The Antiviral Report

A Critical Review of New Antiretroviral Drugs & Treatment Strategies

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Antiviral Committee
Treatment Action Group

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The Treatment Action Group (TAG) fights to find a cure for AIDS and to ensure that all people living with HIV receive the necessary treatment, care, and information they need to save their lives. TAG focuses on the AIDS research effort, both public and private, the drug development process, and our nation's health care delivery systems. We meet with researchers, pharmaceutical companies and government officials, and resort when necessary to acts of civil disobedience, or to acts of Congress. We strive to develop the scientific and political expertise needed to transform policy. TAG is committed to working for and with all communities affected by HIV.

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TAG's website address is *http://www.aidsinfonyc.org/tag*; updated versions of this and other TAG reports may be accessed and downloaded from that site.

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This report is dedicated to

Dr. James C. Hill
Deputy Director of NIAID, 1987-1995

A proud gay man, an early activist ally
and an unceasing fighter against AIDS

d. 26 June 1997

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The Antiviral Report

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I. INTRODUCTION

by Spencer Cox

In January, 1996, at the Third Conference on Retroviruses and Opportunistic Infections in Washington, DC, I found myself standing amidst some very rude scientists with sharp elbows in a generic overcrowded conference hall, staring at the survival curves of patients treated with ritonavir in combination with nucleoside analogues, and I started crying. Over the course of the six month study, ritonavir-treated patients were surviving much more frequently than a similar group of participants who had been treated with a placebo and nucleoside analogues. AIDS research had finally paid off; effective therapy would be available for the hundreds of thousands of HIV-infected people in the United States, including some of those for whom I care most dearly.

After a brief scuffle with my insurance company, which hadn't had time to add the drug to its formulary, I began treatment with ritonavir two days after the drug was approved. After three days on ritonavir, I felt so disoriented and sick that, my partner being away on a business trip, I was forced to call a friend to my apartment in case something serious happened.

Those initial side effects eventually declined to a level that was manageable through diet and careful planning, only to be replaced by severe diarrhea. That too, the literature told me, should wane over time. Mine did not. It reached the point that I had to plan carefully never to be further than quick running distance from a restroom.

In the meantime, my CD4 cell count had increased dramatically from 60 cells/mm^3 to over 300 cells. My viral load had dropped from more than 500,000 copies to less than 3,000 copies/ml. By all laboratory signs I was doing well on the drug, but my quality of life was shot to hell.

Finally, just before I left for Vancouver, my viral load began to rise. With my doctor's permission, I discontinued ritonavir and switched to indinavir, which had no discernable effect on my rapidly-increasing viral load, but which substantially improved my quality of life, despite the Talmudic eating restrictions imposed by the drugs.

That summer in Vancouver at the International Conference on AIDS, the good news kept getting better. More patients – healthier patients – treated with different combinations of drugs were also doing well for as far as we could see. HIV RNA could no longer be detected in the plasma of these patients. As 1996 wore on, the incidence of clinical disease began to decline sharply. The euphoria was in the air, and pharmaceutical company staffers were practically – perhaps literally, for all I know – dancing in the streets. And when David Ho began talking about the possibility of eradicating HIV from the body, the elusive notion of a "cure" began floating out over the airwaves, where it still presumably lingers.

Several therapeutic attempts later, including both new drugs and recycled old drugs, I find myself presumably highly drug resistant, off all therapy, and unsure when the new generation of drugs will be available. As more information emerges about HIV sanctuaries in resting memory CD4 T lymphocytes, the estimated timeline for eradication of HIV has receded into the distance (for an update on some

current thinking about HIV eradication, see the May 1998 issue of *TAGLine*).

And yet, that sense of excitement that I felt in knowing that effective therapy would be available – if not effective for everyone, still enough to make a substantial public health benefit – remains. The advent of highly active anti-retroviral therapy (HAART) has made an enormous public health difference. In study after study, rates of opportunistic infections and death are down, inpatient hospitalization rates are down, and outpatient health care utilization is up.

One study conducted at Tulane University compared two matched cohorts of HIV-infected patients with fewer than 200 CD4 cells. The first group was examined in the eighteen months before protease inhibitors became available, and the second group during the eighteen months after protease inhibitors became available. Incidence of PCP fell from 18% to 11.7%; wasting from 9.5% to 4.8%; KS from 4.3% to 2.5%; MAC from 8.5% to 6.1% and CMV from 4.6% to 3% (Mouton 1998)

In the February 28th, 1997 issue of the Morbidity and Mortality Weekly Report, the Centers for Disease Control and Prevention (CDC) reported a substantial decline in the number of AIDS-related deaths in 1996 – the first such decline in the history of the epidemic. These declines were spread among all racial/ethnic groups, all regions of the country, and transmission categories except for those who acquired HIV through heterosexual sex (probably reflecting the increase of this infection route as a percentage of the overall HIV-infected population). CDC spokesperson Tammy Nunally noted that much of the decrease occurred before the advent of protease inhibitors and that therefore larger reductions were expected in future reports.

Dr. Mary Ann Chaisson, of the New York City Department of Health, presented data at the Fifth Conference on Retroviruses and Opportunistic Infections, showing that New York City was experiencing a downward trend in AIDS-related deaths. AIDS-related mortality increased six-fold from 1983 to 1986 and then by about 11% per year, or 19.4 deaths per day, through 1994. In 1995, the death rate did not increase, but plateaued at about 19.3 deaths per day, and began a significant decline in 1996 from 19.5 per day in January to 11.5 per day in July, a decline of 41%. Like the CDC data, Dr. Chaisson cautioned that most of these results are from periods before the advent of protease inhibitors, and are probably a function of improved diagnosis and treatment, increased prophylaxis against *Pneumocystis carinii* pneumonia (PCP) and *Mycobacterium avium* complex (MAC), and use of d4T and 3TC (Chaisson 1998).

Dr. Gabriel Torres presented data on inpatient/outpatient health resource utilization at St. Vincent's Hospital in New York City. Dr. Torres reported that prior to the availability of protease inhibitor therapy, the average daily number of people hospitalized with AIDS-related illnesses peaked at 136. During 1995, 3TC and protease inhibitors became available through expanded access programs, and the average daily HIV hospitalization rate dropped by 5%. In late 1995, 3TC and Invirase brand saquinavir were approved by the FDA. This was followed by a significant drop in the average daily HIV inpatient count, and a substantial rise in outpatient visits. In the first quarter of 1996 ritonavir and indinavir were approved. From 1995 to 1996, the HIV inpatient census dropped by 24% to an average of 79 patients in 1996. At the same time, inpatient admissions dropped by 10.5%, total inpatient days fell by 23.6%, and the average length of stay was shortened by 15.9%. The medical center experienced a simultaneous 33% increase in ambulatory visits. Dr. Torres noted, "The introduction of protease inhibitors into anti-HIV treatment regimens has had a dramatic effect on treatment patterns in our clinic and on our patients'

daily lives. We are seeing fewer infections and fewer hospitalizations. In addition, greater public awareness of the existence of new, potent treatment options clearly has led more people to seek care before they become seriously ill." (Torres, 1998)

Substantial declines in AIDS-related morbidity and mortality were also noted in San Francisco, Philadelphia, Boston, Chicago, Los Angeles County, Miami, and the State of California. Reductions in end-stage illness were also reported from a large, diverse medical practice in Los Angeles, and in nine medical centers in France. (Cadman 1997, Highleyman 1997, James 1997, Mouton 1998, Palella 1998, Ruane 1998)

These consistent reports suggest that gains are being made across the industrialized world in the struggle to make HIV infection a treatable disease. In places with good Medicaid, Medicare and AIDS Drug Assistance Program (ADAP) formularies, most or all demographic groups are experiencing declining death rates.

However, just as modern society still has that small cadre of persons who continue to fight against the teaching of evolution, a similar group of AIDS activists continues to insist that, as one of their representatives put it, "Nothing has changed." Presumably he was referring to a litany of complaints about current therapy: the drugs are expensive, toxic, difficult to take, and don't work in everyone. My own experience with HAART forces me to acknowledge that all of these objections are true, but they do not alter the fundamental fact that when patients can obtain access, tolerate and adhere to these medications – which, in the developed world, they seem to be doing in numbers sufficient to dramatically affect the public health -- those patients will usually experience remarkable clinical improvements, including reduced risks of opportunistic infection and death, and some immune-system reconstitution. Effective anti-HIV therapy is possible for most patients in the developed world: what we have here is an implementation problem.

One consequence of these improvements in therapeutic efficacy is the need to re-think America's AIDS research infrastructure. Grants that fund both the AIDS Clinical Trials Group (ACTG) and the Terry Beirn Community Program for Clinical Research on AIDS (CPCRA) will be completed next year, and bureaucrats at the National Institute of Allergy and Infectious Disease (NIAID) are considering how best to structure the upcoming request for applications.

The effort to re-think clinical trial structures begin in 1996, when the NIH AIDS Research Program Evaluation Committee, chaired by Arnold Levine released results of its review of all NIH AIDS programs. One of the group's key recommendations was the integration of all existing AIDS clinical research networks into one large structure capable of studying the entire range of HIV disease and the entire spectrum of questions related to the development of effective treatments.

In response to this recommendation, both the NIAID and the NIH Office of AIDS Research (OAR) set up committees to advise how best to structure the next AIDS research funding programs. Unfortunately, no consensus has been reached on how best to structure the future federal AIDS research networks. However, there is, conveniently, a much greater scientific consensus on the range and substance of the scientific questions that need to be answered by the federal programs, including:

- The continued need for new and more durable approaches to minimizing viral replication and tissue burden (new drugs, definition of new targets, identification of salvage therapies),
- The need to develop new approaches to enhance immune reconstitution,
- The need to develop methods for optimizing antiretrovirals and other therapies and to conduct additional research to better understand the consequences of poor adherence,
- The need to address the problems confronted by patients throughout the entire course of HIV disease from acute infection through advanced disease,
- The need for long-term data to guide the choice of both the initial antiretroviral treatment regimen used and the regimens used after virologic failure with the initial and subsequent regimens,
- The need for continued focus on developing better agents and strategies to treat and prevent the complications associated with HIV infection, and
- The need for clinical trials to link the pathogenesis of HIV/AIDS with treatment. *(Marco 1998)*

Furthermore, as the OAR's task force noted, there is the need for funded groups to be able to:

- Conduct a range of clinical trials from small, nonrandomized pharmacokinetic, safety and proof-of-concept trials to large, randomized studies that follow patients for many years to key clinical outcomes,
- Rapidly and efficiently access, enroll, and follow patients in studies from demographically and geographically diverse populations of infected individuals, and
- Enroll patients from diverse research sites (from both academic and community research venues) to include a range of research and primary care perspectives on the critical questions to be answered

The NIAID is expected to issue an RFA (Request for Applications) that looks for a "network or networks" capable of performing all of the kinds of studies that will be needed as AIDS therapy evolves. If applications are not received that would ensure both quality and capacity, then NIAID will have to reserve funding for supplementary programs.

This report is an effort to summarize some of these current challenges are being addressed by science today. After the truly miraculous treatment breakthroughs of the Retrovirus and International Conferences, much of this work is likely to seem mundane: twice-a-day regimens versus three-times-a-day regimens, two-drug regimens versus three-drug regimens, interventions to ameliorate side effects, tests to see if drug A should be given before or after drug B, a trickle of new drugs that are mostly from the same old classes of therapy ... It hardly seems it, but this is the stuff of which dreams of a future for HIV-infected people are made of.

However, as the first real glimmers of hope emerge for people in North America, Western Europe and Australia, the bitter world-wide contrast between the haves and the have nots grows all the more stark. The United Nations (UN) reports that a staggering 16,000 people are newly infected with HIV each day, and a total of 30 million people are now estimated to be living with HIV worldwide. Despite Andrew Sullivan's wistful 1996 pronouncement of "The End of AIDS," observers world-wide report that the global HIV pandemic continues to pick up steam. In September of 1997, Dr. Peter Piot of the UN's Joint

Program on HIV/AIDS (UNAIDS) told delegates to the 37th Interscience Conference on Anti-microbial Agents and Chemotherapy (ICAAC) of the toll which HIV continues to extract world-wide.

According to Piot, 90% of new HIV infections occur in developing countries; 40% occur in women and more than 50% are in persons between the ages of 15 and 25 years of age. The number of cases of AIDS is still greatest in sub-Saharan Africa, South and South-east Asia, followed by Latin America, and then North America and Western and Eastern Europe:

The Future of AIDS

	Previous Estimate (1996)	*Current Estimate (1997)*
People with HIV or AIDS	22,600,000	30,600,000
Sub-Saharan Africa	20,080,000	
South and Southeast Asia	6,000,000	
Latin America	1,300,000	
North America	860,000	
Western Europe	530,000	
East Asia and Pacific	440,000	
Caribbean	310,000	
North Africa, Middle East	210,000	
Eastern Europe, Central Asia	150,000	
Australia, New Zealand	12,000	
	New Infections per Year	
Total	3,000,000	5,800,000
Children	350,000	580,000
	Deaths per Year	
Total	1,500,000	2,300,000
Children	350,000	440,000

(UNAIDS 1998)

AIDS is now thought to cause a level of annual worldwide mortality equivalent to that of malaria, with an estimated AIDS-related 1.5 million deaths annually. Despite the treatment breakthroughs in the developed world, AIDS mortality is dramatically accelerating, with one quarter of all deaths from AIDS having occurred in the last year alone.

Global Infectious Causes of Death

	1996	*1997 (estimate)*
Tuberculosis	3,000,000	2.5-3,000,000
Malaria	1,700,000	1.5-2,700,000
AIDS	1,500,000	2,300,000

(UNAIDS 1998)

The front line of the epidemic today is quite clearly Asia. For example, there are at least five million HIV-infected persons in India, and most of these individuals were infected within the last two to three years.

Seroprevalence among Bombay sex workers is estimated to be 51%; STD clinic patients, 40%; pregnant women, 3%.

In Sub-Saharan Africa, AIDS has been concentrated primarily in the Southern, East Coast and Central African countries, with pockets of disease in the Ivory Coast. HIV prevalence among pregnant women ranged from 17%-40% in these countries, the majority of mothers infected between the ages of 15 and 25.

Among Latin America countries, Brazil has the greatest number of HIV-infected persons; as many as 23% of gay men, 27% of sex workers and 60% of injection drug users being HIV-infected. In the state of Sao Paulo, the economic powerhouse of Brazil, AIDS is now the leading cause of death -- even though Sao Paulo state now pays for triple combination therapy for persons with an AIDS diagnosis.

The projected life expectancy in sub-Saharan Africa, where HIV is endemic, has been reduced by as much as 25 years. The economic and social impact of the epidemic in these countries will be devastating. AIDS is reversing any gains in human development made in this part of the world prior to the onset of the epidemic.

While Africa continues to have the most severe epidemic in the world, Piot warned that we are poised for a "new epidemic explosion" in Eastern Europe and parts of the former Soviet Union, where needle use and heterosexual transmission are the most frequent routes for the disease. Last year, in a series of articles in *Newsday* by Pulitzer-prize winning journalist Laurie Garrett, the author noted that as a result of the collapsed public health system in nations of the former Soviet Union, infectious disease experts were forced to stand by as HIV infection rates increased by up to 300% annually. In addition, Piot warned, Asia -- and particularly India -- comprise the "front line of the epidemic," with skyrocketing rates of new infections.

Piot also noted that HIV was contributing to the resurgence of other infectious diseases: tuberculosis rates, according to data from the UN, is rising in tandem with the HIV pandemic, "like it's shadow." Because the public health infrastructures and economies of the different countries and continents vary widely, the UN has developed a set of strategies for combating HIV infection world-wide.

Amidst all the dire statistics, Dr. Piot explained that significant gains had been made in the prevention of new infections in several parts of the world. In Switzerland, Thailand and Uganda, aggressive sex education (including information on sexually transmitted diseases and condom use) has been met with initial success. In Uganda, for example, rigorous prevention campaigns in prenatal clinics had reduced the HIV seroprevalence rate in pregnant women from 21% in 1990-1993 to 15% in 1994-1995. In Thailand, an aggressive behavioral modification among pregnant women and 21-year old military conscripts from 1989-1995 has led to a significant reduction in the rate of new seroconversions in these populations.

Another success has been the UN's efforts to develop a feasible intervention to prevent vertical transmission in the developing world. The standard regimen of AZT (the 076 regimen) used to interrupt vertical HIV transmission in the developed world is both complicated and expensive. HIV-infected pregnant women are given AZT (100 mg five times daily during the third trimester of pregnancy,

intravenous AZT (1 mg/kg/hour) during delivery, and oral treatment of the newborn infant (2 mg/kg every 6 hours) for the first 6 weeks of life). This regimen was shown to cut the rate of maternal-fetal HIV transmission by two-thirds (from 22.6% to 7.6%). The 076 regimen is largely unrealistic in many developing-world settings where pregnant women often do not enter the healthcare system until late in pregnancy and where delivery rooms may lack the capacity to deliver intravenous medication (Cox 1998, Knox 1998). Without effective preventive therapy, 5-10 million children will become infected with HIV through perinatal transmission before the year 2000, mostly in the developing world. But it is precisely in these impoverished countries hardest hit by HIV that the potential of the "076 regimen," as it has come to be called, has been least realized.

In an attempt to address this reality, officials from the World Health Organization (WHO), the United Nations, the National Institutes of Health (NIH) and the Centers for Disease Control (CDC) gathered in Geneva in June 1994 to design perinatal transmission trials suitable for the developing world. Since that time, 18 randomized, controlled trials of interventions to prevent perinatal HIV transmission have begun which are to evaluate a variety of interventions: antiretroviral drugs such as AZT (usually in regimens less expensive or complex than the ACTG 076 regimen), vitamin A and its derivatives, intrapartum vaginal washing, and HIV immune globulin. These trials involve a total of more than 17,000 women from the following countries: Ivory Coast, Uganda, Tanzania, South Africa, Malawi, Thailand, Ethiopia, Burkina Faso, Zimbabwe, Kenya and the Dominican Republic.

The first of these studies (co-sponsored by the Ministry of Public Health of Thailand and the U.S. Centers for Disease Control and Prevention) to produce results showed that a short course of orally administered AZT given during the last 3-4 weeks of pregnancy resulted in a 50% reduction in the rate of mother-to-infant HIV transmission (from 18.6% to 9.2%). The MOPHT/CDC study marks a watershed in the ability to begin controlling HIV transmission in regions where more costly, lengthy antiretroviral courses are simply not feasible. The regimen used in the Thai study costs an estimated $50-$80 per patient-or less than one tenth the cost of the 076 regimen.

After these study results were announced in February, 1998, pharmaceutical giant Glaxo Wellcome agreed to make its anti-HIV drugs AZT and 3TC (also known as Retrovir and Epivir) available in the developing world at "significantly lower pricing ... than in the West."

According to Piot, the UN program is also attempting to improve access to generic drugs in the developing world, and to assist in bringing antiretroviral therapy to those countries whose public health infrastructures and economies would permit their use. Glaxo-Wellcome has also committed to participate in these efforts to bring effective therapy to the developing world. By working with the World Bank, the UN is making an effort to improve the public health infrastructure in other countries. The World Bank, it seems, is increasingly concerned that the AIDS epidemic is posing a significant barrier to economic development of "third-world" countries.

In his closing summary, Dr. Piot summed up the current situation with AIDS as being "very, very grim." "The AIDS epidemic," he continued, "is far, far from over. And we will have to cope with it for many generations to come."

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