Time From Human Immunodeficiency Virus Seroconversion to Reaching CD4+ Cell Count Thresholds <200, <350, and <500 Cells/mm^3: Assessment of Need Following Changes in Treatment Guidelines

Sara Lodi,[1] Andrew Phillips,[2] Giota Touloumi,[3] Ronald Geskus,[4] Laurence Meyer,[5] Rodolphe Thiébaut,[6] Nikos Pantazis,[3] Julia del Amo,[7] Anne M. Johnson,[2] Abdel Babiker,[1] and Kholoud Porter[1] on behalf of the CASCADE Collaboration in EuroCoord[a]

[1]MRC Clinical Trials Unit, [2]University College London, United Kingdom; [3]Athens University Medical School, Greece; [4]Amsterdam Health Service and Academic Medical Centre, the Netherlands; [5]Paris Sud 11/INSERM U1018, le Kremlin Bicêtre, Paris, [6]INSERM U897, Bordeaux, France; and [7]Instituto de Salud Carlos III, Madrid, Spain

Background. Recent updates of human immunodeficiency virus (HIV) treatment guidelines have raised the CD4+ cell count thresholds for antiretroviral therapy initiation from 350 to 500 cells/mm^3 in the United States and from 200 to 350 cells/mm^3 in mid- and low-income countries. Robust data of time from HIV seroconversion to CD4+ cell counts of 200, 350, and 500 cells/mm^3 are lacking but are needed to inform health care planners of the likely impact and cost effectiveness of these and possible future changes in CD4+ cell count initiation threshold.

Methods. Using Concerted Action on Seroconversion to AIDS and Death in Europe data from individuals with well-estimated dates of HIV seroconversion, we fitted mixed models on the square root of CD4+ cell counts measured before combined antiretroviral therapy (cART) initiation. Restricting analyses to adults (age >16 years), we predicted time between seroconversion and CD4+ cell count <200, <350, and <500 cells/mm^3 as well as CD4+ cell count distribution and proportions reaching these thresholds at 1, 2, and 5 years after seroconversion.

Results. Median (interquartile range [IQR]) follow-up for the 18 495 eligible individuals from seroconversion while cART-free was 3.7 years (1.5, 7). Most of the subjects were male (78%), had a median age at seroconversion of 30 years (IQR, 25–37 years), and were infected through sex between men (55%). Estimated median times (95% confidence interval [CI]) from seroconversion to CD4+ cell count <500, <350, and <200 cells/mm^3 were 1.19 (95% CI, 1.12–1.26), 4.19 (95% CI, 4.09–4.28), and 7.93 (95% CI, 7.76–8.09) years, respectively. Almost half of infected individuals would require treatment within 1 year of seroconversion for guidelines recommending its initiation at 500 cells/mm^3, compared with 26% and 9% for guidelines recommending initiation at 350 and 200 cells/mm^3, respectively.

Conclusions. These data suggest substantial increases in the number of individuals who require treatment and call for early HIV testing.

Currently, approximately 5 million people worldwide are receiving antiretroviral therapy (ART), with another 9 million human immunodeficiency virus (HIV)–positive people awaiting treatment [1]. These numbers will increase as a consequence of the recent updates of the International AIDS Society–United States (IAS-US) [2], Department of Health and Human Services (DHHS) [3], and World Health Organization (WHO) [4] guidelines, which have raised the thresholds for ART initiation from 350 to 500 cells/mm^3 in the United States and from 200 to

Received 8 March 2011; accepted 28 June 2011.

[a]Concerted Action on Seroconversion to AIDS and Death in Europe Collaboration in EuroCoord members are listed in the Supplementary Appendix online.

Correspondence: Sara Lodi, MSc PhD, MRC Clinical Trials Unit, Aviation House, 125 Kingsway, London, WC2B 6NH, United Kingdom (sal@ctu.mrc.ac.uk).

Clinical Infectious Diseases 2011;53(8):817–825

1058-4838/2011/538-0011$14.00
DOI: 10.1093/cid/cir494

350 cells/mm^3 in mid- and low-income countries. The threshold for treatment initiation remains at 350 cells/mm^3 in Europe [5].

The recent changes in guidelines have been mainly motivated by observational studies reporting on the benefits of starting treatment at CD4+ cell counts >350 cells/mm^3 [6–8]. While HIV Prevention Trials Network 052 has recently reported on the benefit of early initiation of therapy on the risk of onward transmission [9], the ongoing randomized Strategic Timing of Antiretroviral Treatment trial [10] is currently addressing the benefits of initiation when the CD4+ cell count falls below 500 cells/mm^3 on mortality, AIDS, and non–AIDS-related morbidity.

Given the current global financial crisis and resultant cuts in government health budgets, planning and prioritizing of resources are ever more crucial to rationalize spending while ensuring that HIV treatment is available to those who need it. Data on the time between HIV seroconversion and CD4+ cell count <200, <350, and <500 cells/mm^3 are lacking but are needed to inform health care planners on potential increases in the number of individuals who need therapy. Costs for treating individuals as CD4+ cell count thresholds for initiating increase need to be assessed against the costs of ensuring that treatment continues to be available to all those who initiate it.

Therefore, we have used a large dataset of individuals with well-estimated dates of HIV seroconversion to estimate (1) the time from seroconversion to CD4+ cell count <200, <350, and <500 cells/mm^3 and (2) the proportion of individuals reaching CD4+ cell counts <200, <350, and <500 cells/mm^3 at 1, 2, and 5 years after seroconversion before combined ART (cART) initiation. This will aid estimation of the number of individuals in need of treatment according to these CD4+ cell count thresholds. We report these statistics overall and according to a number of patient characteristics.

METHODS

Study Population

Concerted Action on Seroconversion to AIDS and Death in Europe (CASCADE) is currently a collaboration of 25 cohorts of persons with well-estimated dates of HIV seroconversion from Europe, Australia, Canada, and sub-Saharan Africa. We used the data set pooled in September 2009 within the EuroCoord Network of Excellence (www.EuroCoord.net), comprising 21240 individuals with seroconversion to HIV infection. The date of seroconversion, used to approximate the date of infection, is estimated by various methods: most frequently (in 89% of cases in this update) as the midpoint between dates of the last negative and first positive HIV antibody test results with a maximum of 3 years between test dates, laboratory evidence of seroconversion (real-time polymerase chain reaction positivity in the absence of HIV antibodies or antigen positivity with <4 bands on a Western blot) (8%), or the date of a seroconversion illness (and an earlier documented negative HIV test result) (2%), or the most likely date of infected factor VIII concentrate infusion for hemophiliacs (1%).

We restricted our analysis to individuals with at least 1 CD4+ cell count before death or cART initiation, defined as a combination of either ≥3 drugs from ≥2 classes or ≥3 nucleoside reverse-transcriptase inhibitors, at least 1 of which was tenofovir or abacavir. We excluded CD4+ cell counts after 10 years after estimated seroconversion date because only a few individuals had CD4+ cell counts measured after this time while ART naive, and these individuals were likely to be a selection of slow progressors. Also, because of their variability in primary infection [11], we excluded CD4+ cell counts obtained within the first 4 weeks after estimated seroconversion. As a sensitivity analysis, we repeated the analyses excluding the CD4+ cell counts recorded in the first 6 months after seroconversion. Individuals from the 2 sub-Saharan African cohorts were excluded because they showed different patterns of CD4+ cell decrease and time to cART initiation [12]. Finally, because patterns of change in CD4+ cell counts may be different for children, and because few children (n = 122) are included in CASCADE, analyses were restricted to individuals ≥16 years of age.

Ethical Approval

All cohorts that contributed data to CASCADE received approval from their individual ethics review boards except for the Danish cohort, which received approval from the National Data Registry Surveillance Agency, because Danish law allowed collection and pooling of anonymized 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 anonymized data for analyses and dissemination.

Statistical Analyses

Linear mixed models on the square root of CD4+ cell count were used to model longitudinal CD4+ cell data. This transformation was chosen among others commonly used because it appeared to better normalize the marker distribution. Time origin was defined as the estimated date of HIV seroconversion. The correlation between individual values at seroconversion and subsequent individual slopes was handled through an unstructured covariance matrix of random effects. Departures from the assumption of linearity were assessed using fractional polynomials [13].

CD4+ cell count distribution at 1, 2, and 5 years after seroconversion was estimated using simulations based on the model's parameters. At each time, we report the proportion of individuals with CD4+ cell counts below 200, <350, and <500 cells/mm^3. Parametric bootstrap with 500 repetitions was used to compute 95% confidence intervals (CIs) for these proportions [14].

On the basis of the fixed effects of the model, we also report the times to CD4+ cell counts of 200, <350, and <500 cells/mm^3, defined as the estimated times for a typical individual (ie, with median CD4+ cell count at seroconversion and median slope in the population) to reach the 3 thresholds, if the individuals were to be continually measured after seroconversion.

Analyses were repeated after adjusting for the following characteristics known to influence progression and therefore of interest to health care planners and modelers: age at seroconversion (<25, 25–29, 30–34, ≥35 years of age, based on quartiles of age distribution in eligible individuals), sex, risk group, whether seroconversion occurred before or after the widespread availability of cART (before 1996 or during 1996 or after), and, where available, HIV subtype. In particular, we present estimates for 3 groups of interest: MSM (men who had sex with men), MSW (men who had sex with women) aged 30–35 years at seroconversion, and WSM (women who had sex with men) aged 25–30 years at seroconversion. The choice of age categories was made on the basis of the median age in each respective risk and sex category.

To investigate the presence of informative drop-out as a result of death and to reduce potential bias, a sensitivity analysis was performed that applied a joint model for CD4+ cell count trajectories and survival time [15]. Because decisions regarding therapy are mainly based on already observed CD4+ cell count values, the censoring mechanism due to cART initiation is likely to be ignorable in maximum likelihood analyses, such as mixed models [15].

RESULTS

Individual Characteristics

Of the 20 530 individuals who experienced seroconversion, 18 495 were included in the current analysis, with 175 746 CD4+ cell counts before cART initiation (Table 1). Overall, the majority of subjects were male (78%), infected through sex between men (55%), and had a median age at seroconversion of 30 years (interquartile range [IQR], 25–37 years). Approximately half (9513) experienced seroconversion before cART became widely available in 1996. The median length of follow-up after seroconversion while cART naive was 3.74 years (IQR, 1.48–7.00 years). A total of 449 patients (2%) died during follow-up before starting cART. Of these, the majority (98%) experienced seroconversion before 1996. Subtype information was available for 3229 individuals (17%), and the subtype was subtype B for 90%.

Proportion of Individuals With CD4+ Cell Count <200, <350, and <500 cells/mm^3

We estimated that, at 1, 2, and 5 years after seroconversion, the median CD4+ cell count was 510 cells/mm^3 (IQR, 341–721 cells/mm^3), 460 cells/mm^3 (IQR, 294–656 cells/mm^3), and 315 cells/mm^3 (IQR, 156–528 cells/mm^3), respectively.

Table 1. Characteristics of the 18 495 Individuals with Human Immunodeficiency Virus (HIV) Seroconversion Included in Analyses

Variable	Subjects with HIV seroconversion (n = 18 495)
Female	3991 (22)
Risk group	
Sex between men	10 096 (55)
Sex between women and men	4379 (24)
Injection drug use	3087 (17)
Hemophilia	212 (1)
Other/unknown	721 (3)
Calendar year of seroconversion	
<1996	9513 (52)
1996–2000	3724 (20)
2001–2008	5258 (28)
Age at seroconversion, median years (IQR)	30 (25–37)
First CD4+ cell count, median cells/mm^3 (IQR)	500 (342–690)
Time to first CD4+ count, median years (IQR)	0.73 (0.35–1.46)
CD4+ measurements per patient, median no. of measurements (IQR)	6 (2–13)
Time to last CD4+ measurement in the analysis, median years (IQR)	3.74 (1.48–7.00)
Interval between CD4+ measurements per patient, median months (IQR)	4.03 (2.63–6.36)
Seroconversion interval, median days (IQR)	280 (137–518)
HIV subtype[a]	
A	35 (1)
B	2909 (90)
C	70 (2)
D	16 (1)
Other	199 (6)

Data are no. (%) of subjects unless otherwise indicated.

Abbreviation: IQR, interquartile range.

[a] A total of 3229 patients with known HIV subtype.

Proportions of individuals with CD4+ cell counts <200, <350, and <500 cells/mm^3 at 1, 2, and 5 years after seroconversion are reported in Figure 1 and Table 2. Should guidelines recommend initiation of therapy at 500 cells/mm^3, 48% (95% CI, 47.4%–49.5%) of HIV-infected individuals would require treatment within 1 year of seroconversion, compared with 26% and 9% for guidelines indicating initiation at 350 cells/mm^3 and 200 cells/mm^3, respectively. At 5 years after seroconversion, 56% of individuals infected with HIV are expected to need therapy for CD4+ cell count thresholds of 350 cells/mm^3, compared with 33% for the 200 cells/mm^3 threshold.

Estimated Time Between Seroconversion and CD4+ Cell Counts <500, <350, and <200 cells/mm^3

The estimated times between seroconversion and CD4+ cell counts of <500, <350, and <200 cells/mm^3 were 1.19 (95% CI, 1.12–1.26), 4.19 (95% CI, 4.09–4.28), and 7.93 (95% CI,

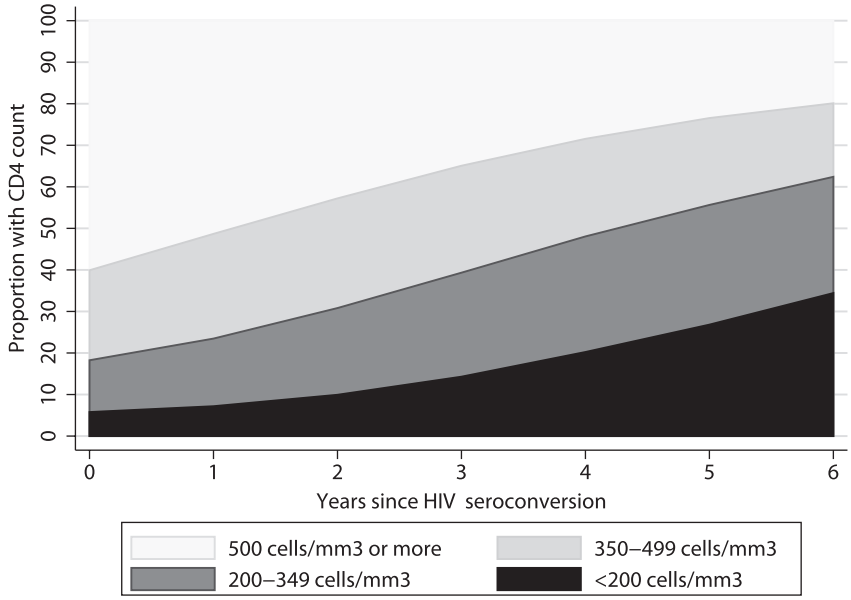

Figure 1. Distribution of CD4+ cell count and percentage of subjects reaching CD4 cell count category and year following HIV seroconversion, estimated from a linear mixed model.

7.76–8.09) years, respectively. Similar estimates of time between seroconversion to the 3 thresholds were found when we excluded CD4+ cell counts within 6 months of seroconversion (1.25, 4.33, and 8.19 years, respectively). Finally, the time to reach the 3 thresholds did not substantially change when we jointly modeled CD4+ cell count trajectories and survival time to account for potential informative drop-out due to death.

Effect of Individual Characteristics

The model for CD4+ cell count decrease on the square root scale is presented in Table 3. Increasing age at seroconversion was associated with lower CD4+ cell count at seroconversion ($P < .001$) and with steeper CD4+ cell count decrease ($P < .001$). Female patients had higher estimated CD4+ cell counts at seroconversion, compared with male patients ($P < .001$). However, there was no evidence that the rate of CD4+ cell count decrease on the square root scale differed by sex ($P = .165$). Individuals who experienced seroconversion in 1996 or earlier had significantly lower estimated mean CD4+ cell count at seroconversion ($P < .001$), compared with those who experienced seroconversion in earlier years. There was also some evidence that such individuals experienced slower rates of CD4+ cell decrease, compared with those seroconverting before 1996 ($P = .031$). Risk group was a significant predictor of rate of decrease ($P < .001$), with individuals infected through sex between men and women or other or unknown risk groups experiencing a shallower decrease, compared with individuals who were infected through sex between men or through injection drug use.

The estimated time between HIV seroconversion and CD4+ cell count <200, <350, and <500 cells/mm^3 by age, sex, risk group, and calendar year of seroconversion are presented in Table 4. As expected, across all groups, the time between seroconversion and need for treatment becomes shorter with increasing CD4+ cell count thresholds for treatment initiation. Median times between seroconversion and needing treatment varied between 8 and 10 years for a CD4+ cell count threshold of 200 cells/mm^3, decreasing to 4–5 years for a threshold of 350 cells/mm^3 and to within 2 years of seroconversion for a threshold of 500 cells/mm^3. Focusing on 3 characteristic groups 2 of HIV-infected individuals, the estimated times between seroconversion to CD4+ cell counts <200, <350, and <500 cells/mm^3 were 10.71, 5.66, and 1.63 years for 25–30-year-old heterosexual females; 7.67, 3.94, and 0.95 years

Table 2. Percentage of Subjects Reaching CD4+ Cell Count <200, <350, and <500 cells/mm^3 at 1, 2, and 5 Years After Seroconversion, Estimated from a Linear Mixed Model

	Estimated subjects reaching the threshold, % (95% confidence interval), by years after seroconversion		
CD4+ cell count, cells/mm^3	1	2	5
<200	8.8 (8.3–9.4)	12.2 (11.5–12.7)	32.3 (31.7–33.5)
<350	26.1 (25.8–27.4)	33.2 (32.4–34.3)	55.0 (54.3–56.1)
<500	48.0 (47.4–49.1)	55.9 (55.5–57.2)	72.7 (71.5–73.3)

Table 3. Effect of Patient Characteristics on CD4+ Cell Count at Seroconversion and Slope Obtained From the Linear Mixed Model Used to Predict Time From Seroconversion to CD4+ Cell Count <500, <300, <250 cells/mm^3

Variable	Coefficient (95% confidence interval)	P[a]
CD4+ cell count intercept		
Baseline[b]	24.167 (23.901–24.433)	<.001
Risk group		
Sex between men	Reference	<.001
Injecting drug use	0.481 (0.167–0.795)	
Sex between men and women	−1.496 (−1.808 to −1.184)	
Hemophilia	5.201 (4.172–6.230)	
Other/unknown	−0.772 (−1.309 to −0.236)	
Age at seroconversion, years		
<25	Reference	<.001
25–29	−0.365 (−0.650 to −0.079)	
30–34	−0.646 (−0.951 to −0.342)	
≥35	−0.944 (−1.229 to −0.659)	
Sex		
Male	Reference	
Female	1.159 (0.841–1.478)	<.001
Calendar year		
<1996	0.367 (0.160–0.575)	<.001
≥1996	Reference	
CD4+ cell count slope[c]		
Baseline CD4+ cell count decrease[b]	−1.159 (−1.243 to −1.075)	<.001
Risk group		
Sex between men	Reference	<.001
Sex between men and women	0.321 (0.225–0.417)	
Injecting drug use	−0.023 (−0.111 to 0.065)	
Sex between men and women	0.321 (0.225–0.417)	
Hemophilia	−0.710 (−0.943 to −0.477)	
Other/unknown	0.207 (0.039–0.376)	
Age at seroconversion		
<25	Reference	<.001
25–29	−0.069 (−0.150 to 0.012)	
30–34	−0.064 (−0.154 to 0.026)	
≥35	−0.173 (−0.258 to −0.088)	
Sex		
Male	Reference	
Female	−0.066 (−0.160 to 0.027)	.165
Calendar year		
<1996	−0.073 (−0.140 to −0.007)	.031
≥1996	Reference	

[a] Wald test for heterogeneity for categorical variables.

[b] Baseline is male with sex between men risk group and age ≤25 years at seroconversion in the post-1996 calendar period.

[c] Estimated average rate of CD4+ cell count change per year (on the square root scale). Negative sign of the slope coefficients implies steeper slopes compared with the baseline group.

for 30–35-year-old homosexual males; and 9.15, 4.08, and 0.04 years for 30–35-year-old heterosexual males. Female subjects consistently experienced longer times (6–12 months longer) to reach CD4+ cell count thresholds than did male subjects of the same age and risk group.

When we restricted the analyses to the 3229 individuals with a known HIV subtype, we found some evidence of an association between subtype and estimated CD4+ cell count at seroconversion ($P = .001$, Wald test). In particular, individuals with subtype D had estimated CD4+ cell counts at seroconversion that were ~179 cells/mm^3 lower than those among individuals with B subtype. However, we detected no overall difference in the rate of decrease by subtype ($P = .612$, Wald test). Similar conclusions were reached after adjusting for potential confounders (results not

Table 4. Estimated Time From Seroconversion to CD4+ Cell Count <500, <350, and <200 cells/mm^3 According to Age at Seroconversion, Sex, and Risk Group in the Post-cART Era (after 1996)

Variable	Median years to CD4+ cell count <500 cells/mm^3 (95% confidence interval), by age at seroconversion							
	<25 Years		25–29 Years		30–35 Years		≥35 Years	
MSM	1.56	(1.36–1.76)	1.17	(1.00–1.34)	0.95	(0.77–1.13)	0.65	(0.50–0.79)
Female MSW	1.63	(1.33–1.92)	1.13	(0.86–1.41)	0.85	(0.56–1.15)	0.49	(0.24–0.74)
Male MSW	0.75	(0.36–1.13)	0.32	(0.02–0.66)	0.04	(0–0.44)	0	(0–0.61)
Female IDU	2.76	(2.48–3.04)	2.34	(2.08–2.60)	2.13	(1.86–2.41)	1.76	(1.51–2.01)
Male IDU	1.94	(1.67–2.20)	1.54	(1.29–1.78)	1.32	(1.06–1.57)	0.99	(0.76–1.22)
Time to CD4+ cell count <350 cells/mm^3								
MSM	4.71	(4.41–5.01)	4.15	(3.91–4.38)	3.94	(3.70–4.17)	3.39	(3.22–3.56)
Female MSW	5.66	(5.14–6.19)	4.89	(4.46–5.31)	4.62	(4.20–5.05)	3.88	(3.57–4.18)
Male MSW	4.77	(4.16–5.38)	4.08	(3.58–4.59)	4.06	(3.45–4.66)	3.35	(2.98–3.72)
Female IDU	5.69	(5.24–6.14)	5.11	(4.72–5.51)	4.92	(4.51–5.32)	4.33	(3.99–4.67)
Male IDU	5.03	(4.63–5.42)	4.46	(4.12–4.79)	4.25	(3.91–4.59)	3.69	(3.41–3.96)
Time to CD4+ cell count <200 cells/mm^3								
MSM	8.65	(8.10–9.20)	7.86	(7.43–8.30)	7.67	(7.22–8.12)	6.82	(6.50–7.13)
Female MSW	10.71	(9.70–11.73)	9.57	(8.73–10.41)	9.34	(8.48–10.20)	8.11	(7.50–8.73)
Male MSW	9.80	(8.65–10.95)	9.15	(8.11–10.19)	8.73	(7.44–10.03)	7.86	(7.13–8.60)
Female IDU	9.35	(8.60–10.10)	8.58	(7.91–9.24)	8.40	(7.71–9.09)	7.54	(6.98–8.11)
Male IDU	8.89	(8.19–9.59)	8.10	(7.52–8.69)	7.91	(7.31–8.52)	7.06	(6.57–7.54)

Estimated from the linear random effect model $\sqrt{CD4_{ij}} = \beta_0 + \beta 1 t_{ij} + bi0 + bi1 t_{ij} + eij$ with bi0 and bi1 as random intercept and slope for patient i as $t = (\sqrt{x} - \beta 0)/\beta 1$ x = 500, 350 and 200 cells/mm^3.

Abbreviations: IDU, injection drug use; MSM, men who have sex with men; MSW, men who have sex with women.

shown). Estimated times between seroconversion and CD4+ cell count < 500, <350, and <200 cells/mm^3 are given in Table 5.

DISCUSSION

Using a large dataset of 18,495 individuals with well-estimated dates of HIV seroconversion, we estimated that CD4+ cell counts <500, <350, and <200 cells/mm^3 are reached, on average, at approximately 1, 4, and 8 years, respectively. We also estimated that, of 100 newly infected individuals, 48, on average, would require treatment within 1 year after seroconversion for guidelines indicating initiation at 500 cells/mm^3, compared with 27 and 9 individuals for guidelines indicating initiation at 350 and 200 cells/mm^3, respectively. At 5 years, 55 of these individuals are expected to reach CD4+ cell counts below 350 cells/mm^3, compared with 33 for CD4+ cell counts below 200 cells/mm^3. These data signify a substantial increase in the number of individuals who require treatment within the first 5 years after becoming infected following the recent changes in the DHHS, IAS-US, and WHO guidelines [2–4]. These estimates, together with information on the distribution of CD4+ cell count at HIV infection diagnosis, will be essential to health care planners estimating the additional costs of increasing the CD4+ cell count thresholds for cART initiation.

Late HIV infection diagnosis, which prevents initiation of cART when its effect on survival would be greatest, has been reported in high-, middle-, and low-income countries [16–19]. Given the short time between seroconversion and the threshold of 500 cells/mm^3 in the current DHHS and IAS-US guidelines (1 year) and 350 cells/mm^3 in European and WHO guidelines

Table 5. Estimated Time From Seroconversion to CD4+ Cell Count <500, <350, and <200 cells/mm^3 According to Human Immunodeficiency Virus (HIV) Subtype

HIV subtype	Years from seroconversion to CD4+ cell count threshold, median years (95% confidence interval)		
	<500 cells/mm^3	<350 cells/mm^3	<200 cells/mm^3
A	0.68 (0–2.13)	3.75 (1.78–5.72)	7.59 (3.84–11.34)
B	1.16 (1.03,1.30)	3.80 (3.62–3.98)	7.10 (6.79–7.42)
C	0 (0,0.81)	2.59 (1.46–3.73)	6.3 (4–8.60)
D	0 (0,1.06)	0.785 (0–2.28)	3.40 (0.60–6.20)

Estimated from the linear random effect model. Zero values indicate CD4+ cell count below the threshold at the estimated date of seroconversion.

(4 years), our data urgently call for a campaign to encourage early HIV testing to ensure that infected individuals receive a diagnosis of HIV infection and access care well before they reach the CD4+ cell count threshold at which the treatment is indicated.

We used data from individuals whose dates of seroconversion have been reliably estimated. In practice, the timing of seroconversion is not known for most individuals with HIV infection; indeed, many individuals are first tested many years after seroconversion, after having reached the CD4+ cell count treatment threshold. Therefore, our estimates of the proportions at various CD4+ cell count thresholds should be interpreted as the maximum proportion in need of treatment and with CD4+ cell count levels being continuously monitored.

To the best of our knowledge, this is the largest study to estimate the time between seroconversion and these 3 CD4+ cell count thresholds for cART initiation. Other smaller studies in high- and low-income countries have provided estimates that were not always consistent. In a meta-analysis of cohort studies from low- and middle-income countries, despite the likely differences in the distribution of HIV subtype and a slightly younger age at seroconversion, the eART-linc collaboration reported results similar to ours, with mean times from seroconversion to CD4+ cell count <200 and <350 cells/mm^3 of 7.6 and 4.0 years, respectively, compared with 7.9 and 4.2 years in our study [20]. In a cohort in rural Uganda, the median time to CD4+ cell count <200 cells/mm^3 or WHO stage 4 was 6.2 years, which is somewhat shorter than the time to CD4+ cell count <200 cells/mm^3 of 7.9 years reported in our study [21]. This may possibly be explained by the difference in subtype distributions as well as by higher background mortality for the Ugandan cohort. In a meta-analysis of cohort studies of homosexual men from high income countries in the pre-cART era (Tricontinental Seroconverter Study), the median time from seroconversion to CD4+ cell count <500 cells/mm^3 varied between 1.2 and 4.4 years, depending of the geographical region [22], whereas in our study this was estimated to be between 1.1 and 1.6 years, depending on the subject's age at seroconversion. Some of the differences in findings may be attributable to different methodological approaches and the availability of more-frequent CD4+ cell count measurements in our dataset.

Consistent with previous reports, we found that injection drug users and individuals infected through sex between men and women had slower CD4+ cell count decreases, compared with those in individuals infected through sex between men [23, 24]. We also found that increasing age at seroconversion predicted considerably shorter times to reaching the various thresholds, consistent with age being an established risk factor for lower CD4+ cell count at seroconversion and faster CD4+ cell count deterioration [23]. We also confirmed previous results that women had CD4+ cell counts at seroconversion that were higher than those of men at seroconversion but had similar rates of CD4+ cell count decrease [23]. In our study, women reached the CD4+ cell count thresholds for cART initiation 2–11 months later than did men of the same risk group, age group, and calendar period of seroconversion. It has been suggested that women seroconvert, develop AIDS, and die at a higher CD4+ cell count than do men [25]. These sex differences have raised concerns as to whether guidelines for therapy should indicate cART initiation in women at lower CD4+ cell counts than in men. However, evidence supporting the impact of different thresholds of cART initiation on long-term outcomes in women is still lacking.

It has been reported that those infected in more recent calendar periods are presenting with significantly lower initial CD4+ cell counts [26] and faster CD4+ cell count decreases [27]. In contrast, a French study indicated no evidence of secular trend in CD4+ cell count in primary HIV infection [28]. It is not clear whether these secular trends, if any exist, are attributable to the emergence of more-virulent strains of HIV in more recent years of the epidemic. We found that individuals who experienced seroconversion before 1996 had significantly higher CD4+ cell counts at seroconversion, compared with those in individuals infected in 1996 or later. However, we also found a marginal tendency for shallower CD4+ cell count decreases in individuals who experienced seroconversion in 1996 or later. Our data do not, therefore, support the hypothesis of increased virulence in more-recent calendar periods.

This study has some limitations. First, the uncertainty around the date of HIV seroconversion could have had an impact on the estimated proportions in need of treatment, particularly at 1 year after seroconversion. However, as the gap between the last negative and first positive test result is relatively narrow (median duration, 280 days), this is unlikely to have affected our results significantly. Second, we used data on individuals with seroconversion who received a diagnosis of HIV infection in high-income countries, with limited numbers known to have been infected with a non-B subtype (10% of those with a known subtype). Therefore, our estimates may not be generalizable to middle- and low-income countries or to populations with different subtype distributions. Indeed, there was some evidence suggesting that individuals with D subtype, which is commonly found in East and Central Africa, had lower CD4+ cell counts at seroconversion than did those with subtype B. Third, guidelines indicate initiation of cART for individuals who develop clinical AIDS regardless of CD4+ cell count. Although most AIDS events occur at CD4+ cell counts well below 200 cells/mm^3, some events, such as tuberculosis and severe bacterial disease, which are the most frequent causes of HIV-related morbidity in Africa, can occur in individuals at higher CD4+ cell counts. Therefore, it is possible that we could have underestimated the proportion of patients in need of treatment, particularly for a threshold of 200 cells/mm^3.

Our findings provide strong support for public health campaigns to encourage early HIV infection diagnosis and testing, especially in targeted populations at an increased risk of HIV infection, enabling those infected to initiate therapy at the optimum time. Given the substantial increase in the number of individuals eligible for treatment as a result of the latest changes in guidelines, it is crucial that the choice of the CD4+ cell count threshold for cART initiation is supported by evidence of benefit from randomized controlled trials and appropriate cost-effectiveness considerations.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://www.oxfordjournals.org/our_journals/cid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Financial support. This work was supported by the European Union Seventh Framework Programme (FP7/2007-2013) under EuroCoord grant agreement 260694.

Potential conflicts of interest. K. P. has received an honorarium from Tibotec. A. P. has received reimbursement for attending a symposium, a fee for speaking, a fee for organizing education, funds for research, funds for a member of staff, or fees for consulting from Roche, Bristol-Meyrs Squibb, GlaxoSmithKline, Abbott, Boehringer-Ingelheim, Gilead, Tibotec, and Oxxon Therapeutics. R. G., G. T., N. P., and A. J. received travel support related to this study through the CASCADE grant. All other authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Towards universal access: scaling up priority HIV/AIDS interventions in the health sector. Progress report 2010. Available at: http://www.who.int/hiv/pub/2010progressreport/en/. Accessed 25 May 2011.
2. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services, **2009**; 1–161. Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed 16 March 2010.
3. Thompson MA, Aberg JA, Cahn P, et al. Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society—USA panel. JAMA **2010**; 304:321–33.
4. World Health Organization (WHO). Antiretroviral therapy for HIV infection in adults and adolescents—2010 revision. Available at: http://whqlibdoc.who.int/publications/2010/9789241599764_eng.pdf. Accessed 21 July 2010.
5. European AIDS Clinical Society. Clinic management and treatment of HIV infected adults in Europe. **2009**. Available at: http://www.europeanaidsclinicalsociety.org/guidelinespdf/1_Treatment_of_HIV_Infected_Adults.pdf. Accessed 16 March 2010.
6. Kitahata MM, Gange SJ, Abraham AG, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. N Engl J Med **2009**; 360:1815–26.
7. Lewden C, Chene G, Morlat P, et al. HIV-infected adults with a CD4+ cell count greater than 500 cells/mm3 on long-term combination antiretroviral therapy reach same mortality rates as the general population. J Acquir Immune Defic Syndr **2007**; 46:72–7.
8. Sterne JA, May M, Costagliola D, et al. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. Lancet **2009**; 373:1352–63.
9. Treating HIV-infected people with antiretrovirals protects partners from infection. *Findings Result from NIH-funded International Study.* http://www.niaid.nih.gov/news/newsreleases/2011/Pages/HPTN052.aspx. Accessed 20 May 2011.
10. Insight start trial. Available at: http://insight.ccbr.umn.edu/start/. Accessed 3 February 2010.
11. Zetola NM, Pilcher CD. Diagnosis and management of acute HIV infection. Infect Dis Clin North Am **2007**; 21:19–48, vii.
12. Pantazis N, Morrison C, Amornkul P. Longitudinal CD4+ cell count evolution during HIV natural history: comparison between European and Sub-Saharn African seroconverter cohorts [Abstract 978]. In: Program and abstracts of the 17th Conference on Retroviruses and Opportunistic Infections, 16–19 February 2010, San Francisco, CA.
13. Royston P, Sauerbrei W. The use of fractional polynomials to model continous risk variables in epidemiology. Int J Epidemiol **1999**; 28: 964–74.
14. Carpenter J, Bithell J. Bootstrap confidence intervals: when, which, what? A practical guide for medical statisticians. Stat Med **2000**; 19:1141–64.
15. Touloumi G, Pocock SJ, Babiker A, Darbyshire J. Estimation and comparison of rates of change in longitudinal studies with informative drop-outs. Stat Med **1999**; 18:1215–33.
16. Borghi V, Girardi E, Bellelli S, et al. Late presenters in an HIV surveillance system in Italy during the period 1992–2006. J Acquir Immune Defic Syndr **2008**; 49:282–6.
17. UK Collaborative HIV Cohort. Late diagnosis in the HAART era: proposed common definitions and associations with mortality. AIDS **2010**; 24:723–7.
18. Sobrino-Vegas P, García-San Miguel L, Caro-Murillo AM, et al. Delayed diagnosis of HIV infection in a multicenter cohort: prevalence, risk factors, response to HAART and impact on mortality. Curr HIV Res **2009**; 7:224–30.
19. Basset I, Regan S, Chetty S, et al. Who starts in Durban, South Africa? … not everyone who should! (abstract WEAD102). In: Program and abstracts of the 5th International AIDS Society Conference on HIV Pathogeneis, Treatmenet and Prevention, Cape Town, South Africa, 19–22 July 2009. Available at: http://www.iasociety.org/Abstracts/A200721911.aspx. Accessed 10 June 2010.
20. The eligibility for ART in lower income countries (eART-linc) collaboration. Duration from seroconversion to eligibility for antiretroviral therapy and from ART eligibility to death in adult HIV-infected patients from low and middle-income countries: collaborative analysis of prospective studies. Sex Transm Infect **2008**; 84:i31–6.
21. Van der Paal L, Shafer LA, Todd J, Mayanja BN, Whitworth JA, Grosskurth H. HIV-1 disease progression and mortality before the introduction of highly active antiretroviral therapy in rural Uganda. AIDS **2007**; 21:S21–9.
22. Veugelers PJ, Schechter MT, Tindall B, et al. Differences in time from HIV seroconversion to CD4+ lymphocyte end-points and AIDS in cohorts of homosexual men. AIDS **1993**; 7:1325–9.
23. Concerted Action on Seroconversion to AIDS and Death in Europe Collaboration. Differences in CD4+ cell counts at seroconversion and decline among 5739 HIV-1 infected individuals with known dates of seroconversion. J Acquir Immune Defic Syndr **2003**; 34:76–83.
24. Pehrson PO, Lindbäck S, Lidman C, Gaines H, Giesecke J. Longer survival after HIV infection for injecting drug users than for homosexual men: implications for immunology. AIDS **1997**; 11:1007–12.
25. Prins M, Robertson JR, Brettle RP, et al. Do gender differences in CD4 cell counts matter? AIDS **1999**; 13:2361–4.
26. Dorrucci M, Rezza G, Porter K, Phillips A. Temporal trends in post-seroconversion CD4 cell count and HIV load: the Concerted Action

on Seroconversion to AIDS and Death in Europe Collaboration, 1985–2002. J Infect Dis **2007**; 195:525–34.

27. Crum-Cianflone N, Ren Q, Eberly L, et al. Is HIV progressing faster after HIV diagnosis over the epidemic? (abstract 980), In: Program and abstracts of the 17th Conference on Retroviruses and Opportunistic Infections, 16–19 February 2010. San Francisco, CA. Available at: http://www.retroconference.org/2010/PDFs/980.pdf. Accessed 12 March 2010.
28. Troude P, Chiax ML, Tran L, et al. No evidence of a change in HIV-1 virulence since 1996 in France: a study based on the CD4+ cell count and HIV RNA/DNA levels at the time of primary infection. AIDS **2009**; 23:1261–7.