Biological, Epidemiological and Clinical Basis of Understanding Human Immunodeficiency Virus Infection

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ABSTRACT

Human immunodeficiency virus (HIV) causes a chronic infection beginning in most individuals with an acute syndrome followed by an asymptomatic stage and progresses in untreated adults over a median of 10 years to the late stage called AIDS. The virus rapidly and enormously replicates from the initiation of infection. The principal immunodeficiency caused by HIV is depletion in the subset of T lymphocytes referred to as helper T cells. New anti-HIV drugs given in potent combination regimens have demonstrated impressive efficacy by both clinical and laboratory measures, and have provided evidence that drugs can suppress HIV replication and disease manifestations. HIV/AIDS is still uncommon in Croatia. In the period from 1986 to 2000, 171 patients with AIDS have been reported of whom 101 (59%) died. The incidence of AIDS in 2000 was about 4 cases per million inhabitants. Recent testing of injection drug users at a needle exchange program (Help, Split) revealed an HIV incidence of about 1%.

Introduction

Untreated human immunodeficiency virus (HIV) infection progresses relentlessly in almost all infected persons from a clinically silent infection detectable only by laboratory tests to a state of severely damaged immunologic function. After a median time of about 10 years a variety of clinical syndromes defining the state of acquired immunodeficiency syndrome (AIDS) emerge. Although with great individual variation, the disease progresses and, if not treated, eventually causes death in almost all cases. Often poorly understood interactions between the host, HIV, and environmental factors determine the particular clinical manifestations.

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and rate of disease progression for each individual.

New advances in basic and clinical research in HIV infection have changed the view of patients, clinicians, and researchers. HIV infection is no longer perceived as a progressive and fatal disease, it is now sought to be a potentially treatable chronic illness. New anti-HIV drugs given in potent combination regimens (HAART from highly active antiretroviral therapy) have demonstrated impressive efficacy by both clinical and laboratory measures, and have provided evidence that appropriate drugs can suppress HIV replication and disease manifestations.

New techniques for measuring HIV RNA have been developed. This enabled more accurate and effective clinical management, and shortened the time required to accumulate evidence for drug efficacy in a clinical trial. The discovery of the high rapid replication rate of HIV in all stages of disease had important therapeutic implications. For example, if replication is not completely suppressed the high replication rate will give rise to mutation and selection for drug-resistant HIV strains. Immune recovery after potent antiretroviral therapy has also been studied. There is evidence that adult thymic function may allow at least partial immune reconstitution in HIV infected patients even in late stages of the disease. However, it seems that specific anti-HIV immune recovery cannot be achieved unless perhaps treatment is begun very early in the course of HIV infection. Unfortunately benefits from recent advances are not available to many individuals, particularly to those from developing countries, but they are very impressive and give hope that the disease might be better controlled on a worldwide scale. In settings were HAART is available problems with adherence, toxicity and resistance have emerged.

History of the Epidemic and Identification of the Etiologic Agent

The initial reports in 1981\textsuperscript{1,2} described Kaposi sarcoma and \textit{Pneumocystis carinii} pneumonia in homosexual men, indicating the presence of a clinical syndrome of immune deficiency. At that time HIV was not discovered and not known to cause this syndrome. The Centers for Disease Control (CDC) introduced the name »acquired immunodeficiency syndrome« (AIDS) and formulated a case definition to identify and report cases, determine the extent of the epidemic, and obtain clues about the cause. Case reporting allowed identification of risk factors associated with the syndrome. The largest risk groups in US and Western Europe were homosexual and bisexual males, the risk being associated with sex with multiple partners. The second largest risk groups were injection drug users. Hemophiliacs, recipients of blood transfusions and heterosexual partners of persons with the syndrome were also identified as being at risk. Subsequently, infants born to mother with the syndrome were also identified as a risk group.

Epidemiological studies showed that major risk groups differ in various world populations, reflecting the predominant transmission mechanisms of the region. Three patterns of transmission (types I, II, and III) were proposed. Type I (North America, Western Europe, and Australia) was characterized by the disease predominantly in homosexual men, injection drug users and their sexual partners, and hemophiliacs and transfusion recipients. Type II (Africa) had an equally prevalent disease in males and females, and reflects predominantly heterosexual transmission. Type III refers to sparse cases usually attributable to imported cases (contaminated blood or contact with an infected person outside the region).

Epidemiological findings strongly suggested a transmissible viral agent as the...
cause of the epidemic, and in late 1983 a group of French scientists isolated a newly recognized retrovirus. In 1984 two other independent laboratories reported the same. Initially different laboratories assigned different names to the new retrovirus, including lymphadenopathy-associated virus (LAV), AIDS-associated retrovirus (ARV), and human T-lymphotropic virus III (HTLV-III). «Human immunodeficiency virus» became the accepted designation for the retrovirus in 1986. Later reports described a second, closely related retrovirus endemic to West Africa with similar modes of transmission and associated clinical syndromes. The initially discovered retrovirus associated with most of the world’s HIV disease is now designated human immunodeficiency virus type 1 (HIV-1), and the virus detected primarily in West Africa and rarely in West Africans residing abroad is now designated human immunodeficiency virus type 2 (HIV-2). However, «HIV» usually indicates HIV-1, because HIV-2 is rare in most parts of the world.

Identification and isolation of HIV enabled the development of techniques for culturing HIV from different specimens. Subsequently, a relatively convenient and cost-effective assay that detected antibody to HIV in the plasma of infected persons became available in 1984 and 1985. This made possible to screen blood products, detect HIV infection in persons who did not have CDC-defined AIDS, identify seroconversions in newly infected persons, and construct prospective studies to describe the course of HIV disease in asymptomatic persons with serologic evidence of HIV infection.

**Current Terminology and Classification**

HIV causes a chronic infection beginning in most individuals with an acute syndrome followed by an asymptomatic stage and progresses in untreated adults over a median of 10 years to the late stage called «AIDS». The virus continuously, rapidly and enormously replicates from the initiation of infection. This gives rise to mutations, and as a result the virus diversifies. Immune system damage also begins upon infection. Major immunopathologic processes occur in lymphoid tissue, and the immune system struggles over years to preserve its function. However, slowly, but relentlessly essential components of the host immune system are destroyed. The host becomes increasingly susceptible to and eventually dies as a result of complications of opportunistic infections and malignancies resulting from immune system dysfunction.

The syndrome called AIDS is the late stage of HIV disease. It was originally defined for surveillance purposes by the CDC prior to the identification of HIV as the etiologic agent. The original case definition was published in September of 1982, the CDC has subsequently revised this definition to include additional syndromes recognized as manifestations of advanced HIV disease (Table 1, 2). The definition of AIDS is complex and comprehensive, however, for the medical management the presence or absence of AIDS is irrelevant. Also, due to the recent advances in antiretroviral therapy, which may produce improvement in immunologic function and a decline of the incidence of opportunistic infection, the concept of AIDS as end-stage immunodeficiency is somewhat inappropriate. The 1987 CDC definition of AIDS still continues to be useful as a definition of an endpoint in clinical research and as criteria for case reporting.

**Natural History and Immunopathogenesis**

The principal immunodeficiency caused by HIV is a reduction in the subset of
T lymphocytes referred to as helper or inducer T cells (CD4+ T lymphocytes). CD4+ T lymphocytes are essential for both cellular and humoral immune responses to microbes and as a result of this depletion, impaired ability of the immune system to recognise and respond to antigens occurs. As the disease progresses, the immune system looses the ability to recognise antigens and the host becomes susceptible to opportunistic infections that are otherwise controlled by T cell mediated immune response in a healthy individual. Therefore, the progressive depletion of CD4+ T lymphocytes results in the development of severe immunodeficiency, increased susceptibility to opportunistic infections and subsequently death.

However, this model is an oversimplification of a complex disturbance of the immune system caused by HIV, which in addition to depletion also includes abnormal activation and profound dysfunction of effector mechanisms of the immune system. Abnormalities of immunological response, for example diminished cellular response to specific antigens in infected individuals, are observed before any substantial depletion in the peripheral blood CD4+ T lymphocytes occurs. Therefore, the exact way in which HIV causes damage the immune system is still controversial.

### Transmission, establishment of infection, initial host immune system response

The virus may enter the host: 1) through mucous membranes of the vagina, rectum or urethra (sexual intercourse) and the upper gastrointestinal tract (swallowed infected semen, vaginal fluid, breast milk) or 2) directly into the bloodstream through infected blood or blood products (transfusions, use of contaminated needles for injecting drugs, sharp-object injuries, maternal to fetal transmission, traumatic sexual intercourse,
exposure of broken skin or an open wound). It seems that the immune response occurring immediately after exposure to HIV influences the clinical course of the disease for years to come.

In case of the mucous membrane transmission of HIV («local» infection), the earliest cells that are infected are mucosal dendritic cells (DC, also known as Langerhans cells)\textsuperscript{22}. DC are antigen-presenting cells (APC) which activate naive T lymphocytes by efficiently processing and presenting immunogenic peptides in association with the major histocompatibility complex (MHC) molecules and by expressing costimulatory molecules and cytokines. Mucosal DC either are themselves infected by HIV or they carry the virus to the regional lymph nodes. Thus CD4\textsuperscript{+} lymphocytes in the regional lymph nodes become infected after contact with DC, and virus replication intensifies prior to the development of an HIV specific immune response. This intensive replication gives rise to primary viremia which leads to wide dissemination of the virus to other lymphoid organs, the brain and other tissues. When the virus enters the bloodstream directly (e.g. contaminated needles) it also reaches lymphoid organs either by the clearing mechanism of the reticuloendothelial system or with or within blood dendritic cells.

DC present HIV antigens to CD4\textsuperscript{+} and CD8\textsuperscript{+} T lymphocytes during antigen presentation processes in draining lymph

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**TABLE 2**

**INDICATOR CONDITIONS IN CASE DEFINITION OF AIDS**

- Candidiasis of esophagus, trachea, bronchi or lungs
- Cervical cancer, invasive\textsuperscript{*}
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis with diarrhea > 1 month
- Cytomegalovirus disease of any organ other than liver, spleen or lymph nodes
- Herpes simplex with mucocutaneous ulcer > 1 month or bronchitis, pneumonitis, esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- HIV-associated dementia: disabling cognitive and/or other dysfunction interfering with occupation or activities of daily living
- HIV-associated wasting: involuntary weight loss > 10\% of baseline plus chronic diarrhea (2 loose stools/day 30 days) or chronic weakness and documented enigmatic fever 30 days
- Isosporosis with diarrhea > 1 month
- Kaposi’s sarcoma
- Lymphoma, immunoblastic, Burkitt’s or primary CNS
- Mycobacterium avium, disseminated
- Mycobacterium tuberculosis, disseminated or pulmonary\textsuperscript{*}
- Pneumocystis carinii pneumonia
- Pneumonia, recurrent-bacterial (2 episodes in 12 months\textsuperscript{*}
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia (non-typhoid), recurrent
- Toxoplasmosis of brain

\textsuperscript{*} Added in the revised case definition 1993.
The appropriate antigen presentation by DC enables the development of HIV-specific cytolytic T lymphocyte (CTL) response that is considered to play a crucial role in the control of primary viremia. The CTL response protects the host via two mechanisms: 1) direct recognition and lysis of HIV-infected cells and 2) the synthesis of cytokines (primarily chemokines) that inhibit HIV replication.

Primary viremia is accompanied in the majority of patients with an acute illness (acute HIV infection) characterized by fever, lymphadenopathy, pharyngitis, rash, myalgia or arthralgia, diarrhea and headache. After primary viremia a level of steady-state viremia, called viral set point, is observed. This set point is usually reached 1 year after infection and has important prognostic implications.

Seroconversion and asymptomatic disease

The CTL response is associated with a sharp reduction in quantitative viral load in blood, and clinical recovery from acute HIV infection. It has been shown that >95% of patients seroconvert, using standard serologic tests, within 5.8 months following HIV transmission. During clinical latency the viral load has reached a set point. However the level of CD4+ T lymphocytes in blood decrease gradually. Major immunopathologic events are noted in lymph nodes. Studies have demonstrated high concentrations of HIV as extracellular virus trapped on the follicular dendritic cell processes within germinal centers of lymph nodes. At this time the lymphoid tissue serves as the major reservoir for HIV, the follicular dendritic cells filter and trap virus and infected CD4+ lymphocytes and the viral burden in peripheral blood mononuclear cells is relatively low. With progressive disease, the lymph node architecture is disrupted and more and more virions are released into blood.

Symptomatic disease

In untreated patients after a variable period, usually measured in years, symptoms, including AIDS defining events occur. When the CD4+ lymphocyte count falls below 200 cells per microliter the patients becomes increasingly susceptible to various opportunistic diseases. As the disease advances further and the CD4+ count drops below 50 cells/mm³, additional, often multiple, opportunistic infections are present. Ultimately death results from extensive disease of vital organs, biochemical abnormalities, hematopoietic and circulatory failure.

Determinants of HIV Disease Progression

The course of HIV infection is quite variable. A few individuals progress rapidly following the acute stage and develop AIDS and die within months. At the other extreme, a few untreated individuals, called »long-term slow progressors« or »long-term non-progressors« (LTNP), remain well after more than 12 years of infection without apparent clinical or laboratory signs of disease progression. In recent years significant progress has been made in identifying some of these factors, although much remains to be learned and the clinical utility of present knowledge is limited. The two most important variables to predict clinical outcome (time to AIDS or death) are viral burden as measured by the level of RNA in plasma and the CD4+ lymphocyte count.

Identified factors for HIV disease progression include HIV characteristics and replication dynamics (viral virulence, replication fitness, and genetic diversity), host genetic determinants (chemokine receptors, HLA), and the immune response (cellular immune response, cytokine milieu).
**HIV determinants**

A few number of LTNP have and were infected initially with a defective virus. Reports describe HIV-infected individuals harboring virus with deletions in the nef gene, rendering the virus nonviral34–36. Throughout all stages of HIV infection there is a high rate of HIV replication. It appears that approximately \(10^{10}\) virions are produced and cleared from the circulation each day37,38.

Strains of HIV can also be characterized by the ability to fuse CD4+ T lymphocytes in vitro, a property called syncytium-induction (SI). HIV strains that are not syncytium-inducing (NSI) are able to replicate in macrophages and CD4+ T lymphocytes (referred to as M-tropic) and are predominant strains in acute infection. SI strains of HIV replicate in CD4+ T lymphocytes but poorly in macrophages and they emerge in advanced HIV disease (Tropic strains) and are associated with disease progression. In vitro cultivation of T-tropic HIV strains in CD4+ T cell lines creates phenotypic and genotypic alterations generating separate, T cell line adapted (TCLA) strains. In vivo infection of CD4+ T lymphocytes is established primarily by SI strains and it correlates with the rapid decline in the population of these cells39.

**Host genetic determinants**

Genetically mediated host factors which are though to influence the rate of HIV replication and the course of infection include: 1) antigen processing characteristics, 2) synthesis of -chemokines, 3) mutations within the genes coding for chemokine receptors, 4) endogenous cytokine synthesis and 5) HLA region polymorphism.

Cytokines are a group of biological response modifiers that mediate the intercellular interactions and participate in the effector phases of both natural and specific immunity. Chemokines are a group of proinflammatory cytokines that act as chemoattractants and activators of leukocytes. Chemokines exert their biological activity by binding to the chemokine receptors. It is now well established that HIV uses chemokine receptors, as coreceptors for entry into a host cells (in addition to the CD4+ molecule). This has profoundly changed our knowledge on HIV infection. M tropic and T tropic HIV strains use different chemokine receptors as coreceptors for the entry into a host cell.

The role of chemokines in the biology of HIV infection was first demonstrated in 199540. The authors demonstrated the inhibitory effect of chemokines RANTES, MIP-1 and MIP-1 on the replication of M-tropic but not on T-tropic strains of HIV. Soon after this discovery, the chemokine receptor CCR5 (expressed on T lymphocytes and macrophages) capable of binding all three chemokines has been identified and shown to act as a primary coreceptor for M-tropic strains of HIV41,42. Subsequent identification of CXCR4 as a coreceptor for T-tropic strains of HIV-1 completed the picture. So briefly, M-tropic strains use the CCR5 coreceptor, TCLA strains use CXCR4 and primary T-tropic strains use both CCR5 and CXCR4. Other chemokine receptors (CCR2b, CCR3, CCR8 and orphan receptors V28, STRL-33 and GPR15) can mediate the entry of some HIV strains in vitro but the significance of this finding in vivo remains to be determined. Paxton et al.43 have identified a group of individuals that have been exposed to HIV but remained uninfected by M-tropic HIV strains. These individuals were subsequently shown to be homozygous for a 32 base pair deletion in the gene coding for a central section of the CCR5 protein (32), the coreceptor used by M-tropic (R5) strains of HIV. In Caucasians, the frequency of the homozygous for -32 CCR5 is 1%, for heterozygotes the frequency is between 15–20%. Homozygosity for the -32 CCR5 allele is asso-
ciated with a significant (not absolute) degree of protection from infection with R5 strains of HIV-1 in vivo\textsuperscript{44–48}. The impact of the heterozygosity of -32 CCR5 mutation on the course of HIV infection is less clear. It has been suggested that heterozygosity might be associated with the slower progression to AIDS and death\textsuperscript{49,50} however, it is not clear whether or not this is real or a methodological (e.g. study design) issue\textsuperscript{51}.

A second genetic variant (CCR2-64I) in the gene coding for the CCR2 receptor might also be associated with slower progression to AIDS in heterozygous or homozygous individuals. It occurs in roughly 2\% of African Americans, Caucasians, Asians, and Hispanics\textsuperscript{52,53}.

A third genetic variant (SDF1–3’A) affects the region of a gene coding for the chemokine SDF-1, which is the ligand (the normal binding molecule) for chemokine receptor CXCR4\textsuperscript{54}. One study has shown that SDF1–3’A occurred in roughly 20\% of Caucasians, 16\% of Hispanics, 6\% of African Americans, and 26\% of Asians infected with HIV. Less than 5\% were homozygous. This genetic variant may offer some protection against infection, although data supporting this concept is limited. However, homozygosity for SDF1–3’A seems to be associated with slower progression, however, this effect seems to be more marked in later stages of HIV disease. It is proposed that the SDF1–3’A variant changes the availability of CXCR4 receptors, perhaps by altering increased synthesis of the SDF-1 protein and thus blocking or decreasing cell surface expression of CXCR4. The role of CXCR4 coreceptor in disease progression is supported by experiments showing that influenza virus increase surface expression of CXCR4 and the rate of infection of HeLa cells by HIV-1 strains which use this coreceptor and not CCR5\textsuperscript{55}.

HLA genes may determine the kinetics and the affinity of the early oligoclonal immune response to an initially homogeneous HIV isolate and determine the disease outcome. The Multicenter AIDS Cohort Studies have shown that the rate of progression is linked to several MHC class I or II genes: HLA B35 or HLA A1-B8-DR3 are associated with progression and HLA B27-A24-DR1 with slower progression of HIV infection\textsuperscript{56}. Other studies support the notion of the genetic determinants of the immune system are important for the control of HIV infection but these data should not be overestimated\textsuperscript{57}. Nevertheless a HLA scoring profile has been shown to predict the risk of HIV disease progression independently of HIV RNA and CD4\textsuperscript{+} cell count\textsuperscript{58}.

The two promotor alleles of the IL-10 gene appear to be another host genetic factor that significantly affects susceptibility to HIV-1 infection and the rate of disease progression. The IL-10-5’-592A allele is associated with decreased IL-10 production, individuals carrying it are at increased risk for HIV-1 infection and experience more rapid disease progression compared with individuals homozygous for the alternative IL-10-5’-592C/C\textsuperscript{59}.

**Immune response and cytokines**

The immune response that follows primary infection is of both humoral and cell mediated type. It is directed against a variety of HIV antigens and viral proteins produced by infected cells. Since HIV infects CD4\textsuperscript{+} cells, T lymphocytes with receptors specific for HIV are most likely to bind to infected cells and themselves become infected and destroyed. Hence, it is postulated that relatively early in the course of infection, specific anti-HIV cellular components of the host defense are infected and destroyed.

Antibodies are produced to multiple HIV antigens but their precise functional significance is unclear. The best studied were antibodies toward the envelope proteins (gp 120 and gp 41). No convincing
association between the presence of neutralizing antibodies and the control of viral replication has been made to date\textsuperscript{60,61}. Analysis of the antigenic structure of gp 120 showed that most of the envelope protein surface is hidden from humoral immune responses\textsuperscript{62}. Most broadly neutralizing antibodies access only two surfaces on gp 120 (one that overlaps the CD4\textsuperscript{+} binding site and another that overlaps the chemokine receptor-binding site). Conformational changes in core gp120 provide additional mechanisms from evasion from the immune response\textsuperscript{63}.

Since it is believed that T cell mediated immunity plays a key role against most viral infections it is also sought to be an important component of the host immune response to HIV. Classic MHC class I restricted, HIV specific CD8\textsuperscript{+} CTLs have been found in the peripheral blood of patients after a few weeks of HIV infection. These cells bind and cause lytic destruction of target cells. The qualitative nature of the HIV specific CD8\textsuperscript{+} lymphocyte response is a important predictor of eventual outcome. Patients who mount a broad CD8\textsuperscript{+} CTL response involving several clonal types, have a more favorable clinical course than patients who mount a more restricted CTL response\textsuperscript{64–68}.

Pathologic consequences of a disrupted and inappropriate cytokine milieu include inappropriate activation with consequent loss of T cells (e.g., by HIV direct killing or by apoptosis), impaired cellular and humoral immune responses, and increased HIV replication. Three types of specific patterns of cytokine production, that become disrupted or inappropriate as HIV disease progresses, have been identified. Type 1 cytokine pattern (also known as Th1) favors a strong cellular immune response (e.g., activation of B cells and antibody production) and consists of higher levels of IL-4, IL-5, IL-10, and IL-13. The third response includes proinflammatory cytokines such as TNF\textsubscript{-}\textalpha, IL-1, and IL-6. These cytokines contribute to immune system activation and in vitro can stimulate HIV replication. Research suggests that as HIV disease progresses, the cytokine milieu shifts from a Type 1 pattern toward a Type 2 and proinflammatory pattern, changes that tend to diminish cellular immune response and increase HIV replication\textsuperscript{69–73}.

**HIV and the Pattern of Lymphocyte Recirculation**

It has been postulated that the principal mechanism responsible for the depletion of CD4\textsuperscript{+} T lymphocytes in the peripheral blood of HIV-infected individuals is virus-mediated cytolysis and that billions of CD4\textsuperscript{+} lymphocytes were produced and destroyed daily\textsuperscript{37,38}. However, studies looking at different T cell compartments have shown depletion of all T cell subsets not only those with the CD4\textsuperscript{+} receptor.

Functionally mature T-lymphocytes emerge from their precursors in the thymus and migrate to the peripheral blood and lymphoid organs. At this point in time they are called naive or virgin cells because they have not yet encountered an antigen. If a naive T lymphocyte encounters an antigen for which it is specific in a lymph node, it will become activated effector. T lymphocytes recognise peptides derived from antigens that are associated with MHC molecules on the surface of APCs. Antigen recognition induces T lymphocyte activation that subsequently leads to the secretion of cytokines, proliferation and the performance of regulatory or cytolytic function. Most of the antigen-specific T lymphocytes die by apoptosis but some of them survive and develop into antigen-specific memory
T lymphocytes that initiate larger secondary immune response upon subsequent exposure to the same antigen.

Over the course of HIV infection there is a progressive decrease in the number of both CD4+ and CD8+ naive T lymphocytes in the peripheral blood. The discovery that the depletion of naïve T lymphocytes during HIV infection is irrespective of the expression of CD4+ molecule and susceptibility to infection suggested alternative mechanisms responsible for this depletion. The discovery that HIV profoundly changes the kinetics of lymphocyte recirculation between peripheral blood and lymphoid organs enabled us to explain these findings. A comprehensive review on this subject has been published by Rosenberg et al.

Lymphocytes circulate in the peripheral blood for a short time before they adhere to high endothelial cells in venules of lymphoid organs (lymph nodes, tonsils, Peyers patches) and migrate through their parenchyma. If lymphocytes do not encounter an antigen during their migra-

### TABLE 3
REGIONAL HIV/AIDS STATISTICS AND FEATURES, DECEMBER 2000

<table>
<thead>
<tr>
<th>Region</th>
<th>Epidemic started</th>
<th>Adults &amp; children living with HIV/AIDS</th>
<th>Adults &amp; children newly infected with HIV</th>
<th>Adult prevalence rate *</th>
<th>Percent of HIV-positive adults who are women</th>
<th>Main mode(s) of transmission for adults living with HIV/AIDS **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-Saharan Africa</td>
<td>late '70s-early '80s</td>
<td>25.3 million</td>
<td>3.8 million</td>
<td>8.8%</td>
<td>55%</td>
<td>Hetero</td>
</tr>
<tr>
<td>North Africa &amp; Middle East</td>
<td>late '80s</td>
<td>400,000</td>
<td>80,000</td>
<td>0.2%</td>
<td>40%</td>
<td>Hetero, IDU</td>
</tr>
<tr>
<td>South &amp; South-East Asia</td>
<td>late '80s</td>
<td>5.8 million</td>
<td>780,000</td>
<td>0.56%</td>
<td>35%</td>
<td>Hetero, IDU</td>
</tr>
<tr>
<td>East Asia &amp; Pacific</td>
<td>late '80s</td>
<td>640,000</td>
<td>130,000</td>
<td>0.07%</td>
<td>13%</td>
<td>IDU, Hetero, MSM</td>
</tr>
<tr>
<td>Latin America</td>
<td>late '70s-early '80s</td>
<td>1.4 million</td>
<td>150,000</td>
<td>0.5%</td>
<td>25%</td>
<td>MSM, IDU, Hetero</td>
</tr>
<tr>
<td>Caribbean</td>
<td>late '70s-early '80s</td>
<td>390,000</td>
<td>60,000</td>
<td>2.3%</td>
<td>35%</td>
<td>Hetero, MSM</td>
</tr>
<tr>
<td>Eastern Europe &amp; Central Asia</td>
<td>early '90s</td>
<td>700,000</td>
<td>250,000</td>
<td>0.35%</td>
<td>25%</td>
<td>IDU</td>
</tr>
<tr>
<td>Western Europe</td>
<td>late '70s-early '80s</td>
<td>540,000</td>
<td>30,000</td>
<td>0.24%</td>
<td>25%</td>
<td>MSM, IDU</td>
</tr>
<tr>
<td>North America</td>
<td>late '70s-early '80s</td>
<td>920,000</td>
<td>45,000</td>
<td>0.6%</td>
<td>20%</td>
<td>MSM, IDU, Hetero</td>
</tr>
<tr>
<td>Australia &amp; New Zealand</td>
<td>late '70s-early '80s</td>
<td>15,000</td>
<td>500</td>
<td>0.13%</td>
<td>10%</td>
<td>MSM, IDU</td>
</tr>
<tr>
<td>TOTAL</td>
<td>36.1 million</td>
<td>5.3 million</td>
<td>1.1%</td>
<td>47%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The proportion of adults (15 to 49 years of age) living with HIV/AIDS in 2000, using 2000 population numbers;

** MSM (sexual transmission among men who have sex with men), IDU (transmission through injecting drug use), Hetero (heterosexual transmission).
tion, they return to the blood via lymph. Lymphocytes in the peripheral blood represent only 2% of the complete lymphocyte pool within the body and they exchange approximately 50 times a day. The kinetics of exit, migration and re-entry of lymphocyte subsets influences the number of a lymphocyte subset and its proportion in relation to other subsets. The most important factors influencing the pattern and the kinetics of lymphocyte recirculation are cytokines IFN-\(\gamma\) and TNF-\(\alpha\). In vivo, the injection of these cytokines causes the depletion of lymphocytes from the peripheral blood by reducing the rate at which they migrate from the lymph nodes back to the blood.

HIV infection changes the pattern of lymphocyte recirculation by altering the composition of CD4\(^+\) and CD8\(^+\) T-lymphocytes and B-lymphocytes within lymphoid organs and peripheral blood. HIV infection also induces the synthesis of various cytokines including IFN-\(\gamma\) and TNF-\(\alpha\) and changes the composition of cells within lymphoid organs. These changes within the lymph nodes of HIV-infected persons include follicular hyperplasia, accumulation of HIV virions attached to the membrane of FDCs and the entrance of HIV-infected lymphocytes and macrophages via afferent lymphatics. The net result of this is the reduction in the lymphocyte migration from the lymphoid tissues back to the blood. Hence, although there is a decrease in peripheral blood lymphocyte subpopulations, the number of CD4\(^+\) T lymphocytes and CD4\(^+\)/CD8\(^+\) ratio in lymph nodes remains unchanged and decreases only when blood CD4\(^+\)/CD8\(^+\) ratio drops to approximately 0.5 (normal value above 1.0). Studies in both human and simian models of infection have shown a marked delay in a decline in the CD4\(^+\)/CD8\(^+\) ratio in lymphoid organs (lymph nodes, tonsils) compared to peripheral blood.

The concept of HIV-mediated change in the pattern of lymphocyte migration provides an explanation how HIV reduces lymphocytes subpopulations (for example naive CD4\(^+\) and CD8\(^+\) T-lymphocytes) in the peripheral blood irrespective of the CD4\(^+\) expression on their membrane. It also explains the initial increase of CD4\(^+\) lymphocytes after initiation of HAART. Successful HAART reduces viral burden, relieving the immune response causing many cells trapped in lymph nodes to become redistributed to the blood\(^{76,77}\).

Global HIV/AIDS Statistics

The latest estimates on the HIV/AIDS pandemic from the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) have been released in December 2000 (Table 3)\(^{78}\). It should be stressed that there are different methods for deriving estimates of an epidemic\(^{79}\). Although we are at the end of the second decade of the HIV epidemic, we cannot see an end to the spread of HIV infection. The success seen in some communities and the dramatic increase in survival in developed countries due to combination antiretroviral therapy have been overshadowed by the numbers of new infections in underdeveloped countries and by the growing epidemic in new regions of the world. Unfortunately on a global perspective, the epidemic seems still out of control.

According to the UNAIDS/WHO estimates a total of 36.1 million people are living with HIV at the end of 2000. About 10 men, women and children around the world were infected per minute during 2000, more than 5 million in all. It is estimated that 1.4 million children live with HIV/AIDS. The total number of AIDS deaths since the beginning of the epidemic reached almost 22 million people. There were 3 million deaths from AIDS in 2000.

More than 95% of all HIV-infected people now live in developing countries. 95% of all deaths occurred also in developing
countries. These deaths occur primarily among young adults, who would normally be in their peak productive and reproductive years. These deaths are reaching critical levels in some parts of the world, particularly sub-Saharan Africa, which has been hardest hit. Child survival is deteriorating, life expectancy has declined 10 to 20 years in some countries, the health care system is now overburdened with AIDS cases, and 20 to 40 million children may become orphaned because of HIV/AIDS.

Sub-Saharan Africa is home of 72% of individuals who became infected with HIV in 2000. Since the start of the epidemic, more than 52 million people living in Sub-Saharan Africa have been infected by HIV, of whom 17 million died. Among newly infected children under age of 15, 9 of 10 infections occurred in this region. Yet only a tenth of the world's population lives in Sub-Saharan Africa. However, for the first time there are signs that HIV incidence may have stabilized in this region. Although new infections are found in all African countries, the bulk of new infections continues to be concentrated in east and particularly in southern Africa. In Botswana, Namibia, Swaziland and Zimbabwe, current estimates show that between 20–26% of people aged 15–49 are living with HIV or AIDS. The epidemic has moved to South Africa as well, which is now considered the hardest hit country. HIV infection is also spreading in countries like Nigeria that had so far a relatively low incidence.

It is now estimated that about 6 million of Asians live with HIV/AIDS, the majority from south and east Asia. The epidemic is now 7 to 9 years old. The fact that HIV epidemic is establishing in the world’s most populated countries such as India and China is of great concern.

Trends in STDs and HIV in Eastern Europe are also alarming. A region which until mid-1990s had only a few cases of HIV/AIDS in now experiencing rising trend particularly in drug injection communities. It is now estimated that 700,000 live with HIV in that region. In Russia, rates of syphilis have increased from around 10 cases per 100,000 people in the late 1980s to over 260 cases per 100,000 in late 1990s. The number of new HIV infections in Russia are showing an exponential growth in recent years. Judging from registered cases a total of about 50,000 new infections occurred in the year 2000. Many eastern European countries (Ukraine, Belarus, Moldova, Estonia) experienced a significant rise in new HIV infections in the late 1990s.

In developed countries (North America, Western Europe), new combinations of anti-HIV drugs continue to reduce deaths significantly. However it seems that there is no significant progress in reducing the number of new infections. Over the last decade the rate of new infections is stable instead of declining. During 2000 it is estimated that about 75,000 persons became infected in North America and Western Europe.

**HIV/AIDS in Croatia**

HIV/AIDS is still relatively uncommon in Croatia. The majority (about 68%) of cases are believed to be imported, hence Croatia can be defined as a «pattern III country». The first cases of AIDS have been diagnosed in 1986 and until December 2000 a total of 171 cases have been reported (Figure 1). 101 (59%) patients have died. There were 14.6% females. The risk behavior associated with transmission were: homo/bisexual in 48% cases, heterosexual 35% cases, and injection drug use in 8.8%. There were only 8 hemophiliacs and only 3 cases of mother to child transmission. The majority of patients were between 30 and 39 years old (37.4%), however, a considerable number were over 40 years old (46.2%). The cu-
The cumulative incidence of AIDS in Croatia is around 38 cases per million inhabitants, the incidence for 2000 being 4 per million. Although the total number of patients is quite small and no definitive conclusion can be made, some regional differences in incidence might exist. The cumulative incidence in the area of Dubrovnik is about 71 per million, Rijeka and Istra 55, Zagreb 42.5 and Split 38.5 per million. In the period 1986 to 1998 the most frequent initial AIDS defining illnesses were *Pneumocystis carinii* pneumonia (20%) and tuberculosis (20%). Prior to the introduction of HAART the median survival after AIDS diagnosis was 15.8 months and was related to the type of presenting illness and CD4+ cell count.

Other available data from HIV testing (blood donors, data from testing sites) also suggest that the incidence of HIV infection in Croatia is low. Rates of syphilis are also constantly low. During 1998 HIV testing of 82 injection drug users at a needle exchange program in Split (Help) revealed only one positive result and similar rates (around 1%) of HIV infection were observed in 1999 and 2000. It is not fully understood why the rate of HIV infection in Croatia remains low. HIV infection was introduced later than in Western countries and educational efforts started relatively early (in 1987). Testing of blood donors began in 1987. Injection drug users were allowed to purchase sterile syringes and needles in pharmacies since 1987. There is a possibility that the pattern of behavior of injection drug users might be different in Croatia than in other countries (for example the frequency of needle and syringe sharing, number of partners, etc). Sexual behavior might also be different. A survey by Rudan, I. (1996, unpublished data) has suggested that adolescents in Croatia have their first sexual intercourse at a relatively older age (26% of 17-year-olds had sexual intercourse). Also about 70% of adolescents from Zagreb used a condom at the first sexual intercourse.

Despite the low incidence of HIV infection in Croatia, there is no room for complacency. For example, the number of injection drug users has increased more
than 5 times in recent years in Croatia. Hence, more needle exchange programs are needed. We must consistently educate our people, especially young ones, about how best to prevent transmission through safer sex practices. Condoms should be available. We should continue screening our blood supply, provide easy access to treatment of STDs, and give antiretroviral therapy to infected pregnant women.

In conclusion, since we still lack a vaccine we must continue to relay on education, behavioral changes, antiretroviral therapy and other preventive measures to combat HIV/AIDS. The development of a protective vaccine remains an uncertainty for the near future, hence we need to invest more into prevention programs.

REFERENCES