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Review

Current status and challenges of antiretroviral research and therapy

José A. Esté[a,*], Tomas Cihlar[b,**]

[a] Retrovirology Laboratory IrsiCaixa, Hospital Germans Trias i Pujol, Universitat Autònoma de Barcelona, Badalona, Spain
[b] Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404, USA

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ABSTRACT

Twenty-five years after the discovery of the therapeutic activity of azidothymidine (AZT), the first antiretroviral drug used in the clinic, infection with the human immunodeficiency virus (HIV) has become, at least in the industrialized world, a manageable chronic disease with a significant improvement in life expectancy and quality. Nevertheless, the number of new infections worldwide continues to rise, particularly in women, and effective drug treatments have not yet reached the vast majority of infected individuals in resource-limited countries. The current status of antiretroviral therapy is therefore encouraging, but significant challenges remain. Although highly active antiretroviral therapy (HAART) provides durable control of virus replication in many patients, it is not devoid of unwanted secondary effects, some of which are now surfacing in aging populations under long-term treatment. The emergence of multidrug resistance and transmission of drug-resistant HIV strains limit the clinical efficacy of current therapy. Further simplification of treatment and identification of more effective drug combinations are needed to improve patient adherence, the most significant cause of treatment failure. Finding new drugs and novel drug targets may lead to redefining the goals of antiretroviral therapy, with an attempt to achieve the ultimate objective: the eradication of infection. Preclinical and clinical biomedical research, rational drug design and a close collaboration with regulatory agencies to set standards for the transition of new treatment concepts into the clinic will be the cornerstones of future progress. This special issue of *Antiviral Research* [85(1), 2010] highlights the principal milestones of antiretroviral research over 25 years of drug discovery and development and offers a comprehensive analysis by leading experts of the efforts being made to meet the challenges of effective control of HIV infection.

This article forms part of a special issue of Antiviral Research marking the 25th anniversary of antiretroviral drug discovery and development, vol. 85, issue 1, 2010.

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* Corresponding author. Tel.: +34 934 656 374; fax: +34 934 653 968.
** Corresponding author. Tel.: +1 650 522 5637; fax: +1 650 522 4890.
E-mail addresses: jaeste@irsicaixa.es (J.A. Esté), Tomas.Cihlar@gilead.com (T. Cihlar).

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1. Introduction

At the present time, more than 33 million people are infected with the human immunodeficiency virus (HIV), with 2.5 million new infections diagnosed in 2008. Sub-Saharan Africa remains most heavily affected by the pandemic, accounting for 67% of all people living with HIV and >70% of deaths from the acquired immune deficiency syndrome (AIDS) in recent years. Globally, the percentage of women among people living with HIV has remained stable at 50% for several years, but women's share of infection is increasing in several countries. The overall number of people living with HIV has increased as a result of new infections and the beneficial effects of more widely available antiretroviral therapy (HIV/AIDS, 2008). The introduction of combination antiretroviral therapy, compounded with the routine use of HIV RNA viral load and CD4+ T-cell counts as surrogate markers of drug efficacy and disease progression (Mellors et al., 1996), has brought about a dramatic increase in life expectancy among HIV-infected patients (The-Antiretroviral-Therapy-Cohort-Collaboration, 2008).

Currently, we recognize the maximal and durable suppression of plasma viremia, i.e. <50 RNA copies/ml, as the most important goal of antiretroviral therapy that minimizes the selection of drug resistance mutations, preserves the CD4+ T-cell count and confers overall clinical benefits to patients (Panel-on-Antiretroviral-Guidelines-for-Adults-and-Adolescents, 2008). Twenty-five years after the discovery of the antiviral effect of AZT (Broder, 2010; Mitsuya et al., 1985), there are 25 approved single antiretroviral drugs in 6 mechanistic classes that can be used to design multiple combination regimens to reach these objectives. As described in articles in this special issue of *Antiviral Research*, these six classes include the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) (Cihlar and Ray, 2010) (Martin et al., 2010), non-nucleoside reverse transcriptase inhibitors (NNRTIs) (de Bethune, 2010), protease inhibitors (PIs) (Wensing et al., 2010), entry/fusion inhibitors (FIs) and CCR5 antagonists (Tilton and Doms, 2010), and integrase inhibitors (McColl and Chen, 2010).

Current treatment options have not yet reached the vast majority of people living with HIV. Although the eradication of HIV infection is unlikely to be a short-term prospect, the voices of experts have begun to herald a change in the future paradigm of HIV treatment by shifting the new long-term goal towards achieving virus control that would allow for durable drug-free remissions (Richman et al., 2009). HIV infection cannot be cured with current treatments and patients are destined to undergo treatment for life. Simplification of therapy, improvement of patient adherence and minimization of drug resistance are foreseeable near-term goals that will likely also be important stepping stones towards achieving long-term drug-free virus control and ultimately finding a cure.

This article is one of three that introduce a special issue of *Antiviral Research* (Esté and Cihlar, 2010) marking the 25th anniversary of the first antiretroviral drug treatment of patients infected with HIV. In the first paper, Samuel Broder describes the development and use of AZT and the impact of antiretroviral therapy on the subsequent course of the HIV pandemic (Broder, 2010). In the second article, Erik De Clercq provides a personal account that places the discovery of antiretrovirals within the overall history of antiviral drug development (De Clercq, 2010). In this third paper, we introduce the topics covered by the many experts who have contributed to the special issue, and offer our own perspective on the past, present and future of antiretroviral therapy.

2. Milestones in the development of antiretroviral therapy

Antiretroviral therapy and HIV/AIDS research have achieved unprecedented series of breakthroughs (Table 1) that have translated into the largely successful management of what is now considered a chronic treatable infection. Soon after the identification of HIV as the etiological agent of AIDS (Barre-Sinoussi et al., 1983; Popovic et al., 1984) a collaboration between the U.S. National Cancer Institute (NCI) and the pharmaceutical company Burroughs-Wellcome led to the discovery that AZT was able to suppress HIV-1 replication in cell culture (Broder, 2010; Mitsuya et al., 1985). AZT, a nucleoside analogue originally synthesized in 1964 as a potential cancer treatment was identified as a DNA polymerase chain terminator with a significant degree of selectivity for the HIV-1 reverse transcriptase (RT). As described by Samuel Broder in this issue, in

Table 1
Timeline of milestones in HIV research and antiretroviral therapy.

• **1981**	*Mortality and Morbidity Weekly Report* (*MMWR*) reports of men treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at three different hospitals in Los Angeles, U.S.A.; All patients showed signs of severe immunodeficiency.
• **1983**	A new human lymphotropic retrovirus (HTLV-III/HIV-1) is isolated from T-cells of immunocompromised patients a retrovirus that is believed to be the underlying cause of the disease.
• **1984**	Etiological link of HIV to AIDS is tentatively demonstrated.
• **1985**	The U.S. Food and Drug Administration (FDA) approves the first ELISA test kit to screen for antibodies to HIV. Zidovudine (AZT) is identified as a candidate agent for antiretroviral therapy. Clinical trials begin.
• **1987**	FDA approval for zidovudine is granted, making it the first antiretroviral therapy to be used as a treatment for HIV/AIDS. The FDA establishes the treatment investigational new drug (IND) mechanism.
• **1992**	FDA adopts an accelerated approval mechanism, allowing for marketing approval of drugs for life-threatening diseases based on surrogate markers, rather than the classical effect on disease morbidity/mortality.
• **1995**	First protease inhibitor (saquinavir) is approved by the FDA.
• **1996**	First NNRTI inhibitor (nevirapine) is approved by the FDA. HAART treatment becomes the standard of care. Viral load assays to measure viral burden are introduced. First cases of resistance to HAART are found and recognized as complications linked to therapy. Combination therapy is used to attempt the eradication of HIV-1 from infected individuals.
• **1997**	The first fixed-dose combination pill to simplify drug adherence, Combivir (AZT + 3TC), is approved. Fast-track approval process allowing for priority review of NDA documentation under abbreviated timelines is formally introduced by the FDA.
• **2000**	Latent HIV reservoirs are identified as a barrier to eradication.
• **2003**	The first fusion inhibitor is introduced (enfuvirtide).
• **2006**	The FDA approves the first single-pill, once-daily full-fixed-dose regimen Atripla™ (TDF + FTC + EFV).
• **2007**	The FDA approves the first CCR5 antagonist (maraviroc) and the first integrase inhibitor (raltegravir).
• **2009**	The first case of long-term control of HIV by CCR5-Δ32 stem-cell transplantation is reported.