MAJOR ARTICLE

$CD4^+$ T Cell Count Decreases by Ethnicity among Untreated Patients with HIV Infection in South Africa and Switzerland

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Background. Estimates of the decrease in $CD4^+$ cell counts in untreated patients with human immunodeficiency virus (HIV) infection are important for patient care and public health. We analyzed $CD4^+$ cell count decreases in the Cape Town AIDS Cohort and the Swiss HIV Cohort Study.

Methods. We used mixed-effects models and joint models that allowed for the correlation between $CD4^+$ cell count decreases and survival and stratified analyses by the initial cell count (50–199, 200–349, 350–499, and 500–750 cells/μL). Results are presented as the mean decrease in $CD4^+$ cell count with 95% confidence intervals (CIs) during the first year after the initial $CD4^+$ cell count.

Results. A total of 784 South African (629 nonwhite) and 2030 Swiss (218 nonwhite) patients with HIV infection contributed 13,388 $CD4^+$ cell counts. Decreases in $CD4^+$ cell count were steeper in white patients, patients with higher initial $CD4^+$ cell counts, and older patients. Decreases ranged from a mean of 38 cells/μL (95% CI, 24–54 cells/μL) in nonwhite patients from the Swiss HIV Cohort Study 15–39 years of age with an initial $CD4^+$ cell count of 200–349 cells/μL to a mean of 210 cells/μL (95% CI, 143–268 cells/μL) in white patients in the Cape Town AIDS Cohort $\geqslant$40 years of age with an initial $CD4^+$ cell count of 500–750 cells/μL.

Conclusions. Among both patients from Switzerland and patients from South Africa, $CD4^+$ cell count decreases were greater in white patients with HIV infection than they were in nonwhite patients with HIV infection.

An understanding of the factors that influence $CD4^+$ T cell counts and their decrease in untreated persons with human immunodeficiency virus (HIV) infection is of importance for clinical management of HIV disease (eg, to inform guidelines on when to initiate antiretroviral therapy [ART]). Such information is also important in the context of public health, because the distribution of $CD4^+$ cell count decreases is required to model time to AIDS and ART eligibility and to project the course of the epidemic and the need for treatment at the population level.

Although the decrease in $CD4^+$ cell counts has been extensively studied in cohorts from North America [1] and Europe [2, 3], there is little data from patients with estimated dates of seroconversion in sub-Saharan Africa [4], where ART has become more widely available in recent years [5]. Data from the Cape Town AIDS Cohort (CTAC), a cohort of seroprevalent patients from Cape Town, South Africa, suggested that mean $CD4^+$ cell count decreases ranged from 21 to 47 cells/mL per year depending on the initial $CD4^+$ cell count strata [6]. Reported decreases for patients from industrialized countries are steeper [1–3], but results may not be directly comparable, because the statistical methodology used to model the trajectories varied. Also, decreases may have been underestimated in the Cape Town cohort, because patients with steeper trajectories are more

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likely to die and to have fewer $CD4^+$ cell counts than those with less rapid decreases [7, 8]. We analyzed $CD4^+$ cell count decreases in the CTAC and the Swiss HIV Cohort Study (SHCS) and assessed the effects of ethnicity, sex, age, and cohort on the rate of $CD4^+$ cell count decrease, taking into account the correlation between survival and $CD4^+$ cell count decrease.

METHODS

CTAC. The CTAC is an observational cohort of patients who received care from public sector clinics affiliated with the University of Cape Town, South Africa. The cohort has been described in detail elsewhere [9, 10]. The clinics mainly served indigent communities, with a predominance of heterosexually transmitted infection [10].

A total of 2086 HIV-infected patients were enrolled in the cohort during the period 1984–2000. Demographic information collected on the first visit included date of birth, sex, marital status, ethnicity/ethnic background, sexual preference, and HIV risk factors. HIV infection diagnosis was confirmed by analysis of 2 separate blood specimens with enzyme-linked immunosorbent assay and/or Western blot. Laboratory data were collected approximately every 6 months and included $CD4^+$ cell count. Some patients with a diagnosis of AIDS or with a $CD4^+$ cell count <200 cells/μL received cotrimoxazole prophylaxis after 1993 [11]. In addition, zidovudine monotherapy was used, although infrequently.

SHCS. Established in 1988, the SHCS is a national prospective cohort study involving HIV-infected patients who were followed up at the outpatient departments of 7 University and Cantonal outpatient clinics in Basel, Bern, Geneva, Lausanne, Zurich, Lugano, and St. Gallen, Switzerland. The study is described in detail elsewhere [12, 13]. Information on demographic characteristics, mode of HIV acquisition, risk behaviors, clinical events, laboratory results, and treatments is collected at registration and then at intervals of 6 months. $CD4^+$ cell counts and other laboratory parameters are measured at least every 3 months. Nonwhite patients who participate in the SHCS are predominantly migrants from sub-Saharan Africa, who are an increasingly important patient group in Switzerland [14].

Patients. We included all patients ⩾15 years of age (CTAC) or ⩾16 years of age (SHCS) with at least 2 $CD4^+$ cell counts obtained while not receiving ART and while they were ART naive. Patients whose initial $CD4^+$ cell count was >750 cells/μL were left censored up to the first cell count <750 cells/μL, because their elevated $CD4^+$ cell count might have been attributable to recent seroconversion, and the $CD4^+$ cell count decreases might have been unrepresentative of the chronic phase of the infection. Patients with initial $CD4^+$ cell count <50 cells/μL were also excluded, because the assumed linearity of decrease of $CD4^+$ cell count on the log scale may not hold below this low level. Finally, we excluded patients from the SHCS whose transmission risk group was injection drug use, because CTAC patients were infected through sexual transmission.

Statistical methods. We used log transformed $CD4^+$ cell count to linearize the relationship with time and make the distribution more symmetric. We considered using square root transformed $CD4^+$ cell count data, which is commonly used to model trajectories [15]; however, models using the log-transformed data were a better fit to the data than those using the square root transformation, and effect estimates may be more easily back transformed to the original scale. We measured time from the first available $CD4^+$ cell count <750 cells/μL and stratified analyses by the initial cell count (50–199, 200–349, 350–499, and 500–750 cells/μL) to allow for different slopes in $CD4^+$ cell count decreases across $CD4^+$ cell count strata. We excluded $CD4^+$ cell counts measured more than 4 years after the first measurement, because models give more weight to patients with many measurements, which might introduce bias, because patients who survive longer than 4 years after the first measurement are more likely than other patients to be slow progressors. We also excluded $CD4^+$ cell counts obtained after ART initiation and deaths that occurred >4 years after the initial $CD4^+$ cell count measurement.

We used mixed effects models with random effects for intercept and slope for $CD4^+$ cell count measurements, to allow for the fitted curve to vary between individuals, and used fixed effects for intercept and gradient terms for sex, age (<40 vs ⩾40 years of age), ethnicity (white vs nonwhite), and initial $CD4^+$ cell count strata. Univariable models were fitted for each potential predictor of $CD4^+$ cell count decrease. We then fitted a multivariable model that mutually adjusted for all other variables separately for each cohort. We used the multivariable model to estimate the mean decrease in $CD4^+$ cell count for different groups of patients for each cohort. The distribution of $CD4^+$ cell count decreases was then estimated using the best linear unbiased predictions of the random effects. The final model was a joint model for $CD4^+$ cell count trajectory and survival time [8] that allowed for the correlation between the $CD4^+$ cell count intercept and slope parameters and the log survival time. The $CD4^+$ cell count model was the model described above, and the survival model assumed a lognormal distribution of survival times with frailty. Results are presented as mean decreases in $CD4^+$ cell counts during the first year after the initial $CD4^+$ cell count measurement with 95% confidence intervals (CIs). These were calculated as the difference between the midpoint of the initial $CD4^+$ cell count strata and the estimated value 1 year later, which is calculated as the product of the exponentiated coefficients from the model and the midpoint value (ie, the calculation uses the ratio of geometric means on the back-transformed log $CD4^+$ cell count).

The estimates of $CD4^+$ cell count decrease are corrected for the bias introduced by informative censoring attributable to death and therefore are the estimates that would hypothetically apply to the whole cohort in the absence of mortality. The comparisons of the $CD4^+$ cell count decreases between the 2 cohorts are therefore not affected by differences in mortality.

RESULTS

Of the 2086 patients enrolled in CTAC, 1766 had ⩾2 visits, and 784 (37.6%) of these had ⩾2 eligible $CD4^+$ cell count measurements and were included in the study. CTAC patients who were excluded from the study were similar with respect to age, sex, ethnicity, sexual preference, or mean initial $CD4^+$ cell count but had shorter mean follow-up time than did those individuals included in the study (18.7 months vs 28.5 months). In the SHCS, there were 7153 patients enrolled before 2000 who were not infected by means of injection drug use; 2030 patients (28.4%) had ⩾2 eligible $CD4^+$ cell counts and were included in the study. SHCS patients who were excluded from the study had lower initial median $CD4^+$ cell counts (220 vs 450 cells/μL), were more likely to be heterosexual (45% vs 42% of patients), and had shorter mean follow-up time than did those who were included in the study (4.2 years vs 8.5 years), but they were similar with respect to age and sex.

A total of 2814 patients and 13,388 $CD4^+$ cell counts were included in analyses. Table 1 shows demographic and clinical characteristics of CTAC and SHCS patients by ethnicity. CTAC had a high proportion of nonwhite patients (81.2%), whereas in SHCS, the majority of patients were white (89.3%). In both cohorts, the proportion of patients who were female was much higher among nonwhite patients than it was among white patients. The median $CD4^+$ cell count at enrolment was lower for nonwhite patients than it was for white patients in both cohorts, and it was lower in CTAC patients than it was in SHCS patients. Patients in CTAC were more likely to have enrolled with a $CD4^+$ cell count <200 cells/μL than to have enrolled with a count >500 cells/μL, whereas the opposite was true for SHCS patients.

Decreases in $CD4^+$ cell count in the first year after the initial $CD4^+$ cell count measurement were similar in men and women, but the trajectory of decrease was steeper in patients with higher initial $CD4^+$ cell counts, in white patients, and in older patients. Therefore, we did not include a term for sex in the final model. Table 2 shows decreases estimated from joint models converted to the original $CD4^+$ cell count scale for each cohort by ethnicity and age group. Decreases ranged from 38 cells/μL (95% CI, 24–54 cells/μL) in nonwhite SHCS patients aged 15–39 years with an initial $CD4^+$ cell count of 200–349 cells/μL to 210 cells/μL (95% CI, 143–268 cells/μL) in white CTAC patients ⩾40 years of age with an initial $CD4^+$ cell count of 500–750 cells/μL. Figure 1 illustrates the distribution of the decrease in $CD4^+$ cell count in 1 year by initial $CD4^+$ cell count strata and ethnicity for both cohorts combined.

The model coefficients with 95% CIs on the log transformed $CD4^+$ cell count scale for gradient and intercept terms from the unadjusted univariable models, the mutually adjusted full multivariable models, and the joint models are available online (Table 3). In the joint model, the adjusted estimate of survival was longer in SHCS than in CTAC. In both cohorts, older patients had shorter survival than did younger patients, and

Table 1. Demographic and Clinical Characteristics of Study Patients from the Cape Town AIDS Cohort and the Swiss HIV Cohort Study by Ethnicity

	Cape Town AIDS Cohort		Swiss HIV Cohort Study	
Variable	White (n = 155)	Nonwhite (n = 629)	White (n = 1812)	Nonwhite (n = 218)
Proportion (%) of total patients in cohort	155/784 (19.8)	629/784 (81.2)	1812/2030 (89.3)	218/2030 (10.7)
Proportion (%) of $CD4^+$ cell counts	606/2594 (23)	1988/2594 (77)	9624/10,795 (89)	1171/10,795 (11)
Patients who died during follow-up	37 (24)	120 (19)	183 (10)	6 (3)
Median no. of $CD4^+$ cell counts per person (IQR)	5 (3–8)	3 (2–5)	8 (5–13)	9 (4–16)
Duration of follow-up, median years (IQR)	1.16 (0.50–2.09)	1.03 (0.57–1.95)	1.33 (0.53–2.45)	0.65 (0.27–1.73)
Age, median years (IQR)	33 (28–42)	31 (25–37)	33 (28–41)	29 (25–33)
Age ⩾40 years	43 (28)	119 (19)	511 (28)	22 (10)
Female sex	14 (9)	364 (58)	379 (21)	139 (64)
$CD4^+$ cell count at enrolment[a]				
Median cells/μL (IQR)	321 (188–495)	279 (174–423)	460 (310–620)	415 (279–580)
50–199 cells/μL	45 (29)	193 (31)	184 (10)	31 (14)
200–349 cells/μL	43 (28)	201 (32)	391 (22)	49 (22)
350–499 cells/μL	34 (22)	133 (21)	506 (28)	60 (28)
500–750 cells/μL	33 (21)	102 (16)	731 (40)	78 (36)

NOTE. Data are no. (%) of patients, unless otherwise indicated. IQR, interquartile range.

[a] Determined by first recorded $CD4^+$ cell count <750 cells/μL.

Table 2. Estimated 1-Year CD4⁺ Cell Count Decrease according to Baseline CD4⁺ Cell Count Stratum, Ethnicity, and Age in the Cape Town AIDS Cohort and the Swiss HIV Cohort Study.

	Cape Town AIDS Cohort				Swiss HIV Cohort Study			
	White		Nonwhite		White		Nonwhite	
Age group, initial CD4⁺ cell count	No. of patients	CD4⁺ cell count decrease, cells/μL (95% CI)	No. of patients	CD4⁺ cell count decrease, cells/μL (95% CI)	No. of patients	CD4⁺ cell count decrease, cells/μL (95% CI)	No. of patients	CD4⁺ cell count decrease, cells/μL (95% CI)
15–39 Years								
50– 199 cells/μL	26	52 (42–60)	154	47 (40–54)	120	46 (40–51)	25	39 (31–46)
200–349 cells/μL	31	65 (38–89)	157	50 (31–69)	276	59 (50–67)	43	38 (24–54)
350–499 cells/μL	22	70 (21–110)	109	44 (8–81)	353	84 (70–94)	55	52 (29–74)
500–750 cells/μL	33	123 (59–180)	90	92 (36–143)	552	98 (87–113)	73	54 (18–87)
⩾40 Years								
50–199 cells/μL	19	65 (55–73)	39	61 (52–68)	83	48 (42–54)	7	41 (33–49)
200–349 cells/μL	11	101 (75–124)	40	91 (67–112)	119	65 (54–75)	6	48 (29–63)
350–499 cells/μL	8	131 (84–172)	20	113 (70–151)	130	94 (81–107)	4	63 (37–91)
500–750 cells/μL	5	210 (143–268)	20	185 (118–242)	179	118 (98–138)	5	71 (30–108)

NOTE. Decreases from the within-group median value in the first year after the initial CD4⁺ cell count measurement are shown with 95% confidence intervals (CIs). Results are from adjusted joint model taking survival time into account.

there was a strong association of survival with initial CD4⁺ cell count strata (the lower the CD4⁺ cell count strata, the shorter the survival time). In the SHCS, nonwhite patients and female patients survived longer than did white patients and male patients, but these associations were not seen in CTAC patients. Compared with the standard mixed-effects multivariable model, the joint model estimated CD4⁺ cell count decreases that were less steep for the highest CD4⁺ cell count strata, in which there is the best survival in the CTAC cohort. In the SHCS, the estimates from both models were similar, probably because of fewer deaths being recorded.

DISCUSSION

We compared the CD4⁺ cell count decreases in untreated patients in a European setting and an African setting and analyzed 2 cohorts from Cape Town, South Africa, and from Switzerland. In both South Africa and Switzerland, nonwhite patients had slower CD4⁺ cell count decreases than did white patients, and older patients had faster decreases than did younger patients. Furthermore, the CD4⁺ cell count decrease was more rapid in patients with higher initial CD4⁺ cell counts than it was in patients with lower counts.

We applied the same analytical approach to the data from the CTAC and SHCS cohorts, and results are therefore directly comparable. We have taken account of the demographic characteristics of the cohorts by excluding injection drug users and adjusting models for age and sex. We focused on estimating short-term CD4⁺ cell count trajectories within 4 years of the first measurement to reduce bias attributable to slow progressors having more CD4⁺ cells than fast progressors. Finally, we examined the effect of deaths on estimated CD4⁺ cell count decrease and found that CD4⁺ cell count decreases in the higher CD4⁺ cell count strata are over-estimated by the standard mixed-effects model. The joint model takes into account survival time and deaths and adjusts for the steeper decrease of CD4⁺ cell counts in very ill patients. A previous analysis of the CTAC data by Holmes et al [6] estimated the CD4⁺ cell count decrease to be 47.1 cells/μL per year for patients with initial CD4⁺ cell counts >500 cells/μL, 30.6 cells/μL for those with CD4⁺ cell counts of 351–500 cells/μL, and 20.5 cells/μL for

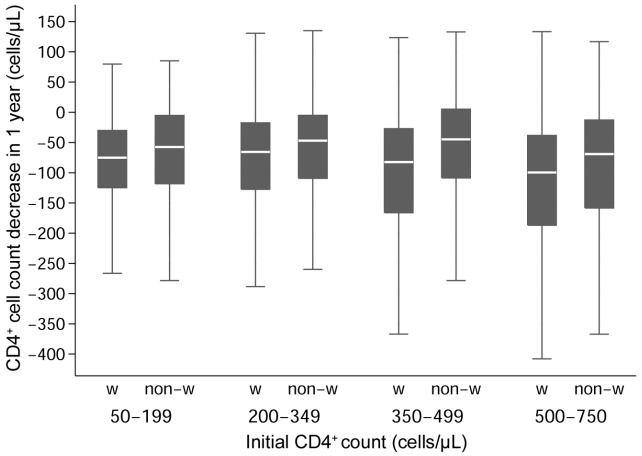

Figure 1. Distribution of CD4⁺ cell count decreases by initial CD4⁺ cell count and ethnicity for the combined Cape Town AIDS Cohort and Swiss HIV Cohort Study population. Box-and-whisker diagrams show the median and quartiles *(box with horizontal line)* and the smallest and largest decrease that are not outliers *(upper and lower whiskers)*. Outliers are defined as points >1.5 times the interquartile range above the 75th percentile or below the 25th percentile. Non-w, nonwhite ethnicity; w, white ethnicity.

Table 3. Model Coefficients with 95% Confidence Intervals on Log Transformed CD4$^+$ Cell Count Scale for Gradient and Intercept Terms and Survival Time for Mortality Model from (i) Unadjusted Univariable Random Effects Models, (ii) Mutually Adjusted Multivariable Random Effects Model, and (iii) Joint Marker and Mortality Random Effects Model (JMRE)

This table is available in its entirety in the online version of the *Journal of Infectious Diseases*

patients with counts of 201–350 cells/μL [6]. Our estimates are somewhat higher. The different methodological approach may at least partially account for the difference between our estimates and those of Holmes et al [6].

Our study has a number of limitations. There were few white patients in CTAC and few nonwhite patients in SHCS. The study thus had limited power to examine whether the effect of ethnicity differed between the 2 cohorts. Also, the follow-up period was short for many patients in CTAC, and therefore, there are few CD4$^+$ cell count measurements for most patients. A further problem with analyzing CD4$^+$ cell count trajectories in seroprevalent cohorts is the lack of data regarding the time of infection, which would be the natural point in time to line up the trajectories. This is, to some extent, overcome by stratifying on initial CD4$^+$ cell count; this reflects what the treating physicians see in practice and are interested in—namely, estimates of short-term CD4$^+$ cell count decrease from the current value. The validity of using first CD4$^+$ cell count measurement as a surrogate for time from infection has been questioned in survival analyses from the Concerted Action on Seroconversion to AIDS and Death in Europe (CASCADE) study, with time to death as the outcome [16], which have shown variation in CD4$^+$ cell count set point associated with rate of subsequent decrease in CD4$^+$ cell count. Our analyses, which examined CD4$^+$ cell count decrease according to initial CD4$^+$ cell count strata, may thus be grouping together patients who have different lengths of time since infection. Furthermore, the mean time since infection for each initial CD4$^+$ cell count strata could vary by cohort or ethnicity.

The data that are available from patients with well-documented seroconversion are limited, and they are particularly limited in resource-limited settings. A recent collaborative analysis of time to ART treatment eligibility was based on just over 2000 individuals with seroconversion from 5 cohorts from sub-Saharan Africa and Thailand [4]. In contrast, the CASCADE collaboration of cohorts in Europe, Canada, and Australia is based on >17,000 patients with documented seroconversion [16]. There are also disadvantages to seroconverter cohorts, which are generally not representative of the HIV-infected population but include many patients who were infected through injection drug use or the transfusion of blood products. Also, independently of the route of transmission, patients whose seroconversion was documented because they experienced symptomatic illness are likely to have more-rapid CD4$^+$ cell count decreases and more-rapid clinical progression, compared with those who were asymptomatic [17, 18].

Other studies involving seroprevalent cohorts that have compared white patients with black patients have also found slower decreases in the black group [19–21]. A recent analysis of the SHCS showed similar differences in CD4$^+$ cell count decreases between patients of African and European descent, but decreases in general were less pronounced, probably because the analysis was restricted to patients in Centers for Disease Control and Prevention clinical stage A with at least 5 CD4$^+$ cell counts and did not take into account informative censoring attributable to death [21]. Interestingly, in CASCADE, nonwhite ethnicity, compared with white ethnicity, was associated with higher odds of spontaneously achieving undetectable viremia and, in those who did have an undetectable viral load, with a longer period of undetectable viremia [22]. Analyses of seroprevalent cohorts, such as the CTAC and SHCS, are helpful to complement and extend the evidence that is available from seroconverter cohorts. In particular, our results are relevant when modeling time to ART eligibility and the need for ART at the population level, as well as when estimating and projecting the future course of the AIDS epidemic [23].

Although the decrease in CD4$^+$ cell count is a determinant of the time from HIV infection to AIDS or death, other factors include the mean CD4$^+$ cell count before infection in the relevant background population and the rapid decrease in CD4$^+$ cell count during the weeks immediately after seroconversion. A study of CD4$^+$ cell count decreases in seroincident and seroprevalent individuals in Tanzania showed that the median initial CD4$^+$ cell count of the seroincident individuals who experienced seroconversion within 1 year before the first CD4$^+$ cell count measurement was ~500 cells/μL, whereas the median CD4$^+$ cell count among infected individuals was ~800 cells/μL, which indicates a decrease of ~300 cells/μL soon after seroconversion [24]. Reference ranges for CD4$^+$ cell counts in people without HIV infection vary across geographical regions, sex, and age and racial groups [25, 26] and are also influenced by lifestyle and biological factors, such as smoking or contraceptive use [27]. A study involving Swiss blood donors found that the reference range was higher for women than for men and that is was lower at older ages [28]. African studies showed heterogeneity across populations, with, for example, markedly lower CD4$^+$ cell counts in Ethiopians [29], and they have also found higher counts in women than in men [25, 30].

The association between ethnicity and CD4$^+$ cell count decreases may have several explanations. Ethnicity reflects the social and economic position of participants within their respective cohorts. In CTAC, nonwhite participants tended to be

of lower socioeconomic position than white participants because of historical limitations on socioeconomic opportunity. In the SHCS, the nonwhite participants are migrants from sub-Saharan Africa who are also generally of a lower socioeconomic position than are white participants. In untreated patients, socioeconomic position may affect $CD4^+$ cell decreases through increased exposure to opportunistic infections and resultant immune activation and by influencing access and adherence to prophylactic therapies and other relevant health behaviors. In the Swiss cohort, but not in South Africa, the slower decrease in $CD4^+$ cell counts appears to have translated into better survival in nonwhite individuals than in white individuals. Of note, once enrolled in the SHCS, access to ART and the prognosis of nonwhite participants is equivalent to that for white participants [14]. Socioeconomic conditions, health-seeking behaviors, access to health care, and exposure to pathogens are more important determinants of mortality in South Africa than is ethnicity [31].

It is also possible that our results relate to host genetic differences. Nonwhite patients may have adapted to frequent infectious diseases by selection over many generations for the ability to survive despite chronic immune activation [20]. Of note, the low immune activation phenotype is also found in HIV-infected patients with slow disease progression in European countries [32] and in asymptomatic nonhuman African primates infected with simian immunodeficiency viruses [33]. A recent study suggested that genetically determined divergent Toll-like receptor signaling and interferon production distinguishes pathogenic ("immune activated") from nonpathogenic infection in the animal model [34]. In white individuals, genetic polymorphisms explained ~15% of the variation in viral load set points during the asymptomatic period of infection [35]. Of note, a recent analysis of the SHCS found that the $CD4^+$ cell count decrease was less rapid for patients of African descent than it was for patients of European descent, independently of whether patients were infected with HIV type 1 subtype B or subtype C [21]. The slower $CD4^+$ cell count decrease in patients of African descent is therefore unlikely to be attributable to infection with less virulent subtypes.

In conclusion, further studies on reference ranges of $CD4^+$ cell counts and on rates of decreases in $CD4^+$ cell counts in different countries and populations are needed to inform the development of guidelines for when to start ART, as well as to improve projections of the epidemic, particularly in resource-limited settings. The methodology used in the present study, which addressed a number of issues not generally considered in previous studies, might serve as a model for future studies.

THE SWISS HIV COHORT STUDY

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