV related lymphoma treated at a single centre over 10 years.

Materials And Methods: A retrospective analysis of all patients with known HIV infection or detection at the time of diagnosis of lymphoma was carried out to assess the incidence of histological types of lymphoma, the degree of immune suppression and viral load at diagnosis, response rates (RR) and overall survival (OS) with chemotherapy and ARV.

Results: 59 patients (Male 47, Female 12; Mean age 45.3yrs) were diagnosed with HIV and lymphoma of whom 32(54.2%) had diffuse large B cell lymphoma (DLBCL), 14(23.7%) had Hodkgins lymphoma (HL), 7(11.8%) had Burkitt's Lymphoma, 1 with primary CNS lymphoma, 2 with Follicular lymphoma, 2 with Marginal zone lymphoma and 1 with Anaplastic large cell lymphoma. 20(33.8%) patients were diagnosed with HIV at the time of presentation. The median time to diagnosis of lymphoma from HIV infection was 918 days (0-4990). At diagnosis, 26 patients were

on treatment with ARV. The mean CD4 count was 31.2%, with a mean viral load of 220124 copies (0-3,761,189). 51(86.4%) had stage 3 or 4 disease, 21(35.5%) had extranodal disease at presentation and 8(13.5%) had performance status of 3 or 4. 48(90.5%) were receiving ARV at the completion of chemotherapy. 3 patients died during treatment and 6 patients were lost to follow-up. 48(90.5%) achieved a complete remission and 45(84.9%) were alive at a median follow up of 854(0-4184) days.

Diagnosis / Treatment	Median Time to diagnosis of lymphoma (days)	Mean CD4 %	RR %	OS %
DLBCL/R-CHOP	916	15	87.5	81.2
HL/ ABVD	924	19.2	85.7	78.5
Burkitt's Lymphoma/ CODOX-M/IVAC	568	31.1	100	100

Conclusion: A high proportion of patients with lymphoma in our catchment area were found to be HIV positive at presentation, and HIV screening should become mandatory for all newly diagnosed cases of lymphoma. Patients on ARV are still at significant risk of developing lymphoma in spite of low viral copy number and high CD4 counts. ARV treatment with standard dose chemo/immunotherapy can be given with high RR and expectation of prolonged free OS.

Shared care and management plans between HIV specialists and Haematologists is crucial for this outcome.

491 LONG-TERM FOLLOW-UP OF RITUXIMAB AND INFUSIONAL CYCLOPHOSPHAMIDE, DOXORUBICIN, AND ETOPOSIDE (CDE) IN COMBINATION WITH HAART IN HIV-RELATED NON-HODGKIN'S LYMPHOMAS (NHL)

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Background: The combination of Rituximab plus chemotherapy (CT) is more effective than CT alone in the treatment of high grade NHL. Objective: To report the long-term follow-up of CDE plus Rituximab in HIV-NHL.

Methods: In June 1998, we started a phase II study using infusional CDE (Cyclophosphamide 187.5 mg/m^2/day, Doxorubicin 12.5 mg/m^2/day and Etoposide 60 mg/m^2/day) administered by continuous intravenous infusion for 4 days every 4 weeks and Rituximab 375 mg/m^2 i.v. on day 1. HAART was given concomitantly with CT.

Results: Seventy-four patients (pts) have been enrolled. The median CD4+ cell count was 161 (range 3-691) and the median Performance Status was 1 (range 0-3). Diffuse large B-cell NHL was diagnosed in 72% of pts and Burkitt in 28%. Seventy per cent of pts had advanced stage (III-IV) disease and 57% of pts had an age-adjusted international prognostic index >2. Fifty-two out of 74 pts (70%) achieved a complete remission (CR), 4/74 (5%) had a partial remission and 18 pts progressed. With a median follow-up of 61 months, only 17% of CRs have relapsed and 41/74 pts are alive. The overall survival, disease free survival and time to treatment failure (TTF) at 5 years were 56%, 81% and 52%, respectively. Four cases of secondary tumours have been observed. No case of late pulmonary or cardiac toxicity has been reported.

Conclusions: The combination of Rituximab and CDE in HIV-NHL treated concomitantly with HAART is very active. CR rate (70%) and TTF at 5 years (52%) are comparable to those observed in high grade NHL of the general population. Our data confirm that in HAART era a high proportion of HIV-NHL can be cured.

492 PHASE II STUDY OF INTRATHECAL LONG ACTING LIPOSOMAL CYTARABINE (DEPOCYTE®) IN THE PROPHYLAXIS OF LYMPHOMATOUS MENINGITIS IN HIV-RELATED NON-HODGKIN'S LYMPHOMA

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Background: Around 5% of patients (pts) with aggressive non-Hodgkin's lymphoma (NHL) develop central nervous system (CNS) progression or relapse during the course of their disease. Pts with HIV-related NHL often develop CNS progression despite the use of adequate prophylaxis. Liposomal cytarabine has shown a significant activity in lymphomatous meningitis but there are limited data in the prophylactic setting.

Methods: Since May 2006, we are running a prospective phase II study of intrathecal liposomal cytarabine (Depocyte®) at the dose of 50 mg in 48 pts with HIV-NHL with the aim to evaluate the feasibility and activity of this drug in the prevention of lymphomatous meningitis.

Results: Forty-two pts were males and the median age was 44 years (range 18-69). As far as the histological subtype of NHL, 47% of pts had a diffuse large B-cell (DLBC) NHL and 40% Burkitt NHL. Stage III-IV was diagnosed in 80% of ps and 68% of DLBC were age-adjusted IPI 2 or more. An extranodal involvement was diagnosed in 70% of pts (gastrointestinal 30%, bone 27%, spleen 10%, liver 22%, bone marrow 17%). Liposomal cytarabine was well tolerated with headache grade I to III being the most frequent side effect in only 32% of pts. Less common toxicity (all grade I) included cortical changes (4%), fever (2%), vomiting (2%), hypertension (2%), chills (2%). With a median follow up of 15.5 months only one pt (2%) with Burkitt lymphoma developed a combined systemic and meningeal relapse. Moreover, in our experience previously the present study, we used methotrexate as practical use in 426 HIV-NHL with a meningeal progression or relapse of 14% (p=0.09). The use of a liposomal formulation allowed to significantly reducing the number of lumbar injections in comparison to the standard schedules (approximately of 50%) with an improvement of quality of life of pts and with a reduction of professional exposure risk for health care staff.

Conclusions: In this first prospective study on prophylaxis of lymphomatous meningitis in HIV-NHL reported in the literature, liposomal cytarabine seems safe and active and it reduces of approximately 50% the number of lumbar punctures and exposure risk for health staff as well.

493 HODGKIN'S DISEASE AND HIV INFECTION (HD-HIV): PROGNOSTIC FACTORS IN 596 PATIENTS (PTS) WITHIN THE EUROPEAN GROUP FOR THE STUDY OF HIV AND TUMOURS (GECAT)

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Background: Hodgkin's disease (HD) is the most common non-AIDS defining tumour diagnosed in HIV setting. The introduction of highly active antiretroviral therapy (HAART) has opened a new prospective in the treatment of pts with HD-HIV as the better control of the underlying HIV infection allows the use of more aggressive chemotherapy regimens, including high dose chemotherapy. However, up to now prognostic factors on overall survival (OS) or time to treatment failure (TTF) have not been identified yet.

Methods: in order to identify prognostic factors, we analyze data on 596 pts with HD-HIV diagnosed and treated in 90 different Institution from 6 European countries from October 1983 to March 2010. All factors were analyzed for OS and TTF.

Results: 86% of pts were male and the median CD4 cell count was 224/dl (range 3-1274); 52% of pts had mixed cellularity subtype, stages III-IV were diagnosed in 72% of cases and 55% of pts had extranodal involvement (bone marrow 35%, spleen 21%, liver 14%). Table 1 summarized the results of multivariate analysis.

Factors	Overall Survival		Time to Treatment Failure	
IPS $\leq$ 2	1		1	
IPS $>$ 2	2.33 (1.61-3.39)	p<0.0001	1.57 (1.09-2.26)	p=0.02
CD4 $\geq$ 200	1		1	
CD4 $<$ 200	1.63 (1.16-2.29)	p=0.005>	1.43 (1.02-2.01)>	p=0.04
European Score				
0	1		1	
1	2.06 (1.40 - 3.02)		1.64 (1.17 - 2.30)	
2	3.08 (2.13 - 4.45)>	p<0.001>	2.31 (1.66 - 3.20)	p<0.001

Conclusion: We identified a new "European Score" for HD-HIV able to predict different outcomes in these patients. This score should be considered for future prospective studies.