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CD4 eligibility thresholds: an analysis of the time to antiretroviral treatment in West African HIV-1 seroconverters

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Abstract

Background—WHO recommends initiating combination antiretroviral treatment (ART) at the minimal threshold of 350 CD4 cells/mm^3. In sub-Saharan Africa, the time for a recently infected patient to reach this threshold is unclear.

Method—We estimated the probability of reaching different CD4 thresholds over time in the ANRS 1220 cohort of HIV-1 seroconverters in Côte d'Ivoire. CD4 slopes were estimated using a mixed linear model. Probabilities of crossing the 350 and 500 CD4 cells/mm^3 thresholds were estimated by the Kaplan-Meier method.

Results—Between 1997 and 2009, 304 recent seroconverters have been enrolled in the Primo-CI cohort (62% men, median baseline age 29 years, median time since the estimated date of seroconversion 9 months). The probability of having a first CD4 count below 500/mm^3 was 0.57, 0.72, 0.79 and 0.84 at study entry, 2, 4 and 6 years, respectively. For a first CD4 count below 350/mm^3, these figures were 0.29, 0.40, 0.55 and 0.67. The time for 75% of patients to reach the threshold was 3.0 years for 500 CD4/mm^3 and 7.0 years for 350 CD4/mm^3.

Conclusion—Almost one third of recent seroconverters had a CD4 count below the current ART eligibility threshold at first contact, about 6% more crossed it each subsequent year, and 25% remained above this threshold after 7 years. If the threshold was raised to 500 cells/mm^3, 57% of recent seroconverters would immediately be eligible, while 14% would remain above the threshold at 7 years. These results should help modelers and treatment providers anticipate the need in antiretroviral drugs.

Introduction

In sub-Saharan Africa, 3,910,000 adults have started combination antiretroviral therapy (ART) within the past five years (1). Despite this unprecedented scaling-up, patients started ART with a mean CD4 count between 100 and 150 cells/mm^3 (2–5). In 2010, the World

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Authors' contributions

Albert Minga, Xavier Anglaret and Charlotte Lewden developed the analysis plan. Albert Minga, Germain Bomisso and Delphine Gabillard performed statistical analyses. All authors contributed to interpretation of the data. Albert Minga, Charlotte Lewden and Xavier Anglaret wrote the report, to which all authors then contributed. Albert Minga and Germain Bomisso have full access to all data. Albert Minga, Charlotte Lewden and Xavier Anglaret had final responsibility for the decision to submit for publication.

Health Organization (WHO) guidelines recommended initiating ART when the CD4 count drops below 350/mm^3 (6). Little is known about the annual number of HIV-infected individuals who reach the CD4 threshold for ART initiation. Estimates of the probability of reaching this threshold in individuals who were diagnosed early would help modelers and drug providers anticipate the need for antiretroviral drugs. Moreover, estimates of the time spent by patients who, with a CD4 above the threshold, are thus unlikely to receive ART, may contribute to the knowledge of the risk of HIV transmission (4).

We estimated the probability of reaching different CD4 thresholds over time in a cohort of HIV-1 adults who recently seroconverted in Abidjan, Côte d'Ivoire.

Methods

Study Population

The ANRS 1220 Primo-CI cohort of seroconverters has been previously described (7). Since 1997, blood donors at the National Blood Bank (centre national de transfusion sanguine, CNTS) in Abidjan, Cote d'Ivoire who were tested HIV-1 positive were offered to be included in the cohort if the time since their estimated date of seroconversion was < 36 months. The estimated date of seroconversion was the midpoint between the last negative and the first positive HIV-1 test. Once included in the cohort, people benefited from a standardized follow-up, which includes a CD4 count every six months (FACScan then FACSCalibur, Becton Dickinson, Aalst-Erembodegem, Belgium). ART was given to patients who fulfilled ART initiation criteria according to WHO guidelines.

Statistical Analysis

We modelled the CD4 decline on the individual level using a linear mixed model with two slopes (before and after 6 months), adjusted for the delay since the estimated date of seroconversion (<6 months, 6–12 months and >12 months), the baseline plasma HIV-1 RNA level (≤4.5 vs >4.5 $\log_{10}$ copies/ml), the baseline CD4 count (<350, 350–500, >500/mm^3), mortality and ART initiation during follow-up. The model was validated by confirming that the simulated CD4 evolution fit the CD4 evolution in the cohort (Figure 1). The probabilities over time of having a CD4 count below 500 cells/mm^3 and below 350 CD4 cells/mm^3 were estimated by the Kaplan-Meier method. The robustness of the results was studied in sensitivity analysis by estimating the probability of the first event among the following: death, loss to follow-up, ART initiation or first CD4 count below the threshold.

Results

From June 1st 1997 to December 31st 2009, 304 HIV-1 infected patients were enrolled in the cohort, of whom 62% were men. The median time between last negative and first positive HIV-1 test was 7.8 months. At study entry, the median time since the estimated date of seroconversion was 9 months (interquartile range [IQR]: 5–18); the median age was 29 years (IQR: 25–34); the median CD4 count was 463 cells/mm^3 (IQR: 327–631); 42% of patients had ≥500 CD4/mm^3, 28% had 350 to 499 CD4 cells/mm^3, 24% had 200 to 349 cells/mm^3, and 6% had <200 CD4 cells/mm^3. The median plasma HIV-1 RNA level was 4.5 $\log_{10}$ copies/ml (IQR: 3.9–5.0); only 11 patients (4%) had a plasma HIV-1 RNA level below the detectability threshold (300 copies/ml), all of whom had CD4 >500/mm^3. All but two of the participants were classified as infected through heterosexual contact. At enrolment, 289 patients (95%) were classified at clinical stage A according to 1993 CDC classification, 13 at CDC stage B and two at CDC stage C. There was a significant difference between men and women in terms of age (men: median 31 years, IQR: 27–37, women: median 27 years, IQR: 24–32, = 0.002), time since seroconversion (men: median 8 months, IQR: 4–19,

women: median 11 months, IQR: 6–19, p = 0.001), plasma HIV-1 RNA (men: median 4.70 log_{10} copies/ml, IQR: 4.00–5.10, women: 4.25 log_{10} copies/ml, IQR: 3.80–4.82, p = 0.02). Baseline CD4 count was not significantly different between genders.

The median follow-up time in the cohort was 5.4 years (IQR: 4.0–8.6). The probability of having a CD4 count <350 cells/mm^3 was 0.29, 0.40, 0.55 and 0.67 at study entry, 2, 4 and 6 years, respectively (Figure 2A). The probability of having a CD4 count <500 cells/mm^3 was 0.57, 0.72, 0.79 and 0.84 at study entry, 2, 4 and 6 years, respectively (Figure 2B). These findings did not change significantly when considering the outcomes of death, loss to follow-up, initiation of ART or first CD4 count below the threshold (Figures 2A and 2B). The time for 75% of patients to reach the threshold was 3 years for 500 CD4 cells/mm^3 and 7 years for 350 CD4 cells/mm^3.

Discussion

In this cohort, almost one third of recent seroconverters had a CD4 count below the current ART eligibility threshold at first contact, about 6% more crossed it each year, and 25% still remained above this threshold until 7 years. If the threshold was raised to 500 cells/mm^3, 57% patients would be immediately eligible while 14% would remain above the threshold at 7 years.

In our study, the median time between the last negative and first positive HIV test was 8 months, and the median delay between seroconversion and enrolment was 9 months. In a study in Thailand, 17% of injection drug users had a CD4 count < 350/mm^3 after a similar time since seroconversion (8), while 65% of blood donors enrolled in another study within 2 years after seroconversion had a baseline CD4 count <500 cells/mm^3 (9). In the Cascade cohort of seroconverters from high income countries, 27% reached the 350 CD4 cells/mm^3 threshold one year after seroconversion and 55% after five years (10). Thus, the time to first CD4 count < 350/mm^3 seems shorter in our population compared to Europe and compared to in injection drug users in Thailand, but close to that reported from blood donors in Thailand. Our population of blood donors includes a high proportion of men and may not be entirely representative of the overall population of HIV-infected adults in Côte d'Ivoire who are predominantly women (11).

Different methods have been proposed to estimate the date of seroconversion. In this cohort, we used the mid point between last negative and first positive test, a method commonly used by others (12–16). Alternative methods, including Weibull analysis, lead to similar estimates (17). In this study, however, we used the date of first contact with care as time zero, rather than the date of seroconversion. Contrary to the latter, the date of entry into care is accurately known and can been used as a landmark by policy makers. We wanted entry into care to be as close as possible to seroconversion, while also being something that could be reached in the real life. Enrolment in a seroconverter cohort represents the earliest entry into care that could be reached in programs offering HIV testing on a pluri-annual basis.

Our findings have two practical implications.

First, the high proportion of individuals whose CD4 count was already below the current threshold for ART strongly suggests that efforts should be made to diagnose HIV-infection as soon as possible after seroconversion. This requires implementation of HIV testing in the general population much more frequently than it is currently done (2), and even more so if guidelines continue to move toward higher CD4 thresholds for ART initiation (18).

Second, even if the CD4 threshold for treatment was raised to 500 cells/mm^3, a minority, but still significant proportion of patients, would remain untreated for many years. Knowing

who these patients are and how they participate in the HIV transmission would be critical in the current debate considering ART as a prevention tool (4).

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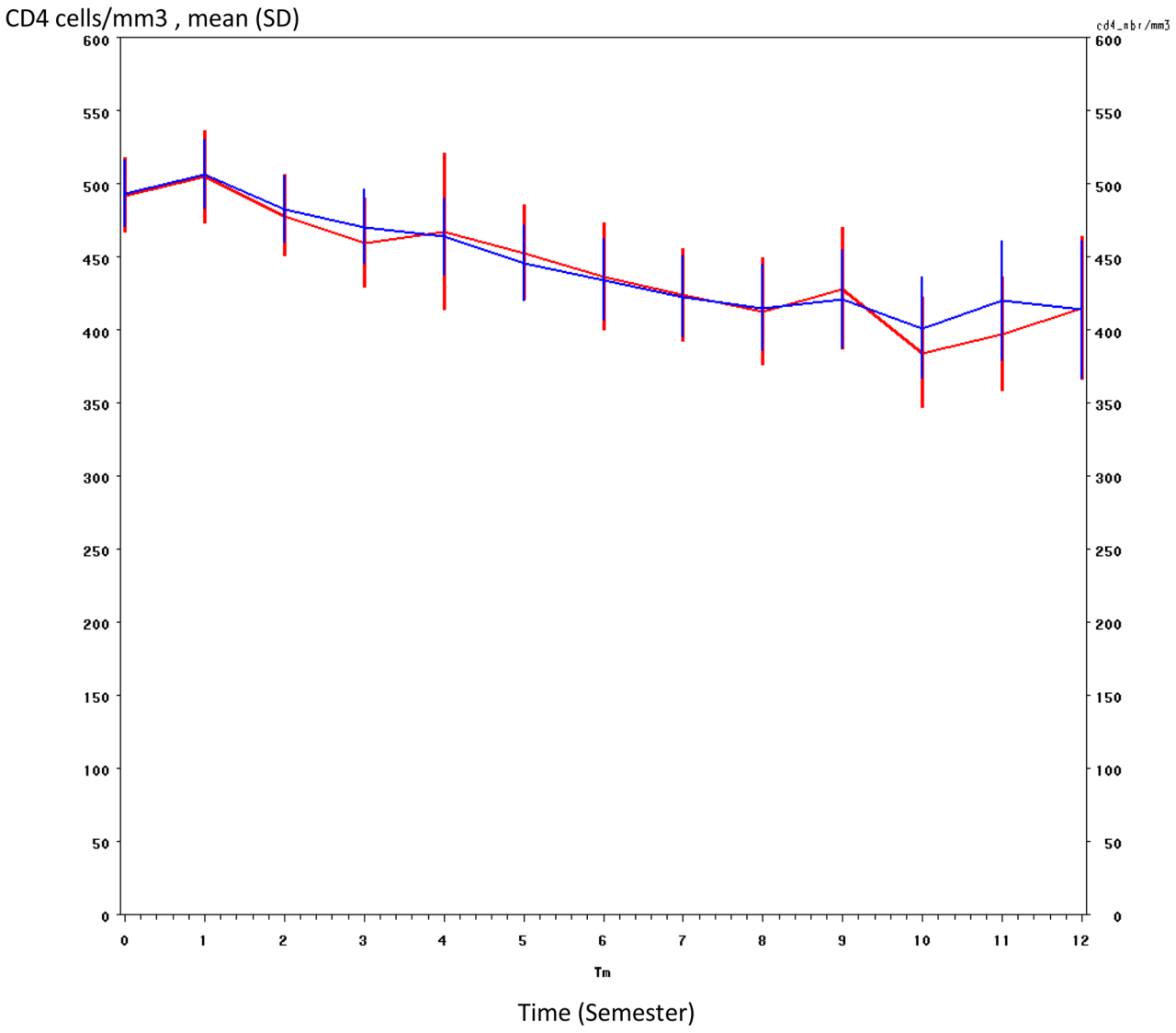
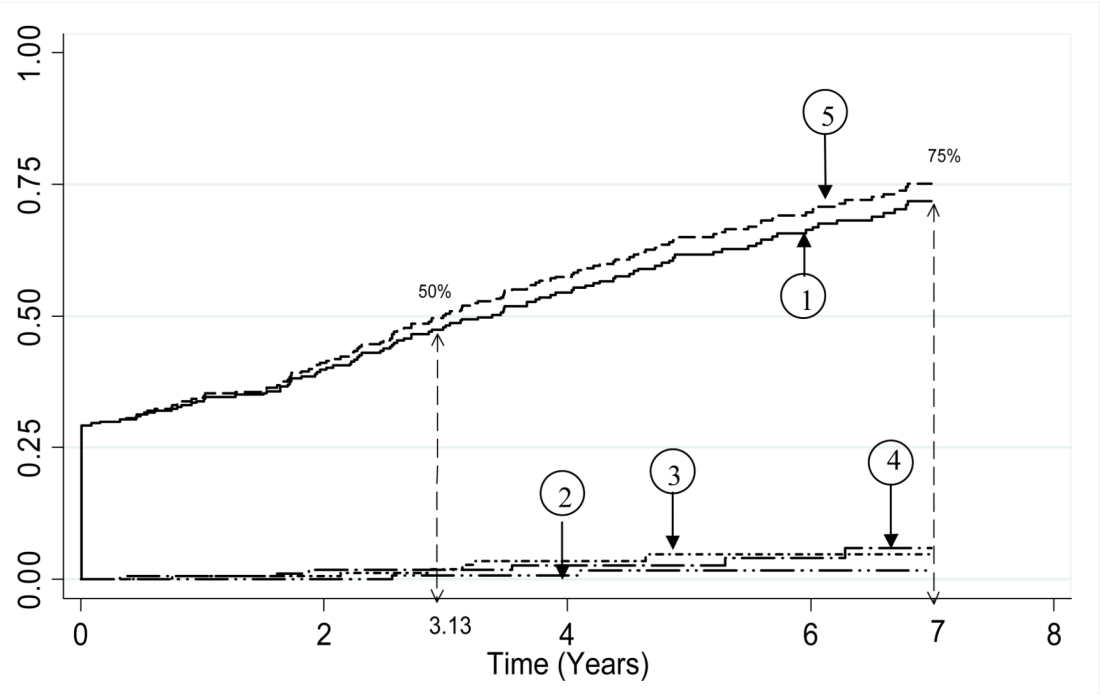


Figure 1. CD4 cell model validation

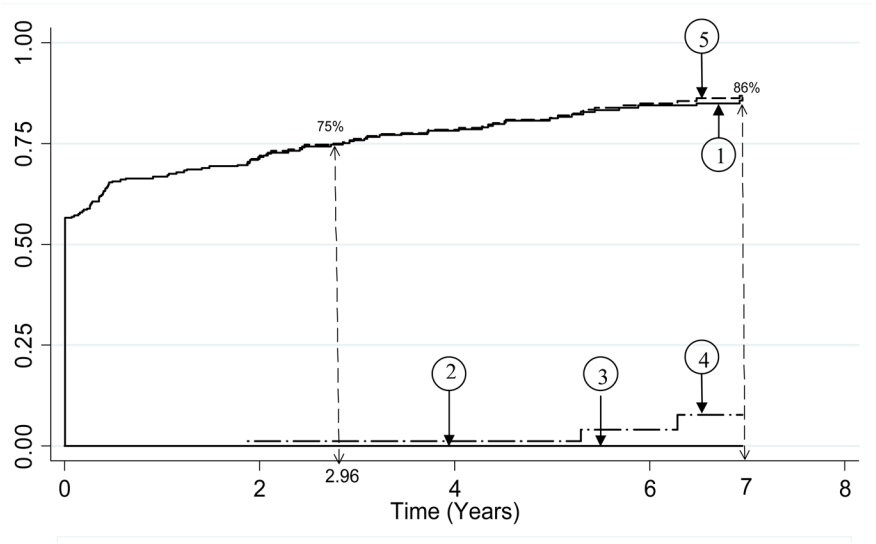
Blue line : predicted by the model

Red line : values actually recorded in the cohort



1. Probability of having a CD4 count below 350 cells/mm^3 (see figures in the table below)
2. Probability of being lost to follow-up
3. Probability of starting antiretroviral therapy
4. Probability of death
5. Probability of the first event among the following: death, ART initiation, LTFU, and CD4 count <350/mm^3

	Time from study entry (years)							
	0	1	2	3	4	5	6	7
Number of events	89	104	123	145	164	180	190	199
Number at risk	304	177	151	128	106	72	55	37
Probability of having a CD4 count below 350 cells/mm^3	0.29	0.34	0.40	0.48	0.55	0.62	0.67	0.75
95% CI	0.25-0.35	0.29-0.40	0.35-0.46	0.43-0.54	0.49-0.61	0.56-0.68	0.61-0.73	0.69-0.81



1. Probability of having a CD4 count below 500 cells/mm^3 (see figures in the table below)
2. Probability of being lost to follow-up
3. Probability of starting antiretroviral therapy
4. Probability of death
5. Probability of the first event among the following: death, ART initiation, LTFU, or CD4 count <500/mm^3

	Time from study entry (years)							
	0	1	2	3	4	5	6	7
Number of events	172	204	216	228	234	240	247	251
Number at risk	304	92	75	63	54	39	28	20
Probability of having a CD4 count below 500 cells/mm^3	0.57	0.67	0.72	0.76	0.79	0.81	0.84	0.87
95% CI	0.51-0.62	0.62-0.72	0.66-0.77	0.71-0.81	0.74-0.83	0.76-0.86	0.80-0.89	0.83-0.91

Figure 2.

Figure 2A: Cumulative probability of having a CD4 count below 350 cells/mm^3 in recently HIV-1 infected adults, ANRS 1220 PRIMO-CI cohort 1997–2009

Figure 2B : Cumulative probability of having a CD4 count below 500 cells/mm^3 in recently HIV-1 infected adults, ANRS 1220 PRIMO-CI cohort 1997–2009