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Difference in Absolute CD4+ Count According to CD4 Percentage between Asian and Caucasian HIV-Infected Patients

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Abstract

We compared the absolute CD4+ count, at different CD4+ percentages (CD4%), between Asian (n=442) and Caucasian (n=674) untreated HIV-infected individuals, using linear regression methods. At any given CD4%, Asians had lower CD4+ count than Caucasians (p=0.001). The difference varied from 38.9 cells/mm^3 (95% CI: 3.3-74.5 cells/mm^3) at CD4% of 15% to 108.7 cells/mm^3 (95% CI: 42.5-174.9 cells/mm^3) at CD4% of 40%. The impact of these differences on prognosis is uncertain, but it may be that the prognostic thresholds for CD4+ count used in Caucasian populations are inappropriate in Asian populations.

Keywords: Race; CD4+ count; CD4+; Asian; Caucasian

Introduction

The CD4+ T-cell lymphocyte count (henceforth CD4+ count) is one of the most important prognostic factors for progression of HIV infection, and forms the basis for international recommendations for antiretroviral treatment and prophylaxis [1]. However, comparative studies between African and European populations suggest that total lymphocyte count (TLC), including CD4+ count, is likely to vary significantly by ethnicity, in both, healthy [2] and HIV-infected individuals [3]. A comparison between French and West-African HIV-infected individuals suggested that the CD4+ count of 200 cells/mm^3 in French individuals would be equivalent to the count of 250 cells/mm^3 in West African individuals, in terms of HIV disease stage [3]. Although similar comparative studies between Asian and Caucasian populations are lacking, previous studies in healthy, and HIV-infected Asian individuals had raised the hypothesis that Asians may have different CD4+ counts than Caucasians [4-8]. A reference-range finding study on healthy Chinese individuals found the CD4+ count to be 727 cells/mm^3 (standard deviation (SD): 255 cells/mm^3), as compared to that of 844 cells/mm^3 (SD 247 cells/mm^3) in Caucasian individuals [9,10]. However, these studies did not evaluate this hypothesis by any formal comparison between the two ethnicities. It is therefore not clearly understood whether Asian HIV-infected population, at any given disease stage of HIV, have different CD4+ count, as compared to their Caucasian counterparts. It is important to investigate the possible racial difference, since most of the clinical research in HIV has been conducted in Caucasian populations and is assumed to hold true for Asian population.

Aim

The aim of this study is to compare CD4+ counts between Asian and Caucasian untreated HIV-infected individuals at various CD4+ percentage (CD4%) strata. We assume that a given CD4% strata indicates similar disease stage of HIV infection in both the populations, as CD4% is known to be the more stable marker of disease stage of HIV infection [11-14] and has been used in similar comparative studies between African and European HIV-infected populations [3].

Methods

Study population

The study population for this analysis were people enrolled in the TREAT Asia HIV Observational Database (TAHOD), who are predominantly Asian and in the ANRS CO3 Aquitaine cohort (French prospective open cohort), who are predominantly Caucasian, for whom pre-treatment TLC and CD4+ counts were available. The detailed methodology of both the cohorts has been published elsewhere [15-17]. Briefly, prospective data collection for TAHOD commenced in 2003, with retrospective data provided where available. In TAHOD, data are collected from 17 clinical sites in Asian region. The Aquitaine Cohort is a prospective hospital-based cohort of HIV-1-infected patients under routine clinical management, initiated in 1987 in the Bordeaux University Hospital and four other public hospitals in Aquitaine (south-western, France) by the Groupe d'Epidemiologie Clinique du Sida en Aquitaine (GECSA) [17]. For the present analysis, we extracted pre-treatment total lymphocyte count, absolute CD4+ count and corresponding CD4%, in addition to baseline variables (Table 1), from participants in both cohorts. The CD4+ counts used for this study were measured as the part of routine care at respective TAHOD and Aquitaine sites by the flow cytometry methods [15,16].

Statistical analysis

TLC and CD4+ counts, after square root transformation to

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normalise the distributions, were compared between the cohorts, after stratification by CD4%, categorised as <5%, 5-10%, 10-15%, 15-20%, 20-25%, and >25%. Linear regression analysis was used to predict CD4+ count based on corresponding CD4% in both cohorts. All analyses were performed using STATA (STATA Corp, USA) version 9.

Results

A total of 442 patients from TAHOD cohort and 674 patients from Aquitaine cohort, with data available before starting treatment, were included in this study, with demographics shown in (Table 1). Compared to Aquitaine patients, TAHOD patients were in a more advanced stage of immune deficiency in terms of AIDS disease stage (40% vs. 18% in CDC category C, $p<0.001$), median CD4+ count (111.5 vs. 260 cells/mm^3, $p<0.001$) and median CD4% (8.1% vs. 16.3%, $p<0.001$).

TLC and CD4+ count from TAHOD and Aquitaine patients, stratified by CD4%, are summarised in (Table 2a) and (Table 2b), respectively. In general, for a given CD4% strata, TAHOD patients had lower TLC and CD4+ count, as compared to Aquitaine cohort (p for heterogeneity= 0.03 and 0.001, respectively). When predicted absolute CD4+ count were calculated according to CD4% for both the cohorts using linear regression, the difference in CD4+ counts between both cohorts was found to be dependent on the level of CD4%, with a larger CD4%, giving a larger estimated difference. The estimated difference in absolute CD4+ count varied from 38.9 cells/mm^3 larger in Aquitaine (Caucasians) (95% CI: 3.3 - 74.5 cells/mm^3) at CD4% of 15% to 66.8 cells/mm^3 (95% CI: 19.0-114.6 cells/mm^3) at CD4% of 25% and 108.7 cells/mm^3 (95% CI: 42.5 - 174.9 cells/mm^3) at CD4% of 40%. (Figure 1) illustrates this relationship between absolute CD4+ counts and CD4% in TAHOD and Aquitaine cohorts, suggesting that the predicted CD4+ counts were overall higher in Aquitaine as compared to the TAHOD and this difference increased with increasing CD4%.

Discussion

In this cross-sectional analysis comparing CD4+ counts in untreated Asian and Caucasian HIV-infected patients, we found that at any given CD4% strata, Asians tended to have lower TLC, and correspondingly lower CD4+ count, compared to Caucasians, and this difference was most prominent at higher CD4%. Several explanations could possibly account for these observed differences in CD4+ count [18]. Firstly, total lymphocyte and CD4+ count is negatively affected by the poor nutritional status [19,20], and the prevalence of under-

Characteristics		TAHOD	%	Aquitaine	%	Characteristics		TAHOD	%	Aquitaine	%
No.		**442**		**674**							
Gender						**Body mass index (kg/m²)**					
	Male	350	79	559	83		Median	19.9		22.1	
	Female	92	21	115	17		IQR	14.2-26.4		14.4-33.7	
Age (years)							Unknown	294	67	118	18
	Median	34		38		**CD4 count cells/mm³**					
	IQR	20-72		19-73			Median	111.5		260	
	Missing	1	<1	121	18		IQR	2-707		2-1078	
Exposure						**CD4 percent**					
	MSM	86	19	337	50		Median	8.1		16.3	
	Heterosexual	308	70	207	31		IQR	0.3-33.9		0.33-43.3	
	IDU	5	1	65	10	**HIV viral load (copies/mL)**					
	Blood transfusion	14	3	14	2		Median	93300		79312.5	
	Perinatal	1	<1	1	<1		IQR	14636-360900		21210-253920	
	Unknown	28	6	50	7		Not tested	283	64	62	9
Clinical classification for HIV infection						**Haemoglobin level (g/dL)**					
	A	203	46	444	66		Median	12.2		13.6	
	B	64	14	108	16		IQR	7-17		6.7-17.1	
	C	175	40	122	18		Not tested	84	19	0	0
Hepatitis B infection						**Hepatitis C infection**					
	No	217	49	576	85		No	187	42	493	73
	Yes	25	6	33	5		Yes	27	6	106	16
	Not tested	200	45	65	10		Not tested	228	52	75	11

Note: CD4 count= CD4+ T-cell count/mm^3, CD4 percent= CD4+ T-cell percentage, TAHOD= Treat Asia HIV Observational Database, BMI= Body Mass Index measured as weight in kg divided by square of height in meters, MSM= Men who have sex with men, IDU= Intravenous drug users, IQR= Inter-quartile range.

Table 1: Demographics of patients before antiretroviral treatment from TAHOD and Aquitaine.

CD4% strata	TAHOD		Aquitaine	
	N	**Mean TLC (SD)**	**N**	**Mean TLC (SD)**
<5	141	1146.1 (676.6)	79	1026.1 (652.1)
5-<10	120	1514.7 (805.4)	95	1613.8 (980.5)
10-<15	92	1523.4 (618.1)	130	1769.9 (907)
15-<20	43	1602.4 (697.6)	125	1690.8 (762.1)
20-<25	30	1610.8 (856.4)	96	1681.0 (720.6)
25+	16	1303.9 (532)	149	1700.9 (540.5)
Total	442	1406.3 (733.5)	674	1618.2 (796.6)
p-value* for heterogeneity		**0.03**		

Table 2a: Mean Total lymphocyte count count (cells/mm^3) from TAHOD and Aquitaine patients, stratified by CD4%.

CD4% strata	TAHOD		Aquitaine	
	N	Mean CD4+ count (SD)	N	Mean CD4+ count (SD)
<5	141	32.1 (30.8)	79	26.8 (26.2)
5-<10	120	110.2 (58.6)	95	120.9 (77.9)
10-<15	92	187.5 (76)	130	219.7 (115.8)
15-<20	43	268.6 (117.3)	125	294.9 (134.1)
20-<25	30	353.5 (181.1)	96	376.8 (166.5)
25+	16	405.6 (167.1)	149	520.6 (182.5)
Total	442	144.0 (136.1)	674	286.0 (209.8)
p-value* for heterogeneity		**0.001**		

*The differences were tested by standard analysis of variance method, where the square roots of TLC and CD4+ counts were used to normalize distributions. TAHOD=Treat Asia HIV Observational Database. TLC= Total Lymphocyte count. CD4+ count = CD4+ T-cell lymphocyte count cells/mm^3. CD4%= CD4+ T-cell percentage. SD=Standard Deviation.

Table 2b: Mean CD4+ count (cells/mm^3) from TAHOD and Aquitaine patients, stratified by CD4%.

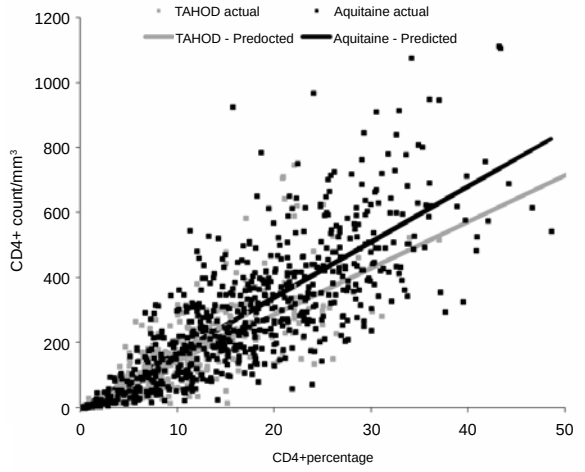

Figure 1: Observed and predicted linear relationship between CD4+ T-cell count/mm^3 and CD4+ percentage for the TAHOD and Aquitaine cohorts.

nutrition is generally higher in Asians [21]. Second, environmental factors including higher prevalence of background infections, such as Tuberculosis in Asian countries [22], may account for some of these differences [23]. Also, these differences may be related to possible variations in other cells of the immune system, such as CD8+ T-cells or Natural Killer (NK) cells [5]. Lastly, these differences could be due to true genetic variations between Asian and Caucasian ethnicity. If similar differences are observed in Asians who are raised in Western countries, then the genetic basis for the observed differences could be asserted.

The clinical impact of the difference in absolute CD4+ count between the two populations is unknown. If a given CD4+ count is found to have the same prognostic value in Asian and Caucasian populations, then these differences are unlikely to be of clinical significance, especially since these differences were only obvious in our data at higher CD4%, where clinical events are less likely to occur. Conversely, if a given CD4+ count is found to have different prognostic value in Asian and Caucasian populations, then it would imply that thresholds defined in Caucasian populations may not be appropriate in Asian populations. Further research in this area should therefore focus on investigating the clinical significance of these differences. Although this could be best investigated in Asians raised in Western countries; comparing large prospective cohorts from Asian countries to those from Western countries could also provide crucial insight into the subject.

This study is limited by the assumption that a given CD4% indicates similar disease stage in two populations. Although CD4% is known to be the more reliable marker of disease stage than CD4+ count [11,12], it may itself vary between the two populations [5]. However, for our analysis, it was the best proxy available for disease stage and duration of HIV infection [3]. Further, the studied populations are highly heterogeneous and our study may not have accounted for all the differences. The variation in laboratorial methods of measuring CD4+ counts could introduce an error; although it is unlikely that it would result in systematic differences in CD4+ counts between the two cohorts, as observed in our study. Also, we did not account for different subtypes of HIV-1 that may be prevalent in the two cohorts [24]. However, there is little evidence of subtype differences in disease progression [25,26]. We did not divide Asian ethnicity into its various sub-types (e.g. Indians, Thai, Chinese etc.), to avoid loss of power. This is unlikely to influence our results as CD4+ counts are known to be largely similar amongst various Asian populations [4,8]. Lastly, co-infection status was not available for a considerable proportion of our study populations, which is especially important as it is known to have detrimental effect on CD4+ count [27].

In summary, we have shown that for a given CD4% strata, Asian (TAHOD) patients have a lower CD4+ count than Caucasian (Aquitaine) patients. The impact of the difference in absolute CD4+ count by CD4% strata on prognosis is uncertain, but it may be that the prognostic thresholds for CD4+ count used in European and North American populations are less appropriate in Asian populations.

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Conflict of Interest

None of the authors declare any conflict of interest.

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