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HIV INFECTION AND AIDS: A BRIEF AND PROSPECTIVE OVERVIEW

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INTRODUCTION

One of the most impressive and dramatic episodes in the history of medical science in the 20th century has been the worldwide impact of the Acquired Immunodeficiency Syndrome (AIDS). AIDS was initially described in 1981 by Gotlieb et al (1) and later on etiologically linked to Human Immunodeficiency virus 1 and 2 (HIV-1, HIV-2). As to October 1989, the World Health Organization (WHO) registered 182,463 cases from over 132 countries with an estimate of actual number of cases close to 600,000. This cumulative number of AIDS cases and the fact of being a disease with an overwhelming mortality and morbidity rate has led WHO to declare AIDS as the number one global public health enemy. Furthermore, the increasing prevalence of HIV infection and AIDS in Third World Countries (particularly Africa and Latin America) add a new formidable obstacle in their quest for survival and development. Within the context of the IX World Congress of Sexology, we will briefly review some of the most relevant aspects of HIV infection, stressing the need to incorporate medical sexology and the action of the medical sexologist in the global fight against AIDS.

EPIDEMIOLOGY

The first cases of AIDS were reported in 1981, when opportunistic infections and unusualley aggresive Kaposi Sarcoma were identified in young male homosexuals. The etiologic agent was soon identified and the transmission routes by which HIV infection can be acquired were linked to sexual activity and blood transmission, either transfused or by means of needle sharing among the Intravenous drug users (IVDU).

A large number of seroepidemiological studies have been conducted in an effort to ascertain the extent of HIV infection in the population at large. Analysis of reported AIDS cases from across the world has led the WHO to the recognition of three distinct geographic patterns of HIV transmission. Pattern I is characterized by having well defined high risk groups, homo/bisexual males and IVDU. These two groups account for over 80% of AIDS cases. Heterosexual transmission is seen in a small percentage of the cases, and male to female ratio ranges from 10:1 to 15:1. Pattern I is typical of industrialized countries and AIDS cases are concealed to urban areas.

Pattern II is dominated by heterosexual transmission, male to female ratio is approximately equal. This pattern accounts for high rates of perinatal

transmission. Blood screening is scarce or absent and health care related infection has been documented by means of syringes and needles poorly maintained. Pattern II countries includes sub-Saharan Africa and some of the Caribbean.

Pattern III is generally restricted to countries which have reported few cases and most are linked to imported blood products or sexual contact with high risk individuals from Pattern I and II countries.

The number of AIDS cases reported to WHO (by continents) as of the end of October, 1989 is as follows:

Africa	31,512	17.3%
Americas	123,343	67.6%
Asia	435	0.2%
Europe	25,589	14.0%
Oceany	1,584	0.9%
TOTAL	182,463	

In the Americas, 88% of AIDS cases reported has been from the United States. Countries with the next highest numbers of cases are Brazil, Canada, Mexico and two countries in the Caribbean basin: Haiti and Dominican Republic.

GLOBAL TRENDS

Since only AIDS cases and not persons with HIV infection are reportable, it is difficult to evaluate changes in current trends. Nevertheless, data collected form all over the world has been used to get some projections for the next few years. At the V International Conference on AIDS, (Montreal, June 1989), Dr. Jonathan Mann, Director of the WHO Global Programm on AIDS (GPA) detailed a Delphi study to predict HIV infection and AIDS in the 1990's: "The study started with the assumption that 5 million adults has already been infected and that during the next decade no effective vaccine or treatment would be available". "The Delphi study predicted that during the 1990's, about three times more HIV infections would occur than had ocurred during the 1980s". "Aproximately nine times more adults will develop AIDS during the 1990s compared with the 1980's". "The HIV/AIDS situation in the decade of the 1990's will be more serious, and perhaps much more serious than what we have experienced during the 1980's". "In particular, the number of people with AIDS will increase greatly and needed health and social services must be planned and developed now".

THIRD WORLD TRENDS

A great effort has been conducted in the industrialized countries to prevent and content the spread of HIV infection. Education and health measures have been enforced at a very high economic cost and the benefits can somehow be evaluated: the risk of HIV transmission to hemophiliacs and blood recipients has greatly diminished and new infected individuals among homosexuals cohorts are also diminishing. In the other hand, the risk is still high among IVDU and their heterosexual partners. Reports from CDC (Atlanta) and others showed an increasing number of HIV infection among minorities in the USA, closely linked to poverty and IV drug abuse.

Conditions affecting minorities in the USA are greatly magnified when we talk about the Third World. In Latin America, increasing rates of HIV infection have been documented in many countries. It is of interest as background information to realize that, in one of the very few detailed epidemiological studies performed in the region, we found that homosexuals who had not travel outside Venezuela and Amerindians living in the Venezuelan Amazonian Territory for the last 15.000 yrs. where free of carrying HIV-1 by 1986 (4). These results allowed us to conclude on the foreign origin of HIV infection in the Venezuelan population. More recently, it has been established that heterosexual transmission (Pattern II) accounts for most of the cases in the Caribbean basin; male to female ratio is 2:4:1 in general, with 9% of AIDS cases in children under 5 yo. On the other hand, Brazil (Pattern I) has 7 millions of "street children" living in absolute poverty, highly linked to prostitution and drugs. Also in Brazil the HIV prevalence among IVDU increased from 3 to 13% in just one year. Malnutrition is a common "disease" in Latin America and Africa, killing millions of children yearly; only in Brazil 2 millions are expected to die of hunger in the next 5 years. Besides malnutrition, Third Word countries are threaten by many other factors, including tropical disease, diarrheas, TBC, illiteracy, lack of health care systems, corruption and colosal external debts that threatens to finsih with the last hope for future wellbeing among the Third World.

Taking into account those many factors affecting our region, it has become very difficult, if not impossible, to implement measures designed to content the spread of HIV. Economic aid is being fueled through the WHO/GPA to the countries governments, but little has been achieved since the problems are so profound that the Third World is actually gasping for life, and HIV infection is disregarded as a real problem when compared to so many threats. It is very sad to hear when the industrialized countries began to talk about AIDS and HIV infection as "a problem of the Third World" which may actually be the most devastating and truthful statement of this new diseases.

Zambian president Kenneth Kaunda Keynote address delivered at the V Inter-

national Conference on AIDS, is pertinent to stress the above mentioned facts: "AIDS is the number one health challenge to all our governments and political systems", he said, "AIDS is a bomb. It is a bomb already impacting on mankind. It's killing is slower but nonetheless lethal and massive, just like bomb". "A cure has to be found at any price, including the highest price... the drastic reduction, indeed stoppage of the program, for the wanton AIDS has come to laugh at mankind, and our wicked plans of mass self-destructions. Fate is showing us that AIDS can do that killing for man worldwide, at no cost in dollars and rubles".

IMMUNOPATHOLOGY OF HIV INFECTION

The immunopathology associated with HIV infection is broad and complex comprising severall cell types (5-7). It is beyond the scope of this presentation torevise in detail the many aspects related to the virus-immune system interaction. CD4+ bearing cells are the main target of HIV (8). As suggested in the initial description of AIDS, the progressive depletion of CD4 lymphocytes is not only a well established immunoclinical finding but today is a definite marker in terms of natural history and prognosis of the disease. CD4 lymphocytes are crucial in the regulation of effector immune responses. Helper effects on antibody synthesis and on the genesis of cytotoxic T lymphocytes (CD3+, CD4-, CD8+) represent two of the most important functions exherted by CD4 lymphocytes. In addition, it has also been established that CD4 may regulate the cytotoxic capabilities of large granular lumphocytes (LGL) (9). These latter cells are of outmost importance as effector cells since both natural cytotoxicity and antibody mediated cellular cytotoxicity are mediated by CD3-, CD4-, CD16+, CD56+ LGL (also known as "natural killer cells"). As far as B lymphocytes, HIV infection induces a state of "over reactive" B lymphocytes manifested by hypergammaglobulinemia, high levels of circulating immune complexes, the detection of auto-antibodies and the presence of a deficient antibody response to new antigenic stimuli (10). Monocyte-macrophage function seems to be associated with a "reservoir" property for HIV (11). The compromised effector functions, particularly those related to virus clearence (T and LGL cytotocicity) probably represent a formidable setback in the infected host. CD8 cytotoxic lymphocytes, which function as a major genetically restricted type of killer cell, is commonly increased in the initial stages of HIV infection but as the disease progress to AIDS, it also declines in number and destructing capability (12). Thus, in a host lacking of these critical effector mechanisms, both opportunistic infections and/or malignancies would become frequent and devastating complications. In relation to central nervous system involvement, the possibility that AIDS dementia complex may be due to direct

HIV infection have been recently stressed (13). HIV may reach the brain barrier employing monocyte-macrophages as carrier. Southern blot analysis and *in situ* hybridization findings have been reported as positive evidence for the presence of viral antigen while IgG antibodies to HIV have been detected in spinal fluid. Since the CD4 epitoge is present in some of the brain cell types, the possibility of direct HIV-CD4 interaction mediating brain injury has also been advanced.

Thus, as stated earlier, a significant group of the immunopathological changes and particularly those related to lymphocyte subpopulations, represent suggestive basis to explain the different aspects of HIV immunoclinical characteristics.

IMMUNOCLINICAL AND DIAGNOSTIC ASPECTS

HIV infection is associated to a wide spectrum of clinical manifestations, ranging from the stage of chronic asymptomatic carrier (AC) to the stage of AIDS. It can be unfrequently diagnosed as an acute viral illness resembling an "infectious mononucleosis-like" syndrome, could stay as AC for up to 10-15 years or else develop a progressive chronic clinical complex, which varies from case to case. It can be stated, that as epidemiological and immunoclinical data is accumulated, HIV-1 or HIV-2 infection may join the chronic viral disease category. Worldwide, the CDC Staging Criteria (Stages I to IV) has been used (14). Stage I is related to the acute onset, stage II to AC, stage III to progressive generalized lymphadenopathy (PGL) and stage IV comprising: the constitutional disease (IVa), AIDS dementia compelx (IVb), secondary infectious diseases (IVc), cancers (IVd) and in stage IVe conditions such as lymphoid intersticial pneumonitis and other constitutional symptoms not meeting sub-groups IVa, b or c criteria. Two other fundamental clinical aspects are being assesed; the proper definition of clinical AIDS and a staging system to delineate the natural history of the disease. For the former, in a recent meeting in Caracas (Workshop on Definition of a case of AIDS, sponsored by Pan American Health Office, February 1989) the clinical definition of an AIDS cases was proposed, in order to provide "provisional case diagnosis" based on symptoms and signs followed by HIV serology testing to reach a final AIDS diagnosis. The list and scoring of the Caracas clinical definition is as follows:

SYMPTOM/SIGN/DIAGNOSIS	Score
A. Kaposi's sarcoma	6
Tuberculosis, disseminated/extrapulmonary/ non-cavitary pulmonary	6
B. Oral candidiasis or hairy leukoplakia	3
Tuberculosis, cavitary pulmonary or TB unspecified	3
Herpes zoster <60 years of age	3
Central Nervous system dysfunction	3
C. Diarrhea 1 month	2
Fever (>38°C) 1 month	2
Cachexia or >10% weight loss	2
Asthenia >1 month	2
Persistent dermatitis	2
Anemia, lymphopenia, thrombocytopenia	2
Interstitial infiltratesm diffuse or bilateral on X-ray	2
Persistent cough	2
"PROVISIONAL CASE" points required:	>6
plus: POSITIVE HIV SEROLOGY	

For the latter, GPA/WHO is currently carrying on a multicentric international assesment to group a number of clinical and laboratory markers which should help the clinician to horizontally stage a given patient with HIV infection. Within this context to choose immunopathological markers which may be applied at the moment of diagnosis and management seems essential. Absolute CD4 lymphocytes count usually parallels worsening and progression of the disease. In our laboratories, we have examined not only the systematic decline of CD4 lymphocytes but some geographical differences. Thus, Vuillier et al (15) showed that diminished total CD4 lymphocytes is accompanied by simultaneous decline of both CD45R suppresor inducer (2H4) and CDw29 helper inducer (4B4) CD4+ subpopulations, while Pérez et al (16) showed that in the Venezuelan serie, patients in the AC stage showed an "early" CD4 depletion when compared to reports from other latitudes. Moreover, in many cases it is possible to correlate the loss of response to specific antigens (systemic anergy) with the degree of CD4 lymphocyte depletion. Recently, we have also reported that LGL may decline in a similar pattern as CD4 lymphocytes, showing a significant decreage in cytotoxic activity against K562 cell line (16). Furthermore, those LGL bearing the phenotype CD3-, CD4-, low density CD8+, CD56+ are identically depleted as CD4 lymphocytes (17).

As the "humoral compartment", neutralizing antibodies can be detected in high levels in the AC stage with a definite declining trend as the disease envolve to AIDS. In addition, circulating HIV antigen (usually P24 levels) may be found in early stages (even in high risk individual which are "seronegative" for antibodies to HIV), to decline when seroconvertion ensued. Most se-

ries would agree that reappearance of P24 antigenemia is linked to worsening and progression of the disease (18). Currently, serum B2-Microglobulin, neopterin and IgA levels are being evaluated as possible "horizontal markers".

Diagnosis of AIDS is routinely established by the sum of the clinical history and the evidence of circulating antibodies to HIV (detected by ELISA and confirmed by Western blot). It is beyond the scope of this review, to detail the many aspects related to testing for HIV antigen and antibodies. It should be pointed out however, the worldwide availability of both clinical and laboratory parameters to properly diagnose and preliminarly stage an HIV infection. From the clinical stand point we would emphasize on the aspects of the HIV infected individual both at the ambulatory and at the bedhound level; much attention have been focused on HIV biology, immunopathology, diagnosis, preventive and educational measures; however, a lack of solid guidelines and the presence of unmodified attitudes of rejection from the health staff toward the HIV infected patient demands new global and local strategies. Furthermore, when WHO projections on the course of the AIDS pandemic to the year 2,000 are taken into consideration (5 to 6 million of cases), more than half the AIDS cases in adults in the 1990's are expected to develop in subjects already infected by 1988, the implementation of those strategies requires immediate action.

TREATMENT

To fight against HIV infection requires not only a broad and systematic approach but a solid knowledge at both international and national level on the current and future trends of the infection. Local policies to propell prevention, education, cultural adjustments, epidemiological survey, implementation of updated massive HIV screening methods (blood, banks, hospitals, private clinics) should comprise along with comprehensive medical care programs (ambulatory and bedbound), an all around disposition to confront the ongoing HIV pandemic.

Since we cannot describe in detail all these aspects, we would emphasize some of the points related to the area of patient care of the HIV infected individual. As we have pointed out, the clinical spectrum ranges from the AC stage to AIDS itself. Thus, monitoring of the former and a global clinical, diagnostic and therapeutic strategies for the later, represents today a formidable task not only in the view of WHO estimates of new cases for the 1990's but because the "rejection" of the "evasive" attitudes from the health staff remains a solid obstacle to improve the patient care level of the HIV infected individual. We propose herein the structuring of a medical team to enhance the outcome of the hospitalized patient and the organization of HIV ambula-

tory clinics to adequately monitor the evolving clinical pattern of a given HIV infected patient. In both cases, the clinical immunologist should assume a definite leadership in coordinating the overall effort and recommendations. At this point, we would emphasize the role of the clinical sexologist in facing the many aspects related to HIV infection. There is a definite role for this new medical specialist in prevention, education and at the patient care level. Lastly, the availability of Deoxynucleosides such as Zidovudine (formerly called Azidothymidine) and more recently the Dideoxy-Cytadine (DDI) has definitely improved the patient outcome and expanded survival and prognosis. In practical terms however, means an additional burden to patient care planning and cost estimates. There is accumulating evidences which suggest that these drugs which are converted by cellular enzymes to 5-triphosphates and are capable of interfering with reverse-transcriptase mediated production of proviral DNA, may delay progression of the disease when administered not only in grade IV patients but in the AC stage, particularly in patients already showing CD4 lymphocyte counts less than 500 cells/mm^3 in the absence of clinical symptoms. Thus, a combined effort of sex counseling, changes of habits, systematic patient care and drug therapy may offer a new outlook to the HIV infected patient, particularly since HIV vaccine research remains intensive and realistic.

CONCLUDING REMARKS

Finally, one main concern, particualrly in developing countries is the social and economical impact of AIDS. The question of resource allocation becomes paramount, since many other formidable health problems need to be tackled. Moreover, since non-governmental and other community based organizations may be active or participating, a solid coordination from health authorities is strongly needed. Hospitalization costs, ambulatory drug treatments, immune function monitoring, surveillance of systemic complications and counseling on sex habits are among the many approach and measures to be taken when dealing with an HIV infected person.

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