Proceedings of the 1st International Symposium of Oncovirology (20/03/2003) at CREAIDS (Centro de Referência Estadual de AIDS), Salvador, Bahia, Brazil

Novel Therapy for Viral Lymphomas

William Harrington

The first clinical studies of AZT in viral lymphomas were conducted in Human T Lymphotropic Virus Type I Adult T Cell Leukemia (HTLV-I ATLL). Two independent groups reported in the New England Journal of Medicine that AZT and Interferon alpha (IFN-α) exhibited potent activity in ATLL. Subsequently, we demonstrated activity of high dose AZT in both AIDS related Epstein Barr Virus (EBV) positive Burkitt's Lymphoma (BL) and primary central nervous system lymphoma (AIDS PCNSL), which led to a trial in the AIDS Malignancies Consortium (AMC). A renal transplant patient followed at Ohio State University developed EBV+ PCNSL and entered sustained (3 years) complete remission after receiving intravenous (IV) AZT and ganciclovir (GCV). This report was recently published in Cancer Research. We have opened a protocol that employs IV AZT and IFN-α for human herpes virus type 8 (HHV-8) associated primary infusion lymphoma (PEL). The first, and only patient treated so far, entered complete remission in only 5 days and remains well 18 months later. Study of the primary tumor cells derived from this patient demonstrated that AZT blocked nuclear translocation of NF-kb and potentiated the pro-apoptotic effect of IFN-α (which induces another death receptor ligand, TRAIL). These data were recently published in Blood. The apoptotic effect of AZT in PEL or EBV+ BL was completely abrogated by the addition of thymidine. Interestingly, chemotherapeutic agents commonly used to treat these lymphomas, etoposide and doxarubicin, actually enhanced NF-kb activity. This is further evidence that AZT induces a specific apoptotic mechanism. These clinical and laboratory data strongly indicate that AZT exhibits potent anti-tumor activity specific in certain viral mediated lymphomas. NF-kb inhibitors represent a new form of therapy for these tumors.

Pathology of HIV Related Lymphomas

Helenemarie Schaer Barbosa

The incidence of non-Hodgkin's lymphomas (NHL) is increased from 60 to 200 fold in HIV-positive patients. The incidence of Hodgkin's lymphoma is increased eight fold. Lymphoma is an AIDS defining disease in 3% to 5% of HIV^+ patients. The use of aggressive multiple anti-viral therapy and prolonged survival of infected patients may change these facts but it is still too early to evaluate their impact. Lymphomas in HIV^+ patients have a tendency to be aggressive, disseminated and extra-nodal. Pathogenic mechanisms are diverse and include prolonged antigenic stimulation, genetic alterations, cytokine deregulation and the role of associated viruses like EBV and Kaposi's Sarcoma Herpes Virus (KSHV). In HIV^+ patients most lymphomas are B-cell, mainly Burkitt's lymphoma or diffuse large B cell lymphoma. There are two quite rare types that practically occur only in HIV^+ patients: primary effusion lymphoma (PEL) associated with KSHV and plasmablastic lymphoma of the oral cavity, which is EBV^+ in around 50% of the cases and KSHV-negative. In Salvador, the majority of lymphomas in HIV^+ patients are diffuse large B-cell. Burkitt's lymphoma was infrequent in a study from cases of HUPES and Hosp. Aristides Maltez. In a study of autopsy of AIDS patients from HUPES 5% presented with diffuse large B-cell lymphoma of the central nervous system. It is possible that HIV associated lymphomas have been underdiagnosed in Salvador since the number of diagnosed cases is low, inferior to the expected number. Other types of B-cell lymphoma have been reported in association with HIV like MALT lymphoma. A few T-cell lymphomas have been described in HIV^+ patients but it is probably a fortuitous association. The diagnosis of Hodgkin's lymphoma

is sometimes difficult due to different histological characteristics with numerous atypical cells, few lymphocytes and frequent extra-nodal involvement. The importance of serology for HIV in all lymphoma patients is reinforced in view of the special characteristics of many HIV-associated lymphomas.

HHV-8 and Kaposi's Sarcoma

Charles Wood

A number of countries found in a contiguous belt stretching from Uganda south to Botswana and South Africa, have HIV prevalence rates far above others. In this area, the proportion of the population in urban areas that is HIV infected (15 to 44 year age group) ranges from 15% to 30%, with distinct urban/rural differences. The association of malignancies, such as non-Hodgkin's lymphoma and Kaposi's sarcoma (KS) has been recognized since the beginning of the HIV epidemic and KS is the neoplasm most commonly found in people infected with HIV. This neoplasm is responsible for extensive morbidity in these individuals and may be associated with increased mortality.

Over the past decade KS has emerged as a significant childhood tumor constituting about 20% of all solid tumors in children in Africa. The cause of KS is not known, but epidemiological evidence suggests that an infectious agent may be involved. A novel Human Herpesvirus-8 (HHV-8) or Kaposi's Sarcoma associated Herpesvirus (KSHV) is consistently being detected in biopsy samples from patients with all types of KS, highly suggesting a causal role of HHV-8 in the pathogenesis of KS.

To study HHV-8 infection in Africa and the effects of HIV-1 infection on HHV-8, we have been studying a cohort in Zambia for HHV-8 and HIV-1 infection. A total 3,161mother/infant pairs that were recruited into the study since delivery were tested for antibodies against HIV-1 and HHV-8. The 3,136 mothers whose specimens were available for testing were divided into four groups based on their serostatus. Group 1 individuals were dually infected by both HIV-1 and HHV-8, Group 2 were infected by HHV-8 alone, Group 3 were infected by HIV-1 alone, and Group 4 individuals were not infected with either virus. Among the 3,136 individuals tested, we found that 1,259 (40%) were infected by HHV-8, 953 (30%) were infected by HIV-1, and 442 (14%) were dually infected by both viruses. These results were similar to our earlier study with a smaller group of non-pregnant women, with an HHV-8 seroprevalence of 40% and an HIV-1 seroprevalence rate of about 30%, suggesting that there is a very high seroprevalence for both HHV-8 and HIV-1 in our studied population. We also found that HHV-8 positive individuals have a much higher HIV-1 seroprevalence rate (46% vs. 37%), with a p value of 0.0001. Our results strongly suggest that there is an association between HIV-1 and HHV-8 infections; infection by one virus predisposes an individual to be more susceptible to infection by the other virus.

The potential routes of HHV-8 transmission remain undefined. The routes may be different among different populations and in different parts of the world. Both sexual and non-sexual routes have been suggested. Epidemiological evidence suggests that the virus is largely transmitted sexually in Northern America and Northern European countries. Besides the potential role of sexual contact in HHV-8 transmission, it is likely that non-sexual routes can transmit HHV-8 as well. In developing countries, HHV-8 infection is widespread in men, women, and in children. This suggests that mother to child (MTC) and horizontal, non-sexual transmission may be the predominant modes of transmission in these countries. To determine whether HHV-8 infection can be acquired perinatally, we have completed and recently published the PCR analysis of maternal and infant DNA from a subpopulation of the cohort. In a group of 89 randomly selected HHV-8 seropositive mothers, we found 13 mothers and two of their infants had detectable HHV-8 DNA at birth. These results demonstrate perinatal transmission of HHV-8 and suggest the infants could have been infected in utero. To confirm these results and

determine whether the HHV-8 infected infants acquired their infection prepartum, peripartum or postpartum, we then focused on children that were found to have seroconverted by 12 months after birth. DNA was extracted from infant PBMC collected at birth, and HHV-8 PCR was carried out to determine the number of seropositive infants infected in utero. Of 34 infant seroconverters tested, 11 were found to be HHV-8 PCR positive with at least two sets of primers. Our findings suggest that in utero infection by HHV-8 could occur but given the high seroprevalence rates in young children in Zambian suggest that horizontal transmission of HHV-8 is the predominant route of transmission of this virus within this group.

Epidemiology of AIDS-related Malignancies

Eduardo M. Netto

Several neoplasias since the beginning of the AIDS epidemic have been identified as being associated with HIV infection. The most striking tumor was Kaposi's Sarcoma, which was the disease most identified with the first cases of HIV. In 1998, Goedert et al., (Lancet 1998;351:1833-9) reviewed cases reported in the U.S. and included several other possibilities along with the already known pathologies such as Non-Hodgkin Lymphoma, Hodgkin's disease, some leukemia, primary brain lymphoma, seminoma and germinoma, but the main finding was that HIV infection is not associated with all neoplasias. Comments on Kaposi's sarcoma (KS); HIV is unlikely to be the sole causative factor, rare in the West, common in Africa, more common in gay men than HIV groups infected by non-sexual routes, Kaposi's sarcoma Herpes virus (HHV-8) is found in all patients with KS (Chang. Science 1994;266:1865-9). Anti-LANA is highly specific and low sensitivity; PCR has low sensitivity (Whitby. Lancet 1995;364:799-802 & Moore, AIDS 1996;10:175-80). Non-Hodgkin's lymphoma: With AIDS, the risk of NHL increases with longer survival (Biggar. Int J Cancer 1996;68:754-58); EBV is linked to roughly half of all cases of systemic AIDS-NHL; EBV is linked to nearly all cases non and AIDS-associated NHL of the brain.

AIDS-related malignancies in Bahia: Review of 55,315 biopsies (1991-1995): 3 different general hospitals; 3821 malignancies diagnosed; 95 patients had a diagnosis of AIDS: 60 (63%) KS (OR: 6.4); 18 (19%) NHL (OR: 9.7); and 10 other different tumors.

Up to Nov/2002, 190 cases of KS were reported in Bahia out of 4577 (4.2%) AIDS cases notified to the AIDS State coordination program. The percentage of cases is decreasing from 6.6% in 1986-8 to 2.1% in 2000-2. Males have almost 3 times more chance to be diagnosed with KS than females; Homosexuals and bisexuals have 2.5 times more chance than heterosexuals; Non-IV drug users have 2 times more chance. 43 cases of Non-Hodgkin lymphoma were reported in Bahia out of 4383 (9.8 per 1000) AIDS cases notified to the AIDS State coordination program. The percentage of cases seems not to be decreasing with the development of the AIDS epidemic in Bahia. Gender is not associated as being IVDU or not. Sexual preferences could not be calculated. Primary Brain lymphoma was reported in 21 cases in Bahia out of 3799 reported (5.5 per 1000). It seems to be decreasing from 7.5 in 1988-90 to 3.6 per 1000 in 2000-2. It was not associated with gender, sexual preference, being IVDU or literacy.

Hepatic Lesions Associated to HIV

Luciano Fonseca

Approximately two-thirds of AIDS patients present with hepatomegaly and abnormalities in the biochemical tests of hepatic function. Apparently these changes do not directly depend upon HIV, but are the result of sole or

combined viral, bacterial, fungal and protozoal infections, adverse drug reactions and neoplasias. We present here the efficiency of hepatic biopsy in clarifying the clinical situation of AIDS patients. One hundred and thirty biopsies were analyzed, all from AIDS patients presenting with at least hepatomegaly and fever of unknown etiology. Besides light and electron microscopic study, morphometry and micro-analytic techniques were also employed. Successful histological diagnoses were achieved in 46 (35.4%) cases, including 22 (16.9%) cases of mycobacterial infections, 9 (6.9%) cases of *Histoplasma capsulatum* infection, 4 (3.1%) cases of *Schistosoma mansoni* infection, 1 (0.8%) case of *Cryptococcus neoformans* infection, 1 (0.8%) case of visceral leishmaniasis, 1 (0.8%) case of Kaposi's sarcoma and 7 (5.4%) cases of granulomatous inflammation with no microorganisms identified. Granulomatous inflammation was the most frequent inflammatory change observed, being present in 29 (22.3%) of the cases. No correlation was observed between serum aminotransferase level and the presence of hepatic changes that required alteration of current therapy for the patient. No significant histological or ultrastructural changes were observed in the hepatic sinusoids. Based on observed data it was concluded that: 1. In AIDS patients presenting with hepatomegaly and prolonged fever of unknown etiology, the result of needle biopsy of the liver can give important clues for the diagnosis of infectious and neoplastic processes. 2. In variance with what occurs in other geographic areas, Mycobacterial, Mycological (Histoplasma capsulatum) and Protozoal (Leishmania) infections are prevalent in our area, and usually represent unsuspected conditions detected by liver biopsy. 3. In the present material, granulomas represented the main histological response to infectious agents, even in those patients with low levels of CD_4^+ lymphocytes in the peripheral blood. 4. Mobilization of sinusoidal cells appeared as an important reaction pattern to the presence of opportunistic infections within the liver. 5. Eletron microscopic analysis of the sinusoidal changes usually failed to reveal significant alterations, others than those detected by light microscopy. 6. No statistically significant direct correlation between serum levels of aminotranferases and hepatic changes, especially those of infectious nature, was disclosed. 7. There was evident correlation between intravenous drug abuse and deposition of a black pigment in hepatic tissue. It is suggested that the presence of the black pigment can even be used as a "Marker" for intravenous drug addiction. 8. Infectious hepatic changes were much more prevalent when compared with neoplastic changes, which were rarely seen in the present material.

Viral Host Response and Intepherom

Glen Barber

Our laboratory has recently shown that vesicular stomatitis virus, VSV, a relatively non-pathogenic, negative-stranded RNA virus, can selectively induce the cytolysis of malignant cells, but not normal cells, through the induction of apoptotic cell death. VSV appears able to selectively replicate in transformed cells since these hosts exhibit the hallmarks of a flawed interferon (IFN) system, which is essential for preventing VSV replication. VSV was found to cause significant tumor regression when administered at sites distal from the tumor, when delivered intravenously, or against syngeneic tumors in immunocompetent hosts. However, the simple genetic constitution of VSV, lack of any known transforming properties, well studied immunobiology and the ability to genetically manipulate this virus affords an ideal opportunity to further enhance the oncolytic potential of this generally innocuous organism. To examine this possibility, we attempted to construct recombinant VSVs that carried either the cytokines IL-4, IL-12 or the Type I or II interferons. Significantly, we determined that such viruses were not only viable but synthesized their heterologous products to extremely high levels. In addition, all engineered viruses exhibited greatly increased attenuation, more potent oncolytic activity against metastatic disease in immunocompetent animals than the wild-type virus and were able to stimulate specific anti-tumor CTL responses. Collectively, our data demonstrates that VSV expressing immunodulatory genes could provide a promising and exciting approach to cancer therapy.

Pathobiology of Viral Lymphomas Pathogenesis of Kaposi's Sarcoma-Associated Herpesvirus (KSHV/HHV-8)

Ethel Cesarman

Kaposis's sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus 8 (HHV-8), is a γ-herpesvirus that is most closely related in humans to Epstein Barr virus (EBV/HHV-4). Not only has infection been shown to precede and predict the development of Kaposi's sarcoma in HIV-infected patients, but also viral DNA has been found in Kaposi's lesions of all types and stages. Furthermore, KSHV is a lymphotropic virus and is present in nearly all cases of primary effusion lymphoma (PEL), a rare malignancy disproportionately affecting HIV-infected individuals. KSHV is also thought to dramatically affect the incidence, type and course of multicentric Castleman's disease, another lymphoproliferative disorder over-represented in individuals with AIDS. While KSHV is clearly causally associated with these diseases, infection is not sufficient for their development. Molecular and immunohistochemical methods for identifying KSHV have been developed, and these are useful for the diagnosis of diseases caused by this virus. KSHV is a lymphotrophic and angiotropic herpesvirus, whose genome encodes many potentially oncogenic products, including several apparently pirated from the human genome. These include various chemokines, cell cycle regulatory proteins, and survival and proliferation factors. A basic understanding of the pattern of expression and functional properties of these viral products is important for the appreciation of the complexity of KS and lymphoma pathogenesis. While in Kaposi's sarcomas lytic genes, in particular vGPCR seem to be critical for pathogenesis, in primary effusion lymphomas latently expressed genes like vFLIP are most important. Knowledge is rapidly accumulating concerning the viral pathogenic mechanisms and host co-factors necessary for KSHV-mediated disease.

Lymphomas Related to Epstein-Barr Virus

William Harrington

The pathogenesis of aggressive non-Hodgkin's lymphoma (NHL) is quite variable. In developing nations the majority of these tumors are associated with Epstein Barr Virus (EBV). Although these NHLs share some histologic and molecular features with those that occur in the United States (U.S.) there are clear distinctions. In the U.S., a minority of Burkitt's (BL) or small non-cleaved cell lymphomas is associated with EBV. This is true for both Acquired Immunodeficiency Syndrome (AIDS) associated and sporadic BL. The site of initial presentation also varies among endemic (the African variant), sporadic and AIDS associated BL. In Africa the initial presentation is usually as a mandibular tumor whereas in sporadic BL the most common site is the abdomen. AIDS related BL usually presents as disseminated disease with concomitant tumor lysis. At the molecular level, there are discrete differences between the breakpoints within the myc oncogene or flanking sequences that may influence transcriptional activity among the various forms of BL. BLs are generally susceptible to chemotherapy however, all variants are recognized as aggressive tumors with a high mitotic index. AIDS associated BL carries a particularly poor prognosis. Recent studies have indicated that a substantial genetic heterogeneity in EBV gene expression exists among endemic BLs. There are also significant differences in the pathogenesis, response to therapy and epidemiology between BLs that occur in affluent versus poor nations. Cyclophosphamide based regimens result in cure rates in endemic BL approaching 60 to 80 percent but relapses are fairly common and most often due to incomplete therapy. Alkylating agents also carry a significant risk of causing secondary refractory myeloid leukemia. Certain inherent molecular features may render NHLs

susceptible or resistant to apoptotic stimuli. Myc overexpression exerts both a transcriptional activation and pro-apoptotic effect and BLs rarely expresses high levels of Bcl-2. Apoptosis occurs in BL despite the presence of p53 mutations that inhibit transactivation of the cell cycle inhibitor p21. In addition, some EBV positive NHLs express high levels of the antiapoptotic Latent Membrane Protein (LMP-1). An important function of LMP-1 is to enforce latency through activation of the transcription factor complex NF-kb. NF-kb refers to a group of proteins involved in inflammatory, immune, pro- and anti-apoptotic cellular responses. NF-kb mediated transactivation occurs through assembly of monomeric subunits at kb binding sites. This binding results in the formation of active homo- and hetero-dimers, which have distinct biological functions. Inhibitor of Kappa b (Ikb) segregates NF-kb in the cytoplasm preventing entry to the nucleus. Upon a variety of stimuli, including cytokines and viral infection, Ikb is phosphorylated by the Ikb kinase complex (IKK) and degraded via the ubiquitin proteosome pathway, allowing for nuclear localization and DNA binding. It is clear that constitutive activation of NF-kb is an important anti-apoptotic mechanism in many types of cancer. Constitutive NF-kb nuclear activity has recently been shown to be a characteristic of activated B cell lymphomas that carry a poor prognosis. Several investigators have demonstrated recently that inhibition of NF-kb in gamma herpes virus associated lymphomas results in induction of apoptosis.

We have previously demonstrated that some gamma herpes virus lymphomas are markedly susceptible to certain antiviral agents. We have found that the prototype antiretroviral thymidine analogue Azidothymidine (AZT) induces apoptosis in EBV positive BL yet is totally inactive in EBV negative BL. We have also found that EBV viral thymidine kinase (TK) is expressed at a basal level in EBV+ BL lines. AZT, rapidly phosphorylated to AZT monophosphate (AZT-MP) in EBV+ BL lines (to levels significantly higher than those seen in EBV- cells), is a potent inhibitor of IKK thereby blocking NF-kb nuclear localization. This effect is not seen with other antivirals such as ddI or ddC. The lack of LMP-1 in EBV+ BL might allow for more facile disruption of NF-kb and subsequent activation of viral gene expression, an event that would also result in apoptosis. Conversely elevated LMP-1 might exert a powerful anti-apoptotic effect in EBV+ NHLs. Investigators have demonstrated that a variety of stimuli including ionizing radiation, chemotherapy, and butyrate activate the lytic cycle of EBV. The unique feature of AZT mediated apoptosis is that the stimulus to activate the virus from latency is not due to dangerous cytotoxic agents but an antiviral that has demonstrated anti-EBV (and HIV) activity. Since blockade of NF-kb activates the lytic program of EBV, phosphorylation of AZT should be enhanced by viral thymidine kinase. This approach exploits the presence of the herpes virus and is a form of simplified, effective gene therapy applicable in impoverished settings where EBV lymphomas are prevalent. This would also avoid potential side effects caused by non-specific inhibitors of NF-kb. A therapy that limits exposure to powerful immunosuppressives like cyclophosphamide and alkylating agents and abbreviates treatment regimens would be an important advance. By studying primary high grade NHLs from an area heavily impacted by HIV and EBV we hope to start to define important functional characteristics of these tumors that can eventually lead to targeted pro-apoptotic therapies.

HPV and HIV Co-infection

José Eduardo Levi

The status of the immune system is considered to be a crucial factor in Human Papillomaviruses (HPV) infections, and may determine the development of persistence after primary infection, which has emerged in several studies as an important risk factor for cervical neoplasia. HPV-associated malignancies occur at increased rates in HIV-infected persons and HPV DNA is commonly detected in the genital mucosa of

HIV-infected women. The prevalence of infection is generally much higher than in control groups comprising seronegative women of similar sociodemographic characteristics. This may be explained by an HIV-impaired immune system, which permits a high HPV viral load and persistent HPV infection and therefore, an increased risk for the development of cervical neoplasia. In addition, individuals practicing unprotected sexual activities have a combined risk to be infected by HIV and HPV since these viruses may share a common mode of acquisition. A group of 208 HIV-infected women in Brazil was studied for the presence of human papillomavirus using the general SPF_{10} PCR primer set. Virtually all (98%) women were found positive for HPV-DNA. Genotyping by the reverse hybridization line probe assay (HPV-LiPA) revealed a high prevalence of multiple genotypes (78.9% of the cases), with an average of 3.1 genotypes per patients (range 1-10 genotypes). HPV 6 was the most prevalent genotype and was observed in 80 (39.2%) patients, followed by types 51 (31.9%), 11 (26.0%), 18 (24.0%) and 16 (22.5%). Twenty-two (10.5%) patients showed normal (Pap I) cytology, 149 (71.6%) patients had inflammation (Pap II), and 28 patients (13.4%) had a Pap III score. The prevalence of high-risk genotypes increased with the cytological classification. There were no significant associations between the number of HPV genotypes detected and the cytological classification, the HIV viral load, and the CD_4 count in these patients. In conclusion, the highly sensitive SPF_{10} LiPA system shows that a very high proportion of HIV-infected women in Brazil are infected with HPV and often contain multiple HPV genotypes.

Care of Patients With AIDS Related Lymphomas (Miami/Bahia)

William Harrington and Glória Bomfim

In the Oncovirologic Clinic of the University Hospital at the Federal University of Bahia, patients receive multidisciplinary care, which includes hematologists, infectologists, surgeons, pathologists, clinical pathologists, nurses and social workers. Patients undergo a standard clinical examination, laboratory tests including viral serology screening, abdominal, thoracic and cranial CT, which determine the Ann Arbor Staging. Central Nervous System involvement is investigated for AIDS-Lymphoma patients. Not available in the clinic, but offered by the hospital structure are advanced laboratory services that perform flow cytometric analysis, bone marrow immunophenotyping, immunogenetics laboratory for HLA typing and an advanced imaging center. Chemotherapy is performed in the Oncovirologic clinic, which has 5 armchairs for the Day-Hospital. If necessary, 12 beds are available for in-patient treatment. Treatment protocols are based on standard regimens, such as CHOP and CHOP-like regimens. Patients are kept or started on HAART therapy. For those patients with highly aggressive lymphomas related to HIV (such as Burkitt's Lymphoma) a special intensive treatment, including high dose chemotherapy (such as methothrexate and Cytarabin) is given.

Co-Infections in Bahia (TB-HIV)

Diana Sampaio

I will present a summary of the papers that our group published in the field of TB/HIV (Campos-Neto A., et al. Tuberculosis 2001 81:353-8). Evaluation of DPPD, a single recombinant *M. tuberculosis* protein as an alternative antigen for the mantoux test. This paper demonstrates that a novel antigen, derived from *M. tuberculosis* (DPPD), produces a bimodal histogram of skin reaction size compared to the standard PPD, which produces a skewed histogram. Because the DPPD gene is not present in non-tuberculous bacilli, these results suggest that this molecule

can be an additional tool for a more specific diagnosis of tuberculosis (Efficacy of Efavirenz 600 mg dose in the ARV therapy regimen for HIV patients receiving Rifampicin in the treatment of tuberculosis. Pedral-Sampaio D.B., et al. 10th Conference on Retroviruses and Opportunistic Infectious). The conclusion is that Efavirenz 600 mg daily is safe and efficacious for use in patients with HIV/TB that includes a Rifampin containing regimen (Use of standard therapy for tuberculosis is associated with increased adverse reactions in patients with HIV. Pedral-Sampaio D.B., et al. Braz J Infect Dis 1997;1:123-30). The frequency of adverse reactions in HIV positive with active tuberculosis is high and poor monitoring could have potentially serious consequences, especially in the first month of therapy. (Epidemiology profile of atypical mycobacteria at Bahia State/Brazil. Pedral-Sampaio D., et al. 38th Annual Meeting of the Infectious Diseases Society of America. New Orleans. Sept. 70-10, 2000). The prevalence of atypical mycobacteria in Bahia is rapidly increasing particularly with high numbers of *M. fortuitum* and *M. kansasii* and *M. avium* (Evaluation of the PCR-Amplicor *Mycobacterium tuberculosis* (TB) in the diagnosis of Pulmonary Tuberculosis (Santos M.M.A., et al. 38th Interscience Conference on Antimicrobial Agents and Chemotherapy. Sept 1998, San Diego). We found that TB-PCR method is as sensitive as the culture method and is significantly higher than the AFB direct smear. It is a rapid and easy test to confirm the diagnosis of pulmonary tuberculosis in patients with negative AFB direct smear examination (Use of GM-CSF in pulmonary tuberculosis patients: preliminary results of a randomized clinical trial. Pedral-Sampaio D.B., et al. 38th Annual Meeting of the Infectious Diseases Society of America. New Orleans. Sept. 70-10, 2000). Summary: GM-CSF did not show toxicity in patients with pulmonary tuberculosis and did not yield a higher rate of cure or time to cure at the dose of 125 mg per square meter.

Co-infections in Bahia (HPV-HIV)

Conceição Queiróz

Cervical squamous carcinoma is the second cause of death due to cancer in women in the world and the first cause of death in Brazil. Cervical squamous carcinoma develops from well-defined pre-neoplastic lesions: low- and high-grade intra-epithelial lesions. Early detection and treatment can prevent the progress of the disease. Epidemiological and molecular studies show that HPV plays a central role in cervical carcinogenesis, however other co-factors such as HIV co-infection are also necessary. More than 100 types of HPV had already been identified, of these, 30 types are related to genital infections and of these 10 types are oncogenic (18, 31, 33, 35, 45, 51, 52, 58, and 59) and involved in more than 95% of cervical cancers.

In a study at the Gynecology service from 1997 to February of 2000 with 110 HIV positive patients from UDAI-HUPES, it was found that 43% had atypical cytologies (31.4% low-grade intra-epithelial lesions (LIE) and 8.1% high-grade LIE). Compared to the general gynecology outpatient clinic, low- and high-grade intra-epithelial lesions rates were respectively 1.4% and 0.6%. These injuries tended to be more serious in women with low CD_4 cell counts. In a previous study, from the same service, an inverse correlation between CD_4 cell counts and presence of cytological abnormalities was found ($p<0.02$). In a recent study, it was observed that all 20 UDAI-HUPES HIV infected patients were also positive for HPV-DNA using PCR technique. Of these 20 patients, 12 had only one HPV type, four had two types, two had 3 types, and two had 5 different HPV types. These results were compared with HIV negative patients and we concluded that the HIV positive patients had infections with higher number of types of HPV than those who were HIV negative. In conclusion, HIV positive patients with precursory injuries of cervical cancer have a lower regression rate, higher persistence and progression, are more refractory to treatment, and relapse more frequently. In addition these tumors needs closer monitoring and more aggressive intervention.

Co-Infections in Bahia (HIV-HTLV)

Carlos Brites

The human retroviruses HIV and HTLV present with different biological behavior. However, they share the same routes of infection, and this makes co-infection by both agents an often-observed phenomenon.

In Bahia, according to some population-based studies, the prevalence of HTLV infection among the general population is around 2%. However, in patients infected by HIV, the prevalence of HTLV co-infection reaches 15% to 20%. It has been demonstrated that co-infection may negatively impact the clinical course of the diseases caused by both agents. Patients co-infected may present with artificially high CD_4 counts, and conversely, co-infected patients may be at increased risk of developing myelopathy.

In Bahia, we evaluated the survival time for patients infected only by HIV-1, compared with those co-infected by HTLV. The survival time was significant shorter for co-infected patients. The major risk factor for co-infection was the use of intravenous drugs and co-infection was more frequent among women than men.

Other retrospective case-control studies showed co-infected patients had higher CD_4 and absolute lymphocyte counts only when they were symptomatic. Asymptomatic patients had similar counts for these cells as those with HIV infection alone. As a consequence, there was a lower chance of co-infected patients being treated with antiretrovirals, compared with single-infected patients with a similar clinical picture.

Recently, another study demonstrated co-infection could increase the severity of scabies. All cases presenting with Norwegian scabies were positive for HTLV antibodies and 85% of them were co-infected by HIV. Among patients with non-crustous, severe forms of scabies (>80% body surface affected), there was also a significant association with HTLV infection.

These results indicate that co-infection by HIV/HTLV is highly prevalent in Bahia and can modify the course of HIV infection.

Co-Infections in Bahia (HCV-HIV)

Nanci Silva

HCV is a worldwide public health problem. It is the main cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma. Today in the United States, HCV is the main cause for liver transplant. Thirty percent of HIV positive patients are co-infected with HCV, and this rate is higher among hemophiliacs (60% to 90% are doubly infected) and intravenous drugs users (50% to 90%). With the introduction of HAART, there was a large reduction of opportunist infections and an increase in the lifespan of HIV patients. In this context HCV appeared as an important cause of mortality in HIV patients. Like the HIV virus, HCV presents with a high replication rate and genetic variability, having the capacity to decrease the host's immune response. HIV co-infection is an important co-factor in the progression of the illness caused by HCV. HIV infection is associated with higher levels of HCV-RNA and leads to faster progression of hepatic disease.

HIV co-infection is a risk factor for rapid development of cirrhosis; moreover, the illness progression rate by HCV seems to be increased when CD_4 counts decline. So, HCV is considered an opportunist pathogen; since the frequency is higher in HIV patients, the disease's severity is greater, and the natural history of HCV infection is accelerated. It is controversial if HCV adversely affects HIV clinical progression. Hepatic disease is becoming an increasing problem in HIV patients, not only for HCV, but also with other viruses. Immunosuppressed patients with HIV, particularly those with CD_4 cell counts < 200, can present with a low or undetectable anti-HCV, and potentially a false negative Elisa. On the other hand, false positives can occur due to hypergammaglobulinemia,

which is common in HIV patients. HCV vertical transmission infection occurs in 2% to 5% of newborns. The mother-to-child transmission increases (7% to 20%) if the mother is co-infected with HIV.

Therefore, HCV infection in patients also co-infected by HIV is associated with faster progression of hepatic illness. Strategies to prevent HCV infection and to modify hepatic progression are urgently needed for those individuals co-infected by HIV and HCV.

Co-infections in Bahia (Burkitt's Lymphoma in children)

José Henrique Barreto

Lymphomas correspond to 16-17% of cancer cases in infancy; about 70% of these cases are Non-Hodgkin Lymphomas (NHL). It is the 3rd most frequent tumor of infancy. In a Specialized Childhood Cancer Service, from 1995 to 2000, 105 cases were seen (56 non-Hodgkin's Lymphoma-Burkitt's Tumor, BL), in 2002, 20 cases were seen (13 BL) and in 2003 8 cases were seen (4 BL). The disease free survival is approximately 65%. The most common presentation is the abdominal form, which represents 80% of the cases. The treatment is multidisciplinary and the current treatment protocol is NHL -2000 (GBTLNH).

There is a recent report "Expression of EBV Gene Products in BL in Northeast Brazil" that presents the first extensive investigation of BL association in Northeastern Brazil. This study showed that 87% of the cases of BL in Bahia expressed EBER molecules; EBV A was the most predominant type. The patients with BL associated with EBV were significantly younger than those who were EBV negative. This difference were also associated with socioeconomic and climatic conditions. The EBV infection rate in the Northeast of Brazil was similar to that observed in Africa, and seems to fall in between the sporadic and endemic BL types. The preferential location is the abdomen, which is different from the jaw location in the North of Africa and suggests the action of common pathogenic mechanisms. However, the nature of these mechanisms needs to be elucidated.

Our data suggest that other researchers corroborate the hypothesis that BL and EBV is probably determined by the age when the infection first occurred for this virus. Probably, competing infections involving the intestinal wall, such as esquistossomose and visceral leishmaniose, can act as local co-factors for the development of this neoplasia, with preferential presentation of the abdominal form.