

J IAPAC

**Journal of the
International Association
of Physicians in AIDS Care**

Vol. 1, No. 1

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battling complacency
advancing commitment

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JIAPAC (ISSN 1081-454X), is published quarterly by IAPAC, 33 N. LaSalle Street, Suite 1700, Chicago, Illinois 60602-2601. Telephone: (312) 795-4930; FAX: (312) 795-4938. E-mail: jiapac@iapac.org. Web site: <http://www.iapac.org>. POSTMASTER: send address changes to IAPAC, 33 N. LaSalle Street, Suite 1700, Chicago, Illinois 60602-2601.

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After terror, more horrors of war

D. William Cameron, MD, FRCPC

Editor-in-Chief, *JIA PAC*



"What's AIDS got to do with it?"

An Afghan boy walks near the Pakistan-Afghan border area at Torkham, northwest of Islamabad, scavenging for food and items of value September 15, 2001. Pakistan said it would comply with all UN resolutions that seek to combat "international terrorism," but its military was unlikely to take part in operations beyond its border.

Aziz Haidari © Reuters 2001

The United States suffered an act of terrorism September 11, 2001, which was designed to kill, hurt, rob, and shock—an act for which the United States has since been responding. We in the West will turn on the perpetrators and protectors of terrorism irrespective of their cause, and will use all necessary and legitimate means to respond. What next?

An effective international response to a "government" which keeps company with organized international terrorism is necessary. Regardless of how it came about, the source of this can be judged by the consequences of other policies, such as the atrocious treatment of women in Afghanistan, the physical labeling of Hindus in their daily life, the destruction of ancient images, and the millions of refugees who have voted with their feet for cold and hunger, over something worse. The Taliban, now the former "government" of Afghanistan, had seized power and did not represent those it governed, and showed no respect for the sanctity and dignity of human life. That government, thus, needed to be organized out of its misery.

When we force military solutions on intractable human problems, we have a war. Whether it is a war on terror, a government, or on a people means little. There are no surgical strikes. There has been further social disorganization, disruption of families, displacement of people, and crowding in the face of poverty. In Afghanistan, and in the crowded refugee camps around that country, we have seen the usual companion of famine and war, namely disease. Visible infections like cholera, hemorrhagic fever, and tuberculosis have emerged there.

The same social factors have promoted the spread of HIV infection in Africa. Decades of migration, displacement, and impoverishment of millions of African people have produced a huge AIDS epidemic. Every major war has had its baggage train of sexually transmitted disease. In the new war, add the economy of injection drug use to the ancient enteric, respiratory, and sexual transmission of infectious disease. Whether these factors will contribute to HIV in Asia is not a matter of *if*, but *when*. And the largest single contributor is war.

Just as for acute infectious diseases, AIDS will be a delayed consequence of the new war on terrorism. While war has denied many their basic human needs, and we participate in war even to bring an end to it, we need to support the civil and human rights of people to their basic needs. Our foreknowledge of this need is the opportunity to act. AIDS is a social disease. ■

Access to medicines is not the business of the pharma industry

Philip J. Brown, PhD

Publisher, *Scrip World Pharmaceutical News*, Surrey, United Kingdom

The trouble with small problems is that they can easily become big ones. Who would have thought that a single shot fired in Sarajevo in 1914 would have led to two world wars and a cold war lasting 50 years? While not on the same scale, but certainly the same principle, who knows where the industry's action against the South African government over the patents on AIDS products will lead?

In my opinion, the industry is heading on a dangerous path in its case against South Africa and its leaders must think very carefully before going any further. The best generals are those who know when to fight and when to withdraw. They will tell you that there is no point in fighting a battle unless there is something substantial to be gained. So what is to be gained in the courtroom in South Africa?

The issue of supplying essential pharmaceuticals to the less developed countries of the world has been going on for years. Access to AIDS drugs for South Africa is nothing new. I first came up against the problem in the early 1970s when Ciba Geigy developed a product for the intestinal parasitic disease, Bilharzia (schistosomiasis). Then, the Egyptian government demanded that it should be supplied at knock down prices on humanitarian grounds given the enormity of the problem for the country at the time.

As I recall, Ciba Geigy stood firm in the face of the Egyptian demands, pointing out that even if those who benefit from the therapy were successfully treated, they would become ill again whenever they went in infected water. The problem was an environmental one and not one of treating sick patients. I believe the issue was solved when Shell came up with a compound which killed the waterborne infectious agent at a very low cost, so matters went no further.

Now, we have a similar situation in South Africa, but here the problem is not an environmental one, rather one of public health, education and general social behavior. In

Editor's Note: This article first appeared in the April 2001 issue of Scrip Magazine and is reprinted here with permission from Scrip World Pharmaceutical News, © 2001.

saying this, I am very aware that we who live in affluent countries must not take a patronizing, "know it all" attitude when discussing the problems of countries which are less well off than ours, which means that we must deal, as far as possible, with hard facts and common sense.

In my analysis of the situation, first I would point out that involvement in treating Third World illnesses is not the core business of the international pharmaceutical industry. The industry operates in the main in developed countries where its industrial property rights, ie patents and trademarks, are accepted and upheld. If pharmaceutical companies did not have this industrial protection, they could not have developed in the way they have for the past 60 years. The patent monopoly granted to a company not only secures its business but also gives it rights to charge the prices needed to sustain its activities. If it is forced to charge generic prices then what is the point of having a patent?

The international R&D-based pharmaceutical industry sells products that treat the diseases of the Western world. At the start of the 21st century, these are diseases of the cardiovascular system, neurological diseases, cancer and illnesses associated with Western lifestyle, obesity and the like. In these cases, affluent countries are prepared to pay up to US\$10,000 a year to treat a patient, which is way beyond the means, and well outside the political will, of poorer countries.

Clearly, when we have a disease which spans both rich and poor countries, such as AIDS, we have a problem. One could ask the question why the pharmaceutical industry should be interested in providing treatment for AIDS since it has a very low incidence in the sophisticated societies where other measures can be taken to combat the condition, such as education and the use of condoms. The fact is that the R&D-based companies have developed AIDS drugs for the wealthy patients of Europe, North America and elsewhere, and not for the poor patients in Africa, just as they have developed drugs for the treatment of cancer, heart disease, Alzheimer's and the like. Around 1.5 billion people benefit from the drugs developed by the international R&D-based pharmaceutical industry, 4.5 billion people do not.

This brings me to the second point, which is that the pharmaceutical industry is not a substitute for a country's national health service. The reason why countries in Europe can afford the prices charged by R&D-based companies is because they commit significant financial resources to the provision of healthcare for their populations. Importantly, they also commit significant financial resources to education, social security, public health, the environment, communication and transportation. The governments in these countries ensure that everything is done to support a healthy and productive society that can thrive and prosper. The pharmaceutical industry is just one component in this mix, a valuable component to be sure, but still just one component.

The problem in the poorer countries is that they do not allocate their service resources in order to maximize the productivity and prosperity of their citizens. They spend disproportionate amounts of money on their armies and weapons systems, national security being their main preoccupation, and in some [countries] huge amounts of state money are siphoned off by corrupt rulers into foreign bank accounts. In many of the poorer countries where TB and malaria are rampant, generic, out of patent drugs are in fact available at costs amounting to a few pence a day, but still they are not deployed to the benefit of the community. As in the Egyptian case, even if individuals were cured of TB and malaria, the problem would not be solved while the environmental hazards remain.

So for the poorer countries, the pharmaceutical industry does not provide the benefits that it does in the wealthier ones. In fact, to bring this point home, I asked a number of pharmaceutical company executives whether they thought that making AIDS drugs available to the poor of South Africa would have any effect on the incidence of the disease in that country, and not one said they would. The treatment of AIDS is not simply a matter of giving a patient a once-a-week pill. It involves multiple dosing with an increasing number of drugs as the condition worsens, and the drugs themselves have serious side effects that have to be tolerated. When such treatments are considered in the context of conditions prevailing in many African countries, one seriously questions whether a beneficial outcome is possible.

It is when one gets down to the specifics of the South African case that things become more complicated, and this leads me to my third point, which is whether the R&D-based pharma industry should become involved in a legal fight with that country's government over patent rights of AIDS drugs.

It is important to remember that South Africa is a special case among the poorer nations of the world because of

the legacy of apartheid. It is special because its black and colored population suffered such abomination at the hand of the whites, and now the black population rules the country, as many think is right and proper. And, of course the transfer of power and authority took place under Nelson Mandela, a man of remarkable qualities whatever one's political point-of-view. If ever an industry wanted to take on a country, the last one it should choose should be South Africa.

Yes, silly things have been said about the nature and origin [of HIV] by Nelson Mandela's successor, Thabo Mbeki. Yes, South Africans are plagued by AIDS and their plight has been brought to the attention of the world by the likes of Oxfam and Médecins Sans Frontières. Yes, the Indian company Cipla has said that it can provide the AIDS drugs at a substantial discount on the price being charged in Europe, and another Indian company has said that it can provide them even cheaper and we have not got to the Chinese yet! Yes, the international companies have claimed that they have patent rights that apply in South Africa. So we have all the makings of a good old-fashioned punch up. Right is on both sides and only a judge can sort it out. Is that what the international industry really wants?

Well now some are not so sure. Thinking has shifted and a number of companies are offering to supply their AIDS drugs at significant discounts. As time passes, these discounts have become more and more significant to the point where they reach levels where there is virtually no difference between the Cipla price and that being offered by the R&D-based companies. But is this the right answer? On the one hand, we have companies which want to have their day in court arguing the rights of their patents. On the other, we have those who are discounting so hard that they have made their products into generics.

Before the South African court comes to order and the lawyers start to argue their cases, just pause for a moment and consider what the outcome will be. On the one hand, the industry could win its case to the embarrassment of the government which would appeal and, I suspect, win on appeal. Or the industry could lose, and have to endure the howls of triumph that would follow not only in South Africa, but in countries throughout the world, both rich and poor. But there would not only be howls of triumph. In the wake of a South African triumph, every health minister in every country, aided and abetted by the local AIDS patients' lobby, would be beating at the doors of the industry demanding that AIDS drugs should be made available at cut prices. And after AIDS, what next?

My advice to the industry is cut and run. Do not fight the South African case. Leave the market to Cipla and

other generic firms whose prices and supply lines may not hold, who knows? I also suggest that one logical conclusion which could be drawn from the South African experience is that companies re-examine their involvement in AIDS R&D and concentrate on research for diseases that relate solely to the Western world which the Western world values. Remember the pharmaceutical companies are businesses, not charities. ■

ISSUE UPDATE

Gregory A. Thompson, MD

Medical Editor, *JIAPAC*

In 1997, South Africa passed the Medicines and Related Substances Act, a controversial piece of legislation meant to allow compulsory licensing and parallel importing of pharmaceutical drugs deemed "vitaly needed" by South Africa's Department of Health. Passage of this legislation sparked international debate over international trade obligations under the World Trade Organization's (WTO) Agreement on Trade-Related Intellectual Property Rights (TRIPS Agreement).

The legislation's implementation was suspended pending the resolution of a legal challenge in South Africa's courts initiated by a coalition of 39 pharmaceutical companies. While the pharmaceutical companies—represented by South Africa's Pharmaceutical Manufacturers Association—ultimately dropped their lawsuit in 2001, dealing a public relations victory to compulsory licensing advocates, the debate continues to roar in South Africa and internationally.

Access to medicines is not a business

Response to the editorial, "Access to medicines is not the business of the pharma industry"
by Philip J. Brown, PhD, in *Scrip Magazine*, April 2001, reprinted on page 9.

Neera Singhal, MBBS, MS, MHA

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The lawsuit launched in February 1998 by 39 pharmaceutical companies against the government of South Africa was intended to protect the companies' rights to patents to AIDS medications. The lawsuit certainly brought into the limelight the long-simmering issue of access to medicines for the people of the poor countries of the world. Before that, other disadvantaged countries were fighting for access to affordable medicines. Under the World Trade Organization's (WTO) Agreement on Trade-Related Intellectual Property Rights (TRIPS), all WTO member countries must give developers the right to set the price of their patented medicines for 20 years. This makes the medicines' cost prohibitive and limits access for the vast majority of people who need them—the 4.5 billion referred to by Dr. Philip J. Brown.

The "general," or the leaders of the pharmaceutical industry, certainly heeded the advice to cut and run, as the case was dropped in April 2001, three years after the decision to launch the lawsuit. Perhaps it became clear to the general that he was in the wrong battle, because those who believe in their cause are known to fight to the bitter end. Just as the South African government was expected by Dr. Brown to appeal an unfavorable decision in the case. Dr. Brown's third point that the pharma industry should not engage in legal fights to limit access to medicines is right. It is not seemly to do so.

In a relatively short span of time, more men, women, and children have fallen victim to the scourge of eventually fatal HIV infection than the total casualties of both world wars, or approximately 60 million men, women, and children. Over 22 million have died and over 13 million children have been orphaned. Almost 95 percent of infected people are in developing countries, more than two-thirds of these in sub-Saharan Africa, so that is where most of the world's supply of AIDS medicines is needed. After all, the World Health Organization (WHO) had a goal of "Health for All" by the year 2000.

Since control of the environment is suggested as the better way to deal with threats to public health, let us first consider the environment of AIDS. Education, socioeconomic status, living conditions, lifestyle, gender, and access to healthcare all play a role in the prevalence of HIV

infection and the course of illness. Whereas the disease emerged among homosexuals in North America, it is now spreading fastest in heterosexuals, especially in developing countries and despite campaigns of public education and awareness. However, the reasons for its now unbridled spread remain primarily tethered to lifestyle. Promiscuity and prostitution are recognized as the main contributors to the spread of HIV in developing countries. The attached stigma and consequent denial make the risk potentially universal, and prevention a challenge. Such is the environment of AIDS. There is still no cure for the disease, and the role of medicines is in prolonging life, alleviating suffering, and reducing transmission. Therefore, treatment and preventive measures must complement each other.

Dr. Brown's first point is that access to medicines is not the business of the pharma industry. How did something as fundamental as access to medicines become reduced to being considered a business? Nevertheless, if it must, the interests of the industry would be well served to remember that when you are in business, everything that affects your product *should* be your business. That makes good business sense. The monopoly created by patents fosters all the ills that come with this institution. The government that favors a company with a patent must ensure that it exercise the privilege in a conscientious manner, rather than just protect its fiscal interests.

Unless the medicine is made available to all who stand to benefit from it, it is equivalent to being given control of the water supply of the world and the power to decide who can be thirsty, or to set the price of this precious commodity. Indeed, it is reminiscent of Marie Antoinette's famous behest that if the people do not have bread let them eat cake. It would be hard to imagine how history may have been shaped if, when discovered, access to penicillin had been restricted due to patent protection.

Proprietary rights, though they protect the interests of companies, are meant for the larger good of society, and give companies a climate free from competition in which to engage in the important task of developing

medicines. However, when patents are in conflict with public interest there should be no argument about who to favor, as corporations do not have human rights.

Just as it took 17 anthrax cases and four deaths in America for the Canadian government to override patent rights of the manufacturer of Cipro, and purchase a generic for mass prophylaxis, forcing the company with the patent to match the generic price. All this was done in short order, with responsible coverage by the news media, and with only token threats of legal action from the affected pharma companies, both the one with the patent and the generic manufacturer. This, of course, is how it should be. And Canada is not even a poor country. It is a moot point if the pharma companies were acting here for reasons of humanitarian concern, public relations and corporate image, or just plain greed. Are the millions who suffer and die in poor countries less deserving of compassion, or are they too insignificant to affect corporate image?

Let us come now to Dr. Brown's second point. Facilitating access to medicines is no substitute for a country's national health service, rather it is the making available of an essential component of the service. As long as the pharma industry is looking for excuses to not help poor countries it will find them—be it in the actions of corrupt despots, in the lack of healthcare infrastructure, or in the poverty and illiteracy, and even the "irresponsible" behavior of the people. Or, perhaps, it takes exception to their temerity in taking over a disease that had been confined to the affluent West, thus creating a demand for their patent-protected drugs where they will not profit from supplying them. Corrupt practices often reflect the economic circumstances of a country and highlight the divide between the rich and poor. Leaders of developed countries, have no qualms about letting the flourishing weapons and tobacco industries accrue huge profits by pandering to the needs of leaders of developing countries and of their people.

These countries often have good health plans, but the prohibitive cost of medicines, and the paucity of their means, make political will ineffectual. It costs approximately US\$10,000 per year to treat a single patient of AIDS in the developed world, which is often two- to three-fold the per capita gross national product (GNP) of developing countries. By United Nations estimates, the annual supply of AIDS medicines in sub-Saharan Africa costs between US\$1,400 and US\$4,200. It is reasonable to expect that, once they have medicines, the governments and responsible healthcare providers will prioritize treatment according to individual need and available support mechanisms. If, as the industry presumably perceives, threat of re-infection or recurrence, and fear of side effects contraindicate treatment, then

there is no place in medicine for antibiotics and anti-cancer agents. Does the pharma industry really want the power to have individual health ministers begging at its door? In addition, in developing countries, the cost of medicines is often borne by the individual, as there is no health insurance.

Cancer, heart disease, and obesity are not the exclusive domain of the rich. Developing countries give precedence to affordable medicines for diseases such as tuberculosis, malaria, and AIDS—diseases that are preventable, are public health risks, or are associated with much suffering. Let the pharma industry try and confine itself, as Dr. Brown suggests, to manufacturing drugs solely for so-called "diseases of the rich" as a solution to its perceived economic woes. It is a safe bet that the pharma industry will not have much success in limiting the geographical scope of diseases.

Essentials such as life-saving or life-prolonging drugs cannot be treated like any other consumer product. Governments look the other way when pharma companies spend twice as much on marketing as they do on research and development. The TRIPS Agreement allows poor countries parallel imports of inexpensive medicines, compulsory licensing, and the right to the manufacture of affordable generics. However, governments of developing countries are often punished for availing themselves of these provisions. The United States has even slapped Special 301 tough trade law sanctions on many countries for passing, and in some cases even for considering, intellectual property rules that do not suit US trade goals.

If each player in the issue of access to medicines remains busy looking at it from their own narrow pecuniary, rather than from a humanitarian, perspective, the problem will persist—this despite the efforts of organizations such as Doctors without Borders and Oxfam to increase awareness. Dr. Brown notes that multinational companies are now beginning to discount prices of AIDS drugs to almost the level of generics. This may well be because the high prevalence of AIDS in developing countries is now making it profitable to sell medicines at cut rates, rather than losing this market altogether to the likes of Cipla, the Indian company which has offered to supply generic AIDS medicines at low prices.

Corporate philanthropy is unpredictable, often targeted to specific populations, and conditional on endorsement of patent rights by the beneficiary country. As a solution, it can only complement a global effort. The recently proposed Global AIDS and Health Fund is commendable, but must strive to be of universal benefit and not at the whim of contributors.

Segmented approaches will always let some aspects of the issue remain unaddressed, and some segments of the global society deprived. Since the problem is international, and the key lies in the hands of multinational companies, the governments that protect them, the political will of needy countries, and the commitment of international health and social organizations, then it may be a safe conjecture that there is some middle ground that offers hope of a solution. History is witness that oblivion and inaction cost the "powers that were" in Marie Antoinette's time their heads. Surely the powers that be in this issue will keep their heads and show much needed leadership in finding a solution to this crisis.

If the decision in the South African case was expected by Dr. Brown to favor the government over the pharma industry, and if both rich and poor countries were expected to applaud such a decision, then who is left? Is this not proof enough where the right lies? It is time to address this issue on a global basis rather than on a case-by-case basis. What better reason to do it than for the sake of the children. ■

Update on didanosine

David A. Cooper, MD, DSc

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Abstract

Didanosine (ddl) has been a cornerstone of HIV management since it was made available in October 1991. Didanosine was originally introduced as an alternative to zidovudine (ZDV) for patients who were intolerant of ZDV or experienced disease progression during ZDV monotherapy. Didanosine is now used extensively as an integral component of multidrug combination regimens in both adults and children with HIV infection, and is now available for once-daily administration in the United States, Canada, and Europe. The recently approved Videx® EC is an enteric-coated didanosine capsule dosed as one capsule, once daily.

This paper provides an update of recently published studies on the use of ddl in combination anti-HIV therapy. In particular, these studies examine the rationale for the use of ddl as first-line anti-HIV therapy, and describe newer findings concerning its long-term efficacy, side effects, compliance, resistance, and once-daily use. The increased survival of HIV-infected patients is largely attributed to the introduction of the triple combination drug therapy but is probably also due to the long-term clinical efficacy of ddl.

Key words: didanosine, combination drug therapy, treatment outcome

Introduction

Didanosine (ddl) is an antiviral agent that belongs to the nucleoside analog reverse transcriptase inhibitor (NRTI) class. The mechanism of action of ddl involves intracellular phosphorylation of the parent drug to its active metabolite, 2', 3'-dideoxyadenosine 5'-triphosphate (ddATP).¹⁻³ ddATP prevents HIV (human immunodeficiency virus) replication by inhibiting the action of the viral reverse transcriptase through competition with

the naturally occurring nucleoside deoxyadenosine triphosphate for incorporation into the growing viral DNA chain. Incorporation of ddATP into viral DNA stops viral DNA elongation, terminating HIV replication.

The antiviral activity of ddl *in vitro* is well established. Didanosine has been shown to effectively inhibit HIV replication *in vitro* in a concentration-dependent fashion and maintain activity in a variety of different cell types.⁴⁻⁶ Antiviral activity *in vitro* may be a useful marker of antiviral potency *in vivo*, but the relationship between *in vitro* antiviral activity of ddl and its clinical efficacy has not been established. The antiviral activity of ddl is additive or synergistic with that of other antiretroviral drugs, a property that increases the activity of combination antiretroviral therapy.

The pharmacokinetics of ddl is linear and dose-proportional following oral single- and multi-dose administration.^{7,8} Didanosine is able to cross the blood-brain barrier and improvement in the symptoms of acquired immunodeficiency syndrome (AIDS)-related dementia has been reported following ddl administration,^{9,10} however, current evidence does not show that ddl achieves therapeutic concentrations in the cerebrospinal fluid. The metabolism of ddl in humans is presumed to occur by the same pathways responsible for the elimination of endogenous purines, and its excretion is primarily renal.¹¹

The antiviral activity and therapeutic efficacy of ddl has been demonstrated in numerous clinical trials both as monotherapy and in combination with other antiretroviral drugs.¹²⁻¹⁶ Most of the earlier studies of the efficacy of ddl were based on clinical endpoints, such as mortality and duration of disease-free survival. Later studies used validated surrogate markers, eg, CD4 T cell count and viral load, as reliable predictors of severity of HIV disease and, by extension, therapeutic efficacy of ddl in arresting HIV disease progression. The vast majority of clinical studies of ddl have been in patients receiving combination therapy with multiple drugs, and as for other therapeutic agents for HIV infection, few placebo-controlled studies with ddl have been conducted for ethical reasons.¹⁷

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JIA PAC 2002;1(1):15-25. © 2002 IAPAC.

Studies have shown that early initiation of combination therapy achieves significant and durable virological and immunological responses, and that such treatment prolongs the duration of disease-free survival in HIV-infected patients.¹⁸⁻²⁰ Findings from ongoing studies will help clarify the effects of early aggressive treatment on immune system reconstitution, body composition changes, and other aspects of long-term HIV management.

The efficacy of all antiretroviral agents is limited to varying degrees by their toxicity and their propensity for the development of viral resistance. Improvement in the survival of HIV-infected patients creates the need for therapeutic interventions with not only sustained clinical efficacy but also long-term tolerability. Long-term clinical efficacy is now a major consideration in the selection of antiretroviral agents for the individual patient, but the sustained efficacy of most anti-HIV drugs, particularly those that have been recently approved, is uncertain. In a five-year follow-up study in 72 patients with advanced HIV infection, ddI was found effective and was well tolerated for over four years.²¹ Such findings underscore the need for antiretroviral agents with sustained efficacy and tolerability for patients at all stages of HIV infection.

Combination therapy

Multiple drug combination therapy is the cornerstone of HIV disease management. This strategy is supported by the findings of pivotal clinical trials that demonstrated improvements in surrogate markers of HIV disease progression, and also in clinical endpoints in patients receiving multiple combination antiretroviral therapy.¹²⁻¹⁶

Two of the primary studies to demonstrate benefit of combination antiretroviral therapy over monotherapy were the Delta trial and the ACTG 175 trial.^{12,13} The Delta trial was a randomized double-blind study comparing zidovudine (ZDV) alone with ZDV plus ddI or ZDV plus zalcitabine (ddC). It included both treatment-experienced and treatment-naïve patients who were followed for a mean of 2.5 years. The trial demonstrated a significant survival advantage for both combination regimens over ZDV alone, and this difference was greatest in the treatment-naïve group. Similarly, the ACTG 175 trial demonstrated a significant advantage of the ddI plus ZDV regimen over ZDV monotherapy, and also showed that ddI monotherapy was significantly better than ZDV alone. The association between clinical endpoints and changes in surrogate markers of HIV disease activity observed in the Delta trial has recently been analyzed.^{22,23} HIV RNA levels and CD4 T lymphocyte counts at baseline and after eight weeks of treatment were significantly associated with survival in all patient

groups.²² Reductions in HIV RNA levels were consistent with clinical results, and the decrease in HIV RNA achieved at 16 weeks was highly predictive of the clinical response.

The INCAS trial was a randomized, controlled, double-blind study of the safety and efficacy of the three-drug combination of ZDV, ddI, and nevirapine (NVP) in 153 treatment-naïve patients with HIV infection.¹⁴ After 52 weeks of treatment, the proportion of patients with HIV RNA levels below 20 copies/ml was 51 percent in patients receiving triple combination therapy, 12 percent in patients receiving ZDV and ddI, and zero percent in those receiving ZDV and NVP. Rates of disease progression or death were significantly lower in the triple combination group (12 percent) than in the ZDV and NVP or ZDV and ddI groups (23 percent and 25 percent, respectively), corroborating the virologic responses.

The efficacy of the triple drug combination of ZDV, ddI, and NVP was examined in a randomized, double-blind trial by Florida et al.¹⁵ In this study, 68 treatment-naïve patients with advanced HIV disease were randomized to receive ZDV and ddI, or the three-drug combination and were followed for 48 weeks. HIV RNA levels decreased and remained below baseline for the duration of the study in both treatment groups, and the decrease was significantly greater in the triple combination group than in the ZDV and ddI group. Body weight increased in all patients during treatment with a trend for greater increases in patients receiving ZDV and ddI. Such treatment of patients with less advanced immune deficiency might be expected to have greater effectiveness.

Triple combination therapy with ZDV, ddI, and NVP proved superior to ZDV alternating with ddI, ZDV and zalcitabine, and ZDV and ddI in a randomized study of 1,313 patients with advanced HIV infection.¹⁶ Although surrogate and clinical endpoints favored triple combination therapy, only CD4 T cell increases were statistically significant between the triple therapy and ZDV and ddI groups. The incidence and severity of treatment-related toxicities were similar in all four groups.

The efficacy of the combination of ZDV, ddI, and NVP may be compromised by drug-drug interactions between ZDV and NVP.²⁴ Zidovudine bioavailability is decreased by about 30 percent in the presence of NVP, whereas NVP does not appear to interfere with ddI bioavailability. Although the decrease in ZDV bioavailability during combination treatment with NVP may be clinically insignificant, it is not known whether the effect of NVP on ZDV bioavailability influences the selection of resistant HIV mutants during combination therapy.

Didanosine has also been studied with the nonnucleoside reverse transcriptase inhibitor (RTI) efavirenz, although to a lesser extent. A once-daily protease inhibitor (PI)-sparing regimen of ddI plus efavirenz plus the investigational nucleoside RTI emtricitabine given to 40 treatment-naïve subjects showed that 98 percent and 93 percent achieved plasma HIV RNA levels less than 400 copies/ml and less than 50 copies/ml at 24 weeks.²⁵

The effective treatment of early HIV infection may be associated with prolonged suppression of viral replication and the preservation of immune function. In a study of 10 patients with primary HIV infection who were treated with the triple combination of ZDV, ddI, and lamivudine (3TC) starting at five to 28 days after the onset of symptoms, all patients achieved undetectable viremia after a mean of 108 days of follow up.²⁶ The plasma HIV RNA response was accompanied by a large viral decrease in multiple compartments and a waning of antibody response in some cases.

An alternative strategy for the treatment of early HIV infection consists of immunotherapy administered in combination with antiretroviral therapy. In a phase II study by Simonelli et al, 12 patients with early stage HIV infection received subcutaneous interleukin-2 with ZDV and ddI for 24 weeks followed by an additional 24 weeks of ZDV and ddI.²⁷ In addition to improvements in CD4 T cell counts and HIV viremia, the combination treatment was associated with improvements in some immunologic functions as indicated by increased expression of CD4 T cell subsets CD25, CD45RO, and CD45RA, and significant decrease in proviral DNA in peripheral blood mononuclear cells. The majority of patients maintained undetectable HIV RNA levels during 24 weeks of follow-up.

The combination of ZDV and ddI with the nonnucleoside RTI delavirdine (DLV) demonstrates significant synergy and antiviral activity *in vitro*.²⁸ A proven combination is that of ddI and stavudine (d4T), a thymidine nucleoside analog, which has been studied as dual NRTI therapy²⁹⁻³⁵ and as part of triple-drug therapy.³⁶⁻⁴³ In a study of 65 heavily pretreated patients with HIV infection who received only ddI/d4T, the CD4 T cell count increased by a mean of 70 x 10⁶/L and the HIV RNA level decreased by a mean of 0.89 log₁₀ copies/ml at week 24.²⁹ Undetectable plasma viremia was achieved by 14 percent of the patients at week 24, and adverse effects were generally mild and observed in 32 percent of the patients.

The most recent evidence of the benefit of ddI in regimens also containing d4T was reported in the START II trial by Eron et al.³⁹ In this 48-week open-label study, 205 HIV-positive patients received initial treatment with

indinavir plus ddI/d4T or indinavir plus ZDV/3TC. In the ddI/d4T arm, the percentage of patients with HIV RNA levels below 50 copies/ml at week 48 was greater (41 percent) compared with that in the ZDV/3TC arm (35 percent), and the CD4 T cell count increase from baseline at 48 weeks was significantly greater (214 and 142 cells/ μ L, respectively; $p = 0.026$).

The results from these and other clinical studies of highly active antiretroviral therapy (HAART) regimens containing the ddI/d4T backbone have shown that ddI/d4T-containing regimens, including those with other protease inhibitors like nelfinavir and ritonavir (only reported as abstracts), were associated with good virologic and immunologic responses (table),³⁶⁻⁴² though concerns for hepatotoxicity must temper such use.

Comparison of didanosine with zidovudine

Drug-related toxicities and the development of resistance limit the beneficial effects of ZDV treatment. Alternating therapy with ZDV and other antiretroviral agents may be a useful strategy for reducing the toxicity of ZDV treatment while maintaining antiviral activity, but the clinical consequences of this approach have not been fully explored. Although no longer appropriate therapy for HIV infection, early monotherapy trials of ddI and ZDV allowed a comparative evaluation of these two drugs without possible confounding influences from the actions of other antiretroviral therapy. These trials showed that switching ZDV for ddI, or alternating treatment with ZDV and ddI on a monthly basis, is associated with greater beneficial effects compared to ZDV monotherapy.⁴³ Significantly greater improvement in survival of patients with CD4 T cell counts less than 100/mL occurred, particularly among those who are ZDV-naïve.⁴⁴ Alternating therapy with ZDV and ddI has no advantage in survival over monotherapy with either drug in patients with higher CD4 T cell counts, but the safety profile of alternating therapy is significantly better than that of ZDV or ddI monotherapy in all patient groups.

The survival of 2,367 HIV-infected patients treated with ZDV was significantly influenced by the use of other nucleoside analog drugs—ddI, ddC, d4T, and 3TC45. As compared with ZDV monotherapy, the relative mortality hazard, with the relative risk of death with ZDV monotherapy considered to be 1.0 in this case, was reduced to 0.41 in patients who added 3TC, 0.79 in those who added ddI, 0.74 for ddC, and 0.67 for d4T. This observational study has limited comparative justification, but consistency of added effectiveness is reassuring.

Once-daily didanosine

To improve compliance, simple and well-tolerated antiretroviral regimens are needed. Treatment adherence

Table. Summary of key studies with triple-drug regimen containing the didanosine/stavudine nucleoside combination

<i>Study</i>	<i>Study group</i>	<i>Study design</i>	<i>Intervention</i>	<i>Key findings</i>
Zurich Prometheus; Flepp (36)	Treatment naïve (<i>n</i> = 30)	Double blind, randomized; 52 weeks	ddl QD/d4T/ nelfinavir	Decrease in mean viral load; decrease in mean CD4 T cell count
VIRGO; Raffi (37)	Treatment naïve (<i>n</i> = 59)	Double blind, placebo- controlled; 48 weeks	ddl QD/d4T/ nevirapine	85 percent of patient at week 24 had achieved viral loads <50 copies/mL.
Atlantic (Murphy, unpublished)	Treatment naïve (<i>n</i> = 235)	Open label, randomized; 48 weeks	ddl QD/d4T/indinavir; ddl QD/d4T/nevirapine; ddl QD/d4T/3TC	The two PI-sparing regimens were as potent and well tolerated as the PI-containing regimen at 48 weeks.
OzCombo1; Carr (38)	Treatment naïve (<i>n</i> = 109)	Open label, randomized; 52 weeks	ddl/d4T/indinavir; d4T/3TC/indinavir; ZDV/3TC/indinavir	All treatments were similar in their virologic and immunologic effects after one year.
START II; Eron (39)	“Limited” prior treatment (<i>n</i> = 205)	Open label, randomized; 48 weeks	ddl/d4T/indinavir; ZDV/3TC/indinavir	Both treatment regimens had potent virologic effects; the ddl/d4T arm had a significantly higher increase in CD4 T cell count (<i>p</i> =0.001).
HIV-NAT; Kroon (40)	Treatment experienced (<i>n</i> = 95)	Open label, randomized; 48 weeks	ddl/d4T/ saquinavir soft gel; ZDV/3TC/ saquinavir soft gel	Both treatments were equally effective in reducing viral load; the ddl/d4T arm had significantly greater improvements in CD4 T counts (<i>p</i> =0.023).
Saimot et al. (41)*	Treatment naïve (<i>n</i> = 36)	Noncomparative	ddl/d4T/ritonavir	After 72 weeks, 87.5 percent achieved viral loads <50 copies/mL
Hengge et al (42)*	Treatment experienced but naïve to nelfinavir (<i>n</i> = 53)	Noncomparative	ddl (200 mg)/ d4T/nelfinavir	Viral load decrease 2.2 log ₁₀ copies/mL and CD4count increase of 230 cells/μL at 24 weeks

* Studies reported as abstracts.

is a major determinant of the clinical and virologic efficacy of antiretroviral drugs, and lack of compliance is a primary contributing factor to the development of drug resistance. The current emphasis on simplifying treatment regimens and improved compliance has shifted attention to once-daily treatments.

The pharmacologic profile of ddl is characterized by sufficient bioavailability and prolonged intracellular half-life to support once-daily dosing.⁴⁶ *In vitro* study has shown the intracellular half-life of the active drug (ddA-TP) is greater than 25 hours.⁴⁷ Using the same total daily dose, the overall plasma exposure with once-

daily dosing, as measured by the area under the concentration time curve (AUC) over 24 hours, was similar to twice-daily dosing.⁴⁸ Although peak concentrations were about 50 percent lower with twice-daily regimen because of the lower dose, the AUC parameters were similar, suggesting once-daily dosing of ddl is appropriate. Early clinical studies of once-daily ddl have suggested that the total daily dosage of ddl rather than the dosage schedule may be a more important determinant of therapeutic response.⁴⁶ Changes in surrogate markers appeared similar whether ddl was administered once or twice daily.

A number of recent studies of the safety and efficacy of once-daily ddI versus twice-daily ddI have been reported.^{30-34,49} All these studies showed once-daily ddI to be as effective as twice-daily ddI, and there was little difference in severity or frequency of adverse events with the two regimens. In a well-controlled, double-blind study of 87 treatment-naïve patients given either d4T plus ddI once daily or d4T plus ddI twice daily, Mobley et al found similar results with nearly a 2 log drop (-1.8 log₁₀ copies/ml) over 2 to 24 weeks of treatment in both groups with similar side-effect profiles.³⁴ The researchers found that gastrointestinal-related side effects occurred more frequently in the twice daily dose group and concluded that ddI once daily may be better tolerated. Further, the results of an open-label study by Monno et al, who also found the same difference between ddI once daily and twice daily dose groups for gastrointestinal side effects, suggested improved adherence with ddI once daily based on time on therapy.³³

Of relevance to current treatment recommendations, once-daily ddI has been shown to be effective as part of various triple-drug therapies containing a protease inhibitor or a nonnucleoside RTI, such as in the VIRGO and Atlantic trials,^{36-38,50,51} (and R. Murphy, unpublished data). Other recent reports, including that by Gathe et al,⁵¹ comparing once-daily ddI with stavudine and nevirapine to a standard triple PI regimen, have so far only been reported as abstracts.

Didanosine in children

The combination of ZDV and ddI has proven superior to monotherapy with either agent alone in children with HIV infection.⁵²⁻⁵⁴ Englund et al randomized 839 children with symptomatic HIV infection to receive ZDV, ddI, or ZDV and ddI, and the primary study endpoint was length of time to death or progression of HIV disease.⁵² After a median follow-up of 23 months, the relative risk of HIV disease progression or death was 0.61 in the dual therapy group as compared with those in the monotherapy groups ($p=0.007$). At the end of the study (median, 32 months), however, the efficacy of ddI monotherapy was similar to that of the combination of ZDV and ddI. Children receiving ddI alone had a significantly lower risk of anemia or neutropenia as compared with those receiving ZDV. Palumbo et al reported similar findings in a review of data from 566 infants and children who participated in a Pediatric AIDS Clinical Trials Group clinical trial (PACTG 152).⁵³ They found no significant difference in mean plasma HIV RNA reductions between children treated with ZDV and ddI and those treated with ddI alone.

Another PACTG study (PACTG 300) assessed the safety and clinical efficacy of the combination of ZDV

and ddI, ZDV and 3TC, and ddI alone as first-line therapy in 615 children with symptomatic HIV infection.⁵⁴ However, enrollment in the ZDV/ddI study arm was halted early when the results of the PACTG 152 study became known, and suggested that equal benefit could be obtained with ddI alone. The 152 study did show that, during a median follow-up of 9.4 months, both ZDV/3TC and ZDV/ddI recipients had a lower risk of both disease progression and death than those receiving ddI alone. The adverse event rates for ZDV/3TC and ZDV/ddI were comparable. In HIV-infected children in stable condition who were previously treated with ZDV alone and with ZDV resistance mutations, switching to ddI monotherapy is associated with a better short-term outcome than is continued ZDV monotherapy or combination therapy with ZDV and ddI.⁵⁵ Among 94 children infected with HIV who had ZDV resistance-associated proviral mutations, clinical deterioration at six months occurred in significantly fewer children who switched to ddI monotherapy (15 percent) than in those who switched to ddI and ZDV (57 percent) or those who received continuous ZDV alone (55 percent). Differences between the groups at one year were not statistically significant.

The combination of ddI and d4T proved to be more effective than treatment with d4T alone in a study of 108 children with HIV infection.⁵⁶ Mean declines in plasma HIV RNA levels at week 12 were 0.49 and 0.18 log₁₀ copies/ml in the ddI/d4T and d4T monotherapy groups, respectively. These differences were maintained during 48 weeks of treatment.

Triple combination therapy is emerging as an important therapeutic strategy for the treatment of HIV infection in infants and children as well as in adults.^{57,58} The safety and efficacy of the combination of ZDV, ddI, and NVP were determined in eight infants with HIV infection who were asymptomatic or only mildly symptomatic at baseline.⁵ Within four weeks, reductions in plasma HIV RNA levels of at least 96 percent were achieved in seven of the eight infants. Over the six-month study period, viral replication was controlled in two infants who began therapy at 2.5 months of age, and viral load was reduced by 0.5 to 1.5 log₁₀/ml in five of the other six infants. The three-drug regimen was well tolerated without clinically important adverse events.

Resistance

Resistance to antiretroviral drugs is a complex issue involving behavioral, pharmacologic, and biological factors. Both genotypic and phenotypic assays for determining antiviral drug susceptibility are available, but the clinical role of these tests is not yet clearly defined, as questions regarding the timing, methodology, and interpretation of drug resistance assays remain unanswered.⁵⁹

The routine incorporation of susceptibility testing into antiretroviral drug trials may be a useful means of increasing the available data on antiviral drug resistance, and refining the clinical usefulness of the test.

Drug-resistant HIV has been detected in patients on all currently available antiretroviral drug regimens.⁶⁰ High-level drug resistance, which is usually defined as greater than 100-fold increase in the 50 percent inhibitory concentration (IC₅₀) of the drug, has been observed in patients treated with ZDV, 3TC, and NVP, whereas treatment with ddI, ddC, and d4T has only produced HIV strains with low-level resistance. However, a number of trials suggest that this low-level resistance may be associated with therapeutic failure of regimens including these drugs. Combination drug regimens can usually delay the emergence of drug-resistant HIV strains, but resistance eventually emerges unless complete suppression of viral replication is achieved.

The HIV RT mutation L74V develops during ddI therapy and confers decreased susceptibility to ddI.⁶¹ This mutation, in conjunction with the ZDV-related mutation Thr215Tyr, also decreases ZDV resistance. In viruses with the L74V mutation, an 11 percent loss of replication ability compared with that of wild-type virus has been demonstrated.⁶² This decreased replication ability provides an explanation for the lower HIV RNA levels observed with ddI therapy compared with ZDV therapy in clinical trials.

Antiretroviral drug resistance may develop in multiple body compartments. Mayers et al evaluated drug resistance mutations in peripheral blood mononuclear cells (PBMC) and lymphoid tissue obtained from 22 HIV-infected patients treated with ZDV alone or in combination with ddI.⁶³ During the eight-week study, 27 percent of the participants showed evidence of ZDV resistance at codon 215 and none of the patients developed the codon 74 mutation associated with ddI resistance. When HIV proviral DNA from PBMC was compared with that from lymphoid tissue, 95 percent of the samples were concordant for the 215 mutation at baseline whereas 86 percent were concordant after eight weeks.

The emergence of multiple drug resistance may occur in patients who are extensively pretreated with anti-HIV drugs. In a European study, multidrug NRTI-resistant HIV-1 strains were detected in four percent of patients treated with multiple dideoxynucleoside analogs for six months or more.⁶⁴ The emergence of HIV-1 strains with unusual combinations of amino acid changes has been reported in extensively pretreated patients not responding to their current antiretroviral combination therapy.⁶⁵ These changes include insertions of amino

acids between codons 68 and 69, in the absence of previously known amino acid changes associated with resistance to ddI, ddC, 3TC, and d4T. Inserts, like point mutations, are selected *in vivo* during antiretroviral therapy and may provide resistance to multiple NRTI drugs.⁶⁶ HIV-1 isolated from a patient receiving combination therapy with ddI and hydroxyurea (HU) was found to have RT amino acid substitutions T69S and K70R flanking a two amino acid insertion.⁶⁷ The amino acid insertions conferred low-level nucleoside analog resistance while the substitutions appeared to represent a compensatory mechanism for the deleterious effects of the insertions on RT activity. Serial passages of HIV-1 in increasing concentrations of the combination of ddI and d4T resulted in mutations at RT codons 57 and 9868. These mutations were associated only with an 11.5-fold increase in the IC₅₀ of ddI and a 4.5-fold increase in the IC₅₀ of d4T. Neither of these mutations was associated with multidrug resistance. The underlying mechanism of NRTI multidrug resistance remains poorly understood.

Didanosine and hydroxyurea

Hydroxyurea (HU) induces the activity of cellular kinases that phosphorylates nucleoside RTIs and preferentially depletes intracellular purines, which may enhance the antiviral activity of ddI; however, hydroxyurea also increases the toxicity of ddI, and the combination may not be helpful. The role for HU in the treatment of HIV infection remains uncertain.

HU has favorable pharmacokinetic properties and has demonstrated good tolerability when used in combination with ddI in patients with HIV infection.^{69,70} In a pilot study of 26 patients with advanced HIV infection treated with ddI who were randomized to receive 500 or 1000 mg/day of HU, median decreases in viral load of 0.02 and 0.63 log₁₀ HIV-1 RNA copies/ml were achieved in the 500 and 1000 mg groups, respectively.⁷¹ HU has been used to intensify regimens and as part of PI-containing regimens. HU improved the efficacy of the combination of ddI and d4T⁷² and was shown to be effective when combined with ddI plus indinavir.⁷³ However, patients treated with ddI in combination with d4T, with or without HU, may be at increased risk for pancreatitis, which may be fatal,^{11,74} and the risk may be too high for use in a clinical setting without further study.

Withdrawal of HU and ddI in patients also treated with both drugs has not been associated with rebound of plasma viremia for at least one year after drug discontinuation.⁷⁵ A possible explanation for the absence of viral rebound following withdrawal of this combination may be that the combination of ddI and HU exerts its antiviral effects in resting cells, as well as in those that are actively replicating. This observation

has possible implications for the role of combination treatment with ddl and HU in persons with early HIV infection with the goals of prolonged suppression of viral replication, delay or avoidance of resistance, and possible viral eradication.^{76,77}

Dosage and administration

The labeling and prescribing recommendations for the use of ddl (Videx[®], Bristol-Myers Squibb) in the United States were extensively revised in April 1998 and again in October 1999, including changes in sections relating to clinical pharmacology, indications and usage, precautions, and dosage and administration of ddl.¹¹ Important changes to US labeling for Videx[®] related to the approval of ddl for once-daily administration and to the potential for increased risk of pancreatitis in patients receiving ddl in combination with d4T, with or without HU. Physicians should be aware of the clinical presentation of pancreatitis in light of the recent labeling changes (see below).

The revised pharmacokinetic information specifies that ddl is rapidly absorbed, with peak plasma concentrations generally observed from a quarter hour to one and a half hours after oral dosing. Increases in plasma ddl concentrations are dose-proportional over the range of oral doses administered in clinical practice, and steady-state pharmacokinetic parameters do not differ significantly from values obtained after a single dose. Binding of ddl to plasma proteins is less than five percent.

Peak plasma concentrations of ddl and the area under the plasma concentration time curve are decreased by about 55 percent when ddl tablets are administered up to two hours after a meal. It is recommended that ddl be taken on an empty stomach at least 30 minutes before or two hours after eating.

The dose of ddl should be reduced in patients with reduced creatinine clearance and in patients receiving maintenance hemodialysis. The pharmacokinetics of ddl in children older than 36 weeks of age is similar to that in adults, and ddl plasma concentrations increase in children in proportion to oral doses ranging from 80 to 180 mg/m².

Drug interactions between ddl and various antiviral, antibacterial, and antifungal drugs have been reported,¹⁷ but an enteric-coated formulation has now eliminated or diminished unwanted interactions that were due to the presence of buffering agents in the tablet formulation (see section on Videx[®] EC below). No clinically significant drug interactions have been demonstrated between ddl and dapsone, loperamide, metoclopramide, ranitidine, rifabutin, stavudine, sulfamethoxazole, trimethoprim, and ZDV.

The warnings accompanying the ddl prescribing recommendations have been revised to note that fatal pancreatitis has occurred during treatment with ddl. The frequency of pancreatitis is dose-related, and the incidence ranged from 1 percent to 7 percent in patients treated with recommended doses. Lactic acidosis and severe hepatomegaly with steatosis have been reported as rare, but potentially life-threatening, adverse effects with the use didanosine and other NRTIs alone or in combination. Fatal lactic acidosis has occurred in pregnant women receiving the combination of didanosine and stavudine.¹¹ This effect is believed to be peculiar to this class of drugs, and the occurrence of lactic acidosis may be more related to the use of stavudine when didanosine and stavudine are given together. Retinal and visual changes have also been observed in patients treated with ddl.

Didanosine is currently indicated as once- or twice-daily dosing in the United States and Europe for the treatment of HIV infection in adults and twice-daily dosing in children. The recommended dosage of ddl tablets is 400 mg once daily or 200 mg twice daily in adults weighing 60 kg or more, and 250 mg once daily or 125 mg twice daily in adults weighing less than 60 kg. The dose should be administered at least 30 minutes before a meal, and the dosing interval should be 12 hours when used twice daily. The recommended dose of ddl monotherapy in children is 120 mg/m² twice daily. There are no data on once-daily dosing in children. Didanosine is supplied as chewable buffered tablets, buffered powder for oral solution, and pediatric powder for oral solution. The tablets and powder preparations of ddl are stored at room temperature. Because of the need for adequate buffering, the 200-mg-strength tablet should only be used as a component of the 400-mg once-daily regimen. For either dosing regimen, two of the appropriate strength tablets at each dose should be administered to provide adequate buffering and prevent degradation by gastric acid.

Videx[®] EC

In October 2000, a new once-daily, enteric-coated formulation of didanosine (Videx[®] EC) was approved in the United States. The enteric-coated formulation permits the use of didanosine without the buffers necessary with previous formulations to prevent degradation of didanosine by stomach acid.

The available efficacy data indicate that the enteric-coated formulation has good antiviral activity. In an open-label trial, 511 treatment-naïve HIV-infected patients received either a triple regimen of nelfinavir plus stavudine and enteric-coated didanosine, or a reference triple regimen of nelfinavir plus zidovudine and lamivudine for 48 weeks.⁷⁸ Both treatments were

found to have similar antiviral activity. The results of the primary efficacy analysis showed that a similar proportion of patients in the enteric-coated ddl regimen and the reference regimen had viral load suppression less than 400 copies/mL (56 percent and 53 percent, respectively). The two treatment groups were also comparable at 48 weeks for suppression below 50 copies/ml (37 percent and 35 percent, respectively) and for median decrease from baseline in viral load (HIV RNA -2.59 and -2.61 \log_{10} copies/ml, respectively) and CD4 T cell count (120 and 162 cells/ μ L, respectively).

The pharmacokinetic data from healthy volunteers and HIV-infected subjects show that peak plasma concentration is reduced (approximately 40 percent) and time to maximum concentration is increased (from 0.67 to 2.0 hours) with the enteric-coated formulation.⁷⁹ However, AUC is equivalent for didanosine when administered as the enteric-coated formulation or the buffered tablet formulation. This indicates equivalent bioavailability of the enteric-coated formulation and the ddl buffered formulation.

The absence of buffering agents has reduced the possible drug interactions with didanosine. In studies of the effects of coadministration of the enteric-coated formulation on the AUC and peak drug concentrations of antimicrobial agents from different classes—ciprofloxacin, indinavir, and ketoconazole, no clinically significant pharmacokinetic interactions were observed.⁷⁹ The use of this once-daily, enteric-coated didanosine formulation, which does not need buffering agents, will probably be associated with fewer gastrointestinal adverse events and fewer drug interactions than previous didanosine formulations. In a six-week open-label, crossover study, tolerability of the enteric-coated formulation of ddl was assessed in 42 HIV-infected patients currently receiving antiretroviral regimens containing the tablet formulation and who had gastrointestinal symptoms, eg, nausea, bloating, diarrhea, gas, cramps, of at least moderate severity.⁸⁰ After switching to enteric-coated ddl, severity of gastrointestinal symptoms and negative impact of side effects on daily activities were significantly reduced ($p < 0.01$) after four weeks. The overall safety profile of enteric-coated ddl is expected to improve the side effect profile of ddl as well as enhance tolerability and promote treatment adherence compared with the current buffered tablet formulation.

Conclusions

The current goal of anti-HIV therapy is to reduce viral replication as low as possible for as long as possible. Numerous clinical trials have demonstrated that prolonged suppression of viral replication is associated with dramatic improvements in long-term survival of

HIV-infected persons. Combination antiretroviral therapy represents the optimal means of achieving long-term suppression of HIV replication.

Didanosine is firmly established as a cornerstone of combination antiretroviral therapy. The safety and efficacy of ddl used alone and in combination with other antiretroviral agents has been demonstrated in both adults and children with either early or advanced HIV infection, and the efficacy of ddl is sustained during long-term therapy. Didanosine has consistent effects on viral load, a favorable pharmacokinetic profile, acceptable toxicity, and low propensity for drug interactions. The introduction of the one capsule, once-daily enteric-coated formulation of didanosine in 2000 provided a means of significantly enhancing the patient adherence and clinical efficacy of ddl, while improving its tolerability and reducing drug to drug interactions as compared with the buffered formulation.

The increasing survival of HIV-infected patients treated with ddl-containing regimens continues to support the major role ddl has in the anti-HIV therapeutic armamentarium. Ongoing studies of the dynamics of HIV replication and the clinical efficacy of newer antiretroviral agents will help further clarify the place of ddl in the management of persons with HIV infection. ■

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Hospitalization in HIV in Chicago

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Supported in part by Contract # 250-OA-13(8), US Health Resource and Service Administration, March 13, 2000.

Abstract

Background: Reduction in HIV-related morbidity and mortality in the highly active antiretroviral therapy (HAART) era has been unevenly distributed in the United States, and its impact on hospitalizations in urban minority populations in the public sector has been poorly characterized.

Methods: We conducted a retrospective analysis of clinical and administrative data sets of an urban public hospital HIV clinic from 1997 and 1998 to identify the correlates of hospitalization early in the HAART era.

Results: 2,647 unduplicated HIV-infected patients were seen in 1997 and 1998 at the CORE Center. There were 31.7 percent women, 71 percent African-Americans and 12 percent Hispanics, and the mean age was 38 years. Men who had sex with men (MSM), injection drug users (IDU), and heterosexuals each made up one third of the population. A majority of the patients had no health insurance, and 27 percent had Medicaid. The median CD4 T cell count was 266 cells/ μ L, and the median viral load was 1,901 copies/ml. Hospitalizations declined significantly from 1997 (1,579) to 1998 (1,160). Admissions were confined to 25 percent of clinic patients, and 16 patients (range 8-15) had eight or more admissions. African-Americans and Hispanics had significantly more and longer hospitalizations than whites, but there was no difference by gender. IDUs had significantly more admissions than non-IDUs (28 percent vs. 21 percent respectively). On multivariate analysis, lower CD4 T cell count and higher viral load predicted risk of admission in all periods. Unexpectedly, hospitalization rates were high in patients in the highest baseline CD4 T cell stratum, >500 cells/ml (45 of 353, 13 percent), and lowest viral load stratum, <500 copies/ml (103 of 675, 15 percent), and rose from 1997 to 1998. HAART (ie, 1 or 2 drug regimens) predicted fewer hospitalizations

compared to 1 or 2 drug regimens. In a subset of patients who filled prescriptions on site, HAART increased from 72 percent to 85 percent and 1-2 drug regimens fell from 28 percent to 15 percent from 1997 to 1998. Regular care was associated with more frequent hospitalization and more hospital days per admission than no regular care. Hospitalized patients had significantly higher mortality than patients not hospitalized (12 percent vs. 2 percent respectively).

Conclusion: HIV-related hospitalizations were frequent in the HAART era and decreased over time. Older age, lack of HAART, lower CD4 T cell count, higher viral load, and minority race predicted hospitalization, while gender did not. However, patients with extremely favorable CD4 T cell and viral load counts also had higher than expected hospitalization rates. Three quarters of patients had no hospitalizations, and clustering of hospitalizations in a small number of patients may enable targeted programs to reduce recidivism.

Introduction

Reduction in human immunodeficiency virus (HIV)-related morbidity and mortality in the era of highly active antiretroviral therapy (HAART), or the concomitant use of three or more drugs, has been unevenly distributed in the United States, with fewer gains in women, minorities, injection drug users, and persons without health insurance.¹ Similar disparities have been reported in HIV ambulatory care outcomes in primary care settings in the US.^{2,3} In contrast, mortality from acquired immunodeficiency syndrome (AIDS) in Chicago declined 65 percent overall from 1995-1997 with no significant difference by race, gender, age, or history of drug use.⁴

The impact of the reduction in morbidity and mortality on hospitalizations in urban minority populations has been incompletely characterized to date. Progress in HIV care in the pre-HAART era may be an important consideration in this regard. Sherer et al reported marked reduction in hospitalizations and in-hospital mortality at Cook County Hospital from 1992 to 1997.⁵ Notably, the observed decline began in 1994, two years before the HAART era. Decline in mortality which preceded the

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JIA PAC 2002;1(1):26-33. © 2002 IAPAC.

HAART era was also reported in 1998 by the New York City Health Department.⁶ Between 1996 and 1998, several reports from the HAART era have shown dramatic reduction in overall hospitalizations as well as reduction in HIV-related morbidity and mortality.^{7,8} More recently, several groups have noted a plateau effect due to relative increase in hospitalizations for non-HIV related reasons, such as drug toxicity, chronic liver disease, and non-HIV associated neoplasia.⁹ For example, Ahmad et al recently reported that, at Cook County Hospital from 1998 to 2000, 38 percent of deaths in in-patients were from non-HIV related causes, and one half of the deaths occurred while plasma viral load was undetectable.¹⁰ Other groups have reported a disproportionate increase in hospitalizations from non-HIV related causes in women and minorities.¹¹

It is clear that the interactions of morbidity, mortality, and hospitalizations due to HIV disease remain complex in the HAART era and vary across various demographic groups. In order to identify predictors of public hospitalization in the HAART era, we investigated hospitalizations during 1997 and 1998, a period of well-documented decline in HIV-related morbidity and mortality in Chicago, in a cohort of patients who receive primary care at Cook County Hospital, the only public hospital in Chicago.

Methods

We examined databases of the HIV Primary Care Center, now named the CORE Center, in order to conduct an observational, retrospective study of all patients enrolled in HIV primary care in 1997 and 1998. This setting will be referred to as the Center. Data collected included patient related information, primary care attendance, and whether they received ancillary services. The methodology used has been described previously.¹² The study population consisted of all adults served by the Center in 1997 and 1998, including those new to care during this time. Unique patient identification unit numbers were used to identify the cohort across all services and databases. From January 1997 through September 1998, the Center was located at the Human Retroviral Disease Clinic (HRD), a 2,000 square foot portion of the Radiation Center of the Fantus Health Center of Cook County Hospital. From October 1998, it was located at the CORE Center, a 74,000 square foot freestanding ambulatory facility for HIV and related infectious diseases.

Outcome variables were mortality, hospitalizations, clinic visits, CD4 T cell counts, and viral loads. For patients enrolled in care prior to 1997, baseline CD4 cell counts were used from the last two months of 1996. Hospitalization data were limited to admissions to Cook County Hospital, as data on admissions to other hospitals were not available for the whole cohort.

Data on reasons for discharge and discharge diagnoses were not available for this analysis.

All patients were analyzed in six-month time periods (periods 1-4) from their entry into care, or from January 1, 1997 for patients enrolled in care before 1997. Follow up for clinical care was through December 31, 1998, while follow up for mortality and retention in care was extended through December 31, 1999. This study was approved by the Cook County Scientific Committee, which is the Institutional Review Board of Cook County Hospital.

Pharmacy records were analyzed for the subset of patients who regularly filled prescriptions at the Cook County Hospital Pharmacy during 1997-8. Patients on three or more antiretroviral drugs were categorized as receiving HAART, and those on one or two drugs as receiving antiretroviral therapy (ART). Aggregate data on treatment for the entire cohort, including patients on no therapy, were not available for this analysis.

SPSS for Windows (V 7.5) was used for data management and statistical analyses. Bivariate relationships between variables were investigated using the chi-square test of association for nominal variables and non-parametric Spearman correlations for non-nominal, statistically non-normal variables. Comparisons of groups with respect to non-nominal, statistically non-normal variables were done with the nonparametric Kruskal-Wallis and Mann-Whitney tests. A 0.05 significance level was used for all statistical tests.

Results

Cohort: 2,647 adults aged 19 and above received primary care at the HIV Center/CORE Center in 1997 and 1998, of whom 32 percent were women. Table 1 shows the baseline characteristics of the cohort according to gender, age, race, payer status, and HIV risk behavior. The majority of patients were African-American, and the median age was 38 years. Two thirds of patients had no insurance at entry into care, 27 percent had Medicaid, and 1.7 percent had private insurance. Significantly more women than men had any form of health insurance ($p < 0.0005$). Approximately one third of patients were men who have sex with men (MSM), one third were injection drug users (IDU), and one third acquired HIV heterosexually.

Of the 2,647 HIV-infected persons at baseline, ie, in period one, 715 (27 percent) persons had AIDS. The median CD4 T cell count at baseline was 266 cells/ μ L, with a range of 1-3,069 cells/ μ L. The median viral load at baseline was 1,901 copies/ml, with a range of <500 copies/ml to 800,000+ copies/ml. Women had significantly higher CD4 T cell counts at baseline than men.

Table 1. Baseline data, n=2,647 patients, 1997

Gender	Male	1807 (68%)	
	Female	840 (32%)	
Age	11-20	1%	
	21-30	19%	
	31-40	44%	
	41-50	28%	
	51-60	6%	
	>60	1%	
Race	African American	71%	
	Hispanic	12%	
	White	11%	
	Other	3%	
	Unknown	3%	
Payer status	Uninsured	61%	
	Medicaid	27%	
	Other public	6%	
	Private	2%	
	Unknown	4%	
Risk behavior	MSM*	29%	
	IDU**	32%	
	Heterosexual	31%	
	Other	2%	
	Unknown	6%	
CD4 count baseline range	<i>Median</i>	<i>266 cells/ml</i>	<i>Normalized</i>
	<50	10%	14.7%
	51-200	17%	25.4%
	201-500	27%	40.3%
	>500	13%	19.5%
	Unknown	32%	
Viral load	<i>Median</i>	<i>1,901 copies/ml</i>	<i>Normalized</i>
	<500	25%	39.3%
	500-10K	16%	25.2%
	10-50K	11%	17.4%
	50-100K	5%	7.3%
	>100K	7%	10.8%
	Unknown	35%	
* men who have sex with men			
** injection drug use			

Disposition: On follow up through December 1999, 139 (5.2 percent) patients had died. 1,188 (45 percent) of patients met the definition of lost to follow up, ie, they had no primary care visits in two consecutive six-month periods. Excluding deaths and patients with return visits in 1999, 688 (29 percent) patients were lost to follow up in 1997 and 1998.

Clinical Outcomes: Demographics and Clinic Visits: 2,528 patients (95.5 percent) had at least one visit in 1997, and 1,457 patients (55 percent) had regular care during 1997, ie, at least one primary care visit in each six-month period. The median follow up interval was 23 months. The median number of primary care visits

was five per year, with a standard deviation of 3.9 visits. 616 (23.3 percent) clients had two or fewer visits, and 1,174 (31.1 percent) had eight or more visits in 1997 and 1998. With older age, the likelihood of receiving any care or regular care, and the total number of visits, increased in both years. African-American and Hispanic patients had more visits than whites in both years (mean visits 8.5 and 8.9 vs. 7.5 respectively, $p=0.045$ and 0.012 respectively). Patients with no insurance had fewer primary care visits in periods 1-3 than patients with insurance (mean 7.8 vs. 9.7, $p=0.004$). Patients with regular clinic care (greater than one visit per six months) had significantly lower viral loads in all periods than those with irregular care.

Hospitalizations: During 1997 there were 1,579 hospitalizations in 623 patients, of which 1,132 (72 percent) were men and 447 (28 percent) were women. There was no statistically significant relationship between gender and hospitalizations or hospital days. Total hospitalizations significantly declined from period 1 (868) to period 4 (585) and from 1997 (1,579) to 1998 (1,160) ($p=0.0005$). Table 2 shows the frequency of hospital admissions for the cohort. 76 percent of patients had no admissions. Of the 24 percent with hospital admissions, 245 (11 percent) patients had one admission, 295 (11 percent) patients had two to four admissions, and 83 (3 percent) patients had five or more admissions. 16 (0.6 percent) patients had eight to 15 admissions during the two years.

Table 2: Frequency of hospital admissions, 1997-1998

No. of admissions	N	%	Cumulative %
0	2023	76.4	76.4
1	245	9.3	85.7
2	146	5.5	91.2
3	100	3.8	95.0
4	49	1.9	96.9
5	30	1.1	98.0
6	27	1.0	99.0
7	10	0.4	99.4
8	3	0.1	99.5
9	4	0.2	99.7
10	4	0.1	99.8
11	2	0.1	99.9
13	1	0.0	99.9
14	1	0.0	100.0
15	1	0.0	100.0
TOTAL	2646	100.0	100.0

Older age was associated with increased admissions and hospital days ($p<0.001$). As shown in Table 3, whites had significantly fewer admissions and shorter hospital stays per period than Hispanics or African-Americans. As expected, there were negative, statistically significant correlations between the mean number of admissions and average number of hospital days, and CD4 T cell counts in each period. Similarly, a positive correlation was observed between admissions and total days, and viral load in each period. These results are shown in Table 4.

Table 3: Mean hospital admissions and hospital days by race

	Mean admissions	Mean hospital days
African American	0.20*	1.76*
Hispanic	0.16*	1.42*
White	0.06*	0.46*

* $p<0.0001$ for African-American and Hispanic vs. white

Hospital admissions during the study period by baseline CD4 T cell count and viral load strata are shown in Tables 5 and 6 respectively. In general, there was a linear increase in admissions among patients in strata with lower CD4 T cell counts and higher viral load. 117 of 266 patients (44 percent) with baseline CD4 T cell counts below 50 cells/ μ L were admitted at least once, compared with 45 of 353 patients (13 percent) with CD4 T cell counts above 500 cells/ μ L. Similarly, 68 of 185 patients (37 percent) with baseline viral loads above 100,000 copies/ml were admitted compared to 103 of 675 patients (15 percent) with viral loads below 500 copies/ml. Nonetheless, admissions among patients with low viral loads and high CD4 T cell counts were high in number, with 10.7 percent (45 of 422) of patients with CD4 T cell counts above 500 cells/ μ L being admitted, and 28.6 percent (103 of 360) of patients with viral loads below 500 copies/ml being admitted. As a proportion of all admissions, admissions in patients with CD4 cells above 500 cells/ μ L increased from 10.7 percent to 16 percent from period 1 to period 4, and admissions in patients with viral load below detection increased from 28 percent to 41 percent (data not shown).

Patients with regular care in both years had more hospital admissions and more hospital days than other patients ($p=0.0005$). Hospitalizations varied by form of therapy received; patients on HAART had significantly fewer hospitalizations than patients on ART after controlling for CD4 T cell count and viral load (mean 0.21 vs. 0.26, $p=0.034$, Mann-Whitney test). The proportion of treated patients on HAART and ART from 1997 to 1998 is shown in Table 7. Patients on HAART, or three or more drugs, rose from 70 percent in period 1 to 82 percent in period 4, and the percent on two drug regimens fell from 30 percent to 18 percent during the study period.

On studying interaction between support services and hospitalization, patients who needed and received case management, mental health services, and transportation assistance were found to have significantly fewer hospitalizations than patients in whom the support service need was unmet ($p<0.015$, Mann-Whitney test for each support service, data not shown).

Mortality was significantly higher in patients who were hospitalized than in other clinic patients. 36 of 2,023 patients (1.8 percent) who were not hospitalized died during the study period compared with 76 of 623 hospitalized patients (12.2 percent, $p<0.0005$).

Discussion

We found that HIV-related hospitalizations in the only public hospital in Chicago were frequent in the HAART era and decreased over time. Importantly, three quarters

Table 4: Correlations of CD4 and viral load with hospital admissions and average hospital days

	<i>Admissions per period</i>		<i>Hospital days per period</i>	
	<i>N</i>	<i>Correlation Coefficient:</i>		<i>p value (t-tailed)</i>
Baseline CD4	1,808	-0.244	-0.253	<0.0001
Period 2 CD4	1,142	-0.274	-0.282	<0.0001
Period 3 CD4	977	-0.289	0.296	<0.0001
Period 4 CD4	791	-0.261	-0.275	<0.0001
Baseline Viral Load	1,716	0.158	0.160	<0.0001
Period 2 Viral Load	1,135	0.142	0.150	<0.0001
Period 3 Viral Load	957	0.236	0.244	<0.0001
Period 4 Viral Load	796	0.154	0.163	<0.0001

Table 5: Admissions by baseline CD4 strata in patients with known CD4 cell count

<i>Baseline CD4 cell count strata</i>	<i>Admitted at least once</i>	<i>Not admitted</i>	<i>Total</i>
<50 cells/ml	149 (10.8%)	117 (27.7%)	266 (14.7%)
51-200 cells/ml	325 (23.4%)	135 (32%)	460 (25.4%)
201-500 cells/ml	604 (43.8%)	125 (29.6%)	729 (40.3%)
>500 cells/ml	308 (22.2%)	45 (10.7%)	353 (19.5%)
Total	1386 (100%)	422 (100%)	1808 (100%)

Table 6: Admissions by baseline viral load in patients with known viral load

<i>Baseline viral load strata (copies/ml)</i>	<i>Not Admitted</i>	<i>Admitted</i>	<i>Total</i>
≤ 500	572 (42.2%)	103 (28.6%)	675 (39.3%)
501-10,000	346 (25.5%)	87 (24.2%)	433 (25.2%)
10,001-50,000	231 (17%)	67 (18.6%)	298 (17.4%)
50,001-100,000	90 (6.6%)	35 (9.7%)	125 (7.3%)
> 100,000	117 (8.6%)	68 (18.9%)	185 (10.8%)
Total	1,365 (100%)	360 (100%)	1,716 (100%)

Table 7: Prevalence of ART (1-2 drug regimens) and HAART (3 or more drug regimens) in patients who regularly filled prescriptions at the Cook County Hospital pharmacy, 1997-1998.

	<i>N</i>	<i>HAART</i>	<i>ART</i>
Period 1	878	616 (70%)	262 (30%)
Period 2	681	486 (71%)	195 (29%)
Period 3	575	449 (78%)	126 (22%)
Period 4	585	479 (82%)	106 (18%)

of patients living with HIV did not require hospitalization during this two-year period. Multiple hospitalizations were clustered in fifteen percent of patients. Older age, lack of HAART, regular clinic care, lower CD4 T cell count, higher viral load, history of IDU, and minority race predicted hospitalization, while female gender did not.

Predictably, we found a linear relationship between baseline CD4 T cell count and viral load, and hospitalization. However, we also found a high proportion of admissions occurred in patients with low viral load and high CD4 T cell counts, and the percent of admissions in these two groups increased significantly during the study period. These data are consistent with other studies of predictors

of HIV disease progression¹³ and several recent reports of increasing hospitalization rates among patients with co-morbid conditions such as hepatitis C and chronic liver disease, drug toxicity, and mental illness.^{14,15}

The significant racial disparity in hospitalization rates in the HAART era was unexpected. We observed higher rates of hospitalization and total hospital days in African-Americans and Hispanics compared with whites after adjustment for CD4 T cell count and viral load. Similar observations have been made in other disease states such as heart disease, asthma, and cancer.¹⁶ Possible explanations have included poor and delayed access to primary care for minority populations, and poorer overall health status in minorities due to a variety of factors, such as inadequate nutrition and greater exposure to environmental pollutants.

Due to the design of the analysis, our data cannot be explained simply by variations in access to regular primary care, to HAART, or to racial disparities in other predictors of HIV disease outcome such as baseline CD4 T cell count and viral load. All patients in the analysis were receiving ambulatory care at no cost with an equal opportunity for regular care. The multivariate analysis adjusted for CD4 T cell count and viral load. In addition, we have already reported the finding of no racial disparities in overall clinical outcomes such as mortality or disease progression as measured by trends in CD4 T cell counts and viral load.¹⁷ Indeed, in this analysis, as in others, lower viral load correlated significantly with lower hospitalization rates and lower mortality, and lower CD4 cell count correlated significantly with higher hospitalization rates and higher mortality, and in both cases these findings were independent of race.

The other unexpected finding of this analysis is the association between regular ambulatory care and a greater risk of hospitalization. The most probable explanations for this observation are selection bias and missing data in patients with irregular care and follow up. Patients in regular care have more opportunity for the identification of medical problems necessitating hospitalization. One limitation of this study is the inability to trace patients who are lost to follow up. The hospitalization data in patients with irregular outpatient care are limited by missing data due to hospitalizations outside of the Cook County Hospital network of which we are unaware. Also, one quarter of the cohort had a baseline CD4 T cell count less than 200 cells/ μ L. Short-term morbidity in this group might not be responsive to short-term interventions, and thus regular care would be expected to increase hospitalizations due simply to selection bias. Finally, public hospitalization is often a short-term remedy to other problems. In addition to medical problems, social ills such as homelessness, domestic

violence, acute drug bingeing or withdrawal, depression, and malnutrition are known to commonly occur in persons with HIV. As shown in other studies, women with HIV are particularly vulnerable to non-HIV related mortality.^{18,19} Further evaluation of disparities and commonalities in causes of hospitalization is needed to better assess their relative contribution to the observations in this study.

A comparison of these data to previously reported hospitalization data at Cook County Hospital from 1992 to 1996 is of interest.⁵ During that period, hospitalizations ranged from 1,575 to 1,781 persons per year with no apparent diminution over time. However, the average length of stay decreased from 13.3 days to 8.5 days, and the average daily census fell from 58 to 33 patients. During the same period, in-patient deaths fell from 116 in 1992 to 74 in 1996. It is noteworthy that these trends preceded the HAART era by several years, and suggest as others have also shown,^{6,8} that receiving regular medical care and prophylaxis for opportunistic infections may also have contributed substantially to the reduction in morbidity and mortality associated with the HAART era. In the current study hospitalizations declined significantly between 1997 and 1998, suggesting a delay in the impact of HAART on hospitalizations in the public sector.

These findings are compatible with numerous reports showing marked reduction in morbidity and mortality from 1996 to 1999.^{3,4,6,14} Most relevant to this analysis is the report from Whitman et al from the Chicago Department of Health that showed a 65 percent reduction in mortality between 1996 and 1998 in the city of Chicago. This reduction was equally distributed in men and women, and in African-Americans, Hispanics, and whites. Our data on hospitalizations and mortality provide a sobering counterpoint to these trends. Although declining, hospitalizations and mortality remain commonplace in the HAART era, and the number of hospital admissions is increasing in patients with well-controlled HIV disease.

The difference in our observations and others between hospitalizations and HIV primary care outcomes is of interest. In related analyses of this data set, IDUs, patients with no insurance, and younger patients were less likely to receive regular primary care.¹² These data are comparable to the national HCSUS data, which showed that women, IDUs, and people of color were less likely to have any care, regular care, access to HAART, and improved morbidity and mortality compared to men, non-IDUs, whites, patients with insurance, and older patients.² Unlike HCSUS, we saw no difference in primary care outcomes, mortality, or CD4 T cell counts and viral load between racial groups.

Finally, we found that hospitalizations were concentrated in a relatively small fraction of the total ambulatory population, as has been seen among HIV positive patients in the private sector.³ In particular, we found that 16 (0.6 percent) individuals had eight or more admissions during the study period. These data provide some hope for targeted programs designed to help such highly hospitalization-prone individuals with the intent of reducing their contribution to the inpatient burden in public institutions. With the success of direct observed therapy (DOT) for tuberculosis, and preliminary success of DOT in HIV-infected populations, DOT-like programs for admission-prone individuals may offer an opportunity to blunt the recidivism rate. Similarly, a related analysis of this cohort found that outreach improved regular clinic care.¹² Targeted programs to improve clinic attendance, adherence to medication, or management of co-morbidities such as chemical dependency, homelessness, or mental illness can substantially improve regular care, and reduce hospitalizations for interval medical or social crises. Although 16 of 2,647 patients may be a proportionately small number for targeted programs, the small number of patients increases the feasibility of beneficial targeted interventions, and the potential benefits in terms of cost and service utilization are large.

There are some limitations to this retrospective observational study. Missing data were common, despite efforts to complete the data set. In particular, one third of patients were lacking viral load and CD4 T cell count data, and complete treatment data for the entire cohort are lacking. Fortunately, the large numbers in the cohort allows for trend analysis of evaluable patients and provides some compensation for this shortcoming. Losses to follow up were common, with about one quarter of the cohort lost to follow up by the end of the study period. These losses explain much of the missing data, and their numbers are comparable to other cohorts in urban public hospitals. This defines the need for better outreach programs, and better strategies to retain patients once they are enrolled. The magnitude of missing data is discouraging, for it has occurred despite extensive efforts to create a "one-stop shopping" model that is convenient for patients with disrupted lives. As noted above, the statistical implications of the losses to follow up are mitigated by the large size of the cohort. Finally, documentation of certain data elements, particularly need for services, was incomplete and not standardized. As a result, more patients received services than were identified with a specific need for the service.

In conclusion, we found that HIV-related hospitalizations were frequent in the HAART era and decreased over time. However, three quarters of patients living with

HIV and in care at an urban public hospital HIV clinic did not require hospitalization during this two-year period. Older age, lack of HAART (ie, one or two drug regimens), lower CD4 T cell count, higher viral load, history of IDU, and minority race predicted hospitalization, while female gender did not. Admissions in patients with well-controlled HIV disease were higher than expected and increased over time. The clustering of hospitalizations in a small number of patients may enable the development of support programs targeted towards these "hospitalization-prone" patients to reduce recidivism. ■

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