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A history of AIDS: Looking back to see ahead

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Since breaking onto the scene 26 years ago, HIV has proven an indefatigable foe. Over 60 million people have been infected with this retrovirus, and 25 million have already died of AIDS. HIV infection is hitting the hardest in the developing world [1]. Tragically, 1600 babies continue to acquire HIV every day from their infected mothers. Over 12 million children have also been orphaned by AIDS, and this number will likely double by 2010. With these sobering statistics as a backdrop, this feature traces the history of the devastating HIV/AIDS pandemic and offers a view for what the future may hold.

Key words: AIDS · Drug design/ discovery · Global pandemic · HIV · Infectious diseases

Unfolding of a pandemic

AIDS was first recognized in the summer of 1981 (Table 1). Young gay men began falling ill and dying of opportunistic infections their immune systems should have fended off [2]. Those afflicted became emaciated and often developed dark purple lesions on their arms and faces due to a relatively rare and aggressive form of cancer called Kaposi's sarcoma. In cities such as New York and San Francisco, prematurely "old" young men became a common sight. Physicians were baffled, and fear spread through the gay community with every new case of what was termed the "gay plague." Almost without fail, patients experienced a rapid downhill course and death as their doctors vainly treated one opportunistic infection after another.

Because the acquired immunodeficiency syndrome (AIDS), a name recommended by the Center for Disease Control (CDC) in September 1982, was most common in gay men and intravenous drug users, early theories about its cause focused on "lifestyle" issues, including "immune overload" from multiple infections, use of amyl or butyl nitrate "poppers," a reaction to semen, infection by an unidentified fungus, and multiple sex partners. The appearance of AIDS in Haiti fueled speculation that the disease had originated there. Although not compelling, these theories stoked the fear and prejudice surrounding the disease.

By late 1982, epidemiologic evidence indicated that AIDS was an infectious disease transferred by bodily fluids and by exposure to contaminated blood or blood products [3]. Without a test for AIDS, blood banks had difficulty safeguarding the blood supply, and most refused to screen donors for homosexuality. Surrogate markers, such as hepatitis B core antigen, proved imperfect at best. Thus, the blood supply remained unsafe for years, and many people were transfused with contaminated blood. One such person was Elizabeth Glaser, who in turn transmitted the disease to her unborn child, Ariel. Their deaths triggered an outcry for more research and ultimately led to the formation of the Elizabeth Glaser Pediatric AIDS Foundation. Approximately 15 000 hemophiliacs in the US became infected with HIV as a result of transfusion with contaminated blood products between 1981 and 1984. Similarly, intravenous drug users were at high risk due to exchange of blood during needle sharing. The first needle exchange program was set up in Amsterdam in 1984; such programs would rapidly spread in Europe but not within the US.

The first clues to the true cause of AIDS stemmed from careful immunological investigations. One consistent manifestation was a rapid decrease in levels of circulating CD4 T cells. Once those levels fell below roughly 200 cells/mm^3, patients became vulnerable to myriad opportunistic infections and various malignan-

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Abbreviations: **CDC:** Center for Disease Control · **HAART:** highly active antiretroviral therapy

cies. Strikingly, this same subset of T cells is the target of the first-described human pathogenic retrovirus, HTLV-I, isolated in 1980 by Robert Gallo and colleagues [4]. However, rather than inducing CD4 T-cell depletion, HTLV-I transforms these CD4 T cells, resulting clinically in adult T-cell leukemia [5]. Early on, serum from HTLV-I-infected patients appeared to weakly stain cells from AIDS patients, suggesting that this new immunodeficiency might be caused by a retrovirus closely related to HTLV-I. While this connection was ultimately proven false, in retrospect, scientists were on the right track in suspecting a retrovirus.

Searching for the cause of AIDS

In 1983, the CDC documented heterosexual transmission of AIDS, a finding that began to change the perception of AIDS as solely a disease in gays [6]. Reports of two "different" epidemics emerged from Europe, one involving homosexuals but a second curiously in immigrants from Central Africa with no known risk factors. Subsequently, it would become clear that heterosexual transmission accounts for more than 80% of new infections worldwide [1] and that sub-Saharan Africa bears the highest infection rates. In 1983, the world also gained its first glimpse of the true cause of AIDS. Using tissue from a "pre-AIDS" patient with acute lymphadenopathy, Luc Montagnier and colleagues at the Pasteur Institute detected a new human retrovirus [7]. By electron microscopy, it appeared to be different from HTLV-I. However, with only a single difficult-to-passage viral isolate in hand, it remained unclear whether this retrovirus was truly the cause of AIDS. A causal link between this virus and AIDS was forged by Robert Gallo and his colleagues at the National Institutes of Health in 1984 [8–10]. Jay Levy and coworkers [11] at UCSF also independently isolated this new retrovirus. In May 1986, the International Committee of the Taxonomy of Viruses chaired by Harold Varmus recommended that this pathogen with many names be called the human immunodeficiency virus (HIV) [12].

Isolation of HIV enabled the development of the first blood test in 1985 [13, 14], a step that offered great hope to both the scientific and lay communities. Margaret M. Heckler, then US Secretary of Health and Human Services, predicted in 1984 that a vaccine against HIV would be available within 2 years. Unfortunately, her enthusiasm belied a limited understanding of the many defenses of HIV. Reflecting the scientific tumult swirling around HIV, in December 1985, Institute Pasteur filed suit against the National Cancer Institute claiming a share of the royalties from the NCI blood test for AIDS.

Understanding what makes HIV tick

In 1985, Ryan White, a 13-year-old boy with hemophilia was banned from school because he was infected with HIV. Rock Hudson died of AIDS – the first such celebrity to be stricken, and President Ronald Reagan finally mentioned the word AIDS during a press conference. More positively, Princess Diana personally visited AIDS patients and shook hands without gloves, visibly demonstrating to the world that the virus is not casually transmitted.

On the scientific front, the sequence of the HIV genome was reported [15–17]. Compared to many other pathogens, its 9-kb RNA genome was rather simple: nine genes encoding 15 proteins. However, HIV would prove anything but a simple virus. First, like a "smart weapon," it seeks out and destroys the very cells that orchestrate the immune response to viral infection, CD4 T lymphocytes. Secondly, because of the error-prone nature of its reverse transcriptase and the recombination that occurs between viruses simultaneously infecting the same cell, HIV evolves at "hyper-light speed" [18, 19]. A swarm of billions of different forms of HIV are present simultaneously in infected patients – a fact that would confound future treatments and vaccine development.

Three enzymes were quickly identified within HIV – reverse transcriptase, protease, and integrase, each a prime therapeutic target (Fig. 1). Indeed, in 1987, AZT, a cancer drug that also inhibits the reverse transcriptase, became the first approved anti-HIV drug. Unfortunately, in what would become a familiar refrain, its therapeutic effectiveness proved short-lived. Drug-resistant variants of HIV rapidly emerged when single antiviral agents were deployed.

A better understanding of the very first interactions of the virus with its target cell pointed the way to new classes of therapies. The CD4 transmembrane protein was identified in late 1984 as one of two receptors needed for viral entry [20, 21]. This finding explained why CD4 T cells are specifically killed by HIV. However, 12 years would pass before the chemokine receptors, CXCR4 and CCR5, were implicated as essential HIV coreceptors [22–24]. A continuing mystery is why CCR5-utilizing strains of HIV are almost uniformly transmitted between people, while CXCR4-tropic viruses only emerge late in the infection and only in about half of patients, often heralding a more rapid clinical decline. Particularly in persons of European descent, a mutated version of the CCR5 gene containing a 32-base pair deletion was detected that prevents cell-surface expression of the receptor; the roughly 1% of individuals homozygous for this mutation proved highly resistant to HIV infection [25]. This "experiment of nature" identified CCR5 as a compelling new drug target and helped galvanize efforts by several pharmaceutical

Table 1. Timeline of important events in the evolution of the global HIV/AIDS epidemic

~1930
Retrovirus passed from chimpanzees to humans subsequently spawns the global AIDS pandemic

1981
First cases of new immunodeficiency disease in gay men in US
Fear of "gay plague" spreads rapidly

1982
Same immunodeficiency disease diagnosed in Europe
Disease named AIDS by the CDC in US, and SIDA in France and Spain

1983
Heterosexual spread of AIDS documented
New retrovirus isolated in pre-AIDS patient by Luc Montagnier's laboratory
Hemophiliacs recognized at great risk for AIDS in US and Europe

1984
Retrovirus isolated by Montagnier group at Pasteur Institute in France, shown to be the cause of AIDS by Robert Gallo laboratory
HHS Secretary argaret Heckler predicts AIDS vaccine in two years
CD4 identified as an HIV receptor
European reports describe two "different" AIDS epidemics in homosexuals and people emigrating from Central Africa

7,700 AIDS cases reported in US and 762 cases in Europe

1985
Blood test for HIV licensed by FDA
Sequence of HIV reported
Genomic diversity of HIV described
Ryan White, a 13-year-old hemophiliac with AIDS, is banned from school
Rock Hudson dies of AIDS
Needle exchange programs spread in Europe
First international AIDS conference held
President Reagan publicly mentions AIDS for the first time

1986
LAV and HTLV-III renamed HIV
"Slim" disease (AIDS) widely recognized in Africa

1987
AZT introduced as first anti-HIV medication
ACT UP, an AIDS activist organization, holds first march in New York
AIDS Memorial Quilt displayed on the mall in Washington DC
HIV-infected persons barred from entering US
Peter Duesberg argues HIV is not the cause of AIDS
Princess Diana shakes hands with AIDS patient without latex gloves

1988
First World AIDS Day held on December 1
"Understanding AIDS" by Surgeon General C. Everett Koop distributed to 107 million households
US Congress prohibits use of federal funds for 'needle exchange' programs
FDA streamlines HIV drug approval process
London Declaration of AIDS Prevention published

1989
ddI made available as part of expanded access program as second HIV drug

1990
Ryan White dies and Ryan White CARE Act becomes law
Dr Jonathan Mann resigns as head of WHO AIDS Program in protest of inadequate UN response

8–10 million HIV-infected persons worldwide

1991
Red ribbon becomes an international symbol of AIDS awareness
ddC approved AZT and ddC used in combination for first time
Earvin "Magic" Johnson states he is HIV-positive and retires from professional basketball
Freddie Mercury, lead singer of Queen, dies of AIDS
French hemophiliacs infected by transfusion sue leading officials

1992
India funds National AIDS Control project with >15% of its health budget

1993
Transmission of AZT-resistant virus documented
HIV replication in lymph nodes demonstrated
Arthur Ashe, tennis champion, dies of transfusion-associated AIDS
Concorde trial results published showing AZT not useful for HIV-infected patients without symptoms
Rapid spread of HIV in Asia appreciated
3TC approved for clinical use
Riga Initiative to contain HIV/AIDS in Central Europe launched

14–15 million HIV-infected people worldwide

1994
AZT shown to reduce mother to child transmission of HIV

1995
First HIV protease inhibitor approved
AIDS named leading cause of death in US of persons 25–44 of age

1996
First use of HAART with dramatic clinical responses
CXCR4 and CCR5 identified as HIV coreceptors
Home testing for HIV approved
Strong protection from HIV infection by homozygous 32-bp deletion in CCR5 gene described
First non-nucleoside reverse transcriptase inhibitor (nevirapine) approved

23 million HIV-infected persons worldwide

1997
Latent HIV reservoirs described
Deaths from AIDS in developed world begin to drop due to HAART
President Clinton sets the goal of an AIDS vaccine in 10 years

UNAIDS revises figures upward, suggesting 30 million people infected with HIV

1998
Glaxo-Wellcome cuts price of AZT by 75% due to evidence that the drug reduces mother-to-child transmission in developing world
VaxGen starts first phase III AIDS vaccine trial
Side effects of HAART including lipodystrophy and fat redistribution syndrome become apparent
Post-exposure prophylaxis program started in San Francisco
Transmission of multi-drug-resistant HIV documented

1999

Origins of HIV traced to chimpanzee virus

Single dose nevirapine shown to reduce mother-to-child transmission of HIV

Explosion of HIV infections in former Soviet Union due to needle sharing

UK offers blood testing for all pregnant women

2000

International AIDS Conference held in Durban, South Africa

The microbicide candidate, nonoxynol-9, shown to enhance rather than decrease HIV transmission

CIA publishes security report emphasizing the threat of AIDS

Oral sex estimated to account for 7% of HIV transmissions in MSM

President Thabo Mbeki of South Africa consults with American scientists who claim HIV is not the cause of AIDS

Botswana officials estimate as many as one in four adults are HIV-positive

34.3 million people worldwide believed to be HIV-positive

2001

HIV budding involving vesicular transport system described

China acknowledges the threat of AIDS to its public health

India drug maker, Cipla, offers to make HIV drugs for less than $1/day

UN Secretary General Kofi Annan calls for establishment of the Global Fund to fight AIDS, Tuberculosis, and Malaria

Peter Piot labels AIDS the most devastating epidemic in human history

South African court orders government to make nevirapine available to pregnant women and to establish nationwide MCT program

2002

Non-random integration of HIV in human chromosomes described

Ukraine reports that 1% of its population is infected with HIV

World Bank reports that one third of teachers in Uganda and Malawi are HIV-positive and teachers in Africa were dying faster than they could be replaced

HIV super infection documented

Powerful anti-HIV host factor, APOBEC3G, discovered

2003

First HIV fusion inhibitor, enfuvirtide, approved

President's Emergency Plan for AIDS Relief (PEPFAR) announced

WHO launches "3 by 5" global program to reverse finding that only 1% of people in Africa needing antiretroviral therapy had access to it

Swaziland reported to have highest HIV infection rate: nearly 40% of population

VaxGen phase III AIDS vaccine trials fail

Vatican Cardinal Trujillo declares that condoms are not safe and do not prevent the transmission of HIV

UNAIDS states that 14,000 people are infected with HIV every day

2004

Activation hypothesis of HIV pathogenesis gains strength

Factor preventing HIV from infecting monkey cells discovered (TRIM5-alpha)

Infectious Diseases Institute opened by President Musevini in Kampala, Uganda to focus on HIV training of African physicians and healthcare workers

FDA approves rapid oral fluid AIDS test

PEPFAR begins full implementation

Botswana succeeds in providing treatment to approximately half of those needing treatment in the country

2005

Nelson Mandela's oldest son dies of AIDS

HIV infection reported to be increasing in the US in African Americans

Growing scientific momentum for testing concept of using antiviral therapy to prevent HIV infection in individuals at high risk for HIV

Global Fund announces its AIDS programs had exceeded 2005 targets

Russia increases AIDS program spending 20-fold

AZT goes off patent; 4 generic forms of AZT go on sale in US

2006

Male circumcision reported to diminish by 50% HIV transmission from infected women to men

Specific targeting of gut-associated lymphoid tissue explored

"Product Red" launched by rock singer Bono and several companies

WHO announces its 3 by 5 program only reached 1.3 million people instead of the 3 million target set

Decline in the prevalence of HIV infection reported in Kenya, Burkina Faso, and Haiti by UNAIDS

First one-a-day pill, Atripla, approved for sale

South African government publicly criticized for its "disastrous, pseudoscientific policies" on HIV/AIDS

Emergency warnings issued by WHO regarding extreme drug-resistant tuberculosis (XDR-TB)

CDC recommends routine testing for HIV for adults and children attending clinics

Nearly 40 million HIV-infected persons; more than 25 million dead of AIDS

Events are coded as follows: scientific (grey shading), **clinical (bold font),** political (normal font), *societal (italics)* and ***societal statistics (italics and bold).***

Interested readers are encouraged to explore many additional details concerning the history of AIDS at www.avert.org.

Information contained on this site formed valuable source material for construction of this timeline table.

companies to develop selective CCR5 inhibitors, the first of which, maraviroc (Selzentry), gained FDA approval in 2007.

Molecular gymnastics are the order of the day when the gp120 env protein sequentially engages CD4 and its chemokine coreceptor (reviewed in [26]). These protein contortions trigger the action of HIV's second envelope protein, gp41, which is responsible for fusing the viral membrane with the target cell membrane. These events allow "microinjection" of the viral core through the fusion pore into the cytoplasm. Understanding the molecular underpinnings of this fusion reaction made it

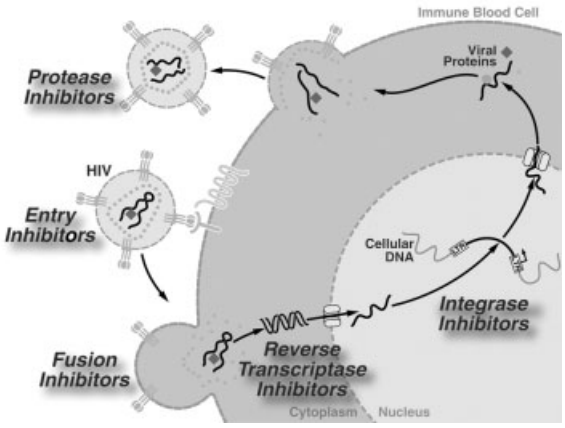

Figure 1. Schematic overview of the HIV life cycle and points of attack by multiple classes of anti-HIV drugs.

possible to develop peptides that blocked a key "hair-pinning" step in the fusion reaction. The first of these peptide inhibitors, enfuvirtide, was approved in March 2003.

Once in the cytoplasm, the viral reverse transcriptase springs into action, generating a double-stranded DNA version of the virus (reviewed in [27]). The viral DNA then wends its way through the nuclear pores to gain entry into the nucleus. HIV integrase then inserts the viral DNA into human chromosomes, where it remains for the life of the cell. Initially, the HIV provirus was thought to insert randomly. However, studies made possible by complete sequencing of the human genome revealed that HIV preferentially integrates into actively transcribed genes [28], a feature that may further enable its replication and spread.

The search for effective HIV integrase inhibitors has been long and frustrating but punctuated with recent success [29]. The key was to look for inhibitors of "strand transfer" in the integration reaction, not the initial binding of integrase to DNA. Integrase inhibitors displaying remarkable antiviral activity are now poised for approval.

Integrated HIV proviruses first express the regulatory proteins Tat, Rev, and Nef and later the structural and enzymatic proteins required for virion assembly [27]. Rev orchestrates this switch, while Tat potently boosts overall expression of all viral genes. Nef appears to optimize the intracellular milieu to support viral replication and spread. In an important study, rhesus macaques infected with SIV lacking Nef showed only low levels of viral replication, greatly delayed progression of disease, and surprisingly robust resistance to wild-type SIV challenge [30]. This induced resistance remains one of the most persuasive experimental findings arguing that an effective HIV vaccine might be possible. Unfortunately, no effective antagonists of Tat, Rev or Nef have emerged, in part because these proteins lack catalytic sites that can be easily targeted with small-molecule inhibitors.

Once all of the viral components are expressed, new virions assemble at the plasma membrane and bud from the cell surface. To achieve complete budding, the virus hijacks components of the cell's vesicular transport machinery [31]. Indeed, this is but one of many examples of how the study of HIV has offered dramatic insights into normal molecular, biochemical, and cellular processes. Specifically, breakthrough discoveries in many areas of fundamental biology, including transcriptional control, RNA export and control of endogenous retroelements, occurred as "byproducts" of HIV investigations [27].

The late 80s and early 90s were a particularly rocky period in the history of AIDS characterized by both medical advances and political turmoil. The epidemic was rapidly expanding yet still there was little that could be done to quell the storm. In 1986, it became abundantly clear that AIDS was common in Africa, where it was commonly referred to as "slim disease" [32]. Sensitive blood tests capable of monitoring circulating levels of HIV also emerged; these tests would ultimately emerge as a cornerstone for clinical management. In 1987, ACT UP, an AIDS activist organization, was formed and held its first march supporting patients' rights in New York City. Cleve Jones started the Names Project, more commonly known as the AIDS Memorial Quilt. On October 11, 1987, the quilt was dramatically displayed to 500 000 people on the mall in Washington, DC; Senator Jesse Helms introduced legislation prohibiting HIV-infected people from entering the US. The first World AIDS Day was held on December 1, 1988, and a world summit of health ministers took place in London to address the expanding AIDS crisis. These meetings culminated in the London Declaration of AIDS Prevention. In October 1989, ddI, another reverse transcriptase inhibitor, joined AZT as the second approved anti-HIV medication.

A few months after Ryan White's death on April 8, 1990, the Ryan White CARE Act was passed by the US. Congress to improve the quality and availability of HIV treatment and to support programs for HIV-infected patients and their families. A third reverse transcriptase inhibitor, ddC was approved by the FDA in the summer of 1991, and the first combination of antiviral drugs, AZT and ddC, began to be used in 1992. The Riga Initiative to control HIV spread in central Europe was launched by European ministers of finance and health. On World AIDS Day, 1993 ACT UP Paris and Benetton place a huge condom on the obelisk in la Place de Concorde to emphasize the importance of HIV prevention. Transmission of AZT-resistant virus was first documented in 1993. In 1994, AZT prophylaxis of HIV-infected mothers and their babies was shown to reduce HIV

transmission from 24 to 8% [33]. Harold Jaffe at the CDC heralded this study as "the most stunning and important result in clinical acquired immunodeficiency syndrome research to date." At nearly the same time, the Russian Duma adopted a law making it compulsory for all foreign residents, tourists, and businessmen to have an HIV test. In 1995, saquinavir, the first of a new class of drugs targeting the HIV protease was approved followed shortly thereafter by the first non-nucleoside reverse transcriptase inhibitor, nevirapine.

Altering the natural history of HIV infection

In 1996, triple-drug antiretroviral drug regimens consisting of various combinations of nucleoside and non-nucleoside reverse transcriptase inhibitors and protease inhibitors – commonly referred to as highly active antiretroviral therapy (HAART) – were introduced [34]. Although the regimens were complex and often difficult to follow, HAART transformed AIDS from an acute, lethal disease to a chronic, manageable infectious process. Patients often experienced what was termed the "Lazarus syndrome." However, these miracle drugs exacted a toll in toxicities ranging from hematological, endocrinological, and cardiovascular complications to disfiguring fat loss and redistribution syndromes.

A cure for HIV-infected patients?

In general, a single HIV-infected T cell produces enough virions to spread the infection to 10 new cells. As such, antiviral therapies that are more than 90% effective should theoretically extinguish the infection over time. Studies in 1995 showed that productively infected CD4 T cells also die after $\sim$1 day, while infected macrophages survive for about 2 weeks [35]. This rather rapid turnover of infected cells raised hopes that treatment with HAART for 2–4 years might completely eradicate the virus in infected patients – in other words a cure might be within reach.

Unfortunately, HIV had another surprise in store – the persistence of small amounts of virus in a latent, drug-insensitive state within resting CD4 memory T cells. While rare (1/100 000 to 1/1 000 000 white blood cells), such latently infected cells display a half-life of at least 44 months; thus, patients will require at least 60 years of treatment before this reservoir is eliminated (reviewed in [36]). Predictably, within weeks of HAART discontinuation, viral loads rebounded in patients to pretreatment levels. If the problem of HIV latency is not solved, a true cure of HIV will not be possible.

Mobilizing a global response

The advent of HAART was associated with unexpected negative consequences. One was a perception that the AIDS crisis was over. Nothing was further from the truth. These lifesaving drugs were costly and not available in those parts of the world where HIV was wreaking its greatest havoc [1]. Developing countries, particularly in sub-Saharan Africa, continued to bear the full brunt of an unchecked AIDS pandemic (Fig. 2). Yet, many leaders in the developed countries looked the other way.

The International AIDS Conference held in Durban, South Africa, in July 2000, proved a turning point. It put the AIDS crisis in the developing world back on the front page of newspapers around the world, increasing awareness among the general population and government leaders and raising a cry heard around the world: "treatment for all, now." Additionally, in 2000, a somewhat less humanitarian but persuasive perspective

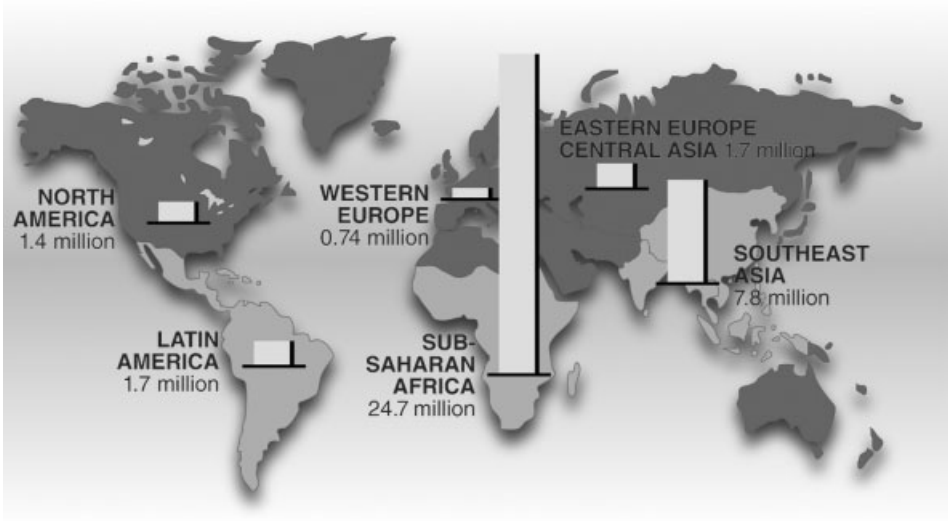

Figure 2. Summary of the global HIV pandemic highlighting regional differences in the numbers of HIV-infected persons at the beginning of 2006.

was offered by the CIA. Their report noted that the AIDS epidemic in Africa and other resource-rich regions was a threat to US national security. This threat emanated from the potential collapse of societal structures and governments. "In our view," the report stated, "the infectious disease burden (AIDS) will add to political instability and slow democratic development in sub-Saharan Africa, parts of Asia, and the former Soviet Union, while also increasing political tensions in and among some developed countries."

Action took many forms. For example, in 2002, the Global Fund initiated a 5-year plan to provide antiretroviral drugs for 1.6 million people, counseling and testing services for 62 million people, and care for more than a million orphans. Its combined HIV, TB, and malaria programs have now invested more that $3.2 billion. In 2003, the US President's Emergency Plan for AIDS Relief (PEPFAR) was launched. This plan called for investing $15 billion over 5 years in what has been termed the largest commitment ever by any nation for an international health initiative dedicated to a single disease. Reflecting a more grass roots commitment of first world consumers and companies, "Product Red" was launched in 2006 to support the activities of the Global Fund in Africa, focusing specifically on the needs of women and children. The Bill and Melinda Gates Foundation also made HIV prevention a top priority. Through 2006, it has provided more than $7.7 billion in funding to combat HIV and other diseases of the developing world. In 2003, the World Health Organization launched its "3 by 5 initiative" to provide antiviral therapy to 3 million people in the developing world by 2005. Although this initiative would ultimately fall short of its goal, 1.3 million people did enter therapy, and singularly broad coverage of the population in need was achieved in some countries, most notably Botswana. While at the start of 2006, only 20% of individuals needing antiviral therapy in the world were receiving it, more that 2 million years of life had been saved by the concerted global effort – an encouraging start that demanded continuing commitment. Distressingly, the funding for the global AIDS response remained $14 billion short of what was truly needed during 2006 and 2007.

Will we ever have an HIV vaccine?

With the turn of the century, increasing interest focused on developing an effective HIV vaccine – without a doubt the "holy grail" of HIV research. So far, the search has not gone well. It should be noted that currently successful vaccines do not block initial infection by the pathogen. Rather they promote clearance of the offending agent before disease develops. Ideally, an HIV vaccine would create a state of sterilizing immunity to block the earliest steps in the retroviral lifecycle preventing integration of the virus in host chromosomes. Such immunity would require high titers of neutralizing antibodies; however the HIV envelope glycoprotein is an ill-suited immunogen for this purpose. Its folding and extensive glycosylation conspire to protect its conserved regions that would yield the type of neutralizing antibody we seek. Rather, the neutralizing antibodies that do appear are limited to hypervariable regions of the envelope that change rapidly, allowing the virus to escape the antibody response. Finally, traditional approaches to vaccine development, including the use of whole killed viruses or live attenuated strains, have been confounded by a lack of potency as well as significant safety concerns.

In 2003, VaxGen completed two phase III efficacy trials using the gp120 subunit of HIV as the immunogen [37, 38]. The initial trial, involving 5400 volunteers in Canada, the Netherlands, and the US, showed no protection against HIV infection. The second trial, performed with 1500 volunteers in Thailand inoculated with both clade B and E envelope proteins, yielded similar negative results. An initial claim of increased activity within particular ethnic groups was suggested, but the trial was not sufficiently powered for such subgroup analyses, and the beneficial claim was dismissed.

Currently, only one other phase III HIV vaccine study is under way. This trial of 16 000 volunteers in Thailand is examining a "prime-boost" vaccine combination of a canarypox-virus-based priming vaccine followed by a gp120 subunit booster. More promising, but less advanced, efforts are focusing on the use of DNA and adenoviruses as vectors to deliver multiple HIV gene products as a vaccine. These vaccines induce robust T-cell immune responses against HIV but do not elicit strong neutralizing antibodies. As such, the goal of these "imperfect" vaccines is to suppress viremia and HIV transmission. The effectiveness of these vaccines will likely be undermined by viral immune escape mutants that are no longer contained by the vaccine-induced CD8 cytotoxic T cells.

Further emphasizing the US' commitment to development of an AIDS vaccine, in May 1997, President Bill Clinton called for the establishment of the Vaccine Research Center (VRC) at the National Institutes of Allergy and Infectious Diseases. In addition, the Global HIV Vaccine Enterprise was launched. One of its two major projects, the Collaboration for AIDS Vaccine Discovery, is funded by the Bill and Melinda Gates Foundation. The other is the Center for HIV/AIDS Vaccine Immunology (CHAVI), funded by the NIH. These programs are providing a coordinated forum for HIV vaccine research. We can only hope that these efforts prove successful.

Looking to the future

The history of HIV research has been a roller coaster ride of soaring achievement and frank disappointment. Thus far, our best efforts against HIV have not been enough – the global pandemic continues to expand. Last year, 4.1 million people were newly infected while 2.8 million died of AIDS [1]. However, gratifyingly, the developed world is now engaged with the developing world to provide antiretroviral drugs and to build health care infrastructure. Novel insights have prompted exciting research on new questions in HIV biology. Why do HIV-related retroviruses cause no disease in their natural monkey hosts [39]? Does the activation of our immune system that accompanies HIV infection fuel disease progression [40]? Is there something special about how the virus interacts with host mucosal sites like the gut [41, 42]? Can intrinsic immunity genes, such as APOBEC3G [43] and TRIM5-alpha [44], be manipulated to stem HIV replication? How can we exploit the finding that circumcision cuts by half a man's risk of acquiring HIV from an infected woman [45]? Can a single anti-retroviral pill a day prevent infection in individuals at high risk [46]?

Dealing with the scientific, clinical, political, economic, and social problems posed by HIV/AIDS will continue to be a major struggle requiring unwavering commitment. However, the fact that the world as a whole has acknowledged their shared responsibility is reason for optimism. Hopefully, the next roundup of HIV immunology will include a description of a successful vaccine and how the tide was finally turned. Nevertheless, historians will assuredly describe HIV/AIDS as one of the most devastating infectious pandemics ever confronted by humankind.

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