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THE PAST AND FUTURE OF AIDS

E. Toniato[1,2*], D. De Amicis[3] and S. Martinotti[1]

[1] Center of Advanced Studies and Technology, Department of Innovative Technology in Medicine and Dentistry, University of Chieti, Chieti, Italy;
[2] Department of General Pathology, UniCamillus-International Medical University, Rome, Italy;
[3] Department of Orthopedics and Traumatology, Hospital "Val Vibrata" of Sant'Omero, ASL Teramo, Italy.

**Correspondence to*:
Prof. Elena Toniato,
Center of Advanced Studies and Technology,
Department of Innovative Technology in Medicine and Dentistry,
University of Chieti,
66100 Chieti, Italy.
e-mail: e.toniato@unich.it

ABSTRACT

Acquired immunodeficiency syndrome (AIDS) was first described in the 1980s and the human immunodeficiency virus (HIV) that causes it was identified in 1983-1984. The virus is transmitted sexually and through transfusions of infected blood, or from an infected mother to her child during childbirth. Today, greater knowledge of AIDS, both at the epidemiological and transmission levels, has allowed us to better understand the pathogenetic biochemical mechanisms and to create new therapeutic treatments that have saved millions of lives. Despite the new therapies adopted today, HIV still remains a serious threat to the world's population and the lack of a vaccine represents a defeat for the scientific community. The drugs available today for HIV and immunomodulators are able to slow the progression of the disease, but not to cure it definitively. The most important immunological damage caused by HIV is the reduction of CD4+ cells resulting in infection by *Candida albicans* and *Herpes zoster*. Low CD4+ counts cause opportunistic infections, comorbidities, and, in severe cases, death. Antiretroviral therapy (ART) targets different stages of the HIV life cycle, including reverse transcriptase, integrase, and protease enzymes. ART involves oral combinations of drugs that, with different mechanisms of action, inhibit HIV replication, reducing viral load. Still today, HIV and AIDS remain a significant health challenge despite new therapies. New treatments are better at treating the disease and certainly improving the quality of life, but AIDS is still completely incurable.

KEYWORDS: *HIV, AIDS, CD4+, ART, infection, immunity, therapy*

INTRODUCTION

The first known cases of acquired immunodeficiency syndrome (AIDS) were reported in the early 1980s. Initially, it was a mysterious illness affecting primarily gay men, leading to its early designation as gay-related immune deficiency (GRID). In the years 1983-1984, scientists identified the human immunodeficiency virus (HIV) responsible for AIDS. Key researchers such as Luc Montagnier (France) and Robert Gallo (USA) played crucial roles in this discovery (1). By the mid-1980s, HIV had spread globally, affecting diverse populations across all continents (2). The virus spread through unprotected sexual contact, blood transfusions, the sharing of needles, and from mother to child during birth or breastfeeding. The peak of the AIDS epidemic was in the late 1990s and early 2000s, and sub-Saharan Africa was, and remains, the most severely affected region (3,4). Initial responses to the epidemic were hindered by stigma, misinformation, and lack of public awareness. Activism groups such as ACT UP helped to raise awareness and pressured

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governments to take action. Much more substantial progress has been achieved in our understanding of HIV, the virus that causes AIDS. Today, the epidemiology, route of transmission, and complex pathologies caused by HIV have helped to better understand the biochemical mechanisms involved in AIDS and to create new therapeutic treatments, which have saved innumerable lives to this day.

DISCUSSION

Since the AIDS outbreak, the HIV virus has infected more than 75 million individuals globally (5) and continues to cause approximately 1.2 million deaths annually (6). Despite treatment, HIV still remains a serious threat to the world population and the absence of a vaccine represents a defeat for the scientific community. In 2019, the World Health Organization (WHO) reported that approximately 38 million people were living with AIDS (6). The drugs available today for HIV, and immune modulators, are able to slow down progression of the disease, but there is still no definitive curative therapy, nor an effective vaccine that can stop the epidemic. Therefore, HIV infection continues to threaten the world's population and cause deaths around the world.

Most people infected with HIV, even those who are asymptomatic, develop AIDS. This disease generates a lot of fear amongst the population and public awareness should be improved to educate people about the transmission of the virus, which is essential for preventing infection.

HIV infection is linked to a wide spectrum of diseases, ranging from asymptomatic to acute and chronic, with symptoms such as fever, weight loss, malaise, night sweats, chills, and diarrhea (7). Sick and asymptomatic people can develop opportunistic infections and cancers (e.g., Kaposi sarcoma) (8). Infected patients with compromised immune systems are at increased risk of developing AIDS earlier, within the first years of infection. In these cases, a diagnostic error can occur, especially when it does not appear that there is an HIV infection. HIV is difficult to classify, and the prognosis can be different from classic AIDS, which puts infected patients at risk. Therefore, the diagnosis of the disease must be made very carefully.

HIV transmission occurs directly through genital contact or rectal mucosal contact with seminal fluid or vaginal secretion. Furthermore, the virus can be transmitted through contact with contaminated blood, typically by transfusion or by the sharing of needles. Infected pregnant women can transmit the virus through childbirth. Contact with healthy skin is not a means of transmission. It has been noted that among hemophiliacs who receive blood products, the incidence of HIV infection is higher than in healthy subjects (9).

After individuals become infected with HIV, most remain asymptomatic for about 7 years, however, a small minority may develop AIDS within one or more year after infection. Early in the infection, the illness may present as flu-like and is characterized by fever, malaise, lethargy, and lymphadenopathy (10). The most important characteristic of AIDS is the reduction in the number of CD4+ lymphocytes due to the cytopathic effect of the virus (11). When the damage to the immune system worsens with a decrease in CD4+ lymphocytes, infections from *Candida albicans* and *Herpes zoster* begin to occur, which can result in oral hairy leukoplasia (12). Additionally, infections can occur from opportunistic bacteria, protozoa, herpes simplex, zoster, cytomegalovirus, and various types of fungi (13).

Patients infected with HIV may present neurological conditions such as encephalitis, dementia, and headaches (14). Brain cells, such as microglia, become infected when macrophages cross the blood-brain barrier (BBB) and colonize the central nervous system (CNS) (15). Microglia and macrophages are innate immune cells that phagocytose HIV and are a true viral reservoir which risks introducing a high number of viruses into circulation (15). HIV activates macrophages and microglia in the brain to release pro-inflammatory cytokines such as interleukin (IL)-1, tumor necrosis factor (TNF), and IL-6 (16). These cytokines are toxic and damage brain tissue, which leads to neurological disorders or worsens pre-existing ones.

Patients diagnosed with HIV face serious mental health implications, including symptoms of depression (17). In some countries, individuals living with HIV infection have a 2 to 3-fold risk of depression, with a higher rate of anti-depressant use, and an increased risk of committing suicide, compared with the healthy population (18-20). However, the cause for this phenomenon has not yet been ascertained. One possible reason could be attributed to the stress faced by infected patients and also to the chronic nature of the disease, which in the long term, becomes increasingly challenging for the patient.

HIV is a retrovirus with an RNA genome, with an outer envelope with glycoproteins gp120 and gp41 that are essential for viral entry into host cells (21). Concerning the mechanism of entry, HIV primarily infects CD4+ T cells. The gp120 glycoprotein binds to the CD4 receptor and a co-receptor (CCR5 or CXCR4) on the host cell, facilitating viral entry (22). Host genetic factors, such as CCR5-Δ32 mutation, can influence susceptibility to HIV infection and disease progression (23), and the virus employs various strategies to evade the immune system, including latency and direct killing of immune cells.

Therapy and health strategies

Efforts to develop a vaccine against HIV have been ongoing but challenging due to the virus's high mutation rate. Some promising candidates are in advanced trial stages. Research is ongoing into potential cures; a functional cure would control the virus without ongoing treatment, while a sterilizing cure would eradicate the virus from the body.

Strategies to end the AIDS epidemic include widespread testing, treatment, and prevention measures like pre-exposure prophylaxis (PrEP). Furthermore, efforts are being made to address inequalities, to reduce disparities in access to treatment and prevention services, especially in resource-limited settings.

Antiretroviral therapy (ART) is used to treat patients infected with HIV using anti-HIV drugs. Current ART targets different stages of the HIV lifecycle, including reverse transcriptase, integrase, and protease enzymes. Research is exploring new therapeutic targets, such as viral entry inhibitors, latency-reversing agents, and gene-editing technologies such as CRISPR-Cas9 to disrupt the HIV genome.

The therapies available today offer a better quality of life and an extended lifespan for HIV patients who have developed AIDS (24,25). HIV therapy aims to reduce plasma HIV RNA levels to less than 20-50 copies/ml and bring CD4+ cells back to a physiological number. ART is one of the therapies available today and consists of taking oral combinations of drugs which, with different mechanisms of action, inhibit HIV replication, reducing the viral load (Table I). It has been estimated that antiviral therapies have saved approximately 16.5 million AIDS patients since 2001 (26). Drugs that suppress HIV are associated with a higher count of CD4+ cell recovery. A low CD4+ count causes opportunistic infections, comorbidities, and in severe cases, death.

Table I. *Virus replication cycle of HIV.*

a) Reverse transcription:	Once inside the cell, HIV's RNA genome is reverse-transcribed into DNA by reverse transcriptase.
b) Integration:	The viral DNA is integrated into the host genome by the integrase enzyme, allowing the virus to hijack the host cell's machinery.
c) Transcription and translation:	The integrated viral DNA is transcribed and translated into viral proteins.
d) Assembly and budding:	New viral particles are assembled and bud from the host cell, ready to infect other cells.

The effective ART adopted against HIV has also improved neurocognitive disorders. People using ART have milder signs of the disease, although cognitive impairment and neurological damage remain for a long time and the neurological damage may have occurred due to the virus before ART (27). ART reduces the pathogenesis and cellular storage of the HIV virus as well as the destruction of CD4+ T cells, improving the immune response (28). Experiments on primates have shown that with simian immunodeficiency virus (SIV), viral invasion into the brain occurs within 2 weeks after infection (29). The virus also invades the cerebrospinal fluid (CSF), causing inflammation with the production of cytokines and activation of microglia (30).

HIV attacks immune cells such as dendritic cells, CD4+ lymphocytes, and macrophages. Dendritic cells, sentinels of the immune system, phagocytose the virus and present it to T cells, which collaborate with B cells and plasma cells to produce antibodies (Ab) (31). HIV evades the immune system by changing its viral genetic makeup via antigenic escape variants (32,33). The continuous mutation of the HIV virus makes it difficult to generate a vaccine.

ART uses three drugs in combination that significantly slows the disease process and prolongs life but does not cure the disease. This therapy allows immune recovery in patients with low numbers of lymphocytes. A severe and advanced state of the disease is established based on the number of CD4+ cells. Typically, a patient with a CD4+ cell count of less than 200 cells/mcl begins ART, but many individuals do not know they have HIV until too late when it has ravaged their immune system.

ART has been utilized in HIV treatment for years, but it has side effects that undermine its effectiveness. Recently, gene therapy has emerged as a potential option to combat HIV (34). It involves the administration of intracellular nucleic acids to the patient and has so far given promising results. Therefore, satisfactory ART must not only reduce mortality, but also disease progression. Today, many advances have been made in therapeutic technologies which, together with a better understanding of the immune system and viral infection, can lead to more effective treatments and new strategies.

CONCLUSIONS

HIV/AIDS remains a significant global health challenge to this day despite advancements in treatment. Modern ART, introduced in the mid-1990s, has transformed HIV from a fatal disease to a manageable chronic condition. Patients on ART can achieve undetectable viral loads and have a near-normal life expectancy. Additionally, new treatments, including long-acting injectable ART, are improving adherence and quality of life for patients.

While tremendous progress has been made in treatment and understanding the virus, ongoing research and innovative strategies are essential to achieving the ultimate goals of a functional cure, an effective vaccine, and, eventually, an end to the epidemic.

Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Vahlne A. A historical reflection on the discovery of human retroviruses. *Retrovirology*. 2009;6(1). doi:https://doi.org/10.1186/1742-4690-6-40
2. UNAIDS, WHO. *A history of the HIV/AIDS epidemic with emphasis on Africa * UNAIDS and WHO **.; 2003. https://www.un.org/development/desa/pd/sites/www.un.org.development.desa.pd/files/unpd-egm-200309-unaids_whopaper2.pdf
3. UNAIDS. 2007 AIDS epidemic update. www.unaids.org. Published December 2007. https://www.unaids.org/en/resources/documents/2007/20071130_2007_epiupdate_en.pdf
4. UNAIDS. *Uniting the World against AIDS Fact Sheet 08*.; 2008. Accessed February 17, 2022. https://data.unaids.org/pub/globalreport/2008/20080715_fs_ssa_en.pdf
5. UNAIDS. How AIDS changed everything — MDG6: 15 years, 15 lessons of hope from the AIDS response. www.unaids.org. Published July 14, 2015. https://www.unaids.org/en/resources/documents/2015/MDG6_15years-15lessonsfromtheAIDSresponse
6. Joint United Nations Programme on HIV/AIDS. UNAIDS data 2020. [cited 2022 Apr 18]. https://www.unaids.org/sites/default/files/media_asset/2020_aids-data-book_en.pdf
7. Chou SH, Prabhu SJ, Crothers K, Stern EJ, Godwin JD, Pipavath SN. Thoracic diseases associated with HIV infection in the era of antiretroviral therapy: clinical and imaging findings. *Radiographics: A Review Publication of the Radiological Society of North America, Inc*. 2014;34(4):895-911. doi:https://doi.org/10.1148/rg.344130115
8. Yarchoan R, Uldrick TS. HIV-Associated Cancers and Related Diseases. Longo DL, ed. *New England Journal of Medicine*. 2018;378(11):1029-1041. doi:https://doi.org/10.1056/nejmra1615896
9. Zhubi B, Mekaj Y, Baruti Z, Bunjaku I, Belegu M. Transfusion-Transmitted Infections in Haemophilia Patients. *Bosnian Journal of Basic Medical Sciences*. 2009;9(4):271-277. doi:https://doi.org/10.17305/bjbms.2009.2777
10. Chu C, Selwyn PA. Diagnosis and initial management of acute HIV infection. *American family physician*. 2010;81(10):1239-1244.
11. Doitsh G, Greene WC. Dissecting How CD4 T Cells Are Lost During HIV Infection. *Cell Host & Microbe*. 2016;19(3):280-291. doi:https://doi.org/10.1016/j.chom.2016.02.012
12. Moylett EH, Shearer WT. HIV: Clinical manifestations. *Journal of Allergy and Clinical Immunology*. 2002;110(1):3-16. doi:https://doi.org/10.1067/mai.2002.125978
13. Benson CA, Kaplan JE, Masur H, Pau A, Holmes KK. Treating Opportunistic Infections among HIV-Infected Adults and Adolescents: Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America. *Clinical Infectious Diseases*. 2005;40(Supplement_3):S131-S235. doi:https://doi.org/10.1086/427906
14. Ru W, Tang SJ. HIV-associated synaptic degeneration. *Molecular Brain*. 2017;10(1). doi:https://doi.org/10.1186/s13041-017-0321-z
15. Wallet C, De Rovere M, Van Assche J, et al. Microglial Cells: The Main HIV-1 Reservoir in the Brain. *Frontiers in Cellular and Infection Microbiology*. 2019;9. doi:https://doi.org/10.3389/fcimb.2019.00362

16. Borrajo López A, Penedo MA, Rivera-Baltanas T, et al. Microglia: The Real Foe in HIV-1-Associated Neurocognitive Disorders? *Biomedicines*. 2021;9(8):925-925. doi:https://doi.org/10.3390/biomedicines9080925
17. Nanni MG, Caruso R, Mitchell AJ, Meggiolaro E, Grassi L. Depression in HIV infected patients: a review. *Current psychiatry reports*. 2015;17(1):530. doi:https://doi.org/10.1007/s11920-014-0530-4
18. Asrat B, Lund C, Ambaw F, Garman EC, Schneider M. Major depressive disorder and its association with adherence to antiretroviral therapy and quality of life: cross-sectional survey of people living with HIV/AIDS in Northwest Ethiopia. *BMC Psychiatry*. 2020;20(1). doi:https://doi.org/10.1186/s12888-020-02865-w
19. Passos SM, Souza LD, Spessato BC. High prevalence of suicide risk in people living with HIV: who is at higher risk? *AIDS Care*. 2014;26(11):1379-1382. doi:https://doi.org/10.1080/09540121.2014.913767
20. Marzuk PM, Tierney H, Tardiff K, et al. Increased risk of suicide in persons with AIDS. *JAMA*. 1988;259(9):1333-1337.
21. Prabakaran P, Dimitrov AS, Fouts TR, Dimitrov DS. Structure and Function of the HIV Envelope Glycoprotein as Entry Mediator, Vaccine Immunogen, and Target for Inhibitors. *Advances in Pharmacology (San Diego, Calif)*. 2007;55:33-97. doi:https://doi.org/10.1016/S1054-3589(07)55002-7
22. Kalinina OV, Pfeifer N, Lengauer T. Modelling binding between CCR5 and CXCR4 receptors and their ligands suggests the surface electrostatic potential of the co-receptor to be a key player in the HIV-1 tropism. *Retrovirology*. 2013;10(1). doi:https://doi.org/10.1186/1742-4690-10-130
23. Singh KK, Spector SA. Host Genetic Determinants of Human Immunodeficiency Virus Infection and Disease Progression in Children. *Pediatric Research*. 2009;65(5 Part 2):55R63R. doi:https://doi.org/10.1203/pdr.0b013e31819dca03
24. Eyawo O, Franco-Villalobos C, Hull MW, et al. Changes in mortality rates and causes of death in a population-based cohort of persons living with and without HIV from 1996 to 2012. *BMC Infectious Diseases*. 2017;17(1). doi:https://doi.org/10.1186/s12879-017-2254-7
25. Oguntibeju O. Quality of life of people living with HIV and AIDS and antiretroviral therapy. *HIV/AIDS - Research and Palliative Care*. 2012;4:117. doi:https://doi.org/10.2147/hiv.s32321
26. UNAIDS. Global roll-out of HIV treatment has saved millions of lives. www.unaids.org. Published September 6, 2021. https://www.unaids.org/en/resources/presscentre/featurestories/2021/september/20210906_global-roll-out-hiv-treatment
27. Moulignier A, Costagliola D. Metabolic Syndrome and Cardiovascular Disease Impacts on the Pathophysiology and Phenotype of HIV-Associated Neurocognitive Disorders. *Current topics in behavioral neurosciences*. 2020;50:367-399. doi:https://doi.org/10.1007/7854_2019_123
28. Ho DD, Neumann AU, Perelson AS, Chen W, Leonard JM, Markowitz M. Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. *Nature*. 1995;373(6510):123-126. doi:https://doi.org/10.1038/373123a0
29. Chakrabarti L, Hurtrel M, Maire MA, et al. Early viral replication in the brain of SIV-infected rhesus monkeys. *The American journal of pathology*. 1991;139(6):1273-80.
30. Moretti S, Virtuoso S, Sernicola L, Farcomeni S, Maggiorella MT, Borsetti A. Advances in SIV/SHIV Non-Human Primate Models of NeuroAIDS. *Pathogens*. 2021;10(8):1018-1018. doi:https://doi.org/10.3390/pathogens10081018
31. Martín-Moreno A, Muñoz-Fernández MA. Dendritic Cells, the Double Agent in the War Against HIV-1. *Frontiers in Immunology*. 2019;10. doi:https://doi.org/10.3389/fimmu.2019.02485
32. Carrington M, Alter G. Innate Immune Control of HIV. *Cold Spring Harbor Perspectives in Medicine*. 2012;2(7):a007070-a007070. doi:https://doi.org/10.1101/cshperspect.a007070
33. Goulder PJR, Watkins DI. Impact of MHC class I diversity on immune control of immunodeficiency virus replication. *Nature Reviews Immunology*. 2008;8(8):619-630. doi:https://doi.org/10.1038/nri2357
34. Chung J, Rossi JJ, Jung U. Current progress and challenges in HIV gene therapy. *Future Virology*. 2011;6(11):1319-1328. doi:https://doi.org/10.2217/fvl.11.113