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## DECLINING MORBIDITY AND MORTALITY AMONG PATIENTS WITH ADVANCED HUMAN IMMUNODEFICIENCY VIRUS INFECTION

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### ABSTRACT

**Background and Methods** National surveillance data show recent, marked reductions in morbidity and mortality associated with the acquired immunodeficiency syndrome (AIDS). To evaluate these declines, we analyzed data on 1255 patients, each of whom had at least one CD4+ count below 100 cells per cubic millimeter, who were seen at nine clinics specializing in the treatment of human immunodeficiency virus (HIV) infection in eight U.S. cities from January 1994 through June 1997.

**Results** Mortality among the patients declined from 29.4 per 100 person-years in 1995 to 8.8 per 100 person-years in the second quarter of 1997. There were reductions in mortality regardless of sex, race, age, and risk factors for transmission of HIV. The incidence of any of three major opportunistic infections (*Pneumocystis carinii* pneumonia, *Mycobacterium avium* complex disease, and cytomegalovirus retinitis) declined from 21.9 per 100 person-years in 1994 to 3.7 per 100 person-years by mid-1997. In a failure-rate model, increases in the intensity of antiretroviral therapy (classified as none, monotherapy, combination therapy without a protease inhibitor, and combination therapy with a protease inhibitor) were associated with stepwise reductions in morbidity and mortality. Combination antiretroviral therapy was associated with the most benefit; the inclusion of protease inhibitors in such regimens conferred additional benefit. Patients with private insurance were more often prescribed protease inhibitors and had lower mortality rates than those insured by Medicare or Medicaid.

**Conclusions** The recent declines in morbidity and mortality due to AIDS are attributable to the use of more intensive antiretroviral therapies. (N Engl J Med 1998;338:853-60.)

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THE treatment of human immunodeficiency virus (HIV) infection has undergone considerable change.<sup>1-3</sup> Protease inhibitors and non-nucleoside-analogue reverse-transcriptase inhibitors, when used as part of combination drug regimens, can profoundly suppress viral replication, with consequent repletion of CD4+ cell counts.<sup>4-7</sup> Multiple clinical trials have shown the virologic and immunologic efficacy of the newer, highly active antiretroviral-drug combinations<sup>7,8</sup> by measuring the plasma load of HIV RNA and CD4+ cell counts.<sup>9-16</sup> In addition, prophylactic medications are now being used routinely to prevent disseminated *Mycobacterium avium* complex infection.

Several reports have described reductions in mortality and in the rate of hospitalization of HIV-infected patients; however, such reductions have not been clearly related to specific therapeutic regimens.<sup>17-21</sup> We analyzed data collected over 42 months in the HIV Outpatient Study. During this period, rates of chemoprophylaxis against opportunistic infection remained relatively constant even while patterns of antiretroviral therapy were changing. This report outlines the changes in death rates and the incidence of opportunistic infections in a large group of HIV-infected outpatients, many of whom had previously received extensive treatment.

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## METHODS

### The HIV Outpatient Study

The ongoing HIV Outpatient Study, into which patients are continuously recruited, collects summaries of physician-patient interactions and data on the course of disease for more than 3500 HIV-infected, nonhospitalized patients who have been seen at a total of approximately 47,000 outpatient visits since 1992. The present analysis includes data on patients seen from January 1994 through June 1997. The study sites are nine clinics (seven private and two public) in eight U.S. cities (Portland, Oreg.; Tampa, Fla.; Oakland, Calif.; Washington, D.C.; Chicago; Stony Brook, N.Y.; Atlanta; and Denver) that provide care for at least 150 HIV-infected patients each per year. The participating physicians routinely care for hundreds of HIV-infected patients and thus have extensive experience with HIV.<sup>22</sup>

Information in five general categories has been abstracted from the chart for each outpatient visit and entered electronically by trained data abstracters; the data are compiled centrally, reviewed, and corrected before being included in the data base. Because the study physicians are the source of primary care for these patients, all symptoms, diagnoses, and treatments since the previous visit, including interim changes in treatment in any setting, are noted at each clinic visit. The categories of information abstracted are as follows: demographic characteristics and risk factors for HIV infection; symptoms; diagnosed diseases (both definitive and presumptive diagnoses); medications prescribed, including the dose and duration; and laboratory values, including CD4+ cell counts and measurements of plasma HIV RNA.

### Patients

Twelve hundred fifty-five study participants who had ever had a CD4+ cell count below 100 per cubic millimeter were the focus of this analysis, since our goal was to evaluate morbidity and mortality among the persons at greatest risk for illness or death. For 71 percent of the patients, the first CD4+ cell count of less than 100 per cubic millimeter was noted within six months before enrollment or thereafter. For the remaining 29 percent, a CD4+ cell count below 100 per cubic millimeter was documented more than six months before study entry; for these patients, the date of the initial study visit marked the beginning of follow-up. Patients whose CD4+ cell counts later rebounded to 100 per cubic millimeter or higher remained in the analysis.

Data from clinic visits were used to calculate the number of days of observation per quarter for each patient in each of four categories of prescribed antiretroviral therapy. These categories, in increasing order of intensity, were no antiretroviral therapy, monotherapy, combination therapy without a protease inhibitor, and combination therapy that included a protease inhibitor. To ensure that mortality rates were based on patients who received therapy for an adequate time, patients were not included in calculations of follow-up time or events for the first 30 days after any change in therapy. Only deaths that occurred within 90 days after a clinic visit were counted. Patients not seen since March 1997 contributed person-years at risk for a maximum of 90 days after their last study visit. Because enrollment continued during the study period, data from some new patients were included in each quarterly analysis.

### Analysis of Outcomes

Data were analyzed with SAS software (version 6.11; SAS Institute, Cary, N.C.). Morbidity (i.e., opportunistic infections) and mortality were compared for the antiretroviral-therapy categories, adjusted for chemoprophylaxis against opportunistic infection and demographic factors (sex, age, race or ethnic group, and risk factors for HIV infection [men who have sex with men, injection-drug use, heterosexual sex, and other]), CD4+ count at the first study visit, and method of payment (i.e., insurance status). After stratifying the data according to antiretroviral-therapy category

and calendar quarter, we fitted Poisson failure-rate models to the data, using the SAS Lifereg procedure. The models assume the hazard is constant throughout each quarter but allow it to vary between quarters. Rates of mortality and morbidity calculated in this way are equivalent to tabulations of the number of deaths (or events) that occurred in each quarter divided by the number of person-years of observation during that quarter. Death rates per 100 person-years were calculated by totaling the number of person-days of observation in a specified period. Deaths among observed patients were counted, and observation time was standardized to 100 person-years.

Acquired immunodeficiency syndrome (AIDS)-defining opportunistic infections were analyzed in the aggregate; in addition, separate analyses were performed for *Pneumocystis carinii* pneumonia, *M. avium* complex infection, and cytomegalovirus retinitis. Patients with a diagnosis of cytomegalovirus retinitis or *M. avium* complex disease before study entry or during the first 30 days of follow-up and patients with active *P. carinii* pneumonia at the beginning of follow-up were excluded from the analyses of the incidence of that opportunistic infection.

### Statistical Analysis

The possible effect of demographic variables on changes in rates of morbidity and mortality was examined. The distributions of patients according to age, race or ethnic group, sex, and risk factors for HIV infection were examined in each of the 42 months of observation to determine whether the study population had changed over the study period. These demographic variables, the study center, the first recorded CD4+ cell count (categorized as 0 to 49, 50 to 99, or  $\geq 100$  per cubic millimeter), and whether the patient received chemoprophylaxis against *M. avium* complex and *P. carinii* were included with the antiretroviral-therapy category as main effects in the failure-rate model of morbidity and mortality in order to determine whether temporal trends were the result of shifts in the composition of the study population or shifts in the pattern of prophylaxis. Finally, the consistency of the effect of treatment on mortality and morbidity over time was tested by comparing a failure-rate model with separate treatment effects for each quarter with a failure-rate model in which treatment effects were assumed to be constant over time. Statistically nonsignificant effects of the calendar quarter were excluded from the final model, resulting in a Poisson model that assumed a constant effect of treatment over the 42-month observation period. Results are reported as relative risks of death or morbidity (defined as *P. carinii* pneumonia, *M. avium* complex infection, or cytomegalovirus retinitis), with associated 95 percent confidence intervals.

The primary source of payment for medical care was documented for each patient and categorized as private insurance (including fee-for-service care, health maintenance organizations, and preferred-provider organizations), Medicare, Medicaid, self-payment, or prescription programs under the Ryan White Care Act. Mortality and rates of prescription of protease inhibitors per 100 person-years of observation in each quarter were analyzed according to the source of payment.

## RESULTS

### Demographic Characteristics

Our analyses include data on 1255 HIV-1-infected persons with at least one CD4+ cell count below 100 per cubic millimeter who were among the more than 3500 HIV-infected patients seen as part of the HIV Outpatient Study during the period of analysis (January 1994 through June 1997). About 80 percent were 30 to 49 years of age, and the age distribution did not shift during the period of analysis. We observed nonsignificant trends toward increasing

numbers of blacks, Hispanics, and women (making up 20 percent, 9 percent, and 12 percent, respectively, of the total by June 1997) and decreasing proportions of men who reported same-sex sexual activity (accounting for 65 percent of those seen by June 1997). The proportion of patients who reported injection-drug use (about 14 percent) did not change significantly over time.

The proportion of persons whose initial CD4+ cell count at study entry was less than 50 per cubic millimeter decreased slightly (it was 55 percent in 1994, 51 percent in 1995, 44 percent in 1996, and 42 percent in 1997). The proportion of patients whose most recent CD4+ cell count was less than 50 per cubic millimeter diminished significantly (from 67 percent in 1994 to 57 percent in 1995, 43 percent in 1996, and 29 percent in 1997).

#### Use of Antiretroviral Agents

During the study, the pattern of antiretroviral therapy changed dramatically among patients with CD4+ cell counts below 100 per cubic millimeter. The proportion of patients for whom any antiretroviral therapy was prescribed increased, from 72 percent of patients in 1994 to 95 percent by June 1997, with marked increases in the prescription of combination regimens (from 25 percent in 1994 to 94 percent by June 1997). The most dramatic increases were in the rate of use of regimens containing protease inhibitors, from 2 percent in mid-1995 to 82 percent by June 1997. The use of combinations incorporating protease inhibitors differed little according to patients' demographic characteristics, although the study sites varied widely in their rates of use of protease inhibitors. In the first quarter of 1996, site-specific rates of protease-inhibitor use ranged from 6 percent to 71 percent; by the second quarter of 1997, the rates ranged from 40 percent to 95 percent. Publicly funded clinics were slower to use protease inhibitors; however, the proportional increases in use were similar among all sites.

#### Mortality

Mortality declined markedly in 1996 and early 1997, after remaining constant during 1994 and 1995. Death rates decreased from 29.4 per 100 person-years in 1995 to 16.7 per 100 person-years in 1996 and to 8.8 per 100 by the second quarter of 1997 (Table 1 and Fig. 1).

Patterns of reduction in death rates among men and women, white and nonwhite persons, and persons  $\leq 40$  or above 40 years of age were similar and declined in the same way during the 14 quarters of observation. Although mortality decreased proportionally among injection-drug users, they had consistently higher mortality rates than patients who did not report a history of injection-drug use. Although mortality and morbidity differed among the study

sites, declines in both rates were noted at all clinics. The rate of use of prophylaxis against opportunistic infections was consistent during the 42 months of observation: the proportion of patients receiving prophylaxis against *M. avium* complex ranged from 46 percent to 55 percent; the rate of prophylaxis against *P. carinii* ranged from 92 to 94 percent. Death rates among persons receiving these types of chemoprophylaxis were evaluated; the patterns of decreasing mortality were similar to those in the study group as a whole.

Death rates are shown according to antiretroviral-therapy category in Table 1. Death rates declined in virtually every quarter, correlating inversely with the intensity of the antiretroviral therapy prescribed (Fig. 1), and declined most dramatically during the last six quarters covered by the analysis (Table 1).

Differences among the patients in sex, age, race or ethnic group, or risk category did not explain the observed temporal trend in mortality or morbidity when these factors were included in the preliminary failure-rate model. The inclusion of the use of chemoprophylaxis against opportunistic infections in the model also did not explain the trend; however, both the initial CD4+ cell count and the study site were significant ( $P < 0.01$ ) and were therefore retained in the model.

When the effect of treatment was included in the failure-rate model used to evaluate mortality, the effect of the calendar quarter of observation was not significant ( $P = 0.49$ ). The interaction of treatment with quarter was also not significant ( $P > 0.34$ ). Comparisons of mortality in different antiretroviral-therapy categories within this model (Table 2) revealed that for each increase in the intensity of antiretroviral therapy, there was a significant additional benefit in terms of lower mortality. Notably, mortality among patients receiving combination regimens that did not include protease inhibitors was 1.5 times that among patients receiving combination regimens that included a protease inhibitor.

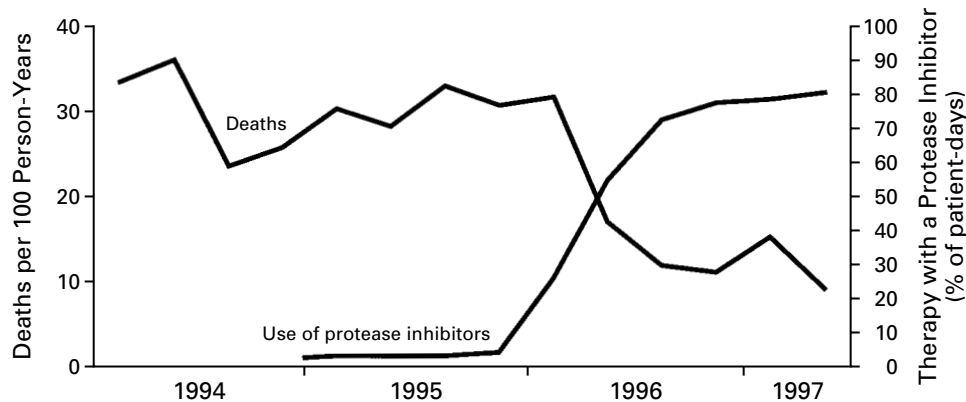
Mortality rates are shown according to patients' primary source of payment for medical services in Table 3. The patients whose care was funded under the Ryan White Care Act prescription programs and those who paid for their own care together made up about 10 percent of the total population and had mortality rates similar to those for patients who were receiving Medicare. Although mortality declined overall among patients covered by Medicaid and those who were privately insured, the death rates for patients insured by Medicaid were higher than the rates in the overall study population in all but two quarters. In 1995, mortality among those covered by Medicaid was 46.9 per 100 person-years; among those with private insurance, it was 24.4 per 100 person-years (data not shown). Patients with private insurance were consistently more likely to receive a

**TABLE 1. MORTALITY AMONG PATIENTS WITH CD4+ T-LYMPHOCYTE COUNTS OF FEWER THAN 100 PER CUBIC MILLIMETER, ACCORDING TO TYPE OF ANTIRETROVIRAL THERAPY AND CALENDAR QUARTER, 1994 THROUGH JUNE 1997.\***

YEAR AND QUARTER	ALL PATIENT†	NO ANTIRETROVIRAL THERAPY	NUCLEOSIDE-ANALOGUE MONOTHERAPY	NUCLEOSIDE-ANALOGUE COMBINATION THERAPY	COMBINATION THERAPY INCLUDING A PROTEASE INHIBITOR	deaths/100 person-yr (no. of deaths/no. of patients)					
1994											
1	35.1 (16/237)	52.7 (6/74)	37.0 (7/122)	29.3 (3/59)	—						
2	35.2 (19/261)	59.9 (8/83)	42.9 (10/130)	8.1 (1/64)	—						
3	23.4 (14/309)	43.3 (7/104)	25.5 (6/147)	7.6 (1/76)	—						
4	23.1 (20/429)	38.2 (9/150)	22.2 (8/219)	19.1 (3/90)	—						
1995											
1	31.2 (34/524)	66.4 (18/178)	31.8 (15/273)	4.9 (1/115)	0 (0/10)						
2	27.4 (34/581)	51.6 (14/172)	33.4 (16/296)	13.4 (4/181)	0 (0/13)						
3	30.8 (41/609)	62.8 (17/183)	34.9 (16/279)	12.1 (5/222)	43.2 (1/11)						
4	28.5 (40/631)	42.0 (13/179)	37.5 (16/256)	23.0 (10/249)	0 (0/35)						
1996											
1	29.4 (41/645)	54.8 (12/150)	55.1 (13/173)	22.7 (9/256)	10.4 (3/201)						
2	15.4 (22/628)	39.3 (6/110)	16.1 (2/85)	18.6 (5/199)	7.8 (5/364)						
3	11.3 (16/608)	21.7 (2/64)	28.5 (2/53)	16.2 (3/123)	9.9 (9/437)						
4	10.8 (15/600)	15.3 (1/47)	0 (0/30)	0 (0/110)	14.4 (14/458)						
1997											
1	14.9 (20/583)	16.1 (1/46)	0 (0/18)	28.0 (5/115)	13.4 (13/462)						
2	8.8 (12/574)	51.6 (3/37)	0 (0/10)	5.8 (1/92)	7.8 (8/460)						

\*The rates shown are deaths per 100 person-years in each quarter among patients who received the specified type of antiviral therapy for at least 30 days. Patients could be included in no more than two categories during a quarter. The period of analysis ran from January 1994 through June 1997. Combination therapy including protease inhibitors was not widely available until 1995.

†This category includes the few patients whose observation time did not fall into any therapy category during the quarter because of frequent changes in therapy.



**Figure 1.** Mortality and Frequency of Use of Combination Antiretroviral Therapy Including a Protease Inhibitor among HIV-Infected Patients with Fewer Than 100 CD4+ Cells per Cubic Millimeter, According to Calendar Quarter, from January 1994 through June 1997.

**TABLE 2. RELATIVE RISK OF DEATH AND MORBIDITY AMONG PATIENTS WITH CD4+ T-LYMPHOCYTE COUNTS OF FEWER THAN 100 PER CUBIC MILLIMETER, ACCORDING TO TYPE OF ANTIRETROVIRAL THERAPY.\***

ANTIRETROVIRAL-THERAPY CATEGORY†	ADJUSTED RELATIVE RISK (95% CI)‡	P VALUE
<b>Mortality</b>		
None vs. monotherapy	1.5 (1.2–2.0)	0.002
None vs. combination	2.9 (2.1–4.2)	<0.001
None vs. combination + PI	4.5 (3.2–6.2)	<0.001
Monotherapy vs. combination	1.9 (1.4–2.7)	<0.001
Monotherapy vs. combination + PI	3.0 (2.1–4.1)	<0.001
Combination vs. combination + PI	1.5 (1.0–2.2)	0.03
<b>Morbidity</b>		
None vs. monotherapy	1.9 (1.2–2.8)	0.003
None vs. combination	2.4 (1.5–3.7)	<0.001
None vs. combination + PI	4.5 (2.8–7.2)	<0.001
Monotherapy vs. combination	1.3 (0.8–1.9)	0.26
Monotherapy vs. combination + PI	2.4 (1.5–3.8)	<0.001
Combination vs. combination + PI	1.9 (1.2–3.1)	0.01

\*Morbidity was defined for this analysis as a diagnosis of *Pneumocystis carinii* pneumonia, *Mycobacterium avium* complex infection, or cytomegalovirus retinitis.

†Antiretroviral therapy was categorized as follows: no antiretroviral therapy, monotherapy, combination therapy without a protease inhibitor (combination), and combination therapy with a protease inhibitor (combination + PI).

‡For mortality, the relative risks have been adjusted for study center and the CD4+ cell count at the first study visit (0 to 49, 50 to 99, or  $\geq 100$  per cubic millimeter); for morbidity, the model included these variables as well as the rate of prophylaxis against *M. avium* complex. CI denotes confidence interval.

protease inhibitor than were patients in any other payer group, although the use of protease inhibitors increased markedly for both privately insured patients and those whose care was publicly funded. The vast majority of patients in all payer groups were prescribed protease inhibitors by the second quarter of 1997. The difference in mortality between patients with private insurance and those covered by public funding narrowed in later quarters; by the second quarter of 1997, mortality among those with private insurance had fallen to 7.7 per 100 person-years; for those covered by Medicaid, mortality was 9.2 per 100 person-years.

In a preliminary failure-rate model with the study center, CD4+ cell count, and payment category as independent covariates, mortality differed significantly ( $P=0.02$ ) according to payment category. However, when the type of antiretroviral therapy was added to this model, the effect of the payment category was not significant ( $P=0.09$ ), suggesting that differences in mortality among payment groups were accounted for by different patterns of treatment.

A subgroup analysis of mortality among patients with a CD4+ cell count below 50 per cubic millimeter mirrored previous findings; there was a decline in mortality from 39.1 per 100 person-years in the first quarter of 1994 to 10.7 per 100 person-

years by the second quarter of 1997. Again, decreases in mortality correlated temporally with the increased use of combination antiretroviral regimens, especially those containing protease inhibitors.

### Morbidity

For the 1255 patients we studied, the incidence of serious opportunistic infections declined markedly in 1996 and early 1997 (Fig. 2). The incidence of any AIDS-defining diagnosis decreased from approximately 50 per 100 person-years in 1994 and 1995 to 28.6 per 100 person-years in 1996; during the last two quarters of 1996, this rate fell to 13.3 per 100 person-years, where it remained during the first two quarters of 1997. To simplify the analysis, we focused on three serious common infections: *P. carinii* pneumonia, *M. avium* complex disease, and cytomegalovirus retinitis. In 1994 the incidence of these three opportunistic infections was 21.9 per 100 person-years; by the second quarter of 1997, it was 3.7 per 100 person-years (Fig. 2). None of the independent demographic variables had a significant effect on the incidence of infection in the failure-rate model, either in the group as a whole or in the various antiretroviral-therapy categories; however, chemoprophylaxis against *M. avium* complex did have a significant effect ( $P=0.001$ ).

The final model for morbidity included the study center, category of antiretroviral therapy, initial CD4+ cell count, and the use of chemoprophylaxis against *M. avium* complex. The effect of time on morbidity was nonsignificant ( $P=0.13$ ) when the first 12 quarters of the observation period were analyzed; apparent temporal trends were explained by changes in antiretroviral-therapy categories. However, when data from the last two quarters of 1997 were included, there appeared to be a confounding effect between the quarter (time) and the type of antiretroviral therapy when both were entered into the model simultaneously; as a result, the effect of time appeared to be significant and the treatment regimen appeared less so. Comparisons in which patients were stratified according to the antiretroviral regimen were problematic because few patients remained in the no-therapy or monotherapy groups and because there were too few opportunistic events in these groups for meaningful comparisons of morbidity among treatment groups. Hence, the fact that time appears to have a significant effect in the later quarters is a reflection of the dramatic redistribution of patients to more aggressive antiretroviral-treatment categories and a consequently lower number of infections. After the strong correlation between these measures had been demonstrated, the calendar quarter was removed from the model, and as expected, the observed benefit was linked to antiretroviral therapy.

The most marked reductions in the overall inci-

**TABLE 3.** MORTALITY AND RATES OF PRESCRIPTION OF PROTEASE INHIBITORS AMONG PATIENTS WITH CD4+ T-LYMPHOCYTE COUNTS OF FEWER THAN 100 PER CUBIC MILLIMETER, ACCORDING TO CALENDAR QUARTER, 1994 THROUGH JUNE 1997.\*

YEAR AND QUARTER	ALL PATIENTS†		PRIVATE INSURANCE‡		MEDICARE		MEDICAID	
	PROTEASE INHIBITORS	MORTALITY	PROTEASE INHIBITORS	MORTALITY	PROTEASE INHIBITORS	MORTALITY	PROTEASE INHIBITORS	MORTALITY
	%	deaths/100 person-yr	%	deaths/100 person-yr	%	deaths/100 person-yr	%	deaths/100 person-yr
1994								
1	—	35.1 (16/237)	—	30.2 (8/129)	—	51.7 (2/20)	—	39.7 (5/70)
2	—	35.2 (19/261)	—	42.2 (13/147)	—	0 (0/16)	—	27.5 (4/70)
3	—	23.4 (14/309)	—	14.8 (5/166)	—	26.1 (1/19)	—	49.3 (8/90)
4	—	23.1 (20/429)	—	27.4 (13/236)	—	0 (0/32)	—	22.2 (5/110)
1995								
1	2.1	31.2 (34/524)	1.4	25.0 (15/279)	0	46.8 (4/41)	1.4	47.2 (13/142)
2	2.4	27.4 (34/581)	2.0	25.6 (17/307)	0	9.8 (1/47)	0.6	38.6 (13/160)
3	4.4	30.8 (41/609)	4.4	23.5 (17/317)	0	34.4 (4/60)	3.1	49.4 (17/161)
4	17.6	28.5 (40/631)	24.8	23.7 (18/335)	9.5	14.4 (2/63)	6.5	44.7 (15/154)
1996								
1	41.6	29.4 (41/645)	49.6	23.5 (18/345)	38.1	60.4 (8/53)	31.6	38.7 (13/158)
2	64.2	15.4 (22/628)	74.8	12.9 (10/330)	53.0	42.5 (6/66)	56.7	14.4 (5/157)
3	75.5	11.3 (16/608)	85.6	7.6 (6/326)	73.0	6.6 (1/63)	67.5	23.7 (8/154)
4	79.3	10.8 (15/600)	88.6	10.1 (8/336)	79.7	14.3 (2/59)	70.0	11.6 (4/150)
1997								
1	81.8	14.9 (20/583)	68.6	10.2 (8/334)	78.3	45.0 (6/60)	71.2	15.8 (5/139)
2	83.6	8.8 (12/574)	89.4	7.7 (6/329)	86.0	21.9 (3/57)	71.7	9.2 (3/138)

\*The mortality rates shown are deaths per 100 person-years in each quarter, with the numbers of deaths and numbers of patients in parentheses. Percentages for protease inhibitors are the percentages of patients who were ever prescribed a protease inhibitor during the quarter. Dashes indicate that protease inhibitors were not yet available.

†This category includes patients for whom the primary payer was not private insurance, Medicare, or Medicaid (e.g., self-payment, Ryan White Care Act, or other programs).

‡This category includes fee-for-service care, private health maintenance organizations, preferred-provider organizations, and similar programs.

dence of opportunistic infections occurred during the last five quarters of analysis and paralleled increases in the frequency of use of protease inhibitors. The number of patients receiving protease inhibitors tripled from the first to the fourth quarter of 1996, and 84 percent of all patients with fewer than 100 CD4+ cells per cubic millimeter received protease inhibitors by the second quarter of 1997.

Comparisons of the incidence of any one of the three major opportunistic infections among the antiretroviral-therapy categories in the failure-rate model produced findings consistent with the data on mortality (Table 2); with increases in the intensity of antiretroviral regimens, stepwise reductions in morbidity were noted.

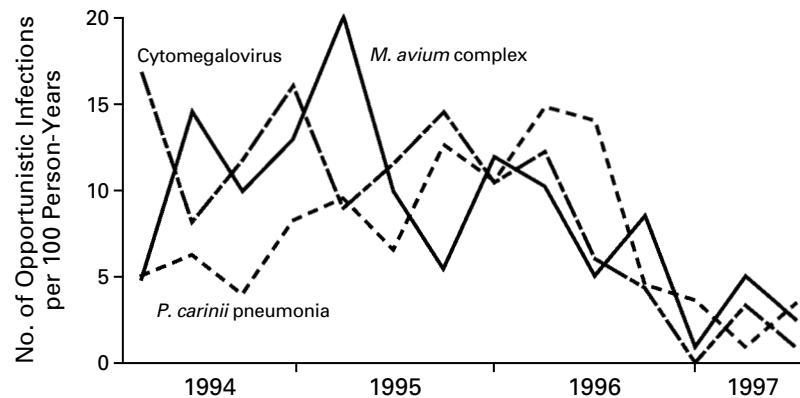
The routine use of measurements of viral load in the participating clinics increased during the period of analysis; by June 1997, at least one such determination had been recorded for 85 percent of patients. Viral-load measurements, which were calculated as the mean of the median values for each patient within each antiretroviral-therapy category, were inversely related to the intensity of therapy. The group mean for those receiving no therapy, expressed as the log of the number of copies of HIV RNA per

milliliter of blood, was 4.10; the corresponding values were 3.66 for those receiving monotherapy, 3.43 for those receiving combination antiretroviral therapy without a protease inhibitor, and 2.97 for those receiving combination regimens that included a protease inhibitor.

## DISCUSSION

The data from the HIV Outpatient Study show a dramatic reduction in morbidity and mortality among patients with CD4+ cell counts under 100 per cubic millimeter. Reductions in death and disease were clearly linked to the increasing use of combination antiretroviral therapy, with the most dramatic reductions coinciding with increases in the use of protease inhibitors. In this analysis, in which we adjusted for the severity of immune compromise, the reductions in morbidity and mortality were seen regardless of sex, race or ethnic group, and risk factor for the transmission of HIV.

The data reflect actual patient care and outcomes in a setting in which the effects of diverse factors, such as access to care and physicians' prescribing preferences, were documented.<sup>23</sup> January 1994 through June 1997 is a period in which use of combinations



**Figure 2.** Rates of Cytomegalovirus Infection, *Pneumocystis carinii* Pneumonia, and *Mycobacterium avium* Complex Disease among HIV-Infected Patients with Fewer Than 100 CD4+ Cells per Cubic Millimeter, According to Calendar Quarter, from January 1994 through June 1997.

of antiretroviral agents that included protease inhibitors increased,<sup>24</sup> while the rate of use of routine prophylaxis to prevent serious opportunistic disease remained constant.

Several types of bias might have affected the results of this study of over 1200 patients. The patients and the physicians may not have been representative of the typical patient with HIV or the typical clinician, although the geographic sites of the clinics and the demographic characteristics of the patients were diverse and roughly representative of the HIV-infected population receiving medical care in the United States. There were some differences in demographic factors between patients for whom combination therapy was prescribed and those for whom it was not prescribed (this was especially true for combination regimens that included protease inhibitors), but demographic factors were found to have no significant effect on morbidity or mortality. The part of the observation period during which the use of protease inhibitors was common was fairly brief, and our analysis cannot address the effects of antiretroviral-therapy combinations that included non-nucleoside-analogue reverse-transcriptase inhibitors.<sup>25</sup>

When we analyzed the reductions in morbidity and mortality according to patients' antiretroviral-therapy category, it became clear that benefit was directly linked to the intensity of treatment. Antiretroviral-drug combinations were more beneficial than monotherapy, and combination regimens (usually three-drug combinations) that included protease inhibitors were of greater benefit than combination regimens without these drugs. These findings are consistent with the reported virologic and immunologic benefits of protease inhibitors in previously reported data.<sup>7,16</sup>

We found reductions in opportunistic infections

overall and in the proportions of patients who had *P. carinii* pneumonia, *M. avium* complex disease, and cytomegalovirus retinitis. The most marked reduction occurred at a time when the use of protease inhibitors became widespread. The rates of use of prophylaxis against *P. carinii* and *M. avium* complex remained essentially constant throughout the period of analysis, confirming the role of antiretroviral therapy as the principal factor in the observed reductions in morbidity and mortality. The results of a subgroup analysis of patients with CD4+ cell counts under 50 per cubic millimeter were consistent with these findings.

Patients with private insurance were more likely to be prescribed a protease inhibitor than were those covered by Medicare or Medicaid, perhaps reflecting a lag in the availability of protease inhibitors in clinics treating patients whose care was covered under public programs. By June 1997, when protease inhibitors had been available for well over a year, there remained a marked discrepancy in the rates of prescription of protease inhibitors between patients with private insurance and those covered by public insurance. Despite this disparity, the rates of use of protease inhibitors did not differ significantly when patients were grouped according to sex, race or ethnic group, or age. Injection-drug users were less likely than other patients to receive protease inhibitors, but injection-drug use was not significantly associated with morbidity ( $P=0.70$ ) or mortality ( $P=0.87$ ) in the models. Death rates were lower for those with private insurance than for the study population overall and for those in other payer categories; this effect is attributable to differences in the rate of prescription of protease inhibitors.

Our analysis describes the rate and extent of the adoption of new antiretroviral therapies outside the setting of controlled clinical trials, in a group of pa-

tients that is reasonably representative of patients with HIV in the United States. During the observation period, the increased routine use of quantitative plasma measurements of HIV RNA may have affected the extent to which new therapies were adopted by providing a timely gauge of the efficacy of treatment. Stratification of patients according to measurements of viral load indicated that this variable had an inverse relation with the intensity of antiretroviral treatment; this finding is consistent with data from earlier reports.

In conclusion, the routine use of increasingly intensive antiretroviral therapies has resulted directly in dramatic declines in morbidity and mortality among HIV-infected patients with advanced immune depletion. These declines occurred during an era in which antiretroviral therapies became more numerous and more potent. As more patients receive more effective antiretroviral-drug combinations, analyses to determine the optimal duration and timing of therapy<sup>26</sup> will become increasingly necessary. Our data suggest that an intensive combination drug-therapy regimen that includes a protease inhibitor should be considered the standard of care for patients with advanced HIV infection.<sup>27</sup>

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## APPENDIX

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## REFERENCES

- Ho DD, Neumann AU, Perelson AS, Chen W, Leonard JM, Markowitz M. Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. *Nature* 1995;373:123-6.
- Perelson AS, Neumann AU, Markowitz M, Leonard JM, Ho DD. HIV-1 dynamics *in vivo*: virion clearance rate, infected cell life-span, and viral generation time. *Science* 1996;271:1582-6.
- Coffin JM. HIV population dynamics *in vivo*: implications for genetic variation, pathogenesis, and therapy. *Science* 1995;267:483-9.
- Hammer SM, Katzenstein DA, Hughes MD, et al. A trial comparing nucleoside monotherapy with combination therapy in HIV-infected adults with CD4 cell counts from 200 to 500 per cubic millimeter. *N Engl J Med* 1996;335:1081-90.
- Delta Coordinating Committee. Delta: a randomised double-blind controlled trial comparing combinations of zidovudine plus didanosine or zalcitabine with zidovudine alone in HIV-infected individuals. *Lancet* 1996;348:283-91.
- Bartlett JA, Benoit SL, Johnson VA, et al. Lamivudine plus zidovudine compared with zalcitabine plus zidovudine in patients with HIV infection: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1996;125:161-72.
- Gulick R, Mellors J, Havlir D, et al. Potent and sustained antiretroviral activity of indinavir (IDV), zidovudine (ZDV) and lamivudine (3TC). In: Supplement to the XI International Conference on AIDS, Vancouver, B.C., July 7-12, 1996. Vancouver, B.C.: XI International Conference on AIDS Society, 1996:19. abstract.
- Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. *N Engl J Med* 1997;337:725-33.
- Ho DD. Viral counts count in HIV infection. *Science* 1996;272:1124-5.
- Hughes MD, Johnson VA, Hirsch MS, et al. Monitoring plasma HIV-1 RNA levels in addition to CD4+ lymphocyte count improves assessment of antiretroviral therapeutic response. *Ann Intern Med* 1997;126:929-38.
- O'Brien WA, Hartigan PM, Daar ES, Simberkoff MS, Hamilton JD. Changes in plasma HIV RNA levels and CD4+ lymphocyte counts predict both response to antiretroviral therapy and therapeutic failure. *Ann Intern Med* 1997;126:939-45.
- O'Brien WA, Hartigan PM, Martin D, et al. Changes in plasma HIV-1 RNA and CD4+ lymphocyte counts and the risk of progression to AIDS. *N Engl J Med* 1996;334:426-31.
- Mellors JW, Rinaldo CR Jr, Gupta P, White RM, Todd JA, Kingsley LA. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. *Science* 1996;272:1167-70.
- Mellors JW, Munoz A, Giorgi JV, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med* 1997;126:946-54.
- Saag MS, Holodniy M, Kuritzkes DR, et al. HIV viral load markers in clinical practice. *Nat Med* 1996;2:625-9.
- Katzenstein DA, Hammer SM, Hughes MD, et al. The relation of virologic and immunologic markers to clinical outcomes after nucleoside therapy in HIV-infected adults with 200 to 500 CD4 cells per cubic millimeter. *N Engl J Med* 1996;335:1091-8.
- Update: trends in AIDS incidence, deaths, and prevalence — United States, 1996. *MMWR Morb Mortal Wkly Rep* 1997;46:165-73.
- Chaisson MA, Berenson L, Li W, Schwartz S, Mojica B, Hamburg M. Declining AIDS mortality in New York City (NYC). In: Program and abstracts of the Fourth Conference on Retroviruses and Opportunistic Infections, Washington, D.C., January 22-26, 1997. Washington, D.C.: IDSA Foundation for Retrovirology and Human Health, 1997:133. abstract.
- Mouton Y, Cartier F, Dellamonica P, et al. Dramatic cut in AIDS defining events and hospitalization for patients under protease inhibitors (PI) and tritherapies (TTT) in 9 AIDS reference centers (ARC) and 7,391 patients. In: Program and abstracts of the Fourth Conference on Retroviruses and Opportunistic Infections, Washington, D.C., January 22-26, 1997. Washington, D.C.: IDSA Foundation for Retrovirology and Human Health, 1997:208. abstract.
- Torres RA, Barr M. Impact of combination therapy for HIV infection on inpatient census. *N Engl J Med* 1997;336:1531-2.
- Hogg RS, O'Shaughnessy MV, Gataric N, et al. Decline in deaths from AIDS due to new antiretrovirals. *Lancet* 1997;349:1294.
- Kitahata MM, Koepsell TD, Deyo RA, Maxwell CL, Dodge WT, Wagner EH. Physicians' experience with the acquired immunodeficiency syndrome as a factor in patients' survival. *N Engl J Med* 1996;334:701-6.
- Markson LE, Cosler LE, Turner BJ. Implications of generalists' slow adoption of zidovudine in clinical practice. *Arch Intern Med* 1994;154:1497-504.
- Carpenter CC, Fischl MA, Hammer SM, et al. Antiretroviral therapy for HIV infection in 1996: recommendations of an international panel. *JAMA* 1996;276:146-54.
- D'Aquila RT, Hughes MD, Johnson VA, et al. Nevirapine, zidovudine, and didanosine compared with zidovudine and didanosine in patients with HIV-1 infection: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1996;124:1019-30.
- Concorde Coordinating Committee. Concorde: MRC/ANRS randomised double-blind controlled trial of immediate and deferred zidovudine in symptom-free HIV infection. *Lancet* 1994;343:871-81.
- Carpenter CCJ, Fischl MA, Hammer SM, et al. Antiretroviral therapy for HIV infection in 1997: updated recommendations of the International AIDS Society — USA panel. *JAMA* 1997;277:1962-9.