Timing of HAART Initiation and Clinical Outcomes in Human Immunodeficiency Virus Type 1 Seroconverters

*Writing Committee for the CASCADE Collaboration**

Background: To estimate the clinical benefit of highly active antiretroviral therapy (HAART) initiation vs deferral in a given month in patients with CD4 cell counts less than 800/μL.

Methods: In this observational cohort study of human immunodeficiency virus type 1 seroconverters from CASCADE (Concerted Action on SeroConversion to AIDS and Death in Europe), we constructed monthly sequential nested subcohorts between January 1996 and May 2009, including all eligible HAART-naive, AIDS-free individuals with a CD4 cell count less than 800/μL. The primary outcome was time to AIDS or death in those who initiated HAART in the baseline month compared with those who did not, pooled across subcohorts and stratified by CD4 cell count. Using inverse probability-of-treatment weighted survival curves and Cox proportional hazards regression models, we estimated the absolute and relative effects of treatment with robust 95% confidence intervals (CIs).

Results: Of 9455 patients with 52 268 person-years of follow-up, 812 (8.6%) developed AIDS and 544 (5.8%) died. In CD4 cell count strata of 200 to 349, 350 to 499, and 500 to 799/μL, HAART initiation was associated with adjusted hazard ratios (95% CIs) for AIDS/death of 0.59 (0.43-0.81), 0.75 (0.49-1.14), and 1.10 (0.67-1.79), respectively. In the analysis of all-cause mortality, HAART initiation was associated with adjusted hazard ratios (95% CIs) of 0.71 (0.44-1.15), 0.51 (0.33-0.80), and 1.02 (0.49-2.12), respectively. Numbers needed to treat (95% CIs) to prevent 1 AIDS event or death within 3 years were 21 (14-38) and 34 (20-115) in CD4 cell count strata of 200 to 349 and 350 to 499/μL, respectively.

Conclusion: Compared with deferring in a given month, HAART initiation at CD4 cell counts less than 500/μL (but not 500-799/μL) was associated with slower disease progression.

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THE INTRODUCTION OF HIGHLY active antiretroviral therapy (HAART) in 1996 reduced morbidity and mortality rates in human immunodeficiency virus type 1 (HIV-1)–infected individuals.[1] Randomized controlled trials[2,3] conducted in immunocompromised patients (eg, those with a CD4 cell count ≤200/μL) demonstrated that rates of AIDS or death were halved in patients starting HAART compared with rates in patients treated with drugs from only 1 class during approximately 1 year.

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A central unresolved issue in the care of HIV-1–infected patients is when HAART should be initiated. Randomized evidence is unlikely to be available before 2015.[4] Observational studies of 3 large multicenter seroprevalent cohorts[5-7] have suggested clinical benefit to initiating therapy at CD4 cell counts greater than 350/μL, but the magnitude and thresholds for benefit were quite different.

See Invited Commentary at end of article

The objective of the present study was to provide clinically relevant information about the relative and absolute benefits of HAART initiation at different CD4 cell counts to support treatment decisions for AIDS-free, HAART-naive individuals living with HIV. We applied a novel approach to a cohort of 9455 HIV-1 seroconverters to estimate the benefit of initiating vs deferring HAART on long-term disease progression and death.

METHODS

STUDY POPULATION

Patients included in this analysis were enrolled in 1 of 23 clinical cohorts in Europe, Australia, and Canada participating in the CASCADE (Concerted Action on SeroConversion to AIDS and Death in Europe) Collaboration, which pools

data on individuals with a well-estimated date of seroconversion (<2 years between the last negative and first positive HIV test results).[8] Individuals 13 years and older at seroconversion were included in this analysis.

All the clinical cohorts participating in the CASCADE Collaboration received approval from their individual ethics review boards except the Danish cohort, which received approval from the National Data Registry Surveillance Agency because Danish law allowed collection and pooling of anonymous clinical data with approval from this agency alone. Two ethics review boards deemed their cohort participants exempt from providing signed informed consent. Signed informed consent was obtained from all others. Approval was also given by all ethics review boards to pool anonymous data for analyses and dissemination. This analysis was reviewed by the institutional review board at the University of North Carolina and was determined to be exempt from further review.

STUDY DESIGN

We created a set of sequential nested subcohorts (a special case of a nested structural model[9,10]) rather than a marginal structural model, as used in a recent analysis.[5] We first considered all individuals who were eligible as of January 1, 1996, and imagined a cohort study in which the subsequent disease progression of those who initiated HAART during this month was compared with that of patients who did not initiate HAART during this month (**Figure 1**). In patients who remained HAART naive and otherwise eligible at the end of January 1996, we defined a new cohort for February 1996 to compare individuals who first initiated HAART in this month with those who did not initiate HAART during this month. We created a new subcohort with all eligible individuals for each month between January 1996 and May 2009, classified each treatment-naive individual in the subcohort according to whether they initiated HAART in the index month, pooled data across all 161 subcohorts, stratified data into separate analyses based on CD4 cell count at baseline, and, finally, estimated the absolute and relative measures of association with HAART initiation. We used a robust variance[11] to account for the fact that the same individual could contribute to more than 1 subcohort. To emulate the clinical scenario in which treatment decisions are made, we did not select a single alternative treatment strategy. Rather, we allowed the comparison group to encompass the range of treatment strategies present in this population. Thus, the survival times of patients who deferred HAART in the index month were used to represent the average population prognosis of individuals who were AIDS free and HAART naive with a CD4 cell count in the specified stratum but did not start HAART immediately, weighted by the number of trials each individual contributed in the CD4 stratum.

HAART was defined as any regimen containing 3 or more antiretroviral agents. Patients were eligible if they (1) were HAART naive as of the first of the month, (2) had not experienced the end point of interest (ie, AIDS or death) as of the end of the month, (3) had no more than 21 days (cumulative) of monotherapy or dual therapy, and (4) had a qualifying CD4 cell count (<800/μL ≥180 days after seroconversion and in the previous 365 days). Eligibility criteria were time varying. A patient who did not have a qualifying CD4 cell count available at the time of the first subcohort for which he or she was otherwise eligible could still be included in a subsequent subcohort as soon as a qualifying CD4 cell count was recorded.

ASCERTAINMENT OF AIDS AND DEATH

The primary outcome of interest was the combined end point of time to first AIDS diagnosis or death from any cause. Analyses were repeated using death from all causes as the sole outcome. For each subcohort, follow-up began on the first day of the next month. Patients who did not experience an outcome of interest during follow-up were censored when they were last known to be alive.

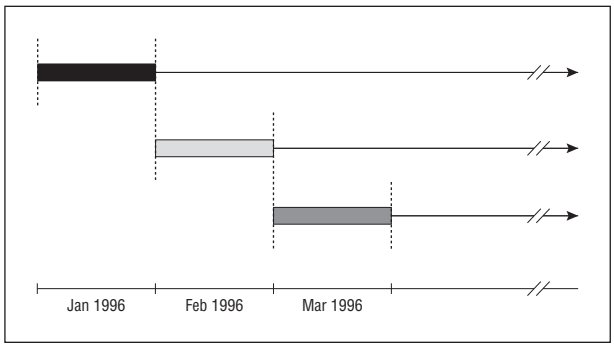

Figure 1. Construction of sequential nested subcohorts. Step 1: Identify all eligible patients, assess covariates, and determine exposure group during January 1996 to create the first subcohort. Step 2: Measure days from February 1, 1996, to the date of first AIDS diagnosis, death, or censoring for each patient. Step 3: Repeat steps 1 and 2 for each month between February 1996 and May 2009, resulting in 161 subcohorts.

ASSESSMENT OF COVARIATES

We considered the following potential confounders: female sex, injecting drug use (IDU) as likely mode of transmission, documented seroconversion illness, and hepatitis B and hepatitis C virus co-infection. Time-varying covariates included age, duration of infection, calendar year, CD4 measures (most recent, nadir, number of tests, and days since last test), and viral load measures (availability of ≥1 tests, most recent [$\log_{10}$ copies per milliliter], peak [$\log_{10}$ copies per milliliter], number of tests, and days since last test). All time-varying characteristics were measured before the first day of follow-up.

STATISTICAL ANALYSIS

Kaplan-Meier survival curves were used to visualize the crude (unadjusted) effect of initiating HAART compared with not initiating HAART in the index month, pooling across subcohorts. We estimated the hazard ratios (HRs) for initiating HAART compared with deferring HAART during the index month separately for 5 CD4 strata (0-49, 50-199, 200-349, 350-499, and 500-799/μL) using Cox proportional hazards regression models. All analyses followed an intent-to-treat approach and did not consider treatment changes (ie, interruptions, discontinuations, and later initiations).

To account for potential differences in the baseline prognosis of participants who initiated HAART compared with those who deferred HAART during the index month, we estimated inverse probability-of-treatment weights as a function of baseline covariate values. We used these weights to create adjusted Kaplan-Meier survival curves,[12] to estimate adjusted HRs using weighted Cox proportional hazards regression models, and to estimate the adjusted absolute effect of HAART initiation on the cumulative risk of AIDS and death.[13] Weights were truncated at the 0.05th and 99.95th percentiles to reduce their variability and improve the stability of the final effect estimates.[14] Confidence intervals (CIs) on risk differences were obtained by bootstrap with 1000 complete resamples with replacement from these data.[15,16] We assumed a normal approximation of the parameter distribution and used the empirical standard error.

Table 1. Participants Who Initiated HAART Compared With Those Who Deferred HAART at Baseline by CD4 Cell Count Strata[a]

Characteristic	Initiated HAART	Deferred HAART
0-49/μL (N_u = 183)		
Subcohort observations, No.	107	527
Follow-up, median (IQR), person-years	3.3 (1.4-7.1)	1.5 (0.4-6.7)
Female sex, No. (%)	24 (22.4)	75 (14.2)
Injecting drug use, No. (%)	20 (18.7)	350 (66.4)
Hepatitis C virus co-infection, No. (%)	21 (19.6)	270 (51.2)
Hepatitis B virus co-infection, No. (%)	30 (28.0)	207 (39.3)
Year of seroconversion, median (IQR)	1996 (1992-1999)	1992 (1988-1995)
Age at seroconversion, median (IQR), y	28 (25-36)	29 (25-33)
Duration of infection, median (IQR), y	5.3 (1.3-8.9)	7.2 (3.6-10.5)
CD4, median (IQR)		
Count, /μL	25 (15-38)	28 (15-37)
Nadir, /μL	25 (15-37)	28 (15-37)
Age, d[b]	19 (10-34)	76 (27-161)
Viral load		
None available, No. (%)	15 (14.0)	204 (38.7)
Most recent, median (IQR), log copies/mL*	5.1 (4.5-5.7)	3.6 (0.0-4.9)
Peak, median (IQR), log copies/mL*	5.4 (4.6-5.7)	4.5 (0.0-5.1)
Age, median (IQR), d*[c]	18 (4-35)	18 (0-105)
50-199/μL (N_u = 1521)		
Subcohort observations, No.	832	5259
Follow-up, median (IQR), person-years	3.4 (1.4-6.2)	3.7 (1.3-8.0)
Female sex, No. (%)	197 (23.7)	1165 (22.2)
Injecting drug use, No. (%)	117 (14.1)	1612 (30.7)
Hepatitis C co-infection, No. (%)	151 (18.1)	1680 (31.9)
Hepatitis B co-infection, No. (%)	188 (22.6)	1743 (33.1)
Year of seroconversion, median (IQR)	1999 (1994-2002)	1993 (1990-1998)
Age at seroconversion, median (IQR), y	31 (26-38)	29 (25-35)
Duration of infection, median (IQR), y	3.2 (1.4-6.4)	5.3 (2.9-9.1)
CD4, median (IQR)		
Count, /μL	149 (110-176)	157 (119-180)
Nadir, /μL	140 (104-170)	147 (108-173)
Age, d[b]	23 (13-39)	53 (19-117)
Viral load		
None available, No. (%)	45 (5.4)	1203 (22.9)
Most recent, median (IQR), log copies/mL*	5.0 (4.4-5.4)	4.4 (2.2-5.0)
Peak, median (IQR), log copies/mL*	5.1 (4.7-5.6)	4.7 (2.9-5.3)
Age, median (IQR), d*[c]	24 (13-43)	34 (2-100)
200-349/μL, (N_u = 4459)		
Subcohort observations, No.	1792	33 824
Follow-up, median (IQR), person-years	3.0 (1.3-6.1)	3.6 (1.6-6.9)
Female sex, No. (%)	371 (20.7)	6755 (20.0)
Injecting drug use, No. (%)	175 (9.8)	5546 (16.4)
Hepatitis C virus co-infection, No. (%)	226 (12.6)	6788 (20.1)
Hepatitis B virus co-infection, No. (%)	361 (20.1)	8652 (25.6)
Year of seroconversion, median (IQR)	2000 (1995-2003)	1997 (1992-2001)
Age at seroconversion, median (IQR), y	31 (25-38)	30 (25-36)
Duration of infection, median (IQR), y	2.8 (1.5-5.6)	4.0 (2.1-7.2)
CD4, median (IQR)		
Count, /μL	270 (238-309)	297 (260-324)
Nadir, /μL	251 (219-288)	270 (228-306)
Age, d[b]	24 (13-44)	57 (24-111)
Viral load		
None available, No. (%)	66 (3.7)	4971 (14.7)
Most recent, median (IQR), log copies/mL*	4.7 (4.1-5.1)	4.3 (3.4-4.8)
Peak, median (IQR), log copies/mL*	5.0 (4.5-5.4)	4.6 (3.9-5.1)
Age, median (IQR), d*[c]	26 (14-49)	47 (12-102)

(continued)

SENSITIVITY AND SUBGROUP ANALYSES

We assessed the sensitivity of the results to alternative ways of conducting the analysis. These alternatives included (1) shortening the period during which CD4 cell counts were considered eligible from 365 days to 45 days, which decreased the number of subcohorts in which an individual participated when his or her CD4 cell count had not been obtained immediately before or during the subcohort month; (2) beginning follow-up in January 1998 rather than in January 1996 to assess

Table 1. Participants Who Initiated HAART Compared With Those Who Deferred HAART at Baseline by CD4 Cell Count Strata[a] (continued)

Characteristic	Initiated HAART	Deferred HAART
350-499/μL (N_u = 5527)		
Subcohort observations, No.	1005	62 734
Follow-up, median (IQR), person-years	4.6 (1.8-8.0)	3.7 (1.6-7.3)
Female sex, No. (%)	222 (22.1)	12 457 (19.9)
Injecting drug use, No. (%)	119 (11.8)	8651 (13.8)
Hepatitis C virus co-infection, No. (%)	172 (17.1)	11 017 (17.6)
Hepatitis B virus co-infection, No. (%)	201 (20.0)	15 040 (24.0)
Year of seroconversion, median (IQR)	1998 (1994-2001)	1997 (1993-2002)
Age at seroconversion, median (IQR), y	30 (25-37)	30 (25-36)
Duration of infection, median (IQR), y	2.4 (1.2-4.7)	3.5 (1.9-6.4)
CD4, median (IQR)		
Count, /μL	408 (375-447)	425 (390-460)
Nadir, /μL	369 (320-413)	376 (326-423)
Age, d[b]	23 (13-42)	70 (32-128)
Viral load		
None available, No. (%)	63 (6.3)	8371 (13.3)
Most recent, median (IQR), log copies/mL*	4.6 (3.7-5.1)	4.1 (3.3-4.7)
Peak, median (IQR), log copies/mL*	4.9 (4.2-5.3)	4.5 (3.7-5.0)
Age, median (IQR), d*[c]	25 (14-47)	58 (17-117)
500-799 cells/μL (N_u = 5162)		
Subcohort observations, No.	615	78 483
Follow-up, median (IQR), person-years	5.8 (2.4-8.5)	4.1 (1.8-7.6)
Female sex, No. (%)	144 (23.4)	16 824 (21.4)
Injecting drug use, No. (%)	79 (12.8)	10 689 (13.6)
Hepatitis C virus co-infection, No. (%)	100 (16.3)	13 383 (17.1)
Hepatitis B virus co-infection, No. (%)	137 (22.3)	18 901 (24.1)
Year of seroconversion, median (IQR)	1997 (1994-2000)	1997 (1993-2001)
Age at seroconversion, median (IQR), y	29 (25-35)	29 (25-36)
Duration of infection, median (IQR), y	2.2 (1.2-4.8)	3.4 (1.8-6.2)
CD4, median (IQR)		
Count, /μL	588 (538-660)	611 (550-690)
Nadir, /μL	513 (411-594)	517 (429-597)
Age, d[b]	19 (11-32)	78 (38-141)
Viral load		
None available, No. (%)	38 (6.2)	12 201 (15.5)
Most recent, median (IQR), log copies/mL*	4.4 (2.8-5.0)	3.8 (2.7-4.4)
Peak, median (IQR), log copies/mL*	4.7 (3.8-5.1)	4.1 (3.2-4.7)
Age, median (IQR), d*[c]	21 (10-38)	63 (16-128)

Abbreviations: HAART, highly active antiretroviral therapy; IQR, interquartile range; N_u, number of unique individuals.

[a] Number of participants is not unique in a given CD4 stratum owing to an individual participant potentially contributing to multiple subcohorts. All the descriptive statistics were based on 185 178 subcohort observations except for rows marked by an asterisk (*), for which the denominator is only subcohort observations with a viral load measure available.

[b] CD4 age is defined as the number of days between the last CD4 cell count and the start of follow-up.

[c] Viral load age is defined as the number of days between the last viral load measure and the start of follow-up.

the effect of early suboptimal HAART regimens; and (3) requiring a baseline viral load for subcohort eligibility. We examined the impact of nonstandard treatment in the comparison group by censoring follow-up at the earliest of the 22nd day of cumulative monotherapy or dual therapy or 6 months after the patient's first CD4 cell count less than 200/μL if he or she remained HAART naive at this point. We also conducted a second version of this sensitivity analysis censoring individuals 6 months after their first CD4 cell count less than 350/μL if they remained HAART naive. Because the effect of HAART may differ in patients with a history of IDU, we conducted subgroup analyses of patients with (IDU+) or without (IDU–) a history of IDU.

RESULTS

Of 18 347 patients in the CASCADE Collaboration as of May 2009, nine thousand four hundred fifty-five were included in this analysis. Most patients excluded from this analysis were no longer alive, AIDS free, antiretroviral therapy naive, or in active follow-up at the beginning of the study (January 1, 1996) or 6 months after seroconversion. Many patients were no longer AIDS free and antiretroviral therapy naive at enrollment or at the time of their first eligible CD4 cell count. Thus, we analyzed data from 9455 HIV-1 seroconverters who were eligible for 1 or more subcohorts after January 1, 1996, with 52 268 person-years of follow-up (median = 4.7 years, interquartile range [IQR] = 2.0-9.1 years). Most participants were male (n = 7367 [77.9%]) and were infected through sex between men (n = 5341 [56.5%]) or sex between men and women (n = 2363 [25.0%]). The median age at seroconversion was 30.3 years (IQR = 25.4-36.8 years), and the median duration of infection was 1.3 years (IQR = 0.8-3.4 years) at the time of entry into the first subcohort. During follow-up, 812 patients (8.6%) developed

Table 2. Crude Incidence Rates (IRs), Crude Hazard Ratios (cHRs), and Adjusted HRs (aHRs) With 95% CIs for the Effect of Initiating (I) Compared With Deferring (D) HAART at Baseline on Time to First AIDS Event or Death and Death Alone Stratified by CD4 Cell Count[a]

		AIDS or Death					Death				
			IR/1000 PY					IR/1000 PY			
CD4 Cell Count, /μL	PY FU_u	$Events_u$	D	I	cHR (95% CI)	aHR (95% CI)[b]	$Events_u$	D	I	cHR (95% CI)	aHR (95% CI)[b]
0-49 (N_u = 183)	664	102	193.3	55.0	0.30 (0.19-0.48)	0.32 (0.17-0.59)	44	88.8	21.2	0.23 (0.12-0.46)	0.37 (0.14-0.95)
50-199 (N_u = 1521)	6934	353	56.6	22.0	0.36 (0.28-0.47)	0.48 (0.31-0.74)	144	27.8	9.7	0.34 (0.24-0.50)	0.55 (0.28-1.07)
200-349 (N_u = 4459)	22 106	732	29.4	18.7	0.62 (0.51-0.75)	0.59 (0.43-0.81)	261	14.1	8.9	0.64 (0.50-0.83)	0.71 (0.44-1.15)
350-499 (N_u = 5527)	29 653	815	20.8	17.2	0.82 (0.66-1.03)	0.75 (0.49-1.14)	277	9.1	7.5	0.81 (0.57-1.14)	0.51 (0.33-0.80)
500-799 (N_u = 5162)	28 631	696	18.5	14.9	0.79 (0.59-1.05)	1.10 (0.67-1.79)	237	8.5	6.8	0.78 (0.51-1.20)	1.02 (0.49-2.12)

Abbreviations: CI, confidence interval; $Events_u$, number of unique events in the CD4 stratum; HAART, highly active antiretroviral therapy; N_u, number of unique individuals in the CD4 stratum; PY FU_u, unique person-years of follow-up in the CD4 stratum.

[a] The reference group for all estimates is composed of subcohort observations during which HAART was not initiated during the index month.

[b] Adjusted via weighting for injecting drug use, human immunodeficiency virus test interval shorter than 30 days (indicator of seroconversion illness), female sex, time since seroconversion, age, calendar year, hepatitis C virus co-infection, hepatitis B virus co-infection, CD4 cell count, days between last CD4 cell count and the start of follow-up, CD4 nadir, number of previous CD4 measures, most recent viral load (log_{10}), days between last viral load and the start of follow-up, peak viral load (log_{10}), and number of previous viral load measures.

AIDS and 544 patients (5.8%) died. On average, each individual contributed to 12 (IQR=4-26) subcohorts (eTable 1; http://www.archinternmed.com).

At baseline, participants who initiated HAART had a poorer prognosis in some respects (higher viral loads, shorter duration of infection, and slightly lower CD4 cell counts) compared with those who deferred HAART in a given month (**Table 1**). In other respects, they had a better prognosis (less likely to have a history of IDU and less likely to be co-infected with hepatitis). Across all CD4 strata, CD4 cell counts were more recent in those initiating therapy, and these patients were more likely to have available viral load measures. Most deferring patients eventually went on to HAART, generally in the same CD4 stratum or the next lower stratum (eTable 2). The only exception was the 500 to 799/μL stratum in which nearly half of patients remained HAART naive at last follow-up. Of these HAART-naive patients, most had CD4 cell counts greater than 350/μL at the last follow-up. The use of all–nucleoside reverse transcriptase inhibitor regimens containing abacavir in the first HAART regimen was similar between those who initiated and those who deferred (eTable 3).

Unadjusted incidence rates and adjusted HRs (aHRs) stratified by CD4 cell count are presented in **Table 2**. Considering first the combined end point of AIDS or death, the effect of initiating rather than deferring HAART in a given month was protective at CD4 cell counts lower than 350/μL. At CD4 cell counts of 350 to 499/μL, there was a 25% reduction in the hazard of AIDS or death (aHR, 0.75; 95% CI, 0.49-1.14). At CD4 cell counts of 500 to 799/μL, AIDS-free survival was not different in the 2 groups after adjusting for covariates (aHR, 1.10; 95% CI, 0.67-1.79). In the analysis of all-cause mortality, HAART initiation seemed to have a stronger effect on death than on the combined end point at CD4 cell counts of 350 to 499/μL (aHR, 0.51; 95% CI, 0.33-0.80). We observed no benefit at CD4 cell counts of 500 to 799/μL (aHR, 1.02; 95% CI, 0.49-2.12).

Weighted survival curves, stratified by CD4 cell count, are presented in **Figure 2**, with estimates of the absolute risk of AIDS or death or at 3 years for those initiating and deferring therapy in **Table 3**. At CD4 cell counts of 200 to 349/μL, the absolute difference in the proportion of patients who died or progressed to AIDS increased from –1.3% at 1 year to –6.4% at 5 years. The estimated number needed to treat (NNT) to prevent 1 event decreased from 79 to 16 at 5 years. Risk reduction was one-third as large for patients with CD4 cell counts of 350 to 499/μL with NNTs of 229 and 45 at 1 and 5 years, respectively. We found no reduction in the absolute risk of AIDS or death at CD4 cell counts of 500 to 799/μL.

When death from all causes was evaluated as the sole outcome, the absolute difference in the proportion of patients who died increased from essentially no difference at 1 year to –2.1% at 5 years for those with CD4 cell counts of 200 to 349/μL. The NNT decreased from approximately 8000 to 49 during this period. Similarly, the cumulative risk of death for patients with CD4 cell counts of 350 to 499/μL differed by –0.3% at 1 year and by –2.8% at 5 years, with corresponding NNTs of 328 and 35, respectively. In patients with CD4 cell counts of 500 to 799/μL, there was no reduction in the risk of death at 1 and 5 years, although there was a small difference at 3 years that favored HAART initiation.

Results of sensitivity analyses suggest that these findings are robust to alternative ways of defining the eligible population and censoring outcomes of those who received nonstandard treatment (**Figure 3**). We also found that excluding individuals with previous IDU did not have a meaningful effect on the magnitude of the association between HAART initiation and time to AIDS or death (eTable 4).

COMMENT

This analysis of 9455 HIV-1 seroconverters confirms the clinical benefit of initiating HAART with CD4 cell counts

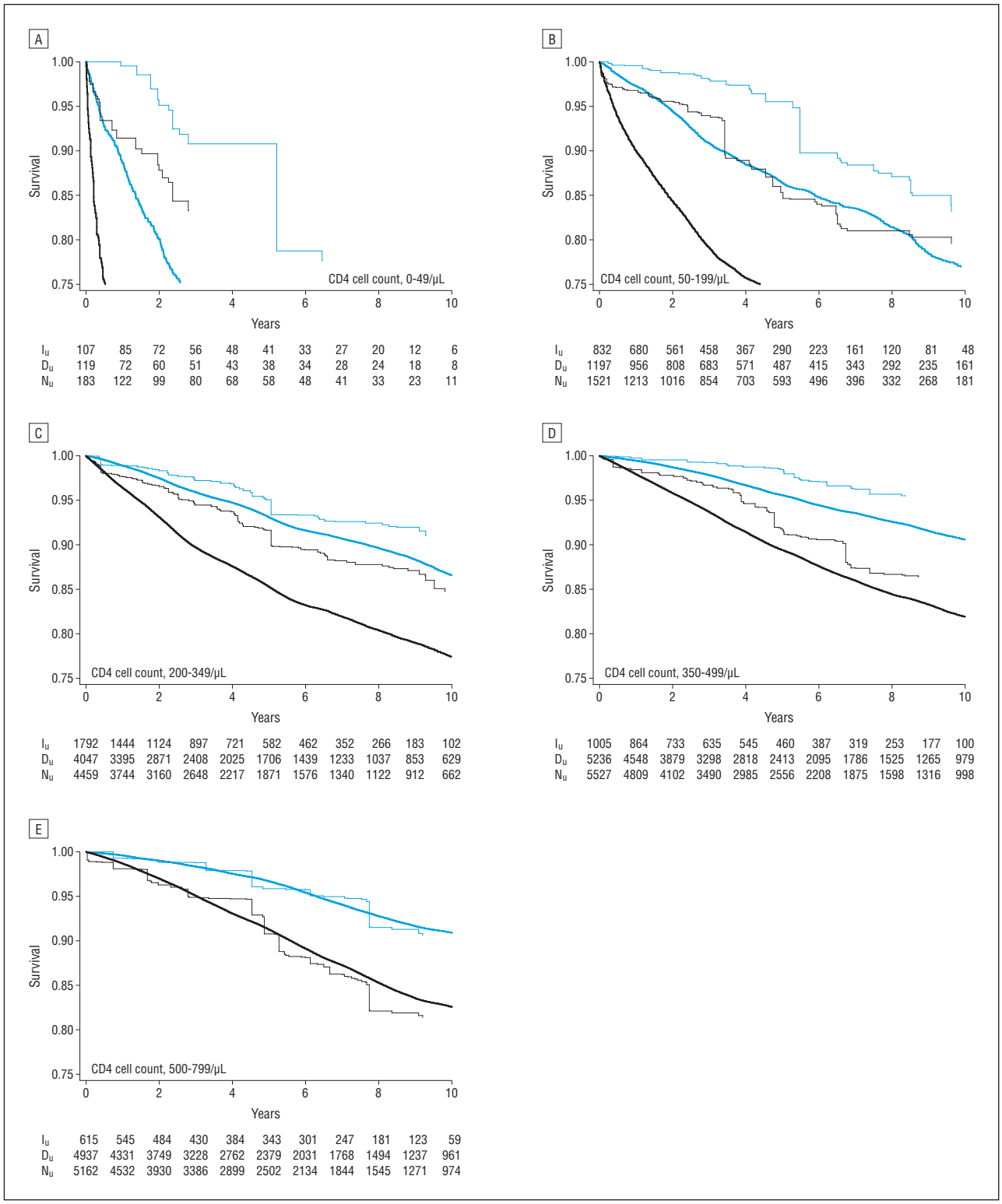

Figure 2. Weighted semiparametric survival curves for time to combined end point of first AIDS diagnosis or death from all causes (black lines) or death alone (blue lines) comparing patients who initiated (thin lines) or deferred (thick lines) highly active antiretroviral therapy (HAART) stratified by CD4 cell count: 0 to 49/µL (A), 50 to 199/µL (B), 200 to 349/µL (C), 350 to 499/µL (D), and 500 to 799/µL (E). D_u indicates number of unique individuals in the HAART deferral group who remained in the risk set at time *t*; I_u, number of unique individuals in the HAART initiation group who remained in the risk set at time *t*; N_u, number of unique individuals in the CD4 stratum overall who remained in the risk set at time *t*.

of 200 to 349/µL. We estimated a 25% reduction in the relative hazard of AIDS or death and a 49% reduction in the relative hazard of death from all causes at CD4 cell counts of 350 to 499/µL. The relatively low incidence of AIDS and death in individuals with CD4 cell counts of 350 to 499/µL indicates that patients and health care providers need to weigh the risks and benefits for each individual over an extended period of treatment.

Table 3. Adjusted Estimates of the Cumulative Percentage of Patients Who Would Experience AIDS or Death or Death Alone Within 3 Years of Follow-up After Deferring (D) or Initiating (I) HAART at Baseline, Estimated Risk Differences (RDs), and Number Needed to Treat (NNT) With Bootstrapped 95% CIs[a]

CD4 Cell Count, /μL	AIDS or Death				Death Alone			
	D	I	RD (95% CI), %	NNT (95% CI)	D	I	RD (95% C), %	NNT (95% CI)
0-49	46.6	16.6	−30.0 (−45.1 to −15.0)	3 (2 to 7)	26.8	8.6	−18.2 (−32.0 to −4.4)	6 (3 to 23)
50-199	20.7	5.7	−15.0 (−19.7 to −10.3)	7 (5 to 10)	9.1	1.9	−7.2 (−10.1 to −4.4)	14 (10 to 23)
200-349	10.3	5.5	−4.8 (−7.0 to −2.6)	21 (14 to 38)	4.1	2.7	−1.4 (−3.0 to 0.3)	74 (33 to ∞)
350-499	6.3	3.4	−2.9 (−5.0 to −0.9)	34 (20 to 115)	2.1	0.7	−1.4 (−2.2 to −0.6)	71 (45 to 165)
500-799	4.9	5.2	0.3 (−3.7 to 4.2)	∞	1.7	1.2	−0.4 (−2.0 to 1.2)	239 (49 to ∞)

Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy.

[a]All the estimates were adjusted via weighting for injecting drug use, human immunodeficiency virus test interval less than 30 days (an indicator of seroconversion illness), female sex, time since seroconversion, age, calendar year, hepatitis C virus co-infection, hepatitis B virus co-infection, CD4 cell count, days between last CD4 cell count and the start of follow-up, CD4 nadir, number of previous CD4 measures, most recent viral load (log_{10}), days between last viral load and the start of follow-up, peak viral load (log_{10}), and number of previous viral load measures.

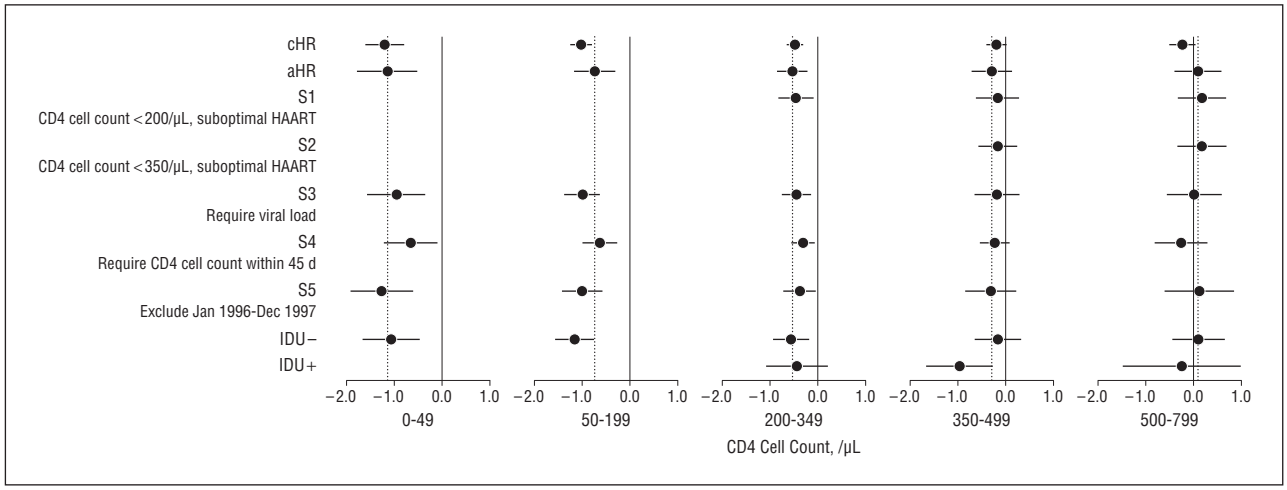

Figure 3. Assessing model sensitivity and results of subgroup analyses. Log hazard ratios (HRs) and 95% confidence intervals for crude (cHR) and adjusted (aHR) estimates for the combined end point of first AIDS diagnosis or death from all causes. Sensitivity analyses include censoring outcomes of patients who initiated monotherapy and dual therapy or who did not start highly active antiretroviral therapy (HAART) within 6 months after first CD4 cell count less than 200/μL (S1), censoring at monotherapy and dual therapy or for failure to initiate HAART within 6 months of first CD4 cell count less than 350/μL (S2), requiring baseline viral load measure (S3), requiring CD4 cell count within the last 45 days of baseline (S4), and beginning follow-up in January 1998 (S5). Subgroup analyses are presented for those without and with a known injecting drug use (IDU) history.

Although many studies have compared disease progression in patients starting HAART at different stages of disease with follow-up beginning at the time of treatment initiation, it is now appreciated that this study design is not ideally suited to inform the "when to start" question due to unobserved lead time and clinical events that occur during the time when patients are deferring therapy.[17,18] Kitahata et al,[5] Sterne et al,[6] and Cain et al[7] report findings from observational analyses tailored to estimate the effect of early HAART initiation on clinical outcomes using data primarily from seroprevalent cohorts. Although the comparison groups differ and, thus, the effect estimates from these studies estimate different parameters, one can compare the conclusions of the studies in broad terms. The present findings agree with those of Kitahata, Sterne, and Cain and their colleagues, who found that deferring HAART to a CD4 cell count less than 350/μL is detrimental. Kitahata et al,[5] but not Sterne et al,[6] further conclude that deferring HAART to a CD4 cell count less than 500/μL is detrimental. (Cain et al[7] began observing patients at first CD4 cell count less than 500/μL and, thus, do not report effect estimates for treatment at CD4 cell counts greater than 500/μL.) Unlike Kitahata et al, we did not observe a benefit at the population level for initiation at 500 to 799/μL after adjusting for confounding.

The absolute risk of AIDS-related morbidity and mortality in the population can drive the degree to which HAART initiation is beneficial at a particular stage of disease. In the present study, the weighted survival curves, absolute risks of disease progression, and NNT provide additional insight regarding the benefit that patients in resource-rich settings can expect from HAART at different CD4 strata. At CD4 cell counts of 350 to 499/μL, the benefits of treatment initiation become evident only beyond 2 years, suggesting that patients need to consider the long-term course of treatment, including the risk of adverse effects of HAART during an extended period.[19]

The decision to initiate therapy is a dynamic process, influenced by changes in the patient's condition and readiness to adhere to the lifelong regimens that are available to treat HIV. We reflected this dynamic process in the analy-

sis by considering each month while a patient was AIDS free and HAART naive as a point in time when therapy could have been initiated rather than representing patients at a single point in time, such as the first measured CD4 cell count in a particular range. We then observed these individuals during an average of 4.7 years as they experienced the clinical consequences of initiating HAART (or not) at that point in time. By allowing individuals to contribute to multiple subcohorts as long as they remained eligible, we effectively estimated a weighted average of the benefit of initiating therapy at any time while an individual had a CD4 cell count in a given CD4 stratum compared with the prognosis that they would have experienced if they had not initiated HAART at that time. The resulting relative and absolute effect estimates can be used to help inform patient decisions about whether the benefit of therapy at this particular stage of disease is sufficient to outweigh the challenge of adhering to treatment, the risk of adverse effects, and the financial cost of medications over a longer period of treatment.

We acknowledge that if the ultimate treatment patterns of the deferrers had been different, the results of the study would have been different. In eTable 2, we describe the type and timing (relative to CD4 cell count) of antiretroviral drug therapy received by patients who composed the deferred group for each CD4 strata. To evaluate the potential effect of individuals who were not treated consistent with the current standard of care, we censored the outcomes of those who waited too long or used suboptimal regimens, but the magnitude of the effect estimates was unaffected (S1 and S2 in Figure 3). We also considered the possibility that the null effect in the 500 to 799/μL stratum was due to individuals who deferred HAART only briefly, but these patients composed only approximately 5% of the deferred group. Although the comparison groups did not follow standardized treatment algorithms, they do represent the real-world experience of thousands of HIV-infected patients in care during the study period. We believe that these findings complement those from other recent studies[5-7] that explicitly compared 2 specific, narrowly defined treatment alternatives.

Patient well-being is adversely affected by many serious non-AIDS–defining conditions. For example, immunodeficiency and uncontrolled viremia have been implicated in the development of cardiovascular disease[20,21] and non-AIDS–defining malignancies.[22,23] Although CASCADE does not pool data on non-AIDS morbidity, this analysis reflects the most serious outcome (death) due to non-AIDS conditions.

We considered several alternative approaches to conducting this analysis in an effort to assess the robustness of these findings. We examined the effect of more restrictive inclusion criteria. To address confounding, we adjusted for a set of 20 covariates that we had a priori reason to suspect were associated with different rates of disease progression. We examined a wide range of possibilities for truncating the weights before deciding on a method that controlled for confounding without introducing instability in the estimates (eTable 5). Despite this, we cannot rule out the possibility that patients who initiated therapy had an inherently better or worse prognosis than did those who deferred therapy related to unmeasured factors. We were reassured that in the 50 to 199/μL CD4 strata, where we can compare with results from a randomized trial conducted in a resource-rich setting, the present estimate is similar to that from the trial.[3]

In the absence of results from well-conducted, long-term, randomized trials in patients with CD4 cell counts greater than 350/μL, treatment decisions will need to be made based on the available evidence from observational cohorts. We used a novel approach applied to a unique cohort of seroconverters to reduce the potential for lead time bias. We found that treatment initiation at CD4 cell counts of 350 to 499/μL was associated with slower disease progression. We did not observe any benefit to treatment initiated at 500 to 799/μL.

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Online-Only Material: The eTables are available at http://www.archinternmed.com.

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INVITED COMMENTARY

HAART for HIV-1 Infection

Zeroing In on When to Start

Great strides have been made in the treatment of HIV-1 infection since HAART was introduced almost 25 years ago. The result has been a dramatic reduction in cases of AIDS and AIDS-related mortality in industrialized countries; a similar impact is being made in resource-limited settings with the rollout of HAART during the last decade. Whereas the benefits of HAART are uncontested, the question of when to start HAART remains controversial. There is consensus that HAART should be offered to HIV-infected patients with CD4 cell counts lower than 350/μL, and for those with symptomatic HIV infection or AIDS-defining conditions regardless of CD4 cell count[1-4]; whether to offer HAART to asymptomatic patients with higher CD4 cell counts is unresolved.

Current guidelines of the US Department of Health and Human Services for antiretroviral therapy (ART) expand the indications for ART to patients with CD4 cell counts below 500/μL, and suggest considering ART for all patients from the time of HIV diagnosis.[3] Support for these recommendations comes from several sources, including the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), which showed a survival advantage for those who initiated ART at CD4 cell counts above 500/μL compared with those who deferred therapy to lower CD4 cell counts.[5] The occurrence of non-AIDS complications as a consequence of immune activation in HIV-1 infection provides an additional rationale for an earlier start to ART.[6] However, another large cohort study (Antiretroviral Therapy Cohort Collaboration [ART-CC]) did not find a statistically significant benefit for starting ART at CD4 cell counts above 500/μL.[7]

In this issue of the *Archives*, the Writing Committee of Jonsson Funk et al[8] addresses the "when to start" question by analyzing outcomes among patients enrolled in the Concerted Action on Seroconversion to AIDS and Death in Europe (CASCADE) Collaboration. Using data from CASCADE, the authors constructed a series of sequential nested cohorts of patients who did or did not start HAART between January 1996 and May 2009. A unique and innovative aspect of the study design is that the authors considered each month during which a patient remained off HAART as an opportunity to initiate treatment, thereby constructing a weighted average of the benefit of starting HAART at any time within a given CD4 cell count stratum. The hazard ratio for starting or deferring HAART was estimated by Cox proportional hazards regression models. Because survival bias could be introduced by patients who defer HAART in a given month and "survive" to enter the next sequential cohort in the subsequent month, the authors applied inverse probability-of-treatment weighting.

Jonsson Funk et al found a 41% reduction in the risk of AIDS or death for patients with baseline CD4 cell counts