Antiviral Research 85 (2010) 1–18

Contents lists available at ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

Review

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

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ARTICLE INFO

Article history:
Received 18 May 2009
Accepted 10 October 2009

Keywords:
HIV-1
AIDS
Antiretroviral therapy
Zidovudine
Nucleoside reverse transcriptase inhibitors

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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doi:10.1016/j.antiviral.2009.10.002

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)

Table 1
Approved antiretroviral drugs. Adapted from: *Drugs Used in the Treatment of HIV Infection*, U.S. FDA, http://www.fda.gov/oashi/aids/virals.html. Drugs are listed in order of FDA approval within each class.

Brand name	Generic name(s)	Manufacturer name	Approval date	Time to approval
Nucleoside reverse transcriptase inhibitors (NRTIs)[a,b]				
Retrovir	Zidovudine, azidothymidine, AZT, ZDV	GlaxoSmithKline (original sponsor Burroughs-Wellcome)	19 March 1987	3.5 months
Videx	Didanosine, dideoxyinosine, ddI	Bristol Myers-Squibb	9 October 1991	6 months
Hivid	Zalcitabine, dideoxycytidine, ddC (no longer marked as of December 31, 2006)	Hoffmann-La Roche	19 June 1992	7.6 months
Zerit	Stavudine, d4T	Bristol Myers-Squibb	24 June 1994	5.9 months
Epivir	Lamivudine, 3TC	GlaxoSmithKline	17 November 1995	4.4 months
Combivir	Lamivudine and zidovudine	GlaxoSmithKline	27 September 1997	3.9 months
Ziagen	Abacavir sulfate, ABC	GlaxoSmithKline	17 December 1998	5.8 months
Videx EC	Enteric coated didanosine, ddI EC	Bristol Myers-Squibb	31 October 2000	9 months
Trizivir	Abacavir, zidovudine, and lamivudine	GlaxoSmithKline	14 November 2000	10.9 months
Viread	Tenofovir disoproxil fumarate, TDF	Gilead Sciences	26 October 2001	5.9 months
Emtriva	Emtricitabine, FTC	Gilead Sciences	02 July 2003	10 months
Epzicom	Abacavir and lamivudine	GlaxoSmithKline	02 August 2004	10 months
Truvada	Tenofovir disoproxil fumarate and emtricitabine	Gilead Sciences	02 August 2004	5 months
Nonnucleoside reverse transcriptase inhibitors (NNRTIs)[c]				
Viramune	Nevirapine, NVP	Boehringer Ingelheim	21 June 1996	3.9 months
Rescriptor	Delavirdine, DLV	Pfizer	4 April 1997	8.7 months
Sustiva	Efavirenz, EFV	Bristol Myers-Squibb	17 September 1998	3.2 months
Intelence	Etravirine	Tibotec Therapeutics	18 Jane 2008	6 months
Protease inhibitors (PIs)				
Invirase	Saquinavir mesylate, SQV	Hoffmann-La Roche	6 December 1995	3.2 months
Norvir	Ritonavir, RTV	Abbott Laboratories	1 March 1996	2.3 months
Crixivan	Indinavir, IDV,	Merck	13 March 1996	1.4 months
Viracept	Nelfinavir mesylate, NFV	Agouron Pharmaceuticals	14 March 1997	2.6 months
Fortovase	Saquinavir (no longer marketed)	Hoffmann-La Roche	7 November 1997	5.9 months
Agenerase	Amprenavir, APV	GlaxoSmithKline	15 April 1999	6 months
Kaletra	Lopinavir and ritonavir, LPV/RTV	Abbott Laboratories	15 September 2000	3.5 months
Reyataz	Atazanavir sulfate, ATV	Bristol-Myers Squibb	20 June 2003	6 months
Lexiva	Fosamprenavir calcium, FOS-APV	GlaxoSmithKline	20 October 2003	10 months
Aptivus	Tipranavir, TPV	Boehringer Ingelheim	22 June 2005	6 months
Prezista	Darunavir	Tibotec, Inc.	23 June 2006	6 months
Fusion inhibitors				
Fuzeon	Enfuvirtide, T-20	Hoffmann-La Roche and Trimeris	13 March 2003	6 months
Entry inhibitors—CCR5 co-receptor antagonists				
Selzentry	Maraviroc	Pfizer	06 August 2007	8 months
HIV integrase strand transfer inhibitors				
Isentress	Raltegravir	Merck & Co., Inc.	12 October 2007	6 months
Multi-class combination products				
Atripla	Efavirenz, emtricitabine and tenofovir disoproxil fumarate	Bristol-Myers Squibb and Gilead Sciences	12 July 2006	2.5 months

[a] Zidovudine (AZT) was the first NRTI to be administered to patients with HIV-1 infection and the first antiretroviral drug to be approved. It is still in use in combination products.
[b] Tenofovir disoproxil fumarate, an acyclic phosphonate nucleotide, was the first antiretroviral nucleotide (NtRTI) approved.
[c] Etravirine exhibits a high genetic barrier to the development of drug-resistance.

there was a large differential between the concentration needed to inhibit HIV-1 replication and viral cytopathic effect in target T cells and monocytes/macrophages compared to their toxicity for uninfected cells; (3) antigen- and mitogen-driven T cell-activation showed a comparable differential between efficacy and toxicity, as did immunoglobulin production by indicator B cells; and (4) a logical structure–activity relationship for the class was evident (Mitsuya et al., 1985; Mitsuya and Broder, 1986; Perno et al., 1988).

In 1984, our central hypothesis was that protecting uninfected cells by blocking viral infection, with its attendant usurpation of the host cell's molecular machinery and iterative cycles of replication, would permit meaningful recovery and restoration of immune function, or at least prevent further loss of immunity, and thereby benefit the patient in tangible ways. This now, in hindsight, seems self-evident, but it definitely was not so at the time. Furthermore, most retrovirologists had little or no experience in clinical drug development, and typically believed that a vaccine program was the higher priority, in any event.

We were open to virtually any drug to treat this lethal and terrifying disease. This applied regardless of a prior intended use—provided that a candidate agent could effectively suppress HIV-1 replication and cytopathic effect at doses that were not toxic to normal host cells. We followed these principles in the newly established antiretroviral drug discovery program in my laboratory (one of the very few in the world with the technical proficiency and willingness to do so at that time). Certain chain-terminating dideoxynucleosides including AZT had been synthesized as potential anti-cancer agents under grants from the National Cancer Institute in the mid-1960s, about 20 years before the discovery of HIV-1 (see timeline of AZT development in Table 2); discussed in (Yarchoan and Broder, 1987). AZT failed in the cancer-drug candidate selections of the time and remained of little interest for applications in human virology. However, we found that AZT was highly active against HIV-1 in vitro, and, indeed, clinical activity was observed even in our very first study to administer zidovudine (AZT) and related drugs such as Hivid® (zalcitibine) or Videx®

Table 2
A timeline of the synthesis, preclinical testing, clinical evaluation and FDA approval of AZT for the treatment of HIV-1/AIDS.

Date	Step in AZT development, evaluation and approval		Reference(s)
1964		With grant support from the NCI, AZT is first synthesized as a potential anti-cancer agent.	Horwitz et al. (1964), also discussed in Yarchoan and Broder (1987)
1974		AZT is shown to suppress the replication of Friend murine leukemia virus *in vitro*.	Ostertag et al. (1974)
Early 1980s		The compound is resynthesized by Burroughs-Wellcome and found to be active against gram-negative bacteria.	Keith et al. (1989), synthesis as described by Lin and Prusoff (1978)
1981		AIDS is first recognized.	CDC (1981)
1983–1984		HIV-1, a novel retrovirus, is identified as the cause of AIDS, in a revolutionary departure from the dogma that pathogenic retroviruses did not cause common human diseases.	Described in Vahlne (2009)
1984	May–August	NCI immediately establishes systems for rapid testing of HIV-1 replication and cytopathic effect in cloned human $CD4^+$ T cells and proves principle that HIV-1 replication can be suppressed by drugs at doses that protect cells against infectivity and cytopathic effects.	Mitsuya et al. (1984), Mitsuya et al. (1987b)
1984	November	In the initial phase of an HIV-1 drug-screening initiative, Burroughs-Wellcome scientists again find AZT active against murine leukemia virus.	
1985	February	Testing at NCI shows that AZT suppresses HIV-1 replication of diverse strains *in vitro* at doses that do not damage viability and function of normal cells.	Mitsuya et al. (1985)
	June 15	Burroughs-Wellcome and NCI file an Investigational New Drug (IND) application to support human testing of AZT. FDA approves it in 7 days.	Wasila and Lasagna (1990)
	July 3	The first patient enrolls in the NCI AZT Phase I trial at the NIH Clinical Center in Bethesda, MD.	Yarchoan et al. (1986)
1986		AZT shown to act through its triphosphate to inhibit the HIV RT.	Furman et al. (1986)
	February 18; last patient entered June 30	A Phase II randomized, placebo-controlled study of AZT efficacy in AIDS patients is initiated, sponsored by Burroughs-Wellcome.	Fischl et al. (1987)
	September 19	The Phase II trial is halted when the Data Safety Monitoring Board (DSMB), after two meetings, announces that patients treated with AZT had a significantly higher survival rate than the placebo group (1 death in 145 vs. 19 of 137).	
	October 11	A treatment IND, based on the NCI model for unlicensed cancer drugs, and makes AZT available for patients on physicians' request.	
1987	March 19	A marketing New Drug Application (NDA) is approved by the FDA in 3.5 months.	

(didanosine) to patients with AIDS (Broder, 1990a; Broder et al., 1990; Yarchoan et al., 1986, 1987, 1988, 1989, 1990a, 1990b; Yarchoan and Broder, 1987).

Perhaps our location in NCI and our longstanding interest in the relationship between immunodeficiency disease and cancer had other benefits (Broder, 1990b). In cancer, under the right conditions, it is possible to reduce tumor burden in a patient, because cancer cells are more sensitive to the actions of a drug or radiation and have less capacity to repair the damage compared to normal cells. Moreover, one may use dose-intensive adjuvant chemotherapy to prevent a future recurrence after surgery or radiation to treat the primary tumor, at a time when no cancer cells are clinically evident. An oncologist typically would not dismiss any therapy that was likely to afford significant palliation, even if a true cure were not possible. Nor would an oncologist hesitate to use combinations of drugs, with different mechanisms of action and side-effect profiles, either because no single drug could deal with proliferating cancer cells and their capacity to become drug resistant, or because excessively dosing one agent alone would result in cumulative organ damage. Indeed, the default assumption is that drugs must be developed with the aim of incorporating them into later combination regimens, even if phase I (dose-seeking) clinical trials must study single agents. Last, but certainly not least, in the therapy of advanced cancers inaction commonly (indeed, all too commonly) poses more of a risk than action. Each of these principles, drawn from the world of cancer, had significant implications for the development of antiretroviral agents, starting with AZT.

As but one example, these were the principles that led Dr. Vincent DeVita and his colleagues at the NCI 40 years ago to dramatically cure certain advanced forms of Hodgkin's disease for the first time using drugs with different mechanisms of action against the tumor and different toxicities against normal tissues (DeVita et al., 1970). Perhaps because we were medical oncologists and worked at NCI, my colleagues and I were inclined to believe that an analogous situation applied to HIV-1, which despite its lethality in human beings, in fact, proved more vulnerable to treatment in practice than in the theory that preceded it.

In any event, we hypothesized that it is not necessary to eradicate the virus to achieve a durable clinical benefit. The latter perspective gave us a sharp and practical focus on drug development with attainable goals for one (small) laboratory. There were no reliable animal models at the time, and we could not await their development.

We also strongly believed then, as we do now, in Voltaire's maxim: "*Le mieux est l'ennemi du bien*," which translated for the AIDS pandemic means, "The perfect is the enemy of the good." Rather than wait for the perfect antiretroviral drug to be developed, we decided to proceed with what we had in hand as rapidly as possible.

It was necessary to take into account the intracellular metabolism of dideoxynucleosides. As a class, these compounds typically require anabolic phosphorylation (activation) and related aspects of intracellular pharmacology to exert an antiretroviral effect (Furman et al., 1986; Cooney et al., 1986, 1987; Hartman et al., 1991). HIV-1 does not carry the relevant enzymes with it, a "simple" fact but one surprisingly overlooked from time to time during the early and often animated discussions of antiretroviral drug activity and the logic of drug-development priorities. In other words, key enzymatic properties of *host* cells (not the virus) can determine the apparent "success" or "failure" of antiretroviral drugs in various test systems, and even the most "minor" chemical modifications could have significant effects on host activating enzymes. Moreover, a dideoxynucleoside may appear inert if the wrong host cell is used, even if its triphosphate serves as a very potent cell-free inhibitor of the HIV-1 RT.

This situation also created opportunities for misinterpretation in using certain animal models, especially common murine systems, whose program of anabolic phosphorylation (or possibly related pathways involving adenylosuccinate synthetase, adenylosuccinate lyase, or purine nucleoside phosphorylase) for a given nucleoside could differ significantly from human cells. By the same token, under certain conditions the intracellular concentrations of fully phosphorylated (activated) *nucleotide* allowed for a longer duration of protection against viral replication in vivo than one might have predicted from monitoring circulating levels of the *nucleoside*. Related products belonging to the class of acyclic phosphonate nucleotide RT inhibitors (NtRTIs) are now available (De Clercq and Holý, 2005; Lee and Martin, 2006). The first drug in this class was tenofovir disoproxil fumarate (TDF), approved in 2001 as Viread®. TDF bypasses the first and often rate-limiting phosphorylation step, and achieves high intracellular concentrations of tenofovir diphosphate, which is functionally equivalent to certain NRTIs in their triphosphate state.

With these basic ideas and observations in mind, we were able to directly initiate clinical trials, a process facilitated by an NIH tradition of locating research labs adjacent to clinical wards and strongly encouraging, if not requiring, physician-investigators to adopt a wholeness of motion from the research lab bench to the hospital bedside, then back to the lab. I cannot overstate how important this was and how much of a liability its absence would have been. This research model is worth preserving and replicating, despite understandable pressures to create a clear division of labor between basic researchers and clinical investigators.

3. The first evidence of antiretroviral activity in the clinic

Several of the drugs studied showed activity in our exploratory clinical trials at the NIH Clinical Center and in other institutions (Broder et al., 1990; Yarchoan et al., 1986, 1987, 1988, 1989, 1990b; Yarchoan and Broder, 1987). For example, in our very first study of AZT, we observed increases in the numbers of circulating helper–inducer $CD4^+$ T cells, an improvement of cytotoxic T-cell response to influenza virus-infected autologous cells, conversion from anergy to positive delayed hypersensitivity skin-test reactions, clearance of fungal infections without specific anti-fungal treatment, and other signs of improved immune function. In many cases, the increase in circulating $CD4^+$ T cells became evident after the second week of therapy (Yarchoan et al., 1986), causing most colleagues not associated with the study to react with incredulity. This created an incongruity between the prevailing pessimism of the time and our own encouraging observations in the clinic.

We also found that peripheral blood mononuclear cells infected with HIV-1 (modern molecular diagnostics had not yet been invented) became negative at therapeutic levels of AZT (Yarchoan et al., 1986). Moreover, we showed the drug had excellent oral bioavailability and penetration into the cerebrospinal fluid (Yarchoan et al., 1986; Klecker et al., 1987), and antiretroviral concentrations were readily achievable in patients, all features that would be important in deciding whether to advance an experimental agent as a therapy for AIDS. These results prompted us to commit to more advanced studies with AZT and also, working with different pharmaceutical sponsors, immediately explore clinical applications of still other dideoxynucleosides that showed good antiretroviral activity in our laboratory systems, both alone and in combination (reviewed in Yarchoan et al., 1990a). We quickly learned that AZT was neither unique nor an anomaly, and other dideoxynucleosides that suppressed HIV-1 replication in our laboratory tests had activity in the clinic and a favorable therapeutic index for long-term administration. Within a short period, we saw signs that AIDS could change from an imminently fatal disease to a manageable illness (Broder et al., 1990).

AZT and related dideoxynucleosides were rapidly advanced into prospective, randomized, multi-center clinical trials endorsed by the National Institute of Allergy and Infectious Diseases (NIAID) and private pharmaceutical companies, initially using clinical endpoints (chiefly survival), as no surrogate markers were then accepted (Naeger et al., 2010). In the case of AZT, the clinical scientists at the corporate sponsor, Burroughs-Wellcome (Wellcome Research Laboratories), made incomparable contributions by rapidly advancing AZT into registration-seeking trials after our initial laboratory and clinical observations (Mitsuya et al., 1985; Yarchoan et al., 1986), and by strongly advancing a drug to treat an "untreatable" disease by means of a history-making, head-to-head comparison of AZT to placebo. Arguably, they risked their corporate careers in undertaking such a project. To those whose experience is informed entirely by the current wide array of safe and effective antiretroviral drugs, this may seem like an exaggeration, but it clearly was not so to those attempting antiretroviral therapy 25 years ago. Moreover, no other group, public or private, was then able to sponsor or shoulder the ultimate responsibility for placebo-controlled, randomized trials in patients with HIV-1/AIDS. After all, HIV-1 was still new and the presumption was that treatment directed at this agent was destined to fail or cause harm, and in any event, the infrastructure for doing multi-center trials in antiretroviral treatment did not then exist. At that nascent stage of antiretroviral drug development, without a positive placebo-controlled trial, a consensus on the safety and efficacy of AZT would have been impossible. A failure to achieve such a consensus would, in turn, have shed more heat than light on the fundamental questions of the day, and antiretroviral programs within my laboratory at the NCI would likely have ended.

Fortune smiled. The randomized controlled trial promptly showed a significant survival advantage for AZT versus placebo, together with improvements in clinical, virological and immunological responses (Fischl et al., 1987; Parks et al., 1988). Such trials, in turn, led to approval by the U.S. Food and Drug Administration (FDA) and by Health Ministries in other countries, with unprecedented velocity. This suddenly changed everything.

As one example, Retrovir® (zidovudine, AZT) was approved in the USA on March 19, 1987 (Table 1). A brief history both of AZT and the road to approval is described in Table 2. An additional perspective is this: Our paper first describing zidovudine's in vitro activity against HIV-1 had only been communicated on June 28, 1985, less than two years prior to FDA approval and we had published the results of the first clinical trial barely one year earlier (Mitsuya et al., 1985; Yarchoan et al., 1986). It was, therefore, possible to move from lab discovery to clinical trials, then on to FDA approval of a novel therapeutic agent, with unprecedented speed against an infectious agent thought to be inherently untreatable, and in the

bargain, during an era when therapy against any virus was basically still quite novel.

Clinical research is not devoid of irony.

There were other sponsors for drugs that we discovered, then advanced into the clinic shortly after AZT. These included Hoffmann-La Roche (zalcitibine) and Bristol-Myers Squibb (didanosine), and they were not far behind (see Martin et al., 2010). However, these sponsors were not required to include placebo-controls in their trials, and they were armed with the knowledge that HIV-1 was not inherently untreatable. That said, the rapid development of two more antiretroviral agents showed that AZT was neither a mere scientific curiosity nor an anomalous outcome. At the time, some members of the public and the lay press seemed to endow AZT with more promise than any single agent could possibly redeem (see further below), a prelude for severe disappointment. Had the development of AZT not been quickly accompanied by the discovery and development of other antiretroviral agents, it is entirely possible that a sense of therapeutic nihilism and of "false hopelessness" would have resurfaced. Indeed, we began clinical testing of other dideoxynucleosides, and undertook combination treatments, as soon as AZT was approved (Yarchoan et al., 1988, 1990a) partly with these considerations in mind. Attempting to do so earlier would have been a practical impossibility, since the regulatory barriers against studying two experimental agents at the same time were (and perhaps still are) extremely high.

A few additional words may help to further maintain a balanced account of this story. The urgent introduction of AZT into the clinic eventually had an unprecedented impact on antiretroviral therapy, and indeed, founded the field as we now know it. However, the limitations of AZT as a single agent, or monotherapy with any available agent, were clear. For example, AZT monotherapy can result in the emergence of viral drug-resistance rather quickly in some patients. Indeed, based on the earlier analogies to cancer drug development, in which successful reliance on a single agent is uncommon, we never considered antiretroviral therapy with a single agent to be a realistic goal, other than to lay the foundation for broader treatment regimens. Thus, clinical researchers quickly adopted various combinations as they became available, comprised of protease inhibitors and other agents, once it was confirmed that no one drug could achieve durable viral suppression or clinical benefit. Therefore, it was often not an automatic requirement to abandon an approved agent – a favorable circumstance for clinical progress. All of these considerations helped foster the development of what is now called highly active antiretroviral therapy (HAART), a catchphrase that signifies both combination treatment and definitive progress.

Dideoxynucleosides that arose from the early period of antiretroviral drug development, such as zidovudine and didanosine (both now generics), are still in use today primarily in combination regimens. More important by far, drugs from that early era facilitated the introduction of second-generation nucleoside/nucleotide agents now in wide use. These include drugs such as Truvada® (a combination of emtricitabine and tenofovir disoproxil fumarate) and related drugs, which remain key ingredients in regimens for previously untreated and treated patients and are crucial experimental agents in trials of pre-exposure prophylaxis (PrEP).

At a minimum, these successes removed the lingering concern that pathogenic retroviruses were somehow *inherently* untreatable and, therefore, that antiretroviral drug development was an impossibility. This in turn had an incalculable effect on both basic and clinical research, and especially on future drug development. In the 1980s, the successful new drug application for AZT at the U.S. FDA altered the strategic thinking of pharmaceutical and biotechnology companies, whose long-term commitment to antiretroviral drug research and development and clear paths to drug approval were essential to success (Naeger et al., 2010).

These successful programs provided a reminder of just how wrong prophecies of doom can be. One can only speculate on the consequences had the outcomes been otherwise.

Indeed, what had been considered to be irreversible neuropathic features of AIDS, e.g., the AIDS dementia complex, responded to dideoxynucleoside therapy—an often astonishing and initially unbelievable event, even for those physicians who witnessed it at first hand. We observed significant reversal of neurologic signs and brain metabolic abnormalities on positron emission tomography (PET scans) in adult patients (Yarchoan et al., 1987; Brunetti et al., 1989). This was not a cure, yet after 12 weeks of therapy we observed a clear pattern of improvements in memory and focused attention and in a range of other neuropsychological deficits, particularly for those patients with central nervous system compromise at entry (Brouwers et al., 1997). Moreover, dideoxynucleosides like zidovudine, alone and in combination, were also quickly shown to improve intelligence-quotient scores, reverse documented brain atrophy, ameliorate abnormal gait and coordination, decrease protein in cerebrospinal fluid, and increase growth velocity in children with AIDS (Pizzo et al., 1988; Pizzo, 1990; De Carli et al., 1991; Wolters et al., 1994; Verwheel et al., 2002). In our own studies, we found consistent and substantial improvement in all 13 children between 6 months and 12 years of age who presented with neurologic or encephalopathic changes before treatment with AZT (Pizzo et al., 1988). Improvements began within three to four weeks. Notable neurologic benefit could occur even in children who had minimal enhancement of immunologic function.

Early viral invasion of the central nervous system can occur, even in asymptomatic patients, primarily within reservoirs of macrophages and microglia. Moreover, HIV-1 expression renders such cells resistant to apoptotic death (Cosenza et al., 2004). From "first principles" some might have argued that our observations on neurological improvements at the bedside were "impossible". We were fortunate the clinical observations pointed to a different conclusion.

The availability of zidovudine also made it possible to reduce the risk of HIV-1 transmission from mother to infant in a groundbreaking clinical trial (Connor et al., 1994). The latter provided the first proof that pre-exposure prophylaxis (PrEP) or an early intervention after HIV-1 contact was possible, no small thing this.

By 1988, 4 years after the discovery of HIV-1 as an "untreatable" new retrovirus, it was possible to conclude that ". . .we now face a totally different future" (Broder and Fauci, 1988). The question at that point was no longer *whether* HIV-1 could ever be successfully treated, but rather *how fast* more therapies could be developed. Moreover, within a five-year period (1985–1990), it became possible to outline a range of very plausible targets for new drug development against HIV-1, with a very high degree of confidence that many would yield clinically useful drugs (Mitsuya and Broder, 1987; Mitsuya et al., 1990), a level of optimism that subsequent trials proved to be well warranted.

4. The special role of the FDA

At this point, a few words on the FDA are in order. This Agency has played a critical (and sometimes unappreciated) role in progress against HIV-1/AIDS by innovatively streamlining the drug approval process, giving priority reviews, and instituting remarkably short timelines for the approval of promising new antiretroviral agents and later for molecular diagnostics (Naeger et al., 2010).

More recently, the FDA has implemented a number of policies to enable distribution of important antiretroviral agents at very low price in the developing world, even if there were still patent or

market exclusivity protection for the product in the U.S.A. This is an unusual, if not unique achievement, and there is no doubt that the policies of the FDA have saved many lives in both resource-rich and resource-poor nations (although the trends are more conspicuous in the former, they are real in both).

In resource-rich nations, there has been an improvement of clinical outcomes with combination antiretroviral therapy, characterized by a dramatic decrease in mortality rates and corresponding increases in life expectancy, which we will revisit briefly later. The FDA played a major role in these and other advances, and the topic is covered in more detail elsewhere in this issue (Naeger et al., 2010). Suffice it to say that it is easy to criticize the FDA, whatever its course of action, including agendas such as the pace of basic research over which it has no control. By contrast, it is vanishingly rare to acknowledge when the Agency performs with great distinction, as is the case here. In the formative years of antiretroviral therapy, the FDA was as much an agent of history as it was a federal agency authorized to review the safety and efficacy of new drugs. This fact is widely overlooked.

5. Molecular/companion diagnostics

The earliest studies successfully developed antiretroviral agents well before HIV-1 molecular/companion diagnostics were accessible in the clinic. A vast majority of available antiretroviral drugs target the HIV-1 RT or the protease (both mutable), and the absence of clinically adaptable measures for circulating viral load and drug-resistance testing contributed to the original skepticism that antiretroviral therapy could ever prove viable outside of the rarified atmosphere of a clinical research institution, if even there.

That changed with the discovery of the polymerase-chain-reaction (PCR) and the development of reliable molecular diagnostic methods that serve as companions to treatment in ordinary medical practice (Kwok et al., 1987; Ou et al., 1988; Sninsky and Kwok, 1993; Piatak et al., 1993; Mulder et al., 1994; Mellors et al., 1996; Larder and Kemp, 1989).

Physicians now have at their disposal automated, sensitive, and reproducible HIV-1 viral load assays that combine fluorescent probe detection with real time PCR amplification (for example, see Swanson et al., 2007; Tang et al., 2007). By the same token, physicians also have access to viral genotyping to determine drug-resistance profiles. This is based on high-throughput processing and capillary electrophoresis platforms that provide integrated systems for nucleotide sequence-based analysis of drug-resistance mutations in the HIV-1 RT and protease (for example, see Eshleman et al., 2004). Such tests have turned many physicians who treat HIV-1/AIDS into "molecular biologists" and transformed therapy-selection (especially after virologic failure), fostered new drug development, and enhanced scientific insights into the mechanisms of drug-resistance (e.g., see Menéndez-Arias, 2010).

Furthermore, besides classic molecular diagnostics for drug-resistance, there may also be increasing research and utilization involving HIV-1 phenotype testing, which measures viral replication in vitro at different concentrations of antiretroviral drugs (Zolopa, 2006; Garcia-Perez et al., 2007). Genotyping and phenotyping are not mutually exclusive. Moreover, the utilization of one assay strategy over another depends on many factors including access, cost, turnaround time, availability of relevant expertise for interpretation, and a range of scientific issues still under study. Genotypic assays can be less expensive with perhaps more rapid turnaround time than phenotypic assays, and have a long history of approval by the FDA or utilization in detecting drug-resistance within the HIV-1 RT or protease (and more recently integrase for research-use only).

In principle, phenotype tests measure the combined effects of all viral mutations, and some physicians find them useful when the treatment history is complex or there is a significant expectation of drug-resistance. Phenotype tests do not require a formal understanding of the connection between genotypes and resistance profiles (something not necessarily desirable for research involving basic mechanisms of resistance). In theory this approach may be useful in resistance testing involving novel drugs or unusual (non-B) viral subtypes. Such tests may also provide information on viral hypersusceptibility (i.e., a lower concentration of drug is necessary to inhibit viral replication than for a control virus), which in turn may help predict short-term virological response to certain drugs, especially NNRTIs. Such tests can also provide information on replication capacity and viral fitness, but it remains unclear how the clinician should incorporate such measures into patient management. One issue worth mentioning is that defining the "clinical cutoff" for these tests is not a simple matter (Zolopa, 2006). Finally, it is important to note that certain phenotype assays focus on viral tropism. Such tests are required to confirm R5 HIV-1 infection status prior to the use of drugs like maraviroc that act as CCR5 co-receptor antagonists (see Table 1). Strictly speaking, this is not a true resistance test, rather it serves to select a drug via its designated target (Dolin, 2008).

The clinical efficacy of individual drugs over time can clearly be limited by resistance due to mutations in the drug targets (see Menéndez-Arias, 2010, for an elegant discussion of the molecular mechanisms of drug-resistance). On a clinical level, accurate viral RNA load determination and drug sensitivity testing are now integral parts of modern treatment (Hirsch et al., 2008), http://aidsinfo.nih.gov/guidelines.

The development of molecular diagnostic methods greatly advanced clinical care in two fundamental and mutually reinforcing ways. First, such diagnostics allowed physicians to provide personalized disease management, using the most appropriate drugs and drug combinations available at any given point, drawn from a wide and continually growing menu of options (Eshleman et al., 2009). Indeed, this has become the classic model for the now extremely popular concept of personalized medicine on a broader front. Second, and no less important, advances in molecular diagnostics made it possible for viral RNA load to act as a surrogate marker in clinical trials, rather than having to rely solely on death or progression of a life-threatening disease – an intensely controversial topic during the development of AZT. This circumvented a host of ethical and practical issues, which might have dramatically impeded trials based solely on clinical endpoints. PCR-based viral RNA testing made it possible for FDA to give pharmaceutical sponsors accelerated approvals of new antiretroviral agents by relying on surrogate markers as a key first step, thereby facilitating patient accrual for any given trial, expediting the development of new therapies, and providing sponsors with focus and clarity for new drug applications.

However, in resource-poor countries, where molecular diagnostics may not be available, it is still possible to make considerable progress against the morbidity and mortality of HIV-1/AIDS, using a population-based approach to antiretroviral therapy by standardizing regimens and medical decisions according to clinical status and $CD4^+$ cell count (if available). The lack of sophisticated molecular diagnostics per se need not impede the scale-up of antiretroviral therapy in the developing world in the hands of properly trained and skilled health care workers.

6. Successful antiretroviral drug development

6.1. Public health consequences in resource-rich nations

The discovery of clinically active antiretroviral agents, and the proof that HIV-1 could, in fact, be treated, led to a precipitous drop in the annual age-adjusted death rate due to HIV-1/AIDS in the United States, reported by the Centers for Dis-

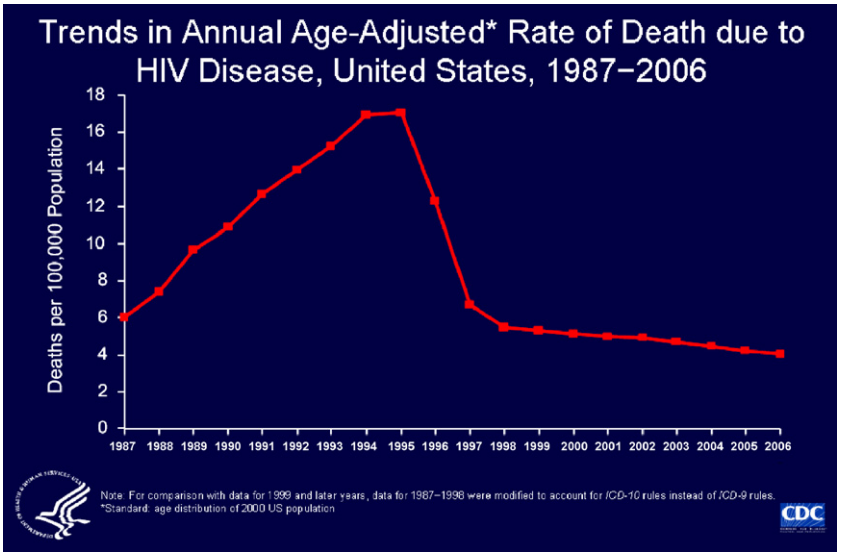

Fig. 1. Trends in annual age-adjusted rate of death due to HIV disease in the USA. Data were compiled from death certificates from all 50 states and the District of Columbia by the National Center for Health Statistics. See Centers for Disease Control and Prevention (CDC): HIV mortality. http://www.cdc.gov/hiv/topics/surveillance/resources/slides/mortality/.

ease Control and Prevention (CDC) starting around 1995, after an inexorable rise (Figs. 1 and 2). See also: http://www.cdc.gov/hiv/topics/surveillance/resources/slides/mortality/

The advent of modern antiretroviral therapy was also associated with a precipitous drop in the incidence of Kaposi's sarcoma (Jones et al., 2000), one of the original disease-defining indicators heralding the onset of the new pandemic (CDC, 1981). The early case-reports quickly rendered disseminated Kaposi's sarcoma in young men a pathognomonic feature of AIDS (Fig. 3) (Hymes et al., 1981; Friedman-Kien, 1981). The clinical challenges in the early 1980s often involved both severe immunodeficiency and serious malignancy, a graphic reminder of the relationship between immunodeficiency disease and cancer (Broder, 1990b).

The impact of highly effective antiretroviral therapy on Kaposi's sarcoma is reflected in the following statistics: the annual incidence among white men in San Francisco rose from about 0.5 per 100,000 in 1973 (the pre-AIDS reference figure) to 32 from 1987 to 1991, then fell by more than 90% to 2.8 in 1998 (Eltom et al., 2002). These population-wide improvements result from the restoration or preservation of the immune system (as reflected in $CD4^+$ count) by antiretroviral therapies. Interestingly, such immunologic amelioration was actually prefigured in the first patient in our first AZT clinical study (Fig. 4) and others who followed.

The morbidity and mortality due to HIV-1/AIDS created a disproportionate burden on relatively young people, and still does in many parts of the world. For example, in the United States in 1994–1995, HIV-1 disease was the leading cause of death among individuals 25–44 years old, and in 1995 caused approximately 32,000 deaths, or 20% of all deaths in this age group. HIV-1 disease mortality fell to 5th place from 1997–2000, and to 6th place from 2001 to 2005. In 2005, HIV-1/AIDS caused about 6000 deaths, or 5% of all deaths in this age group. The decrease in mortality was largely due to the advent and wide availability of effective antiretroviral therapy (Fig. 1), enhanced by FDA approval of viral load kits and other molecular diagnostics.

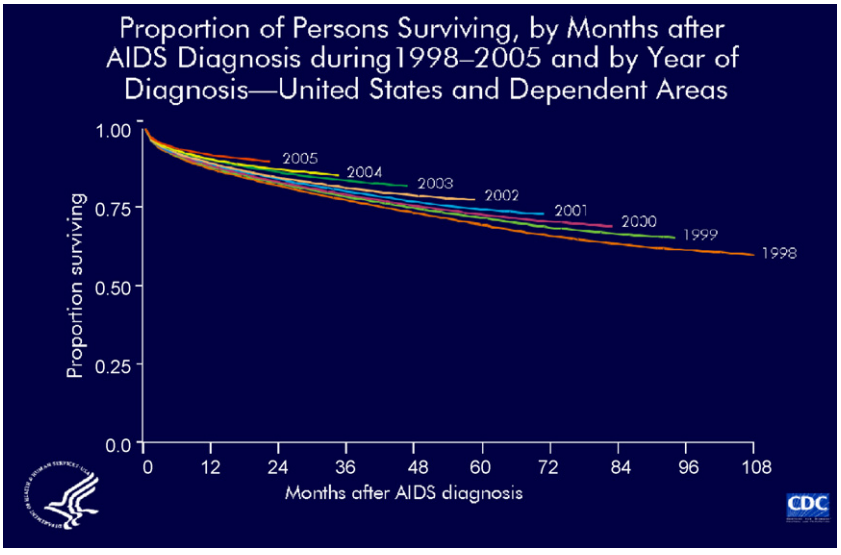

Fig. 2. Proportion of persons surviving, by number of months after AIDS diagnosis, by year of diagnosis—USA and dependent areas See Centers for Disease Control and Prevention (CDC): AIDS Surveillance – General Epidemiology. http://www.cdc.gov/hiv/topics/surveillance/resources/slides/epidemiology.

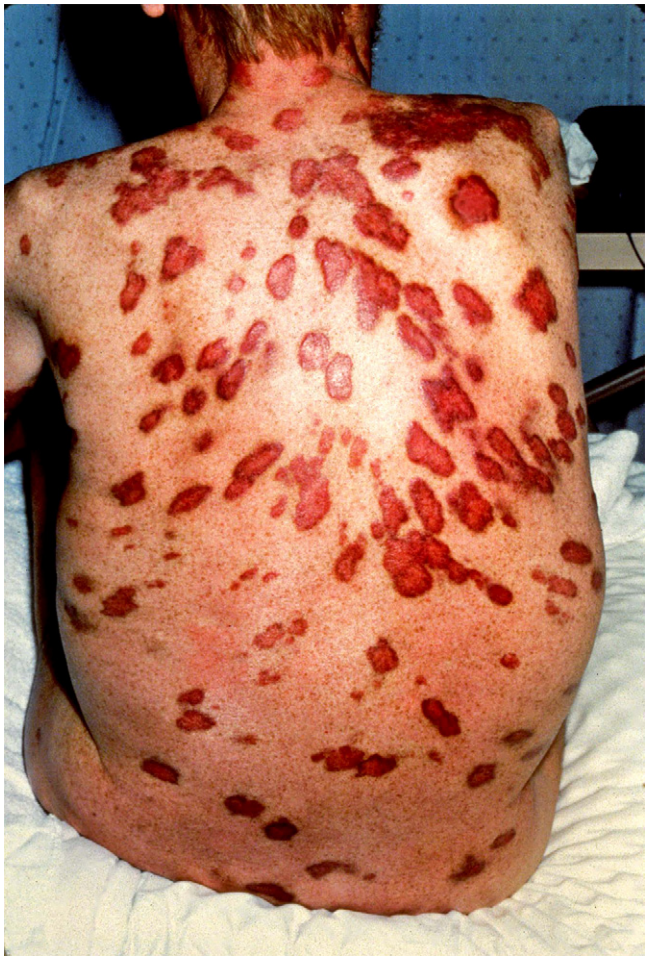

Fig. 3. A patient with AIDS and disseminated Kaposi's sarcoma (KS) undergoing evaluation and therapy by my group at NCI early in the pandemic. One of the most striking features of the early HIV-1/AIDS pandemic was the emergence of an unusual tumor, KS, as a common malignancy among infected individuals. Following the introduction of highly active antiretroviral therapy, its incidence dropped precipitously in nine population-based cancer registries sponsored by the NCI's Surveillance, Epidemiology and End Results (SEER) program.

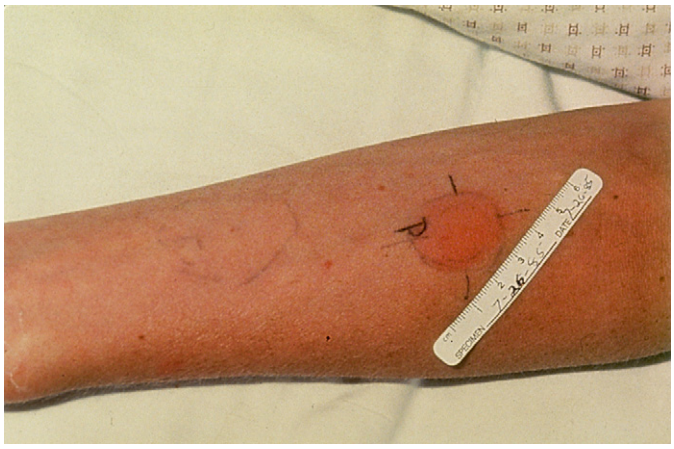

Fig. 4. Patient number 1 in the first study of Retrovir® (AZT) at the NIH Clinical Center in the summer of 1985. The patient, who had a $CD4^+$ T cell count of 33/μL and was anergic at entry, developed a six-fold increase in absolute $CD4^+$ count, and as shown in the figure, displayed a strongly positive delayed hypersensitivity skin reaction to 5 TU PPD approximately two weeks after starting the experimental antiretroviral agent.

There is more to the story. As shown in Fig. 2, the actuarial statistics of people surviving after a diagnosis of HIV-1/AIDS have improved year by year, http://www.cdc.gov/hiv/topics/surveillance/resources/slides/epidemiology.

A typical HIV-1-infected patient in the USA lives about 14 years longer on account of antiretroviral interventions, and if that benefit is denominated in *years-of-life*, millions of life-years have been saved by the development of antiretroviral drugs (Walensky et al., 2006; Vermund, 2006). Other statistical analyses also indicate progressive improvement in life expectancy since the mid-1990s in high-income nations. For example, a 20-year-old individual starting combination antiretroviral therapy is now projected to live well into his sixties, a very substantial increase since the mid-1990s (The Antiviral Therapy Cohort Collaboration, 2008). That said, life expectancy is still below that of the general population, and there is room for further improvement, particularly among injection-drug users and other underserved groups. Moreover, certain antiretroviral agents feature side-effects, including a risk of coronary heart disease and insulin-resistance syndromes or other consequences of chronic therapy, which pose challenges for the future (Hawkins, 2010). Nonetheless, the improvements in life expectancy represent progress without a doubt, and they were beyond any prediction made at the time of the first antiretroviral therapies 25 years ago.

The CDC has concluded that, "Advances in the treatment of HIV infection have resulted in a fundamental shift in its epidemiology, to a potentially chronic and manageable condition." (Hariri and McKenna, 2007). Coming from the governmental agency that brilliantly did so much first to recognize, then to alert the public health community to the pandemic in the early 1980s, this statement is quite significant.

6.2. Public health consequences in resource-poor nations

Sub-Saharan Africa is the epicenter of the HIV-1/AIDS pandemic. Its catastrophic impact in this region is reflected in statistics prepared by the Joint United Nations Programme on HIV/AIDS (UNAIDS): http://www.unaids.org/en/KnowledgeCentre/HIVData/GlobalReport/2008/2008_Global_report.asp, http://www.who.int/hiv/pub/towards_universal_access_report_2008.pdf.

Access to antiretroviral agents also leads to improvements in outcomes for HIV-1/AIDS patients in resource-poor countries (Jahn et al., 2008; Egger and Boulle, 2008; Walensky et al., 2008). For example, data from Malawi and South Africa indicate that a committed scale-up of antiretroviral therapy in populations with high HIV-1 prevalence is followed by a reduction in mortality rates, which becomes evident on a population basis after about one year.

The rapid effect is perhaps related to the clinical condition of those who seek care in the initial phase of a new antiretroviral program, because they are likely to be patients in the most advanced stages of disease, whose prolongation of survival may be the most immediately evident in population-based statistics. This rapid effect on mortality is part of a larger lesson in the power of "secondary intervention" in HIV-1 infection: during the first years of a new antiretroviral public health program, those accessing care or attempting to do so will tend to have the most advanced disease, and the highest mortality rate in the absence of effective treatment. In other words, very sick patients can derive significant benefit from antiretroviral therapy, even in the absence of the sort of health care delivery system found in resource-rich nations. These observations were certainly not obvious 25 years ago, and in fact, they clearly refute early prophesies to the contrary. That said, unless timely diagnosis and therapy-selection are coupled to wide availability of antiretroviral drugs at low cost, patients in resource-poor nations can have less of a mortality-rate reduction compared to those in resource-rich nations.

Table 3
Challenges to the current paradigm of antiretroviral therapy.

Established or emerging challenge	Comments
Integration of provirus and unpredictable viral latency	Viral rebound follows discontinuation of treatment in current paradigm, and therefore, therapy must be undertaken for a lifetime. See siRNA and the topic of transcriptional gene silencing in Table 4.
Drug-resistance, increasing genetic diversity of HIV-1, and the ongoing risk of cross-species infections with new pathogenic retroviruses	Resistance to many available drugs has emerged. The current paradigm of antiretroviral therapy relies heavily on targets encoded by the viral *pol* gene. Other targets are needed. Also, there is an immediate need for more therapeutic agents with a high genetic barrier to the emergence of drug resistant HIV-1 strains (e.g., etravirine) or new inhibitors for resistant virus (e.g., darunavir). Also, beyond classic drug-resistance, non-B HIV-1 subtypes (clades) are becoming more prevalent. Assays for quantifying circulating levels of HIV-1 should be designed to tolerate mismatches and accurately report all known Group M, Group O, and Group N viruses, as well as unexpected and unusual polymorphisms, over a wide dynamic range. There is also a reservoir of retroviruses in non-human primates, which could create opportunities for cross-species jumping of new retroviruses. Careful epidemiologic surveillance programs are important. Three independent cross-species transmissions of *SIVcpzPtt* from chimpanzees are known to have given rise to the human pathogenic retrovirus, HIV-1. Also, more recently, human transpeciation of the gorilla retrovirus, SIVgor, has been documented, and it has been suggested that this be classified within a new HIV-1 Group P.
Cardiac and metabolic complications	Infectious disease specialists will need to manage potentially unfamiliar dyslipidemias, insulin-resistance, and other preventable causes of heart disease. Antiretroviral therapy may represent a modifiable risk factor for heart disease, and may require sequential antiretroviral regimens adjusted for their propensity to induce cardiometabolic side-effects. Determining host genetic endowment for heart disease risk and response to drugs for primary and secondary prevention of cardiovascular conditions (e.g., the statin class in the case of Trp719Arg polymorphism in kinesin-like protein 6) may someday allow more individualized and, therefore, superior treatment selection and better clinical outcomes (Iakoubova et al., 2008).
Lack of either an effective vaccine or practical topical virucide to protect against HIV-1 transmission (see Table 4)	Failure of recent vaccine trials in primary prevention represents a significant setback, from which a rapid recovery is not likely. There is a significant public health need for HIV-1 microbicides (virucides) to protect women against HIV-1 infection.
Pre-exposure prophylaxis (PrEP)	Drugs like tenofovir disoproxil fumarate and emtricitabine hold promise to protect uninfected individuals in high-risk settings (e.g., men who have sex with men or injection drug users). This could also empower women in the developing world. PrEP could be a major advance when the woman cannot convince her partner to use a condom or faces coercive sex. Randomized trials using PrEP are underway. However, efficacy and safety outcomes are not guaranteed and conclusions on long-term outcomes must await pending trials. Cost and compliance issues are not resolved. See clinical studies of pre-exposure prophylaxis for HIV-1 prevention: http://www.cdc.gov/hiv/resources/qa/prep.htm.
The belief that investments in HIV-1/AIDS come at the expense of health systems that are already chronically overburdened	The AIDS pandemic has exposed and focused attention on weaknesses in health care delivery systems in resource-poor nations (and resource-rich ones, for that matter). However, funding and support to fight the pandemic represent major forces for strengthening health systems in developing nations more generally. Reducing the commitment to HIV-1/AIDS, either for research or applied programs, would be detrimental to the public health and pose a threat to global stability and security. See HIV/AIDS and Security: http://data.unaids.org/Topics/Security/fs_security_en.pdf.

There are now effective interventions to reduce or prevent *in utero* and intrapartum transmission of HIV-1 infection. Moreover, such antiretroviral therapies (e.g., extended prophylaxis with nevirapine or with nevirapine plus zidovudine for the first 14 weeks of life) provide a way to reduce maternal-infant HIV-1 transmission via breast milk. Breast feeding is essential for infant survival in many developing countries, but it is also a route for viral transmission, forcing women in resource-poor nations to face wrenching dilemmas in the absence of such therapies (Kumwenda et al., 2008).

Generalizations that modern laboratory-intensive science and technology are dispensable "luxuries," or the exclusive privilege of resource-rich nations, or are immaterial to the most pressing needs of the human condition in places such as sub-Saharan Africa, are sharply refuted by these facts. Moreover, this is yet another example of successful pre-exposure prophylaxis (PrEP) using established antiretroviral drugs, and lays a foundation for even more ambitious programs for prevention, including population-based PrEP or related projects, such as those summarized in Table 3. See Denton et al. (2008), Vissers et al. (2008), Paltiel et al. (2009), Granich et al. (2009); and also: Clinical Studies of Pre-Exposure Prophylaxis for HIV-1 Prevention: http://www.cdc.gov/hiv/resources/qa/prep.htm.

Dr. Peter Piot, the UNAIDS Executive Director, has identified a myth that should be dispelled, namely that investments in AIDS are being undertaken at the expense of health systems that are already fragile, struggling and starved of resources. The reality is quite the opposite. Support for HIV-1/AIDS programs in resource-poor nations is actually a major force for strengthening health care systems, including keeping workers at their posts and helping them perform more effectively (Piot et al., 2009). Indeed, within months of initiating a program of antiretroviral therapy in Rwanda, new hospital AIDS admissions dropped significantly, liberating health workers and resources to satisfy other important health-care needs. Setting up an artificial competition between various disease categories for people in dire need will therefore help none, and will likely harm many. This is true in resource-poor nations, and also in resource-rich ones, for that matter.

While there has been significant progress for patients in resource-poor nations, antiretroviral therapy is available for too few or reaches them too late. It is estimated that three million people in resource-poor or developing nations are currently receiving antiretroviral treatment. This figure would have been difficult to imagine a few years ago; however, at least three times that number are in need of such therapy.

Estimates of need would doubtless be higher still if evidence favoring very early antiretroviral intervention and other factors are taken into account. There may be a tendency to wait until patients are demonstrably ill before initiating treatment, and then to delay switching regimens until a serious health deterioration takes place (Ford et al., 2009). Current guidelines generally recommend initiation of therapy at $CD4^+$ T-cell counts <350 per cubic millimeter or in patients with an AIDS-defining illness. Yet in resource-rich

nations, a growing body of data favors early, rather than deferred, antiretroviral therapy even in asymptomatic, infected patients with baseline $CD4^+$ T-cell counts >500 (Sax and Baden, 2009). Therefore, taking steps to improve access to antiretroviral therapy in the most appropriate regimens in resource-poor nations remains a challenge.

7. Beyond classical public health in the developing world

The global public health consequences of antiretroviral therapy programs are exceedingly important. However, the trajectory of science can move in unexpected directions. Thus, there are also unusual implications for human freedom as a factor dependent on the scale-up and improvement of antiretroviral therapy in certain pandemic regions. This was neither widely anticipated nor discussed 25 years ago. The belief that HIV-1/AIDS was invariably fatal unleashed virulent discrimination and persecution of vulnerable groups. The introduction of effective antiretroviral therapy has changed the perception of AIDS as an automatic death sentence, and has helped to reduce (but not eliminate) the marginalization, violence, eviction, barriers to employment, and other forms of oppression faced by people who are known or believed to be infected by HIV-1 (Piot et al., 2009).

Antiretroviral therapy also has consequences for global economic stability and security (Broder et al., 2002). An emerging body of evidence suggests that infectious diseases (AIDS included) pose a risk to the economic viability of resource-poor nations. In the case of HIV-1/AIDS, a nation may experience grievous losses concentrated within the nucleus of its most productive young adults, disrupting normal economic development, fraying social bonds, and creating orphans for whose care very few resources exist. UNAIDS reports that about 12 million children under the age of 18 in sub-Saharan Africa have lost one or both parents to HIV-1/AIDS, and the numbers continue to rise. In purely economic measures, in sub-Saharan Africa, HIV-1/AIDS can reduce the labor supply and increase a struggling nation's dependence on imports. Moreover, HIV-1/AIDS significantly reduces national economic growth rates (Dixon et al., 2002).

And yet, astonishingly, these statistical measures still do not convey the full extent of what is at stake. There is a direct relationship between AIDS and the probability that a nation will experience armed conflict, an unconstitutional change of government, or other forms of serious instability (Broder et al., 2002). Indeed, a recent report from UNAIDS concluded:

> "*AIDS and global insecurity coexist in a vicious cycle. Civil and international conflict help spread HIV as populations are destabilized and armies move across new territories. AIDS contributes to national and international insecurity, from the instability of societies whose future has been thrown into doubt to the high levels of HIV infection experienced among military and peacekeeping personnel. HIV/AIDS is both cause and effect, initiator and beneficiary, of instability and conflict.*" See: HIV/AIDS and Security (UNAIDS Office on AIDS, Security and Humanitarian Response): http://data.unaids.org/Topics/Security/fs_security_en.pdf

The key point is clear: addressing HIV-1/AIDS is an imperative beyond the traditional boundaries of public health. Antiretroviral therapy alone is certainly not enough—prevention, education, community outreach, and related activities are essential—but treatment is a critical component of any meaningful response to the HIV-1/AIDS pandemic, both in resource-rich and resource-poor nations, and it must not be ignored or supported half-heartedly. Even if current education and preventive measures were to achieve the most optimistic goals possible, this would still leave millions of virus-infected people to their fate.

One of the first groups to recognize the importance of antiretroviral therapy in sub-Saharan Africa was Médecins Sans Frontières, which undertook audacious programs to bring antiretroviral treatment to the poorest nations. Their pilot programs, and others like them, have provided moral examples and stimulated major commitments by resource-rich states. In that spirit, the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) was launched in 2003 to confront HIV-1/AIDS on a global level (http://www.pepfar.gov). PEPFAR works in partnership with resource-poor countries to support the following goals: (1) antiretroviral treatment for at least 3 million people; (2) prevention of 12 million new infections; and (3) care for 12 million people, including 5 million orphans and vulnerable children.

To meet these goals and establish self-renewing local capacity, PEPFAR will support the training of at least 140,000 new health care workers in HIV-1/AIDS prevention, treatment and care. The program will also make available low-cost (generic) versions of the same antiretroviral therapies that are deployed in the developing world, and will help to coordinate other measures to address the AIDS pandemic (Kanki and Marlink, 2009).

The combination of science and political solidarity that gave rise to PEPFAR, and to similar programs of such non-governmental organizations, as the William J. Clinton Foundation and the Bill and Melinda Gates Foundation, has also probably spared the scientific and medical communities from moral dilemmas beyond reckoning. Approximately one year before the initiation of PEPFAR, the macroeconomic effects of HIV-1/AIDS in sub-Saharan Africa were assessed by declaring AIDS to be "more than a medical problem," and therefore requiring "more than medical interventions" (Dixon et al., 2002). One conclusion from this study stands out:

> "...to maintain economic stability it may be necessary to target expensive antiretroviral drugs at highly productive socioeconomic groups in specific industries on the basis of their contribution to economic output rather than their healthcare needs."

This opinion was published in a prestigious peer-reviewed medical journal, and there is no reason to doubt that it was primarily meant to draw attention to a catastrophe-in-the-making, and to buy time for the greater good in the sub-Saharan nations whose economic viability was in grave danger. The conclusion (in effect, a proposal to consider rationing medical care according to a patient's productivity status) did not, however, reckon with

1.) the effectiveness of research on antiretroviral treatment (much of which is covered in this special issue);
2.) the scale-up that becomes possible when political will exists;
3.) the resourcefulness of governmental and private agencies;
4.) the enlightened self-interest of Pharma/Biotech drug sponsors and generic-drug manufacturers (the latter often based in India); and
5.) the solidarity of a galvanized, global AIDS advocacy movement.

all acting in concert to deliver highly effective, practical, and cheap antiretroviral drugs to millions in resource-poor nations.

Although each of these forces is important, everything starts with science. In this case, the science of antiretroviral therapy arguably preempted some unthinkable options. Much of this effort may seem both obvious and inevitable *in retrospect*, as so many things do. The median price of the four most popular first-line combination therapies used in resource-poor nations is $170 per person per year. Even more hopefully, the median price paid for the most widely used first-line treatment (pre-qualified by the WHO) in resource-poor nations is $92 per person per year for

Table 4
Potential new paradigms in treating HIV-1/AIDS.

Technology	Goal	Comments
Proteasomal inhibitors, possibly by adapting marketed products already in use for cancer (Sheehy, 2008; Malim and Emerman, 2008)	Stop depletion of host anti-viral restriction factors by viral proteins that target them for degradation. The viral accessory proteins, Vif, Vpu, and Vpr, are all thought to connect to modular ubiquitin ligases to bring about the polyubiquitylation and proteasomal degradation of cellular host-restriction factor targets.	Might be able to adapt proteasomal inhibitors already approved by FDA or in clinical development for cancer as an antiretroviral regimen, with dose modifications. In the case of Vif, this might protect APOBEC3G or APOBEC3F. In the case of Vpu, this might protect CD4. Low-doses and careful attention to side-effects in directly inhibiting the proteasome would be necessary if such drugs are advanced into clinical trials
Specific small molecule antagonists of Vif (Nathans et al., 2008)	Nullify viral Vif and restore APOBEC3G as an antiretroviral host-restriction factor, featuring (deoxy)cytidine deaminase editing activity.	Several programs underway; a lead compound with antagonistic activity against Vif has been reported. This strategy could restore antiviral activity to carry out nascent DNA strand-editing (viral death by hypermutation or error catastrophe) due to host cytidine deaminases *and/or* cause viral suppression by non-enzymatic mechanisms as well.
Small interfering RNA (siRNA) molecules (Morris, 2008; Verdel et al., 2009; Suzuki et al., 2005; Weinberg et al., 2006; Lim et al., 2008; Han et al., 2007; Suzuki et al., 2008; Kumar et al., 2008; Hawkins et al., 2009; Yamagishi et al., 2009)	Silence viral replication or host "co-factor" genes (e.g., *CCR5*). This involves either post-transcriptional gene silencing or transcriptional gene silencing (TGS).[a] In the latter, promoter-targeted siRNA would likely not exhibit transience of the gene knockdown, saturation of the RNA-induced silencing complex (RISC), or siRNA viral escape mutants.	SiRNA-dependent pathways can cause (1) post-transcriptional gene silencing because siRNAs cleave complementary targeted mRNA in the cytoplasm (classical RNA interference); or (2) transcriptional gene silencing (well known in plants, but until recently less so in animals and humans) because promoter-targeted siRNA in the nucleus may bring about long-term site-specific CpG methylation and a heterochromatic environment at the HIV-1 promoter (medically-induced viral latency) and/or a key host co-factor (e.g., CCR5, in a therapeutic "null mutation").
RNase H-mediated retrovirus destruction triggered by oligodeoxynucleotides ("siDNA") (Heinrich et al., 2009; Wittmer-Elzaouk et al., 2009)	Specifically target polypurine tract of HIV-1, forming a local RNA-DNA hybrid, with mimicry of a natural replication intermediate and RNase H-driven viral self-inactivation.	Might be adapted for systemic therapy or as a virucidal agent in the vagina, inhibitory action can be exerted on viral particles before they infect the cell.

[a] See TGS models: http://www.scripps.edu/mem/morris/tgs/.

the fixed-dose combination of stavudine + lamivudine + nevirapine. There is no reason to believe this is the absolute lowest limit on price.

None of this means that the challenges of cost, infrastructure, and access to antiretroviral drugs have been solved. However, perhaps this is a reminder that theoretical projections setting boundaries on how, when, and where scientific advances can be implemented for the public health can easily give the wrong answers, which if left unchallenged could emerge as self-fulfilling prophesies.

That said, PEPFAR and the model it represents are only a beginning. Current programs are not sufficient, and there may be a number of ways to improve them to achieve a greater consensus on their benefit. For example, see: http://physiciansforhumanrights.org/library/news-2008-03-27.html.

And, yet broadly speaking, we need more "PEPFARs", and we should arm them with even better antiretroviral agents.

8. The future

8.1. Unfinished business

The impression that the HIV-1/AIDS pandemic has been solved, or that it has stabilized and become "manageable" as a global challenge, or that HIV-1/AIDS has "had its day" and it is now time for other conditions to "have their day too" (translation: "Cut funding!") could be a major barrier to further progress, or even result in the abolition of gains already made.

Tables 3 and 4 summarize some of the unfinished business, challenges and opportunities. In some cases (not surprisingly) a challenge is also an opportunity, and both tables reflect this fact. The following narrative may help underscore a few key points and perhaps provide additional perspective for the articles in this special issue.

One challenge, set out in Table 3, is that true eradication of HIV-1 cannot be achieved with technologies now at hand. Preintegration and particularly postintegration viral latency represent serious challenges (discussed by Palmer et al., in this issue). This is true in part because integrated provirus may exist in memory T cells that persist for long periods and represent an inducible retroviral reservoir (Marcello, 2006). This challenge is compounded by reservoirs of the virus within dendritic cells, macrophages, and microglia, the latter two readily providing an infectious viral sanctuary in the brain. As a rule, viral rebound follows discontinuation of therapy, and on that account, therapy must be undertaken for a lifetime.

Twenty-five years ago, when we began implementing the first successful antiretroviral therapies, HIV-1/AIDS was typically expressed as a fulminant immunodeficiency predisposing to life-threatening infections and often accompanied by aggressive Kaposi's sarcoma or other neoplasms with their own rapidly lethal pace. The facts are different now, but even today prolonged survival has a corollary requiring the identification and careful management of the long-term effects of treatment (Hawkins, 2010). In this context, chronic antiretroviral therapy can bring about cardiac and metabolic side-effects, including dyslipidemias, insulin resistance, abnormal body fat re-distribution (lipodystrophy), and related disorders, which can in turn increase the risk for developing heart disease and type 2 diabetes (Sabin et al., 2008; Silverberg et al., 2009; Filardi et al., 2008; Williams et al., 2009). There is probably a higher risk for coronary artery disease in patients who receive protease inhibitors (Friis-Møller et al., 2007).

Thus, several challenges remain in the current paradigm of antiretroviral therapy, with special impact in the developing world. Can we make antiretroviral treatment a modifiable risk factor for

heart disease, perhaps by adjusting therapy according to the cardiac risk profile of both the regimen and the patient, including genetic endowment? In this discussion, one may need to keep in mind that HIV-1 infection per se may be a risk factor for cardiac disease in certain cases (Hsue et al., 2004). Moreover, we cannot precisely forecast the burdens of cardiometabolic side-effects on the health-care systems of resource-poor nations, which may be ill-equipped to handle these chronic conditions. In a recent study evaluating nearly 5000 people infected with HIV-1 for asymptomatic myocardial ischemia, evidence of ischemic heart disease was surprisingly common on electrocardiograms (Carr et al., 2008). More such studies and surveillance should be encouraged.

The issue of long-term sequelae is also part of a discussion of PrEP or related measures that attempt to employ antiretroviral drugs to control the transmission of HIV-1 in individuals who are at risk, but not yet infected.

In any event, the search for safer and more effective therapies is of critical importance, particularly for agents that feature a high genetic barrier to the development of drug-resistance and, whenever possible, fit the realities of AIDS therapy in resource-poor nations. The treatment of HIV-1-infected pediatric patients, particularly children under age 5 or 6, is a clear example of unfinished business, with an unmet need for pediatric formulations, fixed-dose combinations, and a larger range of options for therapy against drug-resistant strains. Fewer drugs are approved for use in such children. There are also uncertainties about the best time to start treatment and dosing guidelines (Giaquinto, 2010).

In other words, it is important to maximize the utility and effectiveness of known drugs and drug classes for both adults and children. The public is likely to intuitively understand all this, but it is also important for the public to understand something a little less obvious: why basic research should proceed unabated. We must acquire fundamentally new targets for therapy to supplement (or perhaps someday supplant) the current ones, while continuing to refine current treatment strategies.

And then, there is the greatest hurdle of them all.

We face the challenge of a continuous pace of new infections. While there has, indeed, been considerable progress in preventing premature deaths through advances in antiretroviral therapy, the annual number of new HIV-1 infections in the USA remains approximately 50,000. Moreover, in 2007 there were 2.7 million new HIV-1 infections globally.

Education and prevention are clearly important, and more must be done. Yet, the ongoing rate of new infections poses a significant risk to individuals and to public health alike. It also presents the difficult-to-quantify risk of introducing more virulent and less treatable strains that could become the new face of the pandemic. Historically, the most prevalent form of HIV-1 infection in the United States and Western Europe has been subtype (clade) B. However, there is now evidence that HIV-1 infections with non-B subtypes are becoming more prevalent (Parkin and Schapiro, 2004; Lin et al., 2006; Taylor et al., 2008). We still do not know the full implications of this trend. This will require significant support for epidemiological surveillance, coupled with an appreciation that new strains of HIV-1 or related pathogenic retroviruses can emerge and migrate quickly around the globe (Taylor et al., 2008), possibly remaining unrecognized for several years.

On an immediate and very practical level, the emergence of non-B subtypes and chimeric HIV strains could have a technical impact on drug-resistance algorithms, which employ subtype B as the consensus sequence (Hirsch et al., 2008). There might also be issues related to quantifying viral load and the overall response to available therapies. Along these lines, progress has been reported in a real-time PCR detection system, for which the primer and probe sequences are targeted to the integrase region of the HIV-1 *pol* gene. Due to the selection of a highly conserved target region and a novel, mismatch-tolerant probe design, the assay can quantify HIV-1 group M subtypes A-H, group O, and group N isolates over a wide dynamic range (Swanson et al., 2007; Tang et al., 2007). All of these topics remain critical issues for ongoing research. One should note a recent case in which some (but not all) commercial tests resulted in an under-quantification of plasma and cerebrospinal fluid viral RNA in an HIV-1 subtype G-infected woman, with serious clinical consequences (Delaugerre et al., 2009). This is a worrisome development.

It is worth noting a separate but related epidemiological issue: AIDS in Africa can be viewed as a zoonosis arising from contact with apes and Old World monkeys (Hahn et al., 2000). Such retroviruses can jump from other primates to humans, particularly in communities whose members hunt and prepare bushmeat as a protein source (Peeters et al., 2002; Wolfe et al., 2004). This applies to chimpanzees (*Pan troglodytes troglodytes*) in the case of HIV-1 in West Central Africa, and sooty mangabeys (*Cerocebus atys*) in the case of HIV-2 in West Africa (Wain et al., 2007; Van Heuverswyn and Peeters, 2007).

For example, HIV-1 arose from three independent ape-to-human transmissions (transpeciations) of simian immunodeficiency virus (SIVcpzPtt) from infected chimpanzees, which in turn gave raise to the three distinct groups M, N, and O, with different epidemiological consequences, group M being the most far-reaching. Molecular clock analyses suggest that one such cross-species transmission (the "founder infection" for group M) occurred around 1930, and group M strains have been diversifying since that time, spreading widely in Africa and around the world. Another virus (the "founder" for group O) likely made the jump to human beings slightly earlier, while cross-species transmission for group N is more recent and restricted. In a *tour de force* of science, it was recently shown that, contrary to original belief, the immediate precursor to HIV-1 can cause an AIDS-like syndrome in free-ranging chimpanzees (Keele et al., 2009). Moreover, the three different cross-species transmissions from chimpanzees to humans were probably enabled by the same host-specific adaptation in the p17, *gag*-encoded viral matrix protein. This is believed to have improved viral "fitness" in the human host, creating what we now call HIV-1, using the same "signature" non-conservative amino acid replacement at the Gag-30 site in the provenance of all three groups of HIV-1, at a site that is otherwise highly conserved among chimpanzee retroviruses (Wain et al., 2007). There is more: Transpeciation of a new human immunodeficiency virus (SIVgor) from gorillas (proposed as the "founding" member of HIV-1, group P) was recently documented in a Cameroonian woman living in Paris (Plantier et al., 2009). Yet again, a commonly used viral load test could not quantify her virus. Moreover, while she is described as being asymptomatic, her CD-4$^+$ T-cell count was below normal. Surprisingly, the signature amino acid replacement at Gag-30 (considered a requisite for efficient replication in human beings) was not found in this new human virus, perhaps signifying that the bar to transpeciation can unfortunately be lower than originally thought.

Some forms of industrialization in sub-Saharan Africa are likely to compound the problem of retroviral zoonoses even further. Commercial logging and its supporting road networks have established mobile populations (including loggers and sex workers) in previously inaccessible forests, while at the same time increasing the demand for bushmeat, all within an environment of ongoing exposure to a primate reservoir of novel retroviruses (new human retroviruses-in-waiting?) This makes future cross-species transmission and new epidemics of AIDS-like pathogenic retroviruses a serious possibility, or at the very least a factor for public health agencies to consider as they plan for the future. Vigilance and optimism are not mutually exclusive.

There is no doubt that we have made considerable progress, but pathogenic retroviruses and the need to confront them with effective antiretroviral drugs represent unfinished business. In this context, opportunities also abound, and many are covered in the articles in this issue. A brief summary will help to set the stage.

8.2. Opportunities

A glance at Table 1 shows that the primary focus of antiretroviral drug development so far has been on classic "druggable" targets of the HIV-1 ***pol*** gene: reverse transcriptase, protease and (more recently) integrase, Indeed, these targets have produced a bountiful supply of active small molecules, and for the most part these have brought about the "triumph for modern medicine" embodied in antiretroviral therapy (Richman et al., 2009). However, the above discussion underscores that it is also important to adapt novel insights on the basic biology of viral replication to the clinic as rapidly as possible (Freed, this issue) and to advance therapeutic strategies beyond classic "druggable" (small molecule) targets. This applies to both systemic treatments and antiretroviral microbicides (Buckheit et al., 2010).

Indeed, there is an immense body of basic research upon which to build future programs of antiretroviral therapy, well beyond the current treatment strategies. Many of these are discussed elsewhere in this special issue (Adamson and Freed, 2010) and in a wide range of publications, of which only a small number are referenced here as examples (Greene et al., 2008; Sheehy, 2008; Takeuchi and Matano, 2008; Nathans et al., 2008; Chiu and Greene, 2008; Malim and Emerman, 2008; Goffinet et al., 2009; Heinrich et al., 2009; Moelling et al., 2006; Matskevich et al., 2006; Matzen et al., 2007; Wittmer-Elzaouk et al., 2009). Indeed, the completion of the human genome project has opened the doors even wider to the discovery of novel gene and protein targets that control the susceptibility and outcomes in microbial diseases generally and HIV-1/AIDS specifically (Broder, 2004; Hutcheson et al., 2008). Moreover, programs to address viral latency and reactivation, possibly including depleting pools of latent HIV-1 infection in vivo, are being explored (Lehrman et al., 2005; Palmer, 2010).

Table 4 contains a short list of potential therapeutic strategies for the future to stimulate further discussion. Attempting to adapt currently available proteasomal inhibitors to stop the depletion of host-restriction factors by viral accessory proteins that target them for degradation would be a logical short-term goal, but likely with dose reductions compared to those used in cancer therapy. It may also be possible to test such ideas first using HIV-1 infected mice featuring a humanized immune system, and thus exhibiting many key features of human HIV-1/AIDS (Denton et al., 2008). A somewhat less immediate, but no less important goal, would be to target the Vif/APOBEC3G axis directly, and in that context, one especially active and promising small molecule with a triphenyl thioether amide structure (RN-18) has been profiled extensively (Nathans et al., 2008). The same general considerations apply to molecules that specifically induce an RNase H-driven viral self-destruction (Heinrich et al., 2009; Wittmer-Elzaouk et al., 2009).

Still another group of treatment strategies relates to RNA-based therapeutics, including antisense molecules, microRNA, and siRNA. While still in its infancy, one such approach could radically shift the paradigm beyond small molecules and canonical "druggable" targets, and at the same time overturn strongly held beliefs on what may be possible to combat HIV-1/AIDS. The strategy is based on small interfering RNAs (siRNAs) directed against promoter regions to silence genes at the point of transcription (transcriptional gene silencing, TGS), a durable effect and one potentially maintained throughout mitosis (see Table 4). The process differs from classic RNA-interference (RNAi) and involves special pathways well known in plants and yeast, but until recently, less so in animals and humans (Morris, 2008; Verdel et al., 2009). TGS specifically enlists the host's own chromatin remodeling apparatus to epigenetically silence the provirus and render it incapable of replication as long as the altered state of chromatin holds (Suzuki et al., 2005, 2008; Weinberg et al., 2006; Lim et al., 2008; Han et al., 2007; Morris, 2008; Hawkins et al., 2009; Yamagishi et al., 2009). Such an approach does not "target" the virus in a conventional way (compare Table 1 with Table 4). The strategy also has deep implications for cancer and many other serious conditions (Swanton et al., 2004; Napoli et al., 2009). Indeed, it has been postulated that one day it may be possible to use siRNA or related molecules to induce permanent epigenetic modifications and thereby achieve highly specific control of the human genome (Morris, 2008).

Whatever specific paradigms of future antiretroviral therapy emerge, *and there will certainly be many*, enormous progress is likely and the ramifications will not be confined to the retroviruses. Almost by definition, the establishment of any new paradigm looks formidable upon first contemplation, and understandably invites caution, unspoken fear of failure, and a reluctance to outline specific developmental timelines. However, a glance to the past shows that certain paradigm-changing goals are in reality no more formidable than many already-achieved goals were when first proposed. Furthermore, almost none need be considered in isolation from current therapies.

9. Conclusion

There has been considerable and perhaps even surprising progress against premature deaths caused by HIV-1/AIDS in the United States and in other parts of the world, starting from the time 25 years ago when HIV-1 was considered inherently untreatable. It turns out that this pathogenic human retrovirus is not inherently untreatable, after all – far from it!

Moreover, the antiretroviral drugs available now are not limited to medical care in resource-rich countries, or at least they need not be if nations acting together have the political will. Those who question whether basic laboratory research can really benefit people in resource-poor nations, both in immediate and fundamental human terms, have their answer.

Undeniably, much unfinished business remains, particularly in the arenas of viral drug-resistance and genetic diversity, long-term complications of therapy, and the need to develop paradigm-shifting agents against new viral targets, host-restriction factors, or both. We should therefore guard against triumphalism, for much remains to be done: the pandemic's toll still rises, and we cannot be certain when it will reach the high water mark.

That said, a strong foundation for a new era of progress against HIV-1/AIDS is already in place. In the near term, we stand to see one of the most rapid and extensive transfers of knowledge from basic research to the clinic in history, a process that will greatly benefit patients with AIDS and many other diseases, in the bargain. Future success will require a wholeness of motion from the lab to the clinic and thence to the remotest dispensaries of resource-poor nations. As the articles in this special issue prove, the available science does not lack for ideas that can take the next phase of antiretroviral therapy to an entirely new level The progress summarized in these papers is a reminder that scientists engaged in basic and clinical research exert a transcendent effect on human beings in peril. Those conducting laboratory research, clinical trials or public health outreach are a truly privileged group.

Acknowledgements

I wish to thank all of my colleagues at the National Institutes of Health for their commitment, dedication, and support during

the discovery and development of the earliest antiretroviral therapies for patients with HIV-1/AIDS. Very special thanks go to Drs. Hiroaki Mitsuya and Robert Yarchoan for their unwavering efforts to advance these programs.

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