Twenty-Five Years of Science

Never before in the history of medicine have the nosology and etiology of a new disease been defined as quickly as in the case of AIDS (acquired immune deficiency syndrome). The worldwide dissemination of human immunodeficiency virus (HIV) over the past 47 years is one of the most catastrophic examples of the emergence, transmission, and propagation of a virus [248].

AIDS was first observed in the USA in 1981 through the study of young homosexual males demonstrating a high rate of Pneumocystis carinii pneumonia (PCP) associated with Kaposi’s sarcoma (KS), also at a visceral level [222]. At the time, KS was considered a rare form of cancer that mainly affected subjects over the age of 60. Reports of cases of pneumocystosis and/or KS, often associated with other severe opportunistic infections, rose to such an extent that 159 cases were reported between June and November 1981 [222]. It was soon discovered that HIV infection had spread above all among young adults from already identified risk categories: homosexuals, drug addicts, hemophiliacs, recipients of transfusions of blood or blood products, or natives of Haiti and Zaire, Rwanda and Burundi [61, 87, 182, 455, 555].

The early cases of HIV infection originated in Central Africa, where it was identified in Kinshasa, Democratic Republic of Congo, [555] in a sample of serum stored since 1959 [599] and then spread outwards to neighboring Tanzania and Uganda in the east, and Congo-Kinshasa in the west [555]. On the basis of the HIV-1 (HIV type 1) sequences obtained from a sample of serum that was stored in 1959 and more recent isolates, it has been estimated that the date of the common ancestor of the main (M) group of HIV-1 is 1931 (1915–1941) [292]. The most recent common isolates of HIV type 2 (HIV-2) have been dated to the 1940s [326]. As early as in 1983 [477] several investigators reported AIDS in children [17, 61, 182, 477], and especially in infants [182]. In addition to HIV-1, a second virus, HIV-2, was subsequently identified in West Africa [107, 108], causing a syndrome that was fully analogous to HIV-1 but was different from an antigenic standpoint [82]. HIV infection is characterized by virus replication in a limited number of cells, including T lymphocytes and macrophages, leading to a CD4 depletion and a profound immune deficiency (ID) [31, 202, 205, 442]. In children, the disease is marked by a short incubation period of even <1 year [494], while in adults it can develop in HIV-infected subjects within a decade (or up to even 19 years following HIV-2 infection) [158]; many of these patients remain asymptomatic for long periods of time, with normal CD4 counts [85] and normal-looking lymph nodes, despite persistent virus replication [423].

The WHO estimated that >40×10^6 people worldwide are currently infected, and AIDS has caused >20×10^6 deaths. In the developing world, where the epidemic is most prevailing, the disease’s adverse social and economic impact should not be underestimated [438]. Sixty-six percent of infected persons are in Africa, and 20% are in Asia, where the epidemic has been growing rapidly in recent years. Global statistics have made it clear that at the end of 2003, an estimated 34.6×10^6 to 42.3×10^6 people throughout the world were living with HIV infection, and the AIDS epidemic has claimed the lives of >20 million people [523, 549]. In addition, because HIV-infected mothers are likely to die of AIDS, 10 million children have been orphaned thus far and an estimated 20 million will be orphaned by 2010 [577].

The WHO now recommends quality-assured, fixed-dose combinations of lamivudine (3TC), stavudine (d4T) and nevirapine (NVP) in a single pill as first-line treatment [576] (see “Treatment”). There, when parents die, they leave orphans, most of whom are not HIV infected, thus HIV infection has a disproportionate impact on children, resulting in the loss through illness or death of those persons who can make the greatest contribution to the social support systems and economic vitality of their regions [191, 208].
As shown in Fig. 23.1, like other retroviruses HIV is composed of two identical copies of RNA, arranged inside a core of viral proteins [301]. The gene structures in the 9 kb that form the RNA strand are reported in Table 23.3 [214, 456]. The genome includes at least nine separate genes with sequences that partially overlap: these chains are flanked on both sides by long terminal repeats (3¢ and 5¢ LTR), which contain the set of essential signals to regulate the provirus transcription and become integrated in the cell genes. It must be noted that some LTR regulatory sequences share cell sequences [214]. For a better understanding of the role of these genes, we can theorize that when the cell encounters activation phenomena, this also involves LTR, whose signals include a promoting part activated by cell RNA, an enhancing part, another with a negative regulatory activity and the tat sequence, a positive HIV replicator that is capable of 1,000-fold acceleration of the production of viral proteins [132].

Schematically, the HIV virion is spherical in shape, has a diameter of 100–120 nm, and a basic structure similar to that of other retroviruses [103, 301, 467, 509]:
- The viral env, a lipid bilayered membrane, is studded with various host cells (including HLA class I and II) and contains 72 external spikes formed by the two major viral-env proteins gp120 and gp41 [100] (Fig. 23.1). These originate from enzymatic splitting of the larger viral pre-protein gp160; they elicit viral entry and syncytium formation. Gp120 has a variable protein domain containing the V3 loop, which triggers a strong immune response [194, 584]. The cell shows mature and budding particles (Fig. 23.2). Within the virus, structural proteins surround an inner viral core that contains enzymes and proteins required for viral replication including protein p24. In addition to p24, the HIV-1 core contains three nucleocapsid proteins, p17, p9 and p7 [226]. These proteins are proteolytically cleaved from a