

Kitahata MM, Gange SJ, Abraham AG, et al. for the NA-ACCORD Investigators. Effect of Early versus Deferred Antiretroviral Therapy for HIV on Survival. *N Engl J Med* 2009;360:1815-26.

The optimal time to initiate antiretrovirals in asymptomatic HIV patients is unclear. Current guidelines suggest starting treatment when the CD4+ count reaches 350, although there is minimal data from RCT's to support this. In this multi-center observational study, patients with CD4+ counts of >500 and CD4+ counts of 350-500 were considered separately. Subjects in both groups were grouped based upon whether they initiated antiretroviral treatment within 6 months of entry into the study or initiated treatment after their CD4+ count fell below the threshold (500 in the first group, 350 in the second group). Among the group who started with CD4+ of 350-500, waiting until the CD4+ count fell below 350 was associated with a 69% increase in the relative risk of death within 1 year, the primary outcome. In the group with >500 CD4+ cells at the outset, deferring therapy until falling below 500 CD4+ cells was associated with a 94% increased risk of death. The major strengths of this trial include its large size and its use of all-cause mortality as an endpoint. There are several potential limitations, including significant baseline differences between the two groups, such as higher rates of Hep C co-infection and higher rates of IVDU in the deferred-therapy group (although these were adjusted for). Appropriately accounting for such differences will require an RCT.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

APRIL 30, 2009

VOL. 360 NO. 18

Effect of Early versus Deferred Antiretroviral Therapy for HIV on Survival

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ABSTRACT

BACKGROUND

The optimal time for the initiation of antiretroviral therapy for asymptomatic patients with human immunodeficiency virus (HIV) infection is uncertain.

METHODS

We conducted two parallel analyses involving a total of 17,517 asymptomatic patients with HIV infection in the United States and Canada who received medical care during the period from 1996 through 2005. None of the patients had undergone previous antiretroviral therapy. In each group, we stratified the patients according to the CD4+ count (351 to 500 cells per cubic millimeter or >500 cells per cubic millimeter) at the initiation of antiretroviral therapy. In each group, we compared the relative risk of death for patients who initiated therapy when the CD4+ count was above each of the two thresholds of interest (early-therapy group) with that of patients who deferred therapy until the CD4+ count fell below these thresholds (deferred-therapy group).

RESULTS

In the first analysis, which involved 8362 patients, 2084 (25%) initiated therapy at a CD4+ count of 351 to 500 cells per cubic millimeter, and 6278 (75%) deferred therapy. After adjustment for calendar year, cohort of patients, and demographic and clinical characteristics, among patients in the deferred-therapy group there was an increase in the risk of death of 69%, as compared with that in the early-therapy group (relative risk in the deferred-therapy group, 1.69; 95% confidence interval [CI], 1.26 to 2.26; $P < 0.001$). In the second analysis involving 9155 patients, 2220 (24%) initiated therapy at a CD4+ count of more than 500 cells per cubic millimeter and 6935 (76%) deferred therapy. Among patients in the deferred-therapy group, there was an increase in the risk of death of 94% (relative risk, 1.94; 95% CI, 1.37 to 2.79; $P < 0.001$).

CONCLUSIONS

The early initiation of antiretroviral therapy before the CD4+ count fell below two prespecified thresholds significantly improved survival, as compared with deferred therapy.

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This article (10.1056/NEJMoa0807252) was published at NEJM.org on April 1, 2009.

N Engl J Med 2009;360:1815-26.

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THE USE OF ANTIRETROVIRAL THERAPY has dramatically reduced disease progression and death among patients with human immunodeficiency virus (HIV) infection,^{1,2} but the optimal time to begin therapy is uncertain.^{3,4} Current guidelines recommend treatment for asymptomatic patients who have a CD4+ count of less than 350 cells per cubic millimeter on the basis of accumulating observational data.^{5,6} However, these guidelines note the lack of data from randomized clinical trials regarding the timing of the initiation of antiretroviral therapy.^{3,4} Data from randomized trials are limited to an analysis of a subgroup of 477 patients⁷ from the Strategies for Management of Antiretroviral Therapy (SMART) trial (ClinicalTrials.gov number, NCT00027352),⁸ which suggested that deferring antiretroviral therapy until the CD4+ count fell below 250 cells per cubic millimeter increased the risk of progression to the acquired immunodeficiency syndrome (AIDS) or death, as compared with initiation of therapy at a CD4+ count of more than 350 cells per cubic millimeter.^{7,9}

Several observational studies have examined the prognosis for patients who begin antiretroviral therapy at different CD4+ counts.^{5,6,10-16} However, these studies do not address the question of when to start antiretroviral therapy, since they do not have a comparison group of patients who deferred therapy.^{17,18} A few studies have compared patients with similar CD4+ counts who either initiated or deferred antiretroviral therapy,¹⁹⁻²⁴ but these studies did not have the statistical power and methods^{18,25,26} to examine differences in outcomes, particularly among patients with higher CD4+ counts.

Since previous studies have enrolled small numbers of patients and had a relatively short follow-up,^{19-24,27} they have required the use of a combined end point of progression to an AIDS-defining illness or death. However, serious conditions that are not traditionally considered to be associated with AIDS have resulted in death and complications in HIV-infected patients,^{8,28} and the risk of these conditions is greater than the risk of AIDS among patients with a CD4+ count of more than 200 cells per cubic millimeter.²⁹⁻³³

Emerging data about the benefits of early antiretroviral treatment, including a better response to therapy and a preservation of immune function,³⁴⁻³⁹ suggest that the initiation of antiretro-

viral therapy earlier in the course of HIV infection may improve long-term outcomes. In a recently established collaboration of research groups in the United States and Canada, we examined all HIV-infected patients with a CD4+ count ranging from 351 to 500 cells per cubic millimeter and all patients with a CD4+ count of more than 500 cells per cubic millimeter who had received no previous antiretroviral therapy and had no history of an AIDS-defining illness to determine whether the initiation of antiretroviral therapy at early stages of HIV infection would be associated with better survival than deferred therapy.

METHODS

STUDY PATIENTS

The data for this study were collected as part of the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of the International Epidemiological Databases to Evaluate AIDS project. Details on the collaboration and sites have been published previously.⁴⁰ Briefly, the NA-ACCORD consists of 22 research groups, representing more than 60 sites. The study was approved by local institutional review boards and used standardized methods of data collection, including routine surveillance of U.S. national and Canadian provincial death indexes. Each group of investigators submitted data regarding demographic characteristics, treatment, and clinical, laboratory, and vital status on enrolled patients.

We conducted parallel analyses on two distinct study groups of patients who received medical care between January 1996 and December 2005, had not had a previous AIDS-defining illness (according to 1993 criteria of the Centers for Disease Control and Prevention⁴¹), and had not undergone previous antiretroviral therapy. The patients were identified from a total of 67,527 patients who underwent screening. For the first analysis, we identified all patients who had a CD4+ count of 351 to 500 cells per cubic millimeter. For the second analysis, we identified patients who had a CD4+ count of more than 500 cells per cubic millimeter.

STUDY DEFINITIONS

Antiretroviral therapy was defined as a regimen containing at least three antiretroviral drugs, including a protease inhibitor, a nonnucleoside re-

verse-transcriptase inhibitor, or three nucleoside reverse-transcriptase inhibitors, including abacavir or tenofovir.

In a study design similar to that of a randomized clinical trial, we compared the rates of death from any cause in the group that initiated antiretroviral therapy when the CD4+ count was within one of the two thresholds of interest (early-therapy group) with the rate in the group that did not initiate antiretroviral therapy until the CD4+ count fell below these thresholds (deferred-therapy group). Follow-up ended at the month of death, at 1 year after the date of the last measurement of the CD4+ count, or on December 31, 2005, whichever occurred first.

STATISTICAL ANALYSIS

The baseline characteristics of patients who initiated antiretroviral therapy early were compared with those who deferred therapy with the use of Wilcoxon and chi-square tests for association. Among the patients in the deferred-therapy group who transitioned to a CD4+ count of either 350 cells or less or 500 cells or less per cubic millimeter, we identified and characterized the subgroup that initiated antiretroviral therapy.

We used multivariate Cox proportional-hazards models with strata for each cohort of patients and each baseline calendar year. Baseline was defined as the date of the first measurement of a CD4+ count either in the range of 351 to 500 or of more than 500 cells per cubic millimeter. To avoid immortal time bias,⁴² patients in the early-therapy group contributed person-time to the deferred-therapy group between baseline and the date of initiation of antiretroviral therapy. After the initiation of antiretroviral therapy, these patients contributed all person-time to the early-therapy group in an intention-to-treat approach that ignored subsequent changes in therapy. In addition to the primary analysis between the early-therapy group and the deferred-therapy group, adjustment was made for sex, age, and the CD4+ count at baseline. Data regarding other prognostic factors in patients with HIV infection (including the HIV RNA level,⁴³ a history injection-drug use,³⁵ the presence or absence of hepatitis C virus [HCV] infection,^{44,45} and race) were available for most of the patients. Thus, we separately fit models that adjusted for these covariates in prespecified subgroup analyses, treating patients with unknown

status as a separate covariate group. Proportional-hazards assumptions were assessed graphically with the use of the methods of Grambsch and Therneau.⁴⁶ A two-sided P value of 0.05 or less was considered to indicate statistical significance.

Since patients did not undergo randomization and data censoring was not performed in a random fashion, we used inverse-probability weighting methods.^{26,47} To investigate the sensitivity of our results to potential unmeasured confounding factors associated with the time to death and deferral of therapy,⁴⁸ we conducted a set of Monte Carlo simulations⁴⁹ (for details on both methods, see the Supplementary Appendix, available with the full text of this article at NEJM.org).

RESULTS

PATIENTS

In the first analysis, 8362 patients (who contributed 23,977 person-years of follow-up) met the inclusion criteria with a CD4+ count of 351 to 500 cells per cubic millimeter (351-to-500 CD4+ count). Of these patients, 2084 (25%) initiated antiretroviral therapy within 6 months after the first CD4+ count was within the range of interest, as compared with the remaining 6278 patients (75%), who deferred therapy until the CD4+ cell count fell below the range (Table 1). Of the patients in the deferred-therapy group, 2829 (45%) were not observed with a CD4+ count of 350 cells or less per millimeter; data from 22% of the patients were censored because the patients initiated antiretroviral therapy beyond the 6-month target window after the first CD4+ count ranged from 351 to 500 cells per millimeter. The other 3449 patients (55%) transitioned to a CD4+ count of 350 cells or less per cubic millimeter; of these patients, 803 initiated antiretroviral therapy within 6 months after the first CD4+ count of 350 cells or less per cubic millimeter.

In the second analysis, 9155 patients (who contributed 26,439 person-years of follow-up) met the inclusion criteria with a CD4+ count of more than 500 cells per cubic millimeter (more-than-500 CD4+ count). Of these patients, 2220 (24%) initiated antiretroviral therapy within 6 months after the first CD4+ count was within the range of interest, as compared with the remaining 6935 patients (76%) who deferred therapy. Of the patients in the deferred-therapy group, 3054 (44%) were not

Table 1. Stratification of Patients According to CD4+ Count at Baseline.*

Variable	351-to-500 CD4+ Count	More-Than-500 CD4+ Count
Patients with a CD4+ count within prespecified range and no history of previous antiretroviral therapy or AIDS-defining disease — no.	8362	9155
Patients who initiated antiretroviral therapy within 6 mo — no.	2084	2220
Patients who deferred antiretroviral therapy — no.	6278	6935
Patients who deferred therapy and who either transitioned to a lower CD4+ count stratum or not		
Transition — no. (no. of cells)	3449 (≤ 350 cells/mm ³)	3881 (≤ 500 cells/mm ³)
No transition — no.	2829	3054
Timing of initiation of therapy among patients who deferred therapy and who transitioned to a lower CD4+ count		
Within 6 mo — no.	803	539
Not within 6 mo — no.	2646	3342

* The CD4+ count was measured in cells per cubic millimeter.

observed with a CD4+ count of 500 cells or less per millimeter. The other 3881 patients transitioned to a CD4+ count below the threshold of interest. Of these patients, 539 (14%) initiated antiretroviral therapy within 6 months after the first CD4+ count of 500 cells or less per cubic millimeter. The proportion of patients who initiated antiretroviral therapy at a CD4+ count of more than 500 cells per cubic millimeter peaked at 15% in 1999 and had dropped to less than 10% by 2003.

Demographic and clinical characteristics of the patients in the two groups are shown in Table 2. In each of the groups with the two thresholds of CD4+ counts, patients in the early-therapy group were slightly older and were more likely to be white men. At study entry, the CD4+ count within each of the two ranges of interest was similar in the early-therapy group and the deferred-therapy group. Among patients with a 351-to-500 CD4+ count, the median count per cubic millimeter was 422 cells in the early-therapy group and 431 cells in the deferred-therapy group; among patients with a more-than-500 CD4+ count, the median count per cubic millimeter was 679 cells in the early-therapy group and 664 cells in the deferred-therapy group.

In the subgroup of patients for whom data were available, fewer patients with a history of injection-drug use and HCV infection were in the early-therapy group. Patients in the early-therapy group were more likely to initiate a protease inhibitor–

based regimen that did not include a ritonavir boost; in the early-therapy group and the deferred-therapy group, the proportions of patients who initiated a protease inhibitor–based regimen with a ritonavir boost were low. The proportions of patients who had an HIV RNA level of less than 500 copies per milliliter within 12 months after the initiation of antiretroviral therapy were clinically similar in the two groups, although among patients with a more-than-500 CD4+ count, there was a statistically significant difference.

OVERALL RISK OF DEATH

Among patients with a 351-to-500 CD4+ count, there were 137 deaths in the early-therapy group and 238 deaths in the deferred-therapy group. The crude rate of death for patients in the early-therapy group was 1.6 deaths per 100 person-years. Among patients with a more-than-500 CD4+ count, there were 113 deaths in the early-therapy group and 198 deaths in the deferred-therapy group. The crude rate of death for patients in the early-therapy group was 1.3 deaths per 100 person-years. A crude rate of death could not be calculated for the deferred-therapy group because of data censoring to address “outside of protocol” violations.

The median time until data censoring was 3.7 years (interquartile range, 1.1 to 5.3) in the early-therapy group and 1.3 years (interquartile range, 0.7 to 2.9) in the deferred-therapy group among patients with a 351-to-500 CD4+ count and 3.7 years (interquartile range, 1.9 to 5.8) in the early-

therapy group and 1.7 years (interquartile range, 0.9 to 3.5) in the deferred-therapy group among patients with a more-than-500 CD4+ count. At the end of the study, data on the cause of death had been obtained for 16% of the patients who had died. The majority of deaths in the early-therapy group and the deferred-therapy group were from non-AIDS-defining conditions, including hepatic, renal, and cardiovascular diseases and non-AIDS-defining cancers in both analyses.

351-TO-500 CD4+ COUNT

Among patients with a baseline CD4+ count of 351 to 500 cells per cubic millimeter, the relative risk of death for deferred therapy, as compared with early therapy, was 1.69 (95% confidence interval [CI], 1.26 to 2.26; $P < 0.001$), as calculated with weighted Cox regression analysis stratified according to cohort of patients and the year of the first CD4+ count of 351 to 500 cells per cubic millimeter (Table 3). An increased risk of death was associated with an older age at baseline (relative risk, 1.68 for each 10-year increment; 95% CI, 1.48 to 1.91; $P < 0.001$) but not with the patient's sex or the baseline CD4+ count (Table 3). These results remained significant and of similar magnitude when data from each of the cohorts were systematically excluded. Graphical and statistical tests did not suggest any deviation from the proportionality assumption of any variable except for age. The results in the deferred-therapy group remained similar after adjustment for age with the use of a cubic regression spline. There were no significant interactions between the effect of deferred therapy and age, sex, baseline HIV RNA level, a history of injection-drug use, HCV infection, cohort, or calendar year; the latter was examined as a continuous or categorical variable.

Some patients had a first CD4+ count of 351 to 500 cells per cubic millimeter in years before the routine availability of HIV RNA testing. When the analysis was restricted to patients for whom data were available regarding the baseline HIV RNA level, the relative risk of death for deferred therapy, as compared with early therapy, was similar to that in the primary analysis (relative risk, 1.63; 95% CI, 1.21 to 2.19; $P = 0.002$). However, the HIV RNA level at baseline was not an independent risk factor for death.

After the exclusion of one group of investigators that did not collect data regarding a history of injection-drug use and the exclusion of patients

with a history of injection-drug use, the risk of deferred therapy, as compared with early therapy, remained significantly elevated (relative risk, 1.66; 95% CI, 1.02 to 2.70; $P = 0.04$). After adjustment for a history of injection-drug use, the risk of death in the deferred-therapy group was attenuated (relative risk, 1.28; 95% CI, 0.85 to 1.93; $P = 0.23$). Patients who had a history of injection-drug use had a higher risk of death than those with no such history (relative risk, 1.64; 95% CI, 1.10 to 2.44; $P = 0.01$).

After the exclusion of two groups of investigators that did not collect data regarding HCV infection, the risk of death in the deferred-therapy group was also similar to that in the primary analysis (relative risk, 1.71; 95% CI, 1.20 to 2.45; $P = 0.003$). The presence of HCV infection was associated with an increased risk of death (relative risk, 1.85; 95% CI, 1.07 to 3.23; $P = 0.03$). After the exclusion of patients with HCV infection, the risk of death for deferred therapy remained significantly elevated (relative risk, 1.52; 95% CI, 1.01 to 2.28; $P = 0.04$).

Female sex was associated with an increased risk of death in the analysis that included the HIV RNA level, but the risk was not significant after adjustment for either a history of injection-drug use or the presence of HCV infection. Race (white vs. all others) was not significantly associated with an increased risk of death, and the inclusion of race as a variable in the model did not have an effect on the results. A small proportion of patients in the deferred-therapy group transitioned to a CD4+ count of less than 200 cells per cubic millimeter, but the exclusion of these patients from the analysis did not change the results.

MORE-THAN-500 CD4+ COUNT

Similarly, among patients who had a CD4+ count of more than 500 cells per millimeter, the risk of death among patients who deferred therapy, as compared with those with early therapy, increased by 94% (relative risk, 1.94; 95% CI, 1.37 to 2.79; $P < 0.001$). After restriction of the analysis to patients for whom data on the baseline HIV RNA level were available, the relative risk for the deferred-therapy group was similar to that in the primary analysis (relative risk, 1.85; 95% CI, 1.20 to 2.86; $P = 0.006$).

After the exclusion of one group of investigators that did not collect data regarding a history of injection-drug use, the risk of death for deferred

therapy remained significantly elevated (relative risk, 1.73; 95% CI, 1.08 to 2.78; $P=0.02$). After the exclusion of patients who had a history of injection-drug use, the risk of death for deferred therapy was of similar magnitude (relative risk, 2.00; 95% CI, 1.15 to 3.46; $P=0.01$). After the exclusion of two groups of investigators that did not collect data regarding the status of HCV infection, the risk of death for deferred therapy was also similar to that in the primary analysis (relative

risk, 2.03; 95% CI, 1.37 to 3.01; $P<0.001$). After the exclusion of patients with HCV infection, the risk of death for deferred therapy remained significantly elevated (relative risk, 1.90; 95% CI, 1.14 to 3.18; $P=0.01$).

Again, the risk of death was not significantly associated with race or the baseline HIV RNA level. Female sex was associated with an increased risk of death, but the risk was not significant after adjustment for the baseline HIV RNA level, a his-

Table 2. Characteristics of the Patients, According to the Timing of Initiation of Antiretroviral Therapy and CD4+ Count at Baseline.*

Variable	351-to-500 CD4+ Count		More-Than-500 CD4+ Count	
	Early-Therapy Group	Deferred-Therapy Group	Early-Therapy Group	Deferred-Therapy Group
No. of patients	2084	6,278	2220	6,935
Follow-up person-years (no.)	8353	15,624	8663	17,776
Deaths within 1 yr after last CD4+ count (no.)	137	238	113	198
Age (yr)				
Median	40	38	40	38
Interquartile range	34–48	32–45	33–48	32–45
Male sex (%)	84	75	82	73
Race (%) †				
White	45	40	49	42
Black	38	44	36	44
Other	17	16	15	14
CD4+ count at baseline (cells/mm ³)				
Median	422	431	679	664
Interquartile range	387–460	391–468	580–840	573–811
HIV RNA at baseline (log ₁₀ copies/ml) ‡				
Median	4.2	4.1	3.5	3.7
Interquartile range	2.9–4.9	3.4–4.6	2.6–4.6	2.7–4.4
Hepatitis C virus infection (%) §	27	33	25	35
History of injection-drug use (%) ¶	15	20	14	21
No. of patients who initiated antiretroviral therapy	2084	803	2220	539
Year of initiation of antiretroviral therapy				
Median	2000	2001	2000	2000
Interquartile range	1998–2001	1998–2003	1998–2001	1998–2003
Interval from first CD4+ count to initiation of antiretroviral therapy (mo)				
Median	3	3	2	3
Interquartile range	2–3	2–4	2–3	2–4
CD4+ count at initiation of antiretroviral therapy (cells/mm ³)				
Median	422	286	679	410
Interquartile range	387–460	228–320	580–840	332–464

Table 2. (Continued.)

Variable	351-to-500 CD4+ Count		More-Than-500 CD4+ Count	
	Early-Therapy Group	Deferred-Therapy Group	Early-Therapy Group	Deferred-Therapy Group
Type of first antiretroviral therapy (%)				
Protease inhibitor–based				
Without boost	48	40	50	43
With boost	9	11	7	9
Nonnucleoside reverse-transcriptase inhibitor–based	33	38	32	38
Protease inhibitor and nonnucleoside reverse-transcriptase inhibitor–based	4	2	4	3
≥3 Nucleoside reverse-transcriptase inhibitors	6	9	6	8
HIV RNA <500 copies/ml within 12 mo after initiation of antiretroviral therapy (%)	75	72	81	71

* The CD4+ count was measured in cells per cubic millimeter. $P < 0.05$ for all comparisons between the early-therapy group and the deferred-therapy group except for the response to the initiation of antiretroviral therapy in the number of HIV RNA copies in patients with a 351-to-500 CD4+ count ($P = 0.16$) and the median year of initiation of antiretroviral therapy in patients with a more-than-500 CD4+ count ($P = 0.72$). HIV denotes human immunodeficiency virus.

† Race was self-reported. Race was evaluated in 7657 patients with a CD4+ count of 351 to 500 cells per cubic millimeter and in 8462 patients with a CD4+ count of more than 500 cells per cubic millimeter.

‡ Baseline HIV RNA levels were evaluated in 6425 patients with a CD4+ count of 351 to 500 cells per cubic millimeter and in 6566 patients with a CD4+ count of more than 500 cells per cubic millimeter.

§ The status of hepatitis C virus infection was evaluated in 4404 patients with a CD4+ count of 351 to 500 cells per cubic millimeter and in 5147 patients with a CD4+ count of more than 500 cells per cubic millimeter. Data on hepatitis C virus infection were not obtained for two cohorts of patients.

¶ The status of injection-drug use was evaluated in 5744 patients with a CD4+ count of 351 to 500 cells per cubic millimeter and in 6087 patients with a CD4+ count of more than 500 cells per cubic millimeter. The use of injection drugs was not evaluated for one cohort.

tory of injection-drug use, or the presence of HCV infection. Very few patients in the deferred-therapy group transitioned to a CD4+ count of less than 350 cells per cubic millimeter. When data from these patients were censored at the first CD4+ count of less than 350 cells per cubic millimeter, the relative risk of death among patients in the deferred-therapy group with a 351-to-500 CD4+ count, as compared with patients in the early-therapy group with a more-than-500 CD4+ count, was 1.80 (95% CI, 1.24 to 2.62; $P = 0.002$).

CONFOUNDING BY UNMEASURED COVARIATES

Finally, we evaluated the extent to which an unmeasured covariate might reduce the relative risk of death. Figure 1 shows the results of the analysis of patients with a 351-to-500 CD4+ count; similar results were seen for the analysis of patients with a more-than-500 CD4+ count. The plot shows that a confounding factor with a relative risk of death of 4.0 and an odds ratio for the deferral of therapy of 4.0 after adjustment for all included vari-

ables would reduce the estimated relative risk for deferred therapy to approximately 1.30.

DISCUSSION

The results of this study suggest that among patients with a 351-to-500 CD4+ count, the deferral of antiretroviral therapy was associated with an increase in the risk of death of 69%, as compared with the early initiation of therapy. Among patients with a more-than-500 CD4+ count, deferred therapy was associated with an increase in the risk of death of 94%. As has been shown in previous studies, an older age was an independent risk factor for death,^{5,50} as were a history of injection-drug use³⁵ and the presence of HCV infection.⁴⁵

Results regarding the risk of deferred therapy on mortality were robust after adjustment for these factors and after the exclusion of patients with a history of injection-drug use, who may have had a higher likelihood of deferring treatment, a poorer level of adherence to therapy, and a higher risk of

Table 3. Risk of Death Associated with Deferral of Antiretroviral Therapy, According to CD4+ Count at Baseline, with Adjustment for HIV RNA Level, Age, and Sex.*

Variable	351-to-500 CD4+ Count		More-Than-500 CD4+ Count	
	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
Without inclusion of HIV RNA data				
Deferral of antiretroviral therapy	1.69 (1.26–2.26)	<0.001	1.94 (1.37–2.79)	<0.001
Female sex	1.21 (0.89–1.64)	0.24	1.85 (1.33–2.59)	<0.001
Older age (per 10-yr increment)	1.68 (1.48–1.91)	<0.001	1.83 (1.62–2.06)	<0.001
Baseline CD4+ count (per 100 cells/mm ³)	1.13 (0.72–1.78)	0.59	0.93 (0.87–0.99)	0.03
With inclusion of HIV RNA data				
Deferral of antiretroviral therapy	1.63 (1.21–2.19)	0.002	1.85 (1.20–2.86)	0.006
Female sex	1.47 (1.02–2.12)	0.04	1.35 (0.85–2.15)	0.20
Older age (per 10-year increment)	1.89 (1.69–2.11)	<0.001	1.81 (1.58–2.07)	<0.001
Baseline CD4+ count (per 100 cells/mm ³)	0.74 (0.55–1.00)	0.06	0.97 (0.89–1.05)	0.45
Baseline HIV RNA level (per log ₁₀ copies/ml)	1.11 (0.96–1.28)	0.15	1.13 (0.96–1.33)	0.14

* The CD4+ count was measured in cells per cubic millimeter. Results were calculated with the use of Cox regression analyses with inverse probability-of-censoring weights. HIV denotes human immunodeficiency virus.

death. The type of the initial antiretroviral regimen and the proportion of patients who achieved viral suppression as a measure of adherence were clinically similar in the early-therapy group and the deferred-therapy group. The increased risk of death for patients who deferred treatment was similar throughout the 10-year study period. The improved rate of survival among patients who initiate antiretroviral therapy at higher CD4+ counts probably can be attributed to multiple factors, including earlier control of viral replication and viral diversity and a greater immunologic benefit.^{34–37} Incomplete restoration of the CD4+ count is common among patients initiating antiretroviral therapy at lower CD4+ counts, despite viral suppression for up to 10 years while receiving therapy, and there may be persistent deficits in immunologic function even with substantial restoration of the CD4+ count.^{38,39}

Studies in which patients were observed only after they began antiretroviral therapy could not provide data regarding AIDS events and deaths that occurred during deferral of therapy, a factor that introduced a lead-time bias.¹⁸ Some investigators have applied methods¹⁸ to impute these missing events,^{21,22,27} using data from patients with HIV infection during the era before the advent of potent antiretroviral therapy, but such methods may not fully address the lead-time bias. In

contrast, our study was not subject to such lead-time bias. An additional strength of our study was the comprehensive ascertainment of mortality through linkage with national death registries in both the United States and Canada.

The benefits of initiating antiretroviral therapy earlier after HIV infection must be weighed against potential adverse effects of treatment. Newer antiretroviral therapies that are more potent, have fewer side effects, and have to be taken less frequently improve adherence and maintain viral suppression at lower levels of adherence⁵¹ than did previous regimens,⁵² which decreases the risk of drug resistance.⁵³ Furthermore, starting therapy at progressively higher CD4+ counts has been shown to lower the risk of some toxic effects associated with antiretroviral therapy, including peripheral neuropathy, anemia, and renal insufficiency.⁵⁴ However, all the potential side effects of long-term antiretroviral therapy are unknown.

The size and duration of our study enabled us to use death as the end point. This was an advantage, since death is a more definitive and all-inclusive outcome measure than progression to an AIDS-defining event, an end point that has been used in previous studies. Non-AIDS-defining conditions may occur at different rates among patients who defer therapy, as compared with those who initiate therapy early. HIV infection and de-

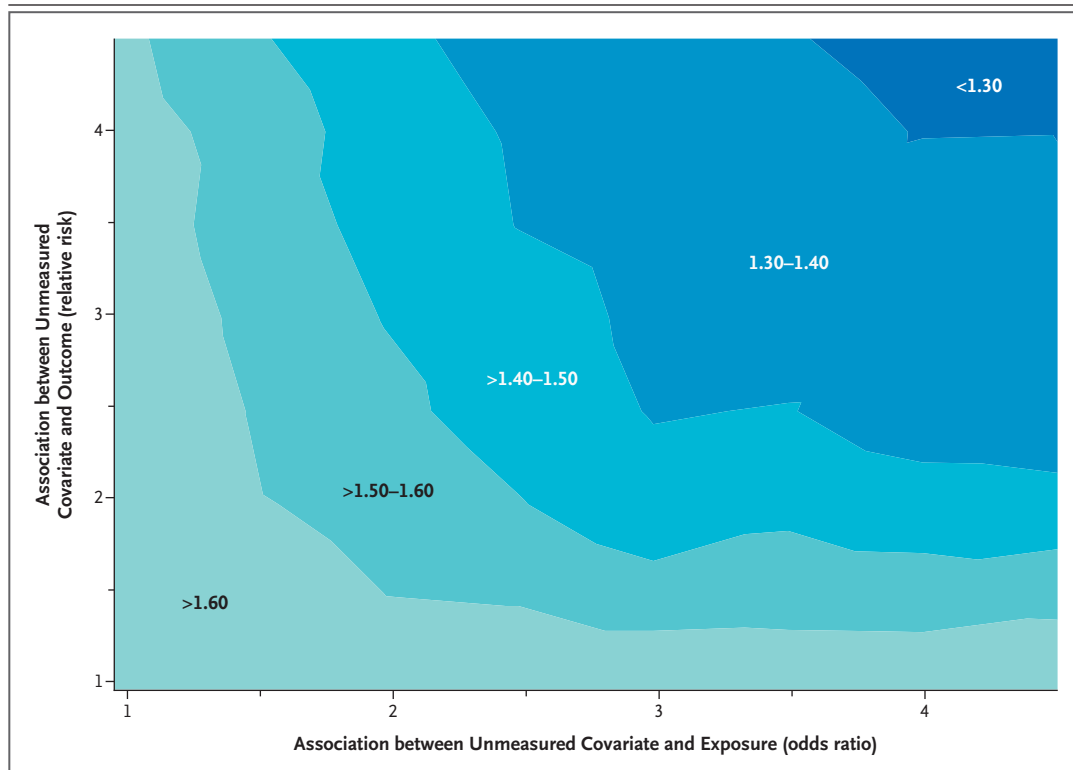


Figure 1. Results of Sensitivity Analyses Examining the Effect of Possible Unmeasured Confounding Factors on the Association between Deferral of Antiretroviral Therapy and Death.

The contour plot shows that a confounding factor with a relative risk for death of 4.0 and an odds ratio for deferral of therapy of 4.0 after adjustment for all included variables would reduce the estimated relative risk for deferred therapy to approximately 1.30.

creasing CD4+ counts are associated with a higher risk of cardiovascular, liver, and renal diseases and non-AIDS-defining cancers, and treatment with antiretroviral therapy appears to reduce the risk of these conditions.^{8,29-33,55,56} Among patients for whom cause-of-death data were available, the majority of deaths were from causes that were non-AIDS-defining conditions.

There remains uncertainty about when to start antiretroviral therapy for asymptomatic patients with HIV infection.^{3,4} Ideally, such data would come from randomized trials.²⁵ Since patients in our study did not undergo randomization, the decision to initiate or defer antiretroviral therapy could have been influenced by multiple factors. To address potential confounding, we adjusted the analyses for established risk factors for death in HIV disease (including age, the CD4+ count, the HIV RNA level, a history of injection-drug use, and the presence or absence of HCV infection), factors that may also affect the decision to defer

treatment. Patients in the early-therapy group and the deferred-therapy group received similar initial antiretroviral therapy regimens. In addition, our analyses were adjusted for potential cohort effects and improvement in survival because of advances in therapies over time.

Our approach had several limitations. As with any observational study, even after adjustment for known prognostic factors, residual confounding may occur because of unmeasured socioeconomic and other factors that may be associated with both deferral of therapy and death. Whereas only a large, randomized trial can balance such unmeasured factors, our sensitivity analyses suggest that the effect size of unmeasured confounding would have to be uncommonly large to mitigate our results. In addition, we made assumptions in our analyses regarding the target and follow-up windows on the basis of clinical practice. However, different assumptions might have had an effect on the magnitude of the relative risk estimates,

and such assumptions warrant future study. More careful assessment of the misclassification inherent in measures of injection-drug use and the presence of HCV infection will provide a better understanding of how such factors are associated with a risk of death.

Recommendations for the initiation of therapy for asymptomatic HIV-infected patients have undergone major shifts since the introduction of potent antiretroviral therapy more than a decade ago. In 1996, antiretroviral therapy was recommended for all HIV-infected patients with a CD4+ count of less than 500 cells per cubic millimeter,⁵⁷ but concern about resistance,⁵⁸ inadequate adherence,⁵² and toxic effects⁵⁹ led to a shift to delay initiation of treatment until later stages of HIV disease. Significant advances in our understanding of the role of HIV infection in inflammation and immune activation resulting in potentially irreversible immune-system and end-organ damage have renewed the impetus for earlier treatment of HIV.^{60,61}

Supported by grants from the National Institutes of Health and from the Agency for Healthcare Research and Quality.

Dr. Saag reports receiving consulting fees from Ardea Biosciences, Avexa, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Monogram Biosciences, Pain Therapeutics, Panacos, Pfizer, Progenics, Roche Laboratories, Tibotec, Tobira Therapeutics, and Viro and research support from Achillion Pharmaceuticals, Avexa, Boehringer Ingelheim, GlaxoSmithKline, Merck, Panacos, Pfizer, Progenics, Theratechnologies, and Tibotec; Dr. Hogg, receiving

grant support from Merck; Dr. Deeks, receiving consulting fees from GlaxoSmithKline, Roche, Gilead, and Boehringer Ingelheim and grant support from Merck, Gilead, Bristol-Myers Squibb, and Pfizer; Dr. Eron, receiving consulting fees from Tibotec, Bristol-Myers Squibb, Merck, GlaxoSmithKline, and Pfizer, lecture fees from Roche, Bristol-Myers Squibb, Tibotec, and Merck, and grant support from GlaxoSmithKline, Merck, and Boehringer Ingelheim; Dr. Gill, receiving consulting fees from Gilead, GlaxoSmithKline, Abbott, Merck, Boehringer Ingelheim, Tibotec, and Pfizer and grant support from GlaxoSmithKline, Abbott, Tibotec, and Pfizer; Dr. Klein, receiving consulting fees from GlaxoSmithKline, Abbott, Pfizer, and Boehringer Ingelheim, lecture fees from Abbott, Gilead, Tibotec, Bristol-Myers Squibb, and GlaxoSmithKline, and research support from the Canadian HIV Trials Network, the Ontario HIV Treatment Network, and Schering-Plough Canada; Dr. Rodriguez, receiving consulting fees from Gilead and Bristol-Myers Squibb, lecture fees from Bristol-Myers Squibb, and grant support from STERIS; Dr. Rachlis, receiving consulting and lecture fees from GlaxoSmithKline, Abbott, Merck, Pfizer, Bristol-Myers Squibb, Gilead, and Tibotec and grant support from GlaxoSmithKline, Tibotec, Boehringer Ingelheim, Abbott, Merck, Pfizer, and Roche; Dr. Horberg, receiving grant support from Gilead, Abbott, and Bristol-Myers Squibb; Dr. Silverberg, receiving grant support from Pfizer, Merck, Gilead, the University-wide AIDS Research Program, and Community Benefit/Kaiser Permanente; Dr. Gebo, receiving consulting fees from Tibotec and grant support from the Johns Hopkins University Richard Ross Award; Dr. Benson, receiving consulting fees from GlaxoSmithKline, Pfizer, Merck, and Achillion and grant support from Gilead; Dr. Collier, receiving consulting fees from Merck, Pfizer, and GlaxoSmithKline and grant support from Schering-Plough, Tibotec-Virco, Gilead, Koronis, and Merck and having an equity interest in Bristol-Myers Squibb and Abbott; and Dr. Moore, receiving consulting fees from Bristol-Myers Squibb and GlaxoSmithKline, lecture fees from Gilead, and grant support from Pfizer, Merck, and Gilead. No other potential conflict of interest relevant to this article was reported.

We thank all the patients, physicians, investigators, and staff who were involved in this study.

APPENDIX

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The investigators in the study were affiliated with the following research groups: G. Kirk (AIDS Link to the IntraVenous Experience); C. Benson, R. Bosch, A. Collier (Adult AIDS Clinical Trials Group Longitudinal Linked Randomized Trials); R. Hogg, R. Harrigan, J. Montaner (HAART Observational Medical Evaluation and Research); J. Brooks (HIV Outpatient Study); K. Gebo (HIV Research Network); R. Moore (Johns Hopkins HIV Clinical Cohort); B. Rodriguez (John T. Carey Special Immunology Unit Patient Care and Research Database, Case Western Reserve University); M. Horberg, M. Silverberg (Kaiser Permanente Northern California); J. Goedert (Multicenter Hemophilia Cohort Study II); L. Jacobson (Multicenter AIDS Cohort Study); M. Klein (Montreal Chest Institute Immunodeficiency Service Cohort); S. Rourke, A. Rachlis (Ontario HIV Treatment Network Cohort Study); L. Calzavara (Polaris HIV Seroconversion Study); M. Kushel (Research in Access to Care for the Homeless Cohort); J. Gill (Southern Alberta Clinic Cohort); S. Deeks, J. Martin (Studies of the Consequences of the Protease Inhibitor Era); M. Saag, M. Mugavero, J. Willig (University of Alabama at Birmingham 1917 Clinic Cohort); J. Eron, S. Napravnik (University of North Carolina, Chapel Hill, HIV Clinic Cohort); M. Kitahata (University of Washington HIV Cohort); A. Justice, D. Fiellin (Veterans Aging Cohort Study); T. Sterling, S. Stinette, P. Rebeiro, D. Haas (Vanderbilt-Meharry Centers for AIDS Research Cohort); S. Gange (Women's Interagency HIV Study).

The committee members for the study were as follows: **Executive Committee:** R. Moore, M. Saag, S. Gange, M. Kitahata, R. McKaig, A. Freeman. **Epidemiology/Biostatistics Core:** S. Gange, B. Merriman, A. Abraham, B. Lau, K. Althoff, J. Zhang. **Data Management Core:** M. Kitahata, S. Van Rompaey, H. Crane, W. Lober, E. Webster, B. Simon. **Administrative Core:** R. Moore, A. Freeman, C. Lent.

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