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The Development of Antiretroviral Therapy and Its Impact on the Global HIV-1/AIDS Pandemic: Lessons from “treating an untreatable” infectious agent.

Abstract

In the last twenty- five years, HIV-1, the pathogenic retrovirus responsible for 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 played a role in the discovery and development of the first generation of antiretroviral agents. We focused on zidovudine (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 is treatable, and such proof provided momentum for new therapies from many sources, directed at a range of viral targets, and at a pace that has been rarely if ever matched in modern drug development. Antiretroviral therapy, despite many prophecies of failure, has brought about a substantial decrease in the death rate due to HIV-1 infection. In resource-rich nations, such therapy has changed the nature of HIV-1 infection from a rapidly lethal disease into a chronic manageable condition, one compatible with very long survival. Most of the available therapies are oral medicines, administered on relatively convenient schedules. Several have been specially formulated as fixed-dose, generic-drug combinations for even greater utility in resource-poor nations. 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.) life-long duration of therapy; 2.) the ultimate role of pre-exposure prophylaxis (PrEP); 3.) 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; 6.) the continued pace of new HIV-1 infections in many parts of the world; and 7.) barriers or inefficiencies in providing state-of-the-art medical care. All of these factors make refining current therapies and developing new therapeutic paradigms essential priorities. Nonetheless, there is a short journey from basic research to public health benefit around the world. The current science will likely lead to new strategies of therapy against HIV-1 with far-reaching implications in the HIV-1/AIDS pandemic. Perhaps there are broader lessons for a wholeness of motion from lab bench to the clinic and back again, with potential relevance to a range of other “untreatable” conditions.