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SPECIAL ARTICLE

HIV/AIDS infection: The beginning of the end for today's greatest pandemic?☆

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Abstract Recently, there have been significant advances in the fight against human immunodeficiency virus, which have increased the hopes of definitively halting its dissemination and of starting the decline of the epidemic it has caused. Transmission of the infection was drastically reduced when infected patients were given antiretroviral treatments, which boosted the diffusion of treatments to middle- and low-income countries. Global therapy coverage has doubled in recent years; meanwhile the incidence of new infections has decreased. Various curative strategies are also actively being investigated, including those aiming to induce cell resistance to the infection through gene therapy and the elimination of latent virus reservoirs. This article reviews the current situation and future developments in terms of controlling the pandemic and, eventually, curing the infection.

PALABRAS CLAVE
VIH;
Epidemia de sida;
Terapia antirretroviral;
Erradicación del VIH;
Curación del VIH

Infección por el VIH/sida: ¿El principio del fin de la primera gran pandemia contemporánea?

Resumen En los últimos años se han producido avances importantes en la lucha contra el virus de la inmunodeficiencia humana que hacen concebir esperanzas de que pueda detenerse definitivamente su diseminación y de que la epidemia que ha provocado entre en fase de declive. Se ha demostrado que el tratamiento antirretroviral de los pacientes infectados reduce drásticamente la transmisión de la infección, lo que ha impulsado la extensión de los tratamientos a los países de renta media y baja. La cobertura terapéutica a escala mundial se ha duplicado

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en los últimos años y de forma paralela se ha reducido la incidencia de nuevas infecciones. Al mismo tiempo se están investigando activamente diferentes estrategias para la curación, entre ellas las encaminadas a inducir resistencia celular a la infección mediante terapia génica y la eliminación de los reservorios de virus latente. En este artículo se revisa la situación actual y las perspectivas futuras para controlar la pandemia y, quizá, curar la infección.

Background

The acquired immune deficiency syndrome (AIDS) pandemic is undoubtedly the most significant of modern times. Of all known viruses, the human immunodeficiency virus (HIV) has one of the highest lethality rates. Since its onset in 1981, HIV has caused the death of more than 30 million individuals. The most recent estimates by the World Health Organization (WHO) and the Joint United Nations Program on HIV and AIDS (UNAIDS) indicate that 37 million individuals are currently infected.[1] Each year, 2 million new infections are produced, and more than 1 million individuals die from the disease worldwide.

In the 35 years of struggle against AIDS, there have been major scientific advances that have been transferred in an exemplary fashion to real life. These advances have helped convert HIV infection into a controllable chronic disease. An important scientific milestone was the identification of HIV in 1983, only 2 years after declaring the first cases of AIDS in the US. Shortly thereafter, the virus' genetic organization was discovered. Studies showed that the main targets of HIV were the T lymphocytes and that the most important cell receptor was the RCA-4 (CD4) protein, although the entry of the virus into the cells also required the binding to other proteins of the cell membrane, called coreceptors, whose natural ligands are different chemokines. The 2 main coreceptors of HIV are CCR5 and CXCR4, and most new infections are caused by viruses that use CCR5 to enter the cells (virus with R5 tropism).[2]

We know that activated T-CD4(+) lymphocytes are often infected, which is where transcription of the HIV genome is started. Within a few hours, massive viral replication occurs, with destruction of the infected cells.[3] Over time, the progressive cell destruction leads to T-CD4(+) lymphopenia, with damage to the architecture of the lymph nodes and other lymphoid tissues, as well as immunoactivation and general dysregulation of the immune function. In a median of approximately 10 years, the patient develops severe immunodeficiency.[3] There is, however, considerable heterogeneity in the outcomes of patients with the infection, ranging from rapid progression to the so-called elite controllers, a rare group of individuals who for years maintain spontaneous control over viral replication without treatment.[4] Variants have also been described in the human genome that confer natural resistance to infection by this virus. The best characterized of these variants is a deletion of a gene segment of coreceptor CCR5 (CCR5-Δ32), which impedes penetration by the virus with tropism R5 in the lymphocytes.[5] Individuals with this homozygous CCR5-Δ32 variant (less than 1% of the white population) are highly resistant to HIV infection, even after repeated exposure to the virus.[6]

Achievements and limitations of antiretroviral therapy

In the last 2 decades, increasingly effective antiretroviral drugs have been developed, and a continuous reduction in overall mortality for AIDS has been documented.[7] The current antiretroviral therapy (ART) regimens can achieve virological suppression (defined by the inability to detect viruses in the blood using highly sensitive molecular techniques) in almost 90% of cases,[8] which has translated in a growing proportion of patients who are virologically controlled. Thanks to the widespread use of prophylaxis with antiretrovirals during pregnancy, the vertical transmission of the infection has been practically eliminated in high-income countries.[9]

Since the first decade of the 21th century, international initiatives have been launched with public and private funds that, aligned with the WHO directives, have implemented ART programs in low to middle-income countries. Thus, in 2009, more than 30% of infected patients in Africa had access to treatment. Following an incessant increase in worldwide mortality from AIDS that exceeded 2.5 million deaths annually, since 2005, there has been a documented reduction in mortality from this cause, which continues to this day.[1]

The achievements of ART have undoubtedly been significant. However, long-term administration of antiretroviral drugs also has many disadvantages[10–13] and does not eradicate the infection. Patients who are kept in a state of virological suppression with ART are known to have proviral DNA with replicative capacity. It has been shown that discontinuing ART in these patients is inevitably followed by a rebound in viremia due to the presence of cellular reservoirs of the virus.[14] These reservoirs are rapidly established after the infection and mainly consist of lymphocytes infected with already integrated virus that enter a state of rest/latency.[15] These lymphocytes with latent infection and without detectable replication represent a small proportion of the total infected lymphocytes (less than one per million) but have a long half-life (months-years). These cells do not express any viral marker or protein on their surface and are