

# A brief history of antiretroviral therapy of HIV infection: success and challenges

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**Summary.** Unprecedented efforts in the fields of biology, pharmacology and clinical care have contributed to progressively turn HIV infection from an inevitably fatal condition into a chronic manageable disease, at least in the countries where HIV infected people have full access to the potent antiretroviral drug combinations that allow a marked and sustained control of viral replication. However, since currently used treatments are unable to eradicate HIV from infected individuals, therapy must be lifelong, with the potential for short- and long-term, known and unknown, side effects, and high costs for health care systems. In addition, different patterns of unexpected systemic complications involving heart, bone, kidney and other organs are emerging. Although their pathogenesis is still under debate, they are likely to originate from chronic inflammation and immune dysfunction associated to HIV infection. A final consideration regards the dishomogenous pattern of HIV disease worldwide. In fact, access to HIV diagnosis, treatment and care are seriously limited in the geographical areas that are most affected, like Africa, which sustains 70% of the global burden of the infection. This is one of the greatest challenges that international institutions are asked to face today.

*Key words:* HIV, antiretroviral therapy, eradication.

**Riassunto** (*Una breve storia della terapia dell'infezione da HIV: successi e problemi aperti*). Grazie a un enorme impiego di risorse nel campo della biologia, farmacologia e ricerca clinica, l'infezione da HIV ha subito una graduale evoluzione, da condizione inesorabilmente fatale a malattia cronica trattabile, almeno nei paesi in cui le persone sieropositive hanno pieno accesso alle potenti combinazioni antiretrovirali che consentono un controllo marcato e persistente della replicazione virale. Tuttavia, poiché le terapie attualmente disponibili non sono in grado di eradicare l'infezione, esse vanno protratte per tutta la vita, esponendo il paziente alla potenziale comparsa di eventi avversi, noti e sconosciuti, a breve e lungo termine, con degli alti costi per i sistemi sanitari. Negli ultimi anni sono inoltre emerse complicazioni inattese a carico di cuore, scheletro, rene e altri organi. Benché la patogenesi di queste complicazioni non sia del tutto chiara, probabilmente esse sono in rapporto con lo stato infiammatorio e il deficit immunologico cronicamente associati all'infezione da HIV. Una considerazione finale riguarda il quadro disomogeneo che la malattia da HIV presenta nelle diverse aree geografiche. L'accesso a diagnosi, trattamento e assistenza, infatti, è fortemente limitato proprio nelle aree del mondo dove maggiore è la prevalenza dell'infezione, come l'Africa, che da sola sopporta il 70% di tutti i casi di infezione da HIV. È, questa, una delle emergenze più impegnative che le istituzioni internazionali sono chiamate oggi ad affrontare.

*Parole chiave:* HIV, terapia antiretrovirale, eradicazione.

## INTRODUCTION

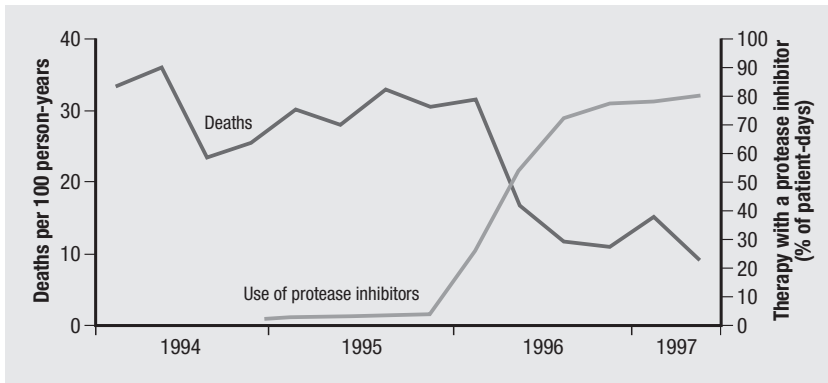
The advances in the knowledge of human immunodeficiency virus (HIV) biology, pathogenesis and therapy, and their dramatic positive consequences on HIV-related morbidity and mortality (*Figure 1*), are quite unique in the history of medicine. Today, antiretroviral (ARV) therapy is potent, convenient and usually well tolerated, capable of reducing HIV blood concentration to undetectable values within a few weeks from treatment initiation and of inducing a robust and sustained CD4 T-cell gain [1, 2].

Despite these unquestioned successes, the problem

is far from being solved: even in countries with full access to antiretroviral treatment, life expectancy of people under ARV therapy remains lower with respect to that of uninfected people [3]. Furthermore, large populations of HIV infected individuals are not diagnosed, remain untreated or enter treatment at a very late stage of diseases. Undiagnosed and untreated population represents an infected reservoir that increases HIV transmission.

### *The HIV epidemic*

After its identification in 1981 as a novel distinct



**Fig. 1** | Decrease of HIV disease mortality after the introduction of potent combined antiretroviral therapy. Reproduced with kind permission from Palella FJ et al. N Engl J Med 1998;338:853-60 [9].

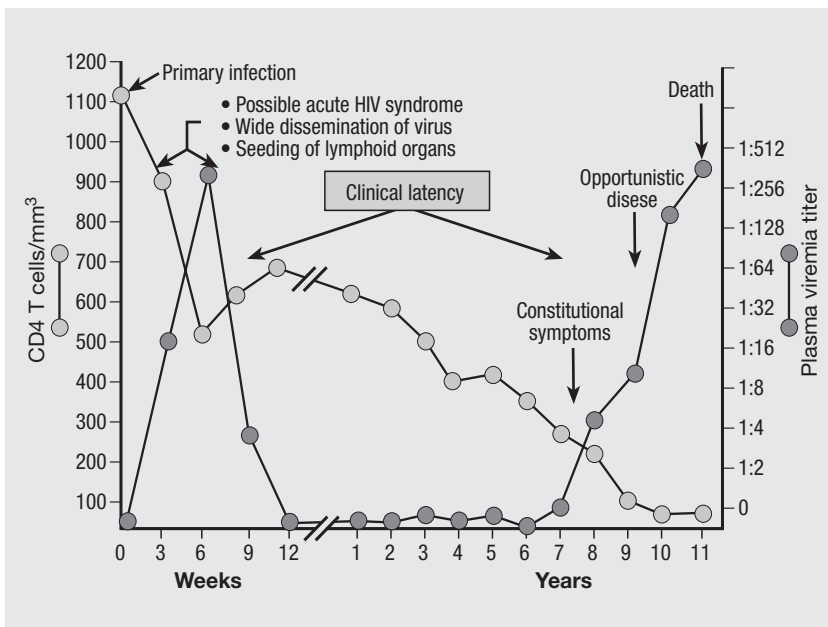
immunodeficiency syndrome (“acquired” rather than “primary”), characterized by a depletion of CD4+ T cells and an expansion of activated CD8+ T cells, in 1983 AIDS was finally associated to HIV in a causative way [4, 5]. Following the development of a diagnostic tool, a huge mass of information on the epidemiology of the disease were rapidly collected. Thanks to huge efforts and resources employment worldwide, most aspects of HIV biology and disease pathogenesis were clarified, allowing pharmacological research to develop, as of today, 23 antiretroviral agents with different mechanisms of action, that can be variously combined.

**The natural history of HIV infection**

HIV is mainly transmitted by parenteral or sexual route. The first step is HIV binding to target cells, followed by its transportation to regional lymphnodes, where it replicates and establishes a productive and permanent infection. In the last few years it has been demonstrated that in the early phases of infection HIV preferentially targets CCR5+CD4+memory

T lymphocytes in the gastrointestinal tract [6]. This results in a rapid, massive and possibly permanent destruction of CD4 cells, rupture of the intestinal mucosa and penetration of microbial translocation products in the systemic circulation. At the same time all body compartments, including the CNS, become infected.

Although being often symptomatic, primary HIV infection is seldom recognized, because symptoms are non specific, consisting in fever, malaise, generalised lymphadenopathy, pharyngitis, diarrhoea and rash, sometimes associated to abnormal laboratory results. Plasma HIV RNA levels are usually high, with an elevated risk of transmitting the infection; formulating an early diagnosis is therefore very important not only for the infected individual but for the whole community as well. After primary HIV infection, a chronic asymptomatic phase ensues of variable duration, with symptomatic disease usually developing when CD4 cell count falls to lower than 350 cells/mm<sup>3</sup> and being characterized by the occurrence of several AIDS- or non AIDS-associ-



**Fig. 2** | Natural history of HIV disease without therapy. Reproduced with kind permission from Pantaleo G et al. N Engl J Med 1993;328:327-35. [15].

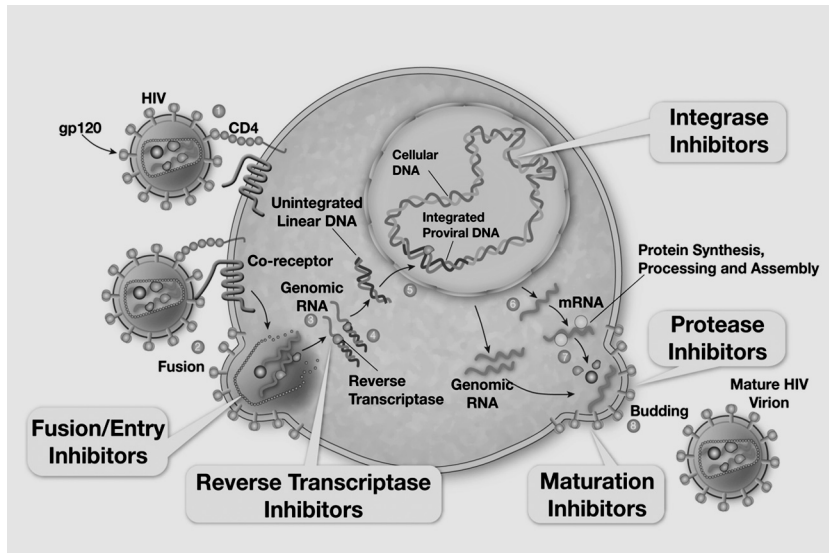


Fig. 3 | Targets of antiretroviral drugs in the HIV life cycle.

ated events (mainly infections or tumors). In the absence of treatment, death is quite unavoidable. However a minority of patients exist, the so-called “élite controllers”, who are able to spontaneously control the infection and maintain low viremia and high CD4 cell count in the absence of therapy. Identifying the mechanisms underlying this natural resistance to HIV is fundamental for approaching two main, still unresolved problems: eradication of the infection and development of an effective vaccine.

While CD4 cell decline is the most specific feature of HIV infection, its mechanism has not been totally clarified (Figure 2). Current opinion is that several factors contribute, the most important being a direct effect of HIV on CD4 cells and a generalized state of inflammation and activation, perhaps due to the chronic translocation of microbial products from the infected gut lumen into the systemic

circulation [7]. Successful long-term antiretroviral therapy is able to reduce, but not to eliminate, the burden of inflammation, that is likely to be causatively associated to some troubling complications of HIV infection, such as cardiovascular diseases, an emerging problem in HIV infected population [8].

**Antiretroviral therapy: successes and limits**

Antiretroviral drugs are classified according to the step they inhibit in the viral life-cycle. A subclassification may be based on their chemical structure. A milestone in the history of HIV disease has been the availability of new classes of drugs, in 1995-96, allowing the introduction of combination ARV therapy (HAART) and the gradual evolution of HIV infection into a chronic, usually non fatal condition [9]. Up to 2010, more than 20 antiretroviral agents have been licensed, in most cases

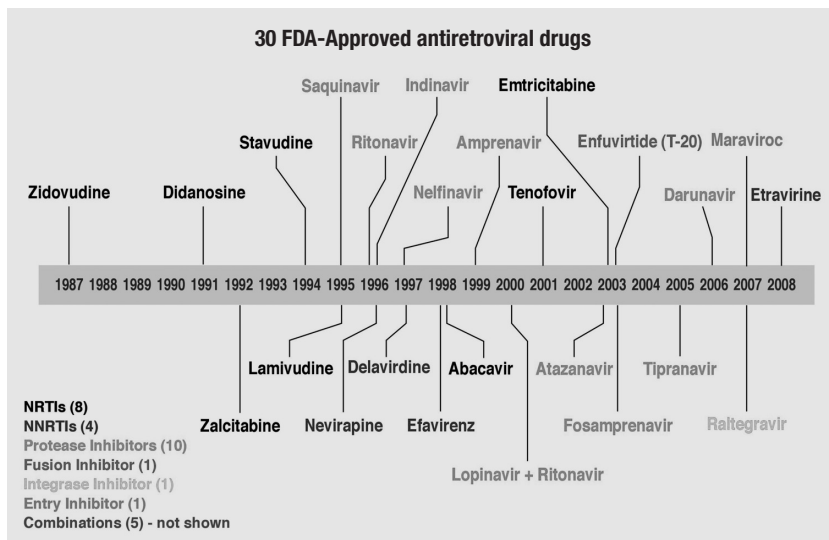


Fig. 4 | Antiretroviral drugs approved for HIV infection.

through an accelerated approval, based not only on clinical efficacy but on their effect on plasma HIV RNA concentration, which is a validated surrogate marker of HIV activity (*Figures 3 and 4*).

Despite these impressive results, several questions still wait for an answer and several issues are still under debate. Furthermore, the emergence of new comorbidities that may be partly associated with ARV therapy and partly with HIV itself represent a new problem in medical practice. When is the best time to start antiretroviral therapy? Which is the best ARV combination to start with? How long should an individual be treated with ARV therapy? These “classic” questions are still open, and they are likely to keep scientists very busy for at least one more decade.

### Present translational research themes

In addition to the “classic” questions on ARV therapy, the clinical research agenda is now shifting toward addressing a new set of questions requiring a complex, multidisciplinary approach. One of these is the very low-level viral replication present in virtually all subjects who achieve plasma HIV RNA concentrations below limits of detectability of commercially available assays (generally around 50 copies per mL) [10]. Regardless of the origin of this residual viremia, it contributes to HIV persistence and, accordingly, to chronic inflammation, persistent immunodeficiency, raised risk for organ damage and accelerate ageing. Another issue is

the long-term immunological response to therapy, which is highly variable. Although the typical patient shows a sustained CD4 cell increase, a remarkable number of subjects never achieve normal ranges of CD4. Old age, the presence of co-infections such as hepatitis C, a lower pretreatment CD4 T-cell nadir, injection drug use and other factors may be associated to a low immunologic recovery, but they don't explain it fully. No effective treatment has been found for these patients.

Does HIV infection accelerate the normal ageing process? This is another question arisen in the last years, due to the higher frequency of organ-specific disease in HIV-infected adults than in uninfected age-matched controls. Cardiovascular disease, bone disease, cancer, renal impairment, and perhaps neurocognitive deficits seem more common in HIV-infected individuals than in age-matched controls [11]. HIV-associated inflammation – which is not fully reversed by therapy – might be a contributing factor, but again it doesn't fully explain the apparent acceleration of ageing process found in HIV infected population.

Does antiretroviral therapy have a role in decreasing transmission at individual and community level? It is well documented that HIV suppression prevents virus transmission from infected women to their newborn babies [12]; similarly sexual transmission in serodiscordant adult couples is reduced in those with lower viral loads. These findings suggest the possibility of HIV treatment as a

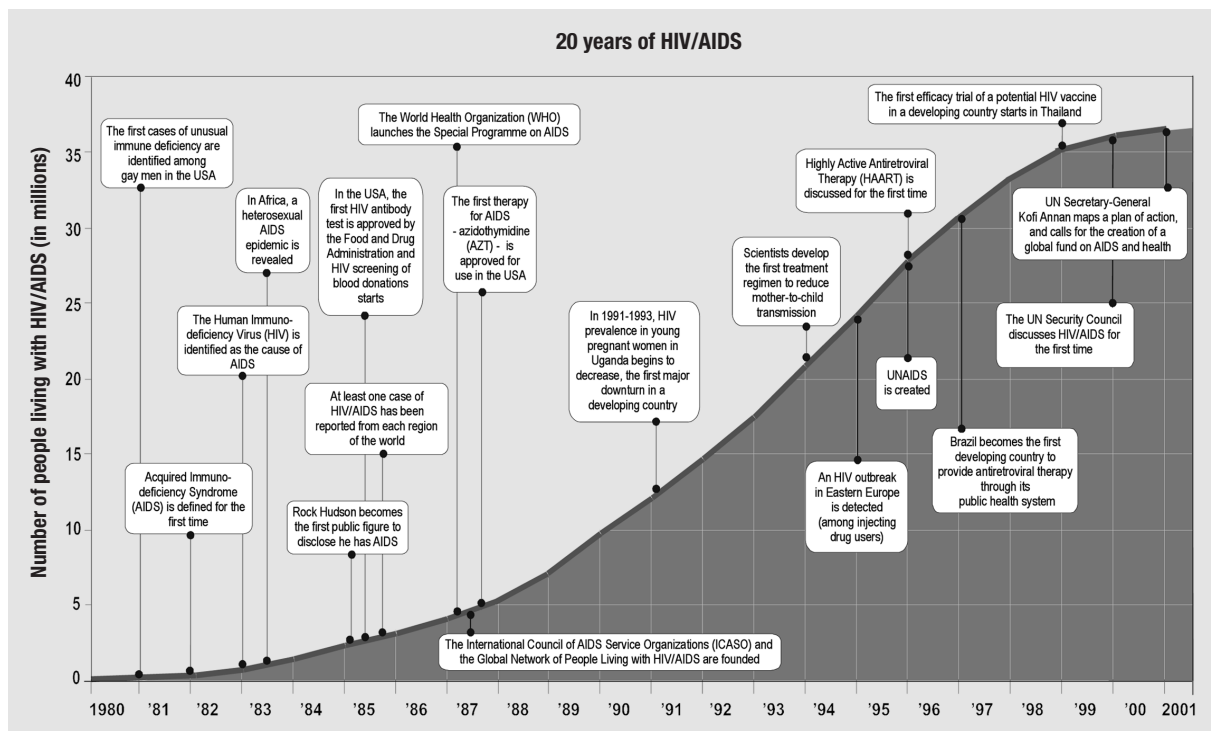


Fig. 5 | Brief history of the AIDS epidemic with milestones. Source: UNAIDS/ONUSIDA, 2001. Reproduced with kind permission.

part of transmission prevention. In fact the strategy of “treatment as prevention” has been successful in the few settings where it has been adopted, and is gaining increasing popularity [13]. A further approach, recently explored in a prospective trial [14] is based on the administration of ARV therapy to uninfected people engaging in risk behaviours. Can HIV infection be cured? In the absence of an effective vaccine, HIV eradication becomes a major goal for global health. However, whether this goal will be achieved is currently unpredictable: although most of HIV-infected cells die, a small proportion of them revert to a dormant stage and survive with HIV DNA persistently integrated in their genome. Since these cells are some of the longest-lived cells in the body, HIV infection can persist for decades in this latent cellular reservoir that is inaccessible to the immune system or present antiretroviral therapy. Several approaches are being considered to reduce or eliminate it, but results are preliminary and controversial. A final question is the drug pipeline: a consequence of the great success of antiretroviral therapy has been a reduced need for new salvage drugs. Accordingly, the pharmaceutical industry has sharply reduced its investment in new therapeutic options. This could eventually prove to be a major problem if an epidemic of multidrug resistant virus develops.

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### CONCLUSIONS

HIV is now a chronic illness in patients with continued treatment access and excellent long-term adherence. Huge efforts are ongoing to reproduce these results even in poor and disadvantaged settings (Figure 5). Although the success of therapy is unquestioned, many issues remain. Since cure is not yet possible, treated people have to maintain lifelong adherence and face the risk of delayed drug toxic effects. Furthermore, even when HIV infection is well controlled, chronic low-level viremia and inflammation can persist, along with a higher than expected risk for many complications often associated with ageing. This represents a challenge for many health-care systems, because the amount of resources needed for effective HIV care is likely to increase in the next future. Political leaders should realize that the epidemic is far from being curbed, rather it is only changing its face.

### Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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