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Review

The development of antiretroviral therapy and its impact on the HIV-1/AIDS pandemic

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ABSTRACT

In the last 25 years, HIV-1, the retrovirus responsible for the acquired immunodeficiency syndrome (AIDS), has gone from being an "inherently untreatable" infectious agent to one eminently susceptible to a range of approved therapies. During a five-year period, starting in the mid-1980s, my group at the National Cancer Institute played a role in the discovery and development of the first generation of antiretroviral agents, starting in 1985 with Retrovir® (zidovudine, AZT) in a collaboration with scientists at the Burroughs-Wellcome Company (now GlaxoSmithKline). We focused on AZT and related congeners in the dideoxynucleoside family of nucleoside reverse transcriptase inhibitors (NRTIs), taking them from the laboratory to the clinic in response to the pandemic of AIDS, then a terrifying and lethal disease. These drugs proved, above all else, that HIV-1 infection is treatable, and such proof provided momentum for new therapies from many sources, directed at a range of viral targets, at a pace that has rarely if ever been matched in modern drug development. Antiretroviral therapy has brought about a substantial decrease in the death rate due to HIV-1 infection, changing it from a rapidly lethal disease into a chronic manageable condition, compatible with very long survival. This has special implications within the classic boundaries of public health around the world, but at the same time in certain regions may also affect a cycle of economic and civil instability in which HIV-1/AIDS is both cause and consequence. Many challenges remain, including (1) the life-long duration of therapy; (2) the ultimate role of pre-exposure prophylaxis (PrEP); (3) the cardiometabolic side-effects or other toxicities of long-term therapy; (4) the emergence of drug-resistance and viral genetic diversity (non-B subtypes); (5) the specter of new cross-species transmissions from established retroviral reservoirs in apes and Old World monkeys; and (6) the continued pace of new HIV-1 infections in many parts of the world. All of these factors make refining current therapies and developing new therapeutic paradigms essential priorities, topics covered in articles within this special issue of *Antiviral Research*. Fortunately, there are exciting new insights into the biology of HIV-1, its interaction with cellular resistance factors, and novel points of attack for future therapies. Moreover, it is a short journey from basic research to public health benefit around the world. The current science will lead to new therapeutic strategies with far-reaching implications in the HIV-1/AIDS pandemic. 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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1. Antiretroviral therapy: "treating the untreatable"

This article introduces a special issue of *Antiviral Research* focusing on progress against HIV-1 and prospects for the future. Physicians now have approximately 30 antiretroviral products, formulated either singly or in combination, to treat patients with human immunodeficiency virus (HIV-1), the pathogenic retrovirus which causes the acquired immunodeficiency syndrome (AIDS) and related conditions (Table 1). Most are oral medicines, administered on convenient schedules. Several have been specially formulated as fixed-dose, generic-drug combinations for even greater utility in resource-poor nations.

The foundational antiretroviral drugs taken into the clinic were nucleoside reverse transcriptase inhibitors (NRTIs) in the form of dideoxynucleosides (Broder, 1990a). After anabolic phosphorylation reactions in host cells, the NRTIs function by competitive inhibition and chain termination against the HIV-1 DNA polymerase (reverse transcriptase, RT). In 1985, animated by a collaboration with scientists at Burroughs-Wellcome (the sponsor of AZT) and Duke University, my colleagues and I at the National Cancer Institute (NCI) were privileged to study these antiretroviral therapies both in our lab and clinic. In 1985–1986, we helped define an orally attainable therapeutic range for AZT, thereby providing the first proof that effective inhibition of HIV-1 was possible, and simultaneously confounding prophesies to the contrary (Mitsuya et al., 1985, 1987a, 1987b, 1988, 1990; Mitsuya and Broder, 1986, 1987, 1988; Yarchoan et al., 1986; Yarchoan and Broder, 1987; Klecker et al., 1987; Johnson et al., 1988). The NRTIs generally (but not always) act with greater specificity for the HIV-1 RT, compared to mammalian DNA polymerases (see Martin et al. and Cihlar and Ray, 2010). There is a separate enzyme (polymerase-gamma) inside the cell that replicates mitochondrial DNA. NRTIs can deplete or impair the function of this enzyme under certain circumstances. Side-effects of these antiretrovirals, while real and not to be discounted, did not preclude their approval as effective therapies for HIV-1/AIDS. AZT is the prototype, but the story is clearly about more than AZT, or any one drug for that matter.

Members of the first generation of NRTIs were eventually joined by nonnucleoside RT inhibitors (NNRTIs), which take aim at a specific 'pocket' binding site within the HIV-1 RT, distinct from the catalytic site (De Clercq, 2004; de Bethune, 2010), and the viral protease inhibitors (Schleif et al., 1988; Kohl et al., 1988; Robins and Plattner, 1993; Hoetelmans et al., 1997; Ghosh et al., 2007; Wensing et al., 2010). Still later came a range of agents targeting other phases of the HIV-1 life cycle, including inhibition of the fusion step for gp41-mediated entry (Kilby et al., 1998), early entry of the virus, such as CCR5 co-receptor antagonists (Kuritzkes, 2009; Tilton and Doms, 2010), and integrase function (Evering and Markowitz, 2007; Cocohoba and Dong, 2008; McColl and Chen, this issue). Indeed, the title of a recent editorial in a prominent medical journal referred to the current availability of antiretroviral drugs for use in the initial treatment of HIV-1 infection as an "embarrassment of riches" (Hirschel and Calmy, 2008). Another recent scientific review named current therapy against HIV-1 infection a "triumph for modern medicine" (Richman et al., 2009).

It was not always this way.

Certain entrenched beliefs complicated the task of developing antiretroviral drugs, including: (1) active (replicating) retroviruses did not exist in human beings; or (2) if they did, they were not associated with human diseases; or (3) in the alternative, even if somehow active human retroviruses did exist, such agents played a relatively minor or "anecdotal" role in the public health (primarily limited to rather rare subacute T-cell leukemias or unusual neurologic syndromes, as in the case of HTLV-1); or (4) even if the first three conditions somehow did not apply, retroviruses by their very nature were inherently untreatable, based primarily on their capacity to integrate into the host genome and/or rapidly mutate due to the error-prone RT. These beliefs were initially a barrier to progress in the prevention, diagnosis, and treatment of AIDS. Overturning them was an essential element for progress in the therapy of HIV-1/AIDS.

The discovery of HIV-1 affected almost every aspect of the public health (Gallo and Montagnier, 2003; Gallo, 2004). Indeed, the proof that a new human retrovirus was the cause of AIDS in 1984 and, particularly, the virtually instantaneous development of an effective screening test for blood donors were astonishing achievements in science, perhaps without parallel in modern times. Recently, Professor Anders Vahlne at the Karolinska Institute published a unique historical perspective on these pivotal discoveries, one that is uncommonly dispassionate and concise (Vahlne, 2009).

There can be no doubt that the rapid application of this knowledge saved countless lives. However, the realization that a retrovirus was the cause of AIDS revived a sense of futility or therapeutic nihilism in many clinical researchers and patients alike. The belief that retroviruses were, by definition, not amenable to therapy remained strong, to the potential detriment of clinical research by creating a self-imposed restriction on what the available clinical science and technology could accomplish, or possibly even try.

We now know that antiretroviral agents can, indeed, improve clinical outcomes in HIV-1 infection, and moreover, such therapies have demonstrably reduced the death rate of AIDS in this country and other parts of the world, but this knowledge did not come easily. The presumed futility of antiretroviral therapy and the "false hopelessness" this engendered in patients (and physicians) are now for the most part forgotten history. (5/30/06 Interview with Martin Delaney, Project Inform; Frontline: The Age of AIDS: interviews|PBS http://www.pbs.org/wgbh/pages/frontline/aids/interviews/.)

2. In the beginning: the earliest programs to identify antiretroviral agents

The discovery of the broad antiretroviral properties of a series of 2′,3′-dideoxynucleosides, the most prominent of which is AZT (3′-azido-2′,3′-dideoxythymidine, zidovudine), showed that treating HIV-1 was possible. The earliest agents still play an important role as ingredients of highly active antiretroviral therapy combinations, but more important, they breached a critical barrier and illuminated a path for other drugs to follow. Such drugs held substantial promise when we first considered them because (1) *in vitro* they were active against widely divergent retroviral isolates; (2)