

Survival Benefit of Initiating Antiretroviral Therapy in HIV-Infected Persons in Different CD4⁺ Cell Strata

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Background: Optimal timing of antiretroviral therapy (ART) initiation for HIV-infected persons remains unclear.

Objective: To assess survival benefit of initiating ART at different CD4⁺ cell counts.

Design: Prospective observational study.

Setting: U.S. clinics in the HIV Outpatient Study (HOPS).

Patients: HIV-infected patients with CD4⁺ cell counts, plasma HIV RNA viral load, and ART use recorded from January 1994 through March 2002.

Measurements: Before initiation of ART, patients were grouped by their CD4⁺ cell counts into three subgroups: 0.201 to 0.350×10^9 cells/L ($n = 399$), 0.351 to 0.500×10^9 cells/L ($n = 327$), and 0.501 to 0.750×10^9 cells/L ($n = 122$). We compared mortality rates for each CD4⁺ subgroup among patients who initiated ART and patients who delayed ART until reaching a lower CD4⁺ subgroup.

Results: Mortality rates for 340 patients who initiated ART and 59 who delayed ART in the CD4⁺ subgroup of 0.201 to 0.350×10^9 cells/L were 15.4 and 56.4 deaths per 1000 person-

years, respectively (rate ratio, 0.27 [95% CI, 0.14 to 0.55]; $P < 0.001$). For the CD4⁺ subgroup of 0.351 to 0.500×10^9 cells/L, mortality rates for 240 patients who initiated ART and 887 who delayed ART were 10.0 and 16.6 deaths per 1000 person-years, respectively (rate ratio, 0.61 [CI, 0.22 to 1.67]; $P = 0.17$). For the CD4⁺ subgroup of 0.501 to 0.750×10^9 cells/L, mortality rates in 55 patients who initiated ART and 67 who delayed ART were 7.5 and 3.1 deaths per 1000 person-years, respectively (rate ratio, 1.20 [CI, 0.17 to 8.53]; $P > 0.2$). Patients in the 0.201 to 0.350×10^9 cells/L and 0.351 to 0.500×10^9 cells/L CD4⁺ subgroups who initiated ART were more likely than those who delayed ART to achieve an undetectable HIV viral load ($P = 0.03$ and 0.04, respectively).

Conclusions: Among HIV-infected persons with CD4⁺ cell counts of 0.201 to 0.350×10^9 cells/L, initiating ART is associated with reduced mortality compared with delaying such therapy. Survival benefits of earlier ART initiation (at CD4⁺ cell counts of 0.351 to 0.500×10^9 cells/L) are possible.

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Optimal timing of antiretroviral therapy (ART) initiation for persons with HIV infection is of great clinical and public health importance. Therapy reduces HIV-related mortality and morbidity for patients with substantial CD4⁺ cell depletion ($<0.100 \times 10^9$ cells/L) who initiate treatment (1). Although data demonstrate the viral suppressive and immunologic (CD4⁺ cell count) benefits of therapy in persons with higher CD4⁺ cell counts (2–8), long-term improvements in disease-associated morbidity and mortality with earlier therapy are less clear (9, 10). In such patients, the potential benefits of ART and highly active ART (HAART) will probably be weighed against possible untoward sequelae of earlier treatment, including the development of metabolic abnormalities; emergence of drug-resistant virus, with resultant exhaustion of effective remaining therapies; cost; and access (9, 11–13). Current treatment guidelines allowing for the delay of ART until a lower CD4⁺ threshold—usually 0.350×10^9 cells/L or, for some patients, 0.200×10^9 cells/L—reflect a lack of consensus on the benefits of earlier initiation of therapy (13, 14).

Sparse data exist on which to base specific recommendations for the initiation of ART relative to CD4⁺ cell count. Longitudinal data comparing ART recipients to appropriate comparison groups not receiving ART (especially patients with CD4⁺ cell counts $> 0.200 \times 10^9$ cells/L) are limited (10, 15). Analyses that include extended

follow-up data on such patients are critical because these patients are unlikely to develop or die of an HIV-related condition over the short term, in contrast to those who start therapy with lower CD4⁺ cell counts. Another challenge is related to the relatively brief time that HAART has been available (since early 1996), making comparative longitudinal studies of sufficient duration difficult.

We compare mortality rates among ambulatory HIV-infected patients who initiated ART and those who delayed ART in various CD4⁺ strata. Patients were enrolled in the HIV Outpatient Study (HOPS), a dynamic cohort of ambulatory HIV-infected patients demographically representative of treated HIV-infected patients in the United States.

METHODS

HOPS

HOPS is an ongoing prospective observational cohort study into which patients have been continuously recruited and followed since 1993 (1, 16). Study sites are 10 clinics (8 private, 2 public) in 8 U.S. cities that provide care for more than 2400 HIV-infected patients per year. Participating physicians have extensive experience treating HIV-infected patients. Information is abstracted from outpatient charts at each visit and entered electronically by trained staff; it is then compiled centrally and reviewed and

edited before being analyzed. Information abstracted includes demographic characteristics and risk factors for HIV infection; symptoms; diagnosed diseases (both definitive and presumptive); medications prescribed, including dose and duration; and laboratory values, including CD4⁺ cell counts and measurements of plasma HIV-1 RNA (viral load).

Selection of Patients for Analysis

We identified HOPS participants who had at least two CD4⁺ measurements and reliable data on ART initiation and use for at least 30 consecutive days from January 1994 through March 2001. We defined HAART as the use of at least three drugs simultaneously, including one protease inhibitor or non-nucleoside reverse-transcriptase inhibitor, or any regimen with at least two full-dose protease inhibitors.

Three patient subgroups were analyzed: those observed to have a pre-ART CD4⁺ cell count of 0.501 to 0.750×10^9 cells/L, those with a pre-ART CD4⁺ cell count of 0.351 to 0.500×10^9 cells/L, and those with a pre-ART CD4⁺ cell count of 0.201 to 0.350×10^9 cells/L. Patients could be in more than one subgroup if they had a pre-ART CD4⁺ cell count in more than one of the defined ranges. Thus, analyses within a subgroup are distinct from analyses in other subgroups. We then stratified patients in each subgroup into one of three treatment groups: those who began ART while still in the same CD4⁺ subgroup range (subsequently called patients who initiated ART), those who began ART after their CD4⁺ cell count decreased to less than the CD4⁺ subgroup range (subsequently called patients who delayed ART), and those who never received ART (untreated patients). The closest (in time) CD4⁺ cell count available within 6 months before or 2 weeks after ART initiation was used to define the CD4⁺ cell count at the start of therapy. By definition, because patients who delayed ART had to have at least 1 additional CD4⁺ measurement during follow-up, patients who initiated ART and those who were untreated were also required to have at least 1 additional CD4⁺ measurement during follow-up to reduce potential bias in the analysis as a result of differential time under observation.

For all treatment groups, time under observation began with the date of the earliest CD4⁺ cell count within the CD4⁺ stratum in which the patient was analyzed. Patients included in the analyses of the CD4⁺ subgroups of 0.201 to 0.350×10^9 cells/L and 0.351 to 0.500×10^9 cells/L were those whose earliest CD4⁺ cell count within the subgroup-defined range was observed after 1 January 1994. The analysis of the CD4⁺ subgroup of 0.501 to 0.750×10^9 cells/L was limited to those whose earliest CD4⁺ cell count within this range was observed between January 1994 and December 1995. This allowed longer elapsed time to observe clinical events. For analysis, the observation period for each patient ended at 6 months after the last contact with a HOPS clinic or at death.

We analyzed all deaths, including those not directly

Context

When to start antiretroviral therapy (ART) for HIV infection is controversial. Starting too early exposes patients to side effects and uncertain benefits. Starting too late deprives patients of benefits.

Contribution

In this cohort study, HIV-infected patients with baseline CD4⁺ cell counts between 0.201 and 0.350×10^9 cells/L who began ART immediately had lower mortality rates than those who started therapy after their CD4⁺ cell count decreased to less than 0.201×10^9 cells/L. Optimal timing of therapy is unclear when the CD4⁺ cell count is greater than 0.350×10^9 cells/L.

Cautions

A randomized, controlled trial is the best way to identify the optimal timing of ART.

—The Editors

due to AIDS or indirectly from conditions exacerbated by HIV infection (such as hepatic, renal, or cardiac disease). Causes of death were ascertained through review of clinic and hospital charts, death certificates, and national AIDS surveillance data. Deaths from suicide (one patient in the CD4⁺ subgroup of 0.201 to 0.350×10^9 cells/L who delayed ART and one patient in the CD4⁺ subgroup of 0.501 to 0.750×10^9 cells/L who initiated treatment) were treated as censored.

Statistical Analysis

We used SAS software, version 8.0 (SAS Institute, Inc., Cary, North Carolina), for all analyses. Patient characteristics were compared by chi-square test or the Fisher exact test for categorical variables and the Wilcoxon rank-sum test or *t*-test for continuous variables. We analyzed mortality rates per 1000 person-years and calculated the relative risk for death, 95% CIs, and approximate two-sided *P* values for each subgroup (17). Cox proportional hazards regression was used to estimate hazard ratios, adjusted for age, sex, race, insurance status, viral load (log scale) at time of first ART (a dummy variable was used to include patients missing viral load data), receipt of HAART, and CD4⁺ cell count at the time of first observation within each stratum.

Role of the Funding Source

The funding source participated in the design, conduct, analysis, and reporting of the study and in the decision to submit the manuscript for publication.

RESULTS

We evaluated data from 1464 HIV-infected HOPS participants. Of these patients, 596 who initiated ART had

Table 1. Characteristics of the HIV Outpatient Study Patients Who Initiated or Delayed Antiretroviral Therapy, by Preantiretroviral CD4⁺ Cell Count Stratum*

Variable	Timing of ART by CD4 ⁺ Cell Count Stratum†								
	0.201–0.350 × 10 ⁹ cells/L			0.351–0.500 × 10 ⁹ cells/L			0.501–0.750 × 10 ⁹ cells/L		
	Initiated (n = 340)	Delayed (n = 59)	P Value	Initiated (n = 240)	Delayed (n = 87)	P Value	Initiated (n = 55)	Delayed (n = 67)	P Value
Demographic characteristics, %									
Age ≤40 y	70.1	64.4	>0.2	69.5	73.6	>0.2	72.7	71.2	>0.2
Men	80.6	81.4	>0.2	80.0	85.1	>0.2	69.1	85.1	0.03
Injection drug user	12.9	11.9	>0.2	11.3	12.6	>0.2	20.0	9.0	0.08
Race/ethnicity									
White	62.7	72.4	0.11	61.9	65.5	>0.2	72.7	78.8	>0.2
African-American	24.6	17.2		28.0	24.1		16.4	15.1	
Hispanic	11.0	5.2		10.0	10.3		9.1	4.6	
Other	1.8	5.2		0.0	0.0		1.8	1.5	
Insurance									
Private	43.2	40.0	>0.2	48.3	34.5	0.07	37.0	47.1	>0.2
Medicare/Medicaid	23.0	27.3		24.4	23.9		29.6	19.1	
Other	24.2	18.2		18.1	29.8		22.2	19.1	
Unknown	9.7	14.6		9.2	11.9		11.1	14.7	
CD4 ⁺ cell counts, ×10 ⁹ cells/L									
Mean cell count at start of observation	275	251	0.008	410	404	>0.2	593	565	0.13
Mean cell count at first ART	280	131	<0.001	421	258	<0.001	601	366	<0.001
Plasma HIV RNA viral load									
Median at first ART, log copies/mL (n)	4.62 (183)	5.03 (35)	0.02	4.44 (141)	4.46 (57)	0.14	4.25 (26)	4.49 (51)	>0.2
Undetectable viral load ever, %‡	63.8	45.8	0.009	70.4	57.5	0.03	65.5	62.7	>0.2
Undetectable viral load at last measurement, %‡	32.4	22.0	0.11	38.7	36.8	>0.2	29.1	26.9	>0.2
Care characteristics									
Median time since ART initiation, y	3.1	2.6	0.06	3.4	2.6	0.02	4.6	3.2	0.02
Patients with treatment interruptions, %	36.8	35.6	>0.2	33.3	33.3	>0.2	36.4	32.8	>0.2
Patients ever receiving HAART, %	77.9	74.6	>0.2	77.1	74.7	>0.2	58.2	83.6	0.002
Median time since HAART initiation, y	3.0	2.7	>0.2	3.2	2.2	0.06	4.5	2.9	>0.2
Follow-up time									
Median time since start of observation, y	3.8	3.9	>0.2	4.1	4.2	>0.2	5.4	5.3	>0.2

* ART = antiretroviral therapy; HAART = highly active antiretroviral therapy.

† Numbers across CD4⁺ strata cannot be added to obtain the total number of persons evaluated because some patients who delayed ART in higher CD4⁺ strata appear as either patients who initiated or patients who delayed ART in lower CD4⁺ strata.

‡ Most viral load measurements were from 1998 and later. Although the lower threshold of detection of assays that were used was variable, most assay results that were undetectable were less than 50 copies/mL of blood.

at least one additional CD4⁺ measurement after ART initiation, and 175 who delayed ART had at least one additional recorded CD4⁺ cell count in a higher stratum before ART initiation. We compared the demographic and baseline characteristics of patients described in this report to those of the larger overall group of HOPS participants and found no meaningful differences (data not shown).

We analyzed data from 399 patients (340 who initiated and 59 who delayed ART) with pre-ART CD4⁺ cell counts between 0.201 and 0.350 × 10⁹ cells/L, 327 patients (240 who initiated and 87 who delayed ART) with pre-ART CD4⁺ cell counts between 0.351 and 0.500 × 10⁹ cells/L, and 122 patients (55 who initiated and 67 who delayed ART) with pre-ART CD4⁺ cell counts between 0.501 and 0.750 × 10⁹ cells/L. Median years of follow-up for patients who initiated and those who delayed ART, by CD4⁺ subgroup, were as follows: 3.8 and 3.9 years for the subgroup of 0.201 to 0.350 × 10⁹ cells/L, 4.1 and 4.2 years for the subgroup of 0.351 to 0.500 × 10⁹ cells/L, and 5.4 and 5.3 years for the subgroup of 0.501 to 0.750 × 10⁹ cells/L, respectively.

Table 1 shows the demographic, immunologic, virologic, and care characteristics of patients who initiated ART and those who delayed ART, by CD4⁺ subgroup. Across subgroups, at least 69% of patients were men, 64% were younger than 40 years of age, 62% were white, and 35% had private health care insurance. Patients who initiated ART and those who delayed ART did not differ significantly except for the following: Patients in the CD4⁺ subgroup of 0.351 to 0.500 × 10⁹ cells/L with private insurance tended to initiate rather than delay ART, and men in the CD4⁺ subgroup of 0.501 to 0.750 × 10⁹ cells/L tended to delay therapy.

In general, most patients in a CD4⁺ subgroup who delayed ART initiated therapy in the next lowest CD4⁺ subgroup, that is, those who did not start in one subgroup started approximately in the middle of the next lowest subgroup. Of patients who delayed ART in the CD4⁺ subgroup of 0.501 to 0.750 × 10⁹ cells/L, 44 (66%) initiated ART in the CD4⁺ range of 0.351 to 0.500 × 10⁹ cells/L, 17 (25%) initiated therapy in the CD4⁺ range of 0.201 to 0.350 × 10⁹ cells/L, and 6 (9%) initiated therapy at a

CD4⁺ cell count less than 0.201 × 10⁹ cells/L. Of patients who delayed ART in the CD4⁺ subgroup of 0.351 to 0.500 × 10⁹ cells/L, 68 (78%) initiated ART in the CD4⁺ range of 0.201 to 0.350 × 10⁹ cells/L, and 19 (22%) initiated ART at a CD4⁺ cell count less than 0.201 × 10⁹ cells/L. Of patients who delayed ART in the CD4⁺ subgroup of 0.201 to 0.350 × 10⁹ cells/L, 41 (69%) initiated therapy at a CD4⁺ cell count between 0.100 and 0.200 × 10⁹ cells/L.

Available data on HIV plasma viral load (representing 47% to 76% of patients in each category) revealed that patients who initiated therapy at CD4⁺ cell counts between 0.201 and 0.350 × 10⁹ cells/L or 0.351 and 0.500 × 10⁹ cells/L were significantly more likely than patients who delayed ART in those subgroups (*P* = 0.009 and 0.03, respectively) to achieve an undetectable viral load (Table 1). Data on viral load were available for the period 1996 to early 2002; most of the data were from 1998 and later. Although the lower threshold of detection of assays that were used varies, most assay results that were “undetectable” were less than 50 copies/mL of blood.

During the observation period, patients who initiated ART and who delayed ART within each CD4⁺ subgroup experienced similar rates of interruptions (about one third) in treatment once it was started. The proportion of patients initiating ART and delaying ART who ultimately received HAART was similar (about three quarters) for the two lower CD4⁺ subgroups, whereas patients in the CD4⁺ subgroup of 0.501 to 0.750 × 10⁹ cells/L who delayed ART were more likely to receive HAART (*P* = 0.002) (Table 1).

Table 2 shows the mortality rates among patients who initiated and patients who delayed ART or HAART in the three CD4⁺ subgroups. Mortality rates were lower in patients who initiated ART with a CD4⁺ cell count of 0.201 to 0.350 × 10⁹ cells/L (rate ratio, 0.27; *P* < 0.001) than in patients in this same CD4⁺ subgroup who delayed ART until reaching a lower CD4⁺ subgroup (<0.201 × 10⁹ cells/L). Mortality rates were also lower in patients who

initiated ART with a CD4⁺ cell count of 0.351 to 0.500 × 10⁹ cells/L (rate ratio, 0.61; *P* = 0.17) than in patients in this same CD4⁺ subgroup who delayed ART until reaching a lower CD4⁺ subgroup (<0.351 × 10⁹ cells/L) (Table 2). We also performed a subanalysis (separate from our main analyses and not presented in the tables) that evaluated mortality rates among 68 patients who delayed ART in the CD4⁺ subgroup of 0.351 to 0.500 × 10⁹ cells/L who initiated treatment after their CD4⁺ cell counts had declined to 0.201 to 0.350 × 10⁹ cells/L (mean CD4⁺ cell count at ART initiation, 0.303 × 10⁹ cells/L). Mortality rates did not differ between these patients and those who initiated ART in the CD4⁺ subgroup of 0.351 to 0.500 × 10⁹ cells/L.

Patients in the highest CD4⁺ subgroup (0.501 to 0.750 × 10⁹ cells/L) had the lowest mortality rates, whether ART was initiated or not. Only four patients in this subgroup died, but none of these deaths were from AIDS or were otherwise unequivocally HIV related.

We evaluated mortality rates in each CD4⁺ subgroup among the subset of patients who were known to have received HAART at some point in their ART history, again comparing patients who initiated and those who delayed ART (Table 2). Although sample sizes were somewhat smaller, time under observation was similar. In the CD4⁺ subgroup of 0.201 to 0.350 × 10⁹ cells/L, patients who initiated therapy had significantly lower mortality rates than those who delayed ART (rate ratio, 0.28; *P* = 0.004). In the CD4⁺ subgroup of 0.351 to 0.500 × 10⁹ cells/L, patients who initiated ART were only about 70% as likely to die as those who delayed therapy (rate ratio, 0.70; *P* > 0.2). In the CD4⁺ subgroup of 0.501 to 0.750 × 10⁹ cells/L, only two patients died (one patient who initiated ART and one who delayed ART); both deaths were unrelated to AIDS. These findings were consistent with observations made in the larger group of ART recipients.

In a series of Kaplan–Meier survival analyses (curves not shown), we observed the same statistical relationships.

Table 2. Mortality Rates in the HIV Outpatient Study Patients Who Initiated or Delayed Antiretroviral Therapy, by CD4⁺ Cell Count Stratum from January 1994 through March 2001*

CD4 ⁺ Stratum	Therapy†	Initiated Therapy within Stratum				Delayed Therapy to Lower Stratum				Rate Ratio (95% CI)	P Value
		Patients	Deaths‡	PY	Deaths/1000 PY	Patients	Deaths‡	PY	Deaths/1000 PY		
<i>× 10⁹ cells/L</i>		<i>n</i>				<i>n</i>					
0.201–0.350	Any ART	340	20	1295.0	15.44	59	13	230.4	56.42	0.27 (0.14–0.55)	<0.001
	Any HAART	265	11	1099.7	10.00	44	7	192.9	36.29	0.28 (0.11–0.71)	0.004
0.351–0.500	Any ART	240	10	992.9	10.07	87	6	362.1	16.57	0.61 (0.22–1.67)	0.17
	Any HAART	185	4	828.0	4.83	65	2	290.7	6.88	0.70 (0.13–3.83)	>0.2
0.501–0.750	Any ART	55	2	295.2	6.77	67	2	354.9	5.63	1.20 (0.17–8.53)	>0.2
	Any HAART	32	1	189.8	5.27	56	1	326.7	3.06	1.72 (0.11–27.5)	>0.2

* ART = antiretroviral therapy; HAART = highly active antiretroviral therapy; PY = person-years of observation.

† Any ART is defined as the use of any HAART or non-HAART regimen. Any HAART is defined as the use of HAART at any time.

‡ Excludes deaths from suicide or trauma.

Survival was clearly better for patients who initiated ART than for those who delayed ART in the CD4⁺ subgroup of 0.201 to 0.350 × 10⁹ cells/L (*P* < 0.001). Analyses of mortality rates again suggested better survival for patients who initiated ART than for those who delayed ART in the CD4⁺ subgroup of 0.351 to 0.500 × 10⁹ cells/L (*P* = 0.19). Because only four patients in the CD4⁺ subgroup of 0.501 to 0.750 × 10⁹ cells/L died, we could not perform these analyses.

We performed Cox proportional hazard analyses comparing patients who initiated and those who delayed ART for each CD4⁺ subgroup. We used a parsimonious statistical model that adjusted only for those covariates found to be independently predictive of death in other analyses (age, insurance status, receipt of HAART, and CD4⁺ cell count at the start of observation within each subgroup). Results from this analysis were similar to those observed in the full model; adjusted hazard ratios were 0.57 (*P* = 0.16) in the CD4⁺ subgroup of 0.201 to 0.350 × 10⁹ cells/L and 0.71 (*P* > 0.2) in the CD4⁺ subgroup of 0.351 to 0.500 × 10⁹ cells/L.

We also analyzed data from patients who never initiated ART during the observation period (data not shown): 68 patients in the CD4⁺ subgroup of 0.201 to 0.350 × 10⁹ cells/L (median follow-up, 1.2 years); 122 patients in the CD4⁺ subgroup of 0.351 to 0.500 × 10⁹ cells/L (median follow-up, 1.5 years); and 54 patients in the CD4⁺ subgroup of 0.501 to 0.750 × 10⁹ cells/L (median follow-up, 2.0 years). Despite shorter follow-up, we observed higher mortality rates for all CD4⁺ subgroups when comparing these patients to those who either initiated or delayed ART: 63.0 per 1000 person-years for the CD4⁺ subgroup of 0.201 to 0.350 × 10⁹ cells/L; 25.3 per 1000 person-years for the CD4⁺ subgroup of 0.351 to 0.500 × 10⁹ cells/L; and 6.9 per 1000 person-years for the CD4⁺ subgroup of 0.501 to 0.750 × 10⁹ cells/L. Notable demographic findings were that untreated patients were more likely to be injection drug users, less likely to be white, and less likely to have private health care insurance than patients who initiated or delayed ART in any CD4⁺ subgroup.

DISCUSSION

Our data indicate that for HIV-infected patients with CD4⁺ cell counts between 0.201 and 0.350 × 10⁹ cells/L, initiation of ART was clearly associated with substantial reductions in observed mortality compared with delaying ART. This finding is consistent with that of several recent reports evaluating the comparative benefit (virologic, immunologic, or clinical) of initiating ART at different immunologic stages of illness (7, 9, 10, 15).

For patients with higher CD4⁺ cell counts (0.351 to 0.500 × 10⁹ cells/L), a group in which relatively few patients died over a comparatively brief follow-up period (approximately 4 years), it is difficult to definitively assess the

potential benefits of starting versus delaying ART (until the CD4⁺ cell count is less than 0.350 × 10⁹ cells/L) on the basis of our data alone. We acknowledge that considerably longer follow-up for those initiating (versus delaying) therapy in this CD4⁺ subgroup may be necessary to clearly demonstrate such benefit. However, in an era in which treatment guidelines advocate delaying ART initiation to ever-lower CD4⁺ cell counts (18), we believe it is our responsibility to suggest that such a benefit may ultimately be shown to exist. Of note, persons who initiated rather than delayed therapy in both the CD4⁺ subgroups of 0.351 to 0.500 × 10⁹ cells/L and 0.201 to 0.351 × 10⁹ cells/L were significantly more likely to achieve an undetectable viral load during the (median) 3 to 4 years of follow-up.

We did not observe a survival benefit for patients in the CD4⁺ subgroup of 0.501 to 0.750 × 10⁹ cells/L who started ART compared with those who delayed ART, but the overall mortality rates seen in this group were, not unexpectedly, quite low (four deaths). Again, substantially longer observation would be necessary in these least immunocompromised HIV-infected persons to discern any differential mortality outcomes between patients who initiated and those who delayed therapy.

Patients who initiated or delayed ART in each CD4⁺ subgroup had, for the most part, similar demographic characteristics, HIV viral loads, rates of initial or eventual HAART receipt, rates of ART interruption, and duration of follow-up. Among HAART recipients, trends indicating a survival benefit for those with lower CD4⁺ cell counts who initiated treatment were consistent with the benefit observed in persons treated with any ART. We do not believe that these findings imply that similar long-term benefits are ascribable to any ART compared with HAART; they do, however, demonstrate that HAART recipients (as a subset of ART recipients) are at least as likely to experience reductions in mortality as a result of earlier therapy. Finally, patients who did not receive ART had the highest mortality rates in each CD4⁺ subgroup, despite shorter follow-up. The fact that these untreated patients were more likely to be injection drug users may have importance.

We believe our analysis is unique in several ways: 1) We provided an overall longer median duration of patient follow-up than other recent reports (9, 10, 15), 2) we sought to provide as direct a comparison as possible of patients who initiated ART in a given CD4⁺ subgroup to otherwise similar “controls” who delayed therapy until after their CD4⁺ count decreased to less than the CD4⁺ subgroup range, and 3) we used the “hardest” and most incontrovertible of all clinical end points, death, as our main outcome measure.

Diverse factors converge to influence the timing of ART initiation for a specific patient (11, 12). While we can show data for discretely measurable factors, such as viral load, health care financing, and HIV risk group, other con-

siderations that we cannot easily measure clearly come into play. Concerns over potential short-term and long-term adverse side effects of treatment, the number and size of pills required, dosing frequency, and cost of therapy have all emerged as important factors that affect a patient's willingness to start and ability to adhere to specific therapeutic regimens. Likewise, these factors influence a clinician's willingness to recommend treatment, especially for asymptomatic or less immunocompromised patients. A common rationale for delaying treatment is the fear that long-term ART will result in exhaustion of available treatment options, especially with the emergence of drug-resistant HIV, leaving few or no effective drugs available for use later in the course of HIV infection. Patients may feel that the start of ART represents the beginning of what is likely to be lifelong therapy. As such, it is an important threshold to which, once crossed, patients may believe they cannot return. Likewise, ART initiation may be the first tangible evidence for many patients that they indeed have a chronic and potentially life-threatening illness.

The limitations of our analyses are apparent but unavoidable. Most important is the limited duration of follow-up and, in the era of effective treatment, number of deaths that would allow a determination of treatment or survival benefit for patients with higher CD4⁺ cell counts. Such challenges affect any long-term cohort study. In addition, it can be difficult to determine causes of death. Although we used several data sources to ascertain and describe deaths, 20% of the deaths analyzed did not have a specified or known cause. Likewise, as more and more deaths among HIV-infected persons cannot be clearly ascribed to AIDS-defining illnesses (19), it is difficult to know the relative contribution of HIV to death-defining conditions, such as end-stage liver disease or kidney disease. In addition, it is usually difficult to precisely assess patient adherence to prescribed therapy; however, data obtained from anonymous surveys about this issue in HOPS indicate that patients who receive ART adhere relatively well to their regimens (>77% "always or almost always" adhere) and those who receive HAART adhere even more so (20; Knoll MD, Chmiel JS, Moorman AC, Wood KC, Holmberg SD, Palella FJ Jr. Factors related and consequences of adherence to antiretroviral therapy in ambulatory HIV patients. Unpublished paper).

We must acknowledge other potential limitations of our analysis, including the possibility that comorbid factors may differentially affect the likelihood of a delay in the initiation of ART and may, as a consequence, adversely affect mortality rates. These factors include recreational substance use, psychiatric illness, and even access to care. In our Cox proportional hazards model, we attempted to control for many potential confounders available to us. However, residual confounding is still possible with potential confounders that we did not measure.

Despite such limitations, these data provide strong evidence that earlier initiation of ART provides survival ben-

efit for HIV-infected patients with CD4⁺ cell counts of 0.201 to 0.350 × 10⁹ cells/L. Optimal timing of ART initiation is not entirely clear for those with CD4⁺ cell counts greater than 0.350 × 10⁹ cells/L. Clinicians should consider these data when evaluating ART initiation for those with HIV infection.

APPENDIX: HOPS INVESTIGATORS AND SITES

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References

1. Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med*. 1998;338:853-60. [PMID: 9516219]

2. Montaner J, Hogg R, Yip B, Chan K, Craib K, O'Shaughnessy M, et al. To start or not to start? Diminished effectiveness of anti-retroviral therapy among patients initiating therapy with CD4⁺ cell counts below 200/mm³ [Abstract]. In: Program and Abstracts of the 13th International AIDS Conference, Durban, South Africa, July 2000: Abstract LbPeB7050.
3. Phillips A, Staszewski S, Weber R, Kirk O, Francioli P, Miller V, et al. Viral load changes in response to antiretroviral therapy according to baseline CD4 lymphocyte count and viral load [Abstract]. In: Program and Abstracts of the Fifth International Congress on Drug Therapy in HIV Infection, Glasgow, Scotland, October 2000: Abstract Pl.3.4.
4. Cozzi-Lepri A, Phillips A, D'Arminio Monforte A, Muro S, DeLuca A, Pezzoti P, et al. When to start HAART in chronically HIV-infected patients? A collection of pieces of evidence from the ICONA Study [Abstract]. In: Program and Abstracts of the Fifth International Congress on Drug Therapy in HIV Infection, Glasgow, Scotland, October 2000: Abstract Pl.3.5.
5. Lane C. What are the differences in immune restoration in response to HAART at different levels of immune suppression in response to HAART at different levels of immune suppression/immunodeficiency at initiation of treatment and do they matter? [Abstract]. In: Program and Abstracts of the Fifth International Congress on Drug Therapy in HIV Infection, Glasgow, Scotland, October 2000: Abstract Pl.7.1.
6. Lederman M, Valdez H, Medvik K, Dorazio D, Asaad R, Pacheko C, et al. Functional significance of CD4 cell numbers on the way down versus the way up [Abstract]. In: Program and Abstracts of the Fifth International Congress on Drug Therapy in HIV Infection, Glasgow, Scotland, October 2000: Abstract Pl.7.4.
7. Kaplan J, Hanson D, Karon J, Cohn D, Thompson M, Buskin S, et al. Late initiation of antiretroviral therapy (at CD4⁺ lymphocyte count < 200 cells/ μ L) is associated with increased risk of death [Abstract]. In: Program and Abstracts of the 8th Conference on Retroviruses and Opportunistic Infections, Chicago, Illinois, February 2001: Abstract 520.
8. Schacker T, Little S, Connick E, Gebhard-Mitchell K, Zhang ZQ, Krieger J, et al. Rapid accumulation of human immunodeficiency virus (HIV) in lymphatic tissue reservoirs during acute and early HIV infection: implications for timing of antiretroviral therapy. *J Infect Dis.* 2000;181:354-7. [PMID: 10608788]
9. Opravil M, Ledergerber B, Furrer H, Hirschel B, Imhof A, Gallant S, et al. Clinical efficacy of early initiation of HAART in patients with asymptomatic HIV infection and CD4 cell count > 350 \times 10(6)/l. *AIDS.* 2002;16:1371-81. [PMID: 12131214]
10. Hogg RS, Yip B, Chan KJ, Wood E, Craib KJ, O'Shaughnessy MV, et al. Rates of disease progression by baseline CD4 cell count and viral load after initiating triple-drug therapy. *JAMA.* 2001;286:2568-77. [PMID: 11722271]
11. Walker BD, Basgoz N. Treat HIV-1 infection like other infections—treat it. *JAMA.* 1998;280:91-3. [PMID: 9660371]
12. Burman WJ, Reves RR, Cohn DL. The case for conservative management of early HIV disease. *JAMA.* 1998;280:93-5. [PMID: 9660372]
13. Dybul M, Fauci A, Bartlett J, Kaplan J, Pua A. Guidelines for using anti-retroviral agent among HIV-infected adults and adolescents: The Panel on Clinical Practices for HIV. *Ann Intern Med.* 2002;137:381-433. [PMID: 12617573].
14. U.S. Department of Health and Human Services and the Henry J. Kaiser Family Foundation. Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents. Washington, DC: U.S. Department of Health and Human Services; February 2001. Accessed at <http://hivatis.org.trtgdlns.html> on 6 February 2003.
15. Phillips AN, Staszewski S, Weber R, Kirk O, Francioli P, Miller V, et al. HIV viral load response to antiretroviral therapy according to the baseline CD4 cell count and viral load. *JAMA.* 2001;286:2560-7. [PMID: 11722270]
16. Moorman AC, Holmberg SD, Marlowe SI, Von Bargen JC, Yangco BG, Palella FJ, et al. Changing conditions and treatments in a dynamic cohort of ambulatory HIV patients: the HIV outpatient study (HOPS). *Ann Epidemiol.* 1999;9:349-57. [PMID: 10475534]
17. Rosner B. *Fundamentals of Biostatistics.* 5th ed. Pacific Grove, CA: Duxbury Pr; 2000:688-9.
18. Yeni PG, Hammer SM, Carpenter CC, Cooper DA, Fischl MA, Gatell JM, et al. Antiretroviral treatment for adult HIV infection in 2002: updated recommendations of the International AIDS Society-USA Panel. *JAMA.* 2002;288:222-35. [PMID: 12095387]
19. Bica I, McGovern B, Dhar R, Stone D, McGowan K, Scheib R, et al. Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. *Clin Infect Dis.* 2001;32:492-7. [PMID: 11170959]
20. Von Bargen J, Moorman A, Holmberg S. How many pills do patients with HIV infection take? [Letter] *JAMA.* 1998;280:29. [PMID: 9660353]

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