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CASE REPORT

Differences and Similarities between Cohorts of HIV-Infected Long-Term Non-Progressors, Elite Controllers and Chronic Progressors, Followed Prospectively in South Africa

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Abstract

Background: We compared sociodemographic, behavioral and clinical characteristics of HIV-infected long-term non-progressors (LTNPs), elite controllers (ECs) and progressors (CPs) to describe differences that may contribute to rates of disease progression. These unique groups of controllers (LTNPs and ECs) provide insights into factors that may influence differential control of HIV infection in the absence of antiretroviral therapy.

Methods: An observational study collecting CD4 and viral load data was conducted prospectively between 2002 and 2016. Three groups were purposively selected: LTNP's with sustained CD4 cell counts >500 cells/dl for at least seven years, EC's with suppressed viral loads <400 copies/ml at least six months apart, and progressors with a progressive CD4 count decline from CD4>500. Fishers-exact and Kruskal-Wallis tests compared categorical and continuous data between groups.

Results: We identified 24 LTNPs, 15 ECs and 109 CPs. Of these, 87.8% were females and median age was 36.3 years. LTNPs had significantly higher median baseline CD4 counts (897 vs 607; p<0.0001) and BMI (31.9 vs 25.5; p=0.0014) than CPs. At the last visit, the median CD4 count of LTNPs (561 vs 205; p<0.0001) and ECs (639 vs 205; p<0.0001) was higher than CPs. CPs were more likely to have reported alcohol use than ECs (67.9% vs 40%, p=0.045).

Conclusions: Our data shows that higher BMI may be a predictor of slower CD4 decline in HIV-infected individuals. Alcohol consumption may hasten disease progression. Understanding these mechanisms requires further research. Universal Test and Treat (UTT) antiretroviral therapy (ART) guidelines make studies on LTNPs and ECs more difficult.

Keywords: Long-Term Non-Progressors; Elite Controllers; Chronic Progressors; Body Mass Index

Abbreviations: LTNP: long term non-progressor; EC: Elite controller; CP: Chronic progressor; BMI: Body mass index; UTT: Universal Test and Treat; ART: Antiretroviral therapy

Introduction

HIV prevalence rates in sub-Saharan Africa are amongst the highest in the world. In 2016, an estimated 53% of HIV-infected individuals resided in sub-Saharan Africa [1]. Heterogeneity in phenotypic responses to HIV infection suggest different rates of progression to AIDS [2-5]. Although the vast majority of HIV-infected individuals are categorized as chronic progressors (CPs) and, in absence of anti-retroviral therapy (ART), will progress to AIDS approximately a decade after seroconversion [6], two controller phenotypic manifestations of HIV infection and progression are described in people in the absence of ART. Long-term non-progressors (LTNP's) are able to maintain their CD4 count above 500 cells/mm^3 in the absence of ART over a period of at

least ten years [7]. Reports from Europe and USA suggest about one tenth of all HIV-infected individuals are LTNP's [8,9] but a far smaller proportion of 2.6% was reported in a cohort study from South Africa [10]. Elite controllers (EC's), comprise less than 1% of HIV-infected individuals and are able to maintain undetectable HIV viral loads for at least six months in the absence of ART [11]. There is a paucity of data from sub-Saharan Africa on the two controller phenotypes, where HIV is most prevalent; EC's have been studied in-depth in North American and European cohorts and provide a model for functional cure of HIV infection [12,13]. Studies from African countries describing controller phenotypes have small sample sizes and various definitions [14-18]. Furthermore, in Africa, there is limited information on elite controllers due to previously limited availability of assays to detect viral loads < 50 [7]. Elite controllers have rarely been described in South Africa, usually single case reports describing sustained viral suppression [19,20].

Universal test and treat (UTT) strategies since September 2016 [21,22] make it increasingly less likely that the controller LTNP and EC phenotypes will be identified and described. However, they may contribute to understanding immune protection. We report a cohort of LTNP's and EC's and compare them to a group of chronic progressors (CPs) to describe clinical, behavioral and sociodemographic differences between the phenotypes.

Methods

We identified adults (≥ 18 years) who fulfilled study case definitions of these phenotypes firstly from several cohorts of HIV-infected adults followed up prospectively in Soweto between 2002 and 2014 in three studies [10,23,24] and secondly from patients identified in routine testing in Soweto, Gauteng Province and Matlosana, North West Province who also had a viral load taken at time of first HIV diagnosis. Eligibility criteria for all three phenotypes were: HIV-infected, antiretroviral naïve adults (age ≥ 18 years) with at least annual CD4 count measurements; and first ever recorded CD4 count record of >500 cells/mm^3. For the purposes of this study, LTNPs were defined by CD4 counts >500 cells/mm^3 for at least 7 years, without a definite downward trend in CD4 count but allowing one CD4 count of >450 cells/ mm^3 during follow up with all subsequent CD4 counts >500 cells/mm^3. ECs were required to maintain HIV viral load <400 copies/ml for at least 12 months or, if follow up was longer than six months, over the entire follow up period, allowing one VL >400 copies/ml, provided it was followed by at least another subsequent VL <400 copies/ml. Our limit of 400 copies/ml is higher than the current definition of 50 copies/ml but in line with previously used definitions before HIV VL tests became more sensitive [9]. The HIV-1 Amplicor viral load test was used during follow up with a viral load cut-off of 200 copies per ml. The lower limit of HIV viral load detection in South Africa at the time when the study started was 400 using an older test. Over time viral load testing improved and detection limits became more sensitive. CPs were defined by their first treatment naïve CD4 count at study entry of >500 cells/mm^3 and to have a clear decline in serial CD4 cell counts over at least 2 years to <350 cells/mm^3. These participants were purposely selected from a larger cohort as a comparative group.

Data of those with the CP phenotype identified and followed up in prior studies were included in this analysis but were not re-contacted. We recontacted those with apparent HIV controller phenotypes (EC and LTNP). If this was successful, they were requested to consent to a new prospective cohort to confirm their controller status. To identify additional adults with the rare EC phenotype, study staff reviewed newly diagnosed HIV-infected adults who had their plasma VL ascertained prior to initiation of ART. Those with initial VL <1000 copies/ml were approached, and once they confirmed their antiretroviral naive status, were requested to consent to prospective follow up. All followed up participants had a similar set of interviews conducted as those who were followed up in prior cohorts.

All prior sociodemographic, behavioral, anthropomorphic, viral load and CD4 data from prior and current cohorts was included in this study as well as that collected in real time follow up. Ethical approval for all studies used in this analysis was granted by the Wits Human Research Ethics Committee. Written informed consent was obtained from each participant prior to initiating any screening procedures.

Statistical Analysis

Frequencies were determined for categorical variables and means (standard deviations) and medians (interquartile ranges (IQR)) calculated for continuous measures. We conducted an overall comparison between LTNP's and EC's against CP's (Table 1). Additionally, a sensitivity analysis was conducted for only women that compared LTNP's and EC's against CP's, since they formed a majority (Supplementary Tables 2a and 2b). Categorical and continuous measures were compared by the Fishers exact and Kruskal-Wallis non-parametric tests respectively.

Variables	Long-term non-progressors	Elite controls (n=15)	Chronic progressors (n=109)	P-Value (LTNP vs CP)	P-Value (EC vs CP)
Female Gender	22 (91.7)	12 (80.0)	96 (88.1)	0.99	0.410
Median age in years (IQR)	36.4 (34.0-39.7)	36.2 (33.2-41.0)	36.2 (32.4-41.1)	0.9068	0.8511
Educational level					
None	0 (0.0)	0 (0.0)	2 (1.8)		
Grade 0-5	1 (4.2)	1 (6.7)	6 (5.5)		
Grade 6-11	11 (45.8)	9 (60.0)	75 (68.8)		
Grade 12	4 (16.7)	3 (20.0)	25 (22.9)		

Variables	Long-term non-progressors	Elite controls (n=15)	Chronic progressors (n=109)	P-Value (LTNP vs CP)	P-Value (EC vs CP)
Degree/Diploma	8 (33.3)	2 (13.3)	1 (0.9)		
Unemployment	11 (45.8)	10 (66.7)	69 (63.3)	0.166	0.99
Income per month#					
0-1000 Rands	13 (54.2)	9 (60.0)	66 (60.6)	-	-
1001-2000 Rands	3 (12.5)	4 (26.7)	29 (26.6)		
>2000 Rands	8 (33.3)	2 (13.3)	14 (12.8)		
Ever smoked cigarettes	7 (29.2)	3 (20.0)	22 (20.2)		0.99
Median cigarettes smoked (IQR)	3.0 (2.0-3.0)	2.0 (2.0-11.0)	5.5 (4.0-10.0)	0.1070	0.4726
Ever consumed alcohol	11 (45.8)	6 (40.0)	74 (67.9)	0.059	0.045
Condom use with regular partner	14 (58.3)	12 (80.0)	50 (60.2)	0.99	0.244
Condom use with casual partner	4 (16.7)	1 (8.3)	6 (7.2)	0.227	0.455
BMI					
Underweight (<18.5)	0 (0.0)	0 (0.0)	1 (0.9)		
Normal (18.5-24.9)	4 (16.7)	7 (46.7)	46 (42.6)	-	-
Overweight (24.9-29.9)	5 (20.8)	5 (33.3)	28 (25.9)		
Obese (>30)	15 (62.5)	3 (20.0)	33 (30.6)		
Mean (SD)	32.5 (7.2)	26.1 (5.6)	27.4 (6.5)	0.0010	0.4671
Median (IQR)	31.9 (28.0-35.1)	26.3 (21.5-29.7)	25.5 (22.3-32.3)	0.0014	0.5364
STI in the past 6 months	3 (12.5)	0 (0.0)	19 (17.4)	0.764	0.210
Lymphadenopathy	3 (12.5)	1 (6.7)	4 (3.7)	0.111	0.481
Ever had TB	2 (8.3)	0 (0.0)	6 (5.5)	0.635	0.99
CD4 Count (cells/mm^3)					
Mean (SD)	867 (198)	807 (236)	661 (172)	<0.0001	0.0050
Median (IQR)	897 (708-971)	859 (620-918)	607 (547-713)	<0.0001	0.0165
Minimum, Maximum	562 to 1290	417 to 1294	500 to 1396		
Viral Load (Copies/ml)					
< 400	Not Applicable	9/11 (81.8)	5/77 (6.5)	Not Applicable	<0.0001
Mean (SD)	Not Applicable	1.8 (0.6)	4.0 (0.7)	Not Applicable	<0.0001
Median (IQR)	Not Applicable	1.6 (1.3-2.2)	4.1 (3.8-4.4)	Not Applicable	<0.0001
Minimum, Maximum	Not Applicable	1.3 to 2.9	1.7 to 5.2		

*Column totals for some variables may not add up to the number enrolled due to missing values

Rand/dollar exchange rate at the time of study (2002) 1 Dollar=10.52 Rands

Table 1: Participant socio-demographic and behavioral characteristics

Variables	Long-term non-progressors (n=22)	Elite controls (n=12)	Chronic progressors (n=96)	P-Value (LTNP vs CP)	P-Value (EC vs CP)
Gender					
Female	22 (100)	12 (100)	96 (100)	-	-
Age-group					
18-35 years	10 (45.5)	6 (50.0)	41 (42.7)	0.816	0.760
>35 years	12 (54.5)	6 (50.0)	55 (57.3)		
Mean (SD)	36.7 (5.9)	34.9 (7.7)	36.7 (6.6)	0.9772	0.3728
Median (IQR)	35.8 (33.7-39.2)	35.3 (30.9-40.0)	36.0 (32.2-40.6)	0.8629	0.6671
Minimum, Maximum	27.2 to 51.1	19.1 to 47.0	24.7 to 59.6		
Educational level					
None	0 (0.0)	0 (0.0)	2 (2.1)	-	-
Grade 0-5	1 (4.5)	1 (8.3)	5 (5.2)		
Grade 6-11	10 (45.5)	6 (50.0)	67 (69.8)		
Grade 12	4 (18.2)	3 (25.0)	21 (21.9)		

Variables	Long-term non-progressors (n=22)	Elite controls (n=12)	Chronic progressors (n=96)	P-Value (LTNP vs CP)	P-Value (EC vs CP)
Degree/Diploma	7 (31.8)	2 (16.7)	1 (1.0)		
Employment					
No	11 (50.0)	9 (75.0)	64 (66.7)	0.151	0.748
Yes	11 (50.0)	3 (25.0)	32 (33.3)		
Own a mobile phone					
No	1 (4.5)	0 (0.0)	6 (6.3)	0.99	0.99
Yes	21 (95.5)	9 (100)	90 (93.8)		
Marital status					
Married	4 (18.2)	2 (22.2)	13 (13.5)	-	-
Other	1 (4.5)	1 (11.1)	20 (20.8)		
Single	17 (77.3)	6 (66.7)	63 (65.6)		
Income per month					
0-1000 Rands	12 (54.5)	7 (58.3)	62 (64.6)	-	-
1001-2000 Rands	3 (13.6)	4 (33.3)	24 (25.0)		
>2000 Rands	7 (31.8)	1 (8.3)	10 (10.4)		
Ever smoked					
No	16 (72.7)	11 (91.7)	86 (89.6)	0.076	0.99
Yes	6 (27.3)	1 (8.3)	10 (10.4)		
Mean cigarettes smoked (SD)	2.6 (0.5)	2.0 ()	7.8 (8.4)	0.1967	0.5257
Median cigarettes smoked (IQR)	3.0 (2.0-3.0)	2.0 (2.0-2.0)	5.5 (4.0-10.0)	0.0640	0.3384
Minimum, Maximum	2.0 to 3.0	2.0 to 2.0	1.0 to 30.0		
Ever taken alcohol					
No	13 (59.1)	8 (66.7)	34 (35.4)	0.054	0.057
Yes	9 (40.9)	4 (33.3)	62 (64.6)		
Ever smoked dagga					
No	20 (90.9)	9 (100)	95 (99.0)	0.089	0.99
Yes	2 (9.1)	0 (0.0)	1 (1.0)		
Age of sexual debut					
< 18 years	11 (50.0)	4 (44.4)	54 (56.3)	0.640	0.510
≥ 18 years	11 (50.0)	5 (55.6)	42 (43.8)		
Mean (SD)	17.7 (1.8)	18.8 (3.2)	17.6 (2.7)	0.9524	0.2382
Median (IQR)	17.5 (16.0-19.0)	19.0 (16.0-20.0)	17.0 (16.0-19.0)	0.5806	0.4807
Minimum, Maximum	15.0 to 22.0	15.0 to 25.0	13.0 to 27.0		
Total lifetime sexual partners					
2-5	13 (59.1)	7 (77.8)	57 (59.4)	-	-
6-1	7 (31.8)	2 (22.2)	32 (33.3)		
>10	2 (9.1)	0 (0.0)	7 (7.3)		
Mean (SD)	6.3 (5.0)	3.8 (1.6)	5.8 (3.5)	0.6150	0.0924
Median (IQR)	4.5 (3.0-8.0)	3.0 (3.0-5.0)	4.0 (4.0-8.0)		
Minimum, Maximum	2.0 to 20.0	2.0 to 6.0	2.0 to 20.0		
Condom use regular partner					
Always	13 (59.1)	9 (75.0)	41 (56.2)	-	-
Never	0 (0.0)	0 (0.0)	3 (4.1)		
No regular partner	5 (22.7)	2 (16.7)	5 (6.8)		
Occasionally	4 (18.2)	1 (8.3)	24 (32.9)		
Condom use casual partner					
Always	2 (9.1)	0 (0.0)	4 (5.5)	-	-
Never	0 (0.0)	0 (0.0)	1 (1.4)		
No regular partner	20 (90.9)	9 (100)	68 (93.2)		

Table 2a: Participant socio-demographic and behavioral characteristics (excluding males)

Variables	Long-term non-progressors (n=22)	Elite controls (n=12)	Chronic progressors (n=96)	P-Value (LTNP vs CP)	P-Value (EC vs CP)
BMI					
Normal	4 (18.2)	5 (41.7)	34 (35.8)	-	-
Obese	14 (63.6)	3 (25.0)	33 (34.7)		
Overweight	4 (18.2)	4 (33.3)	27 (28.4)		
Underweight	0 (0.0)	0 (0.0)	1 (1.1)		
Mean (SD)	32.6 (7.4)	27.0 (5.9)	28.2 (6.5)	0.0070	0.5374
Median (IQR)	31.9 (28.3-35.0)	27.3 (21.8-31.4)	26.5 (23.0-33.4)	0.0126	0.0705
Minimum, Maximum	22.7 to 53.2	20.1 to 37.7	16.6 to 44.3		
Height					
Mean (SD)	160 (4.5)	157 (4.1)	159 (5.0)	0.3044	0.3656
Median (IQR)	160 (157-163)	159 (155-160)	159 (155-162)		
Minimum, Maximum	150 to 168	150 to 163	148 to 172		
Weight					
Mean (SD)	84.0 (22)	65.8 (15)	71.2 (16)	0.0022	0.3339
Median (IQR)	81.4 (71.1-91.1)	68.3 (52.6-77.1)	68.5 (57.5-84.0)		
Minimum, Maximum	55.7 to 150	48.2 to 88.2	40.5 to 120		
STI in the past 6 months					
No	19 (86.4)	9 (100)	77 (80.2)	0.762	0.359
Yes	3 (13.6)	0 (0.0)	19 (19.8)		
Lymphadenopathy					
No	19 (86.4)	11 (91.7)	92 (95.8)	0.119	0.452
Yes	3 (13.6)	1 (8.3)	4 (4.2)		
Ever had TB					
No	20 (90.9)	12 (100)	91 (94.8)	0.613	0.99
Yes	2 (9.1)	0 (0.0)	5 (5.2)		
CD4 Count					
Mean (SD)	866 (186)	782 (246)	663 (176)	<.0001	0.0377
Median (IQR)	897 (736-969)	816 (585-918)	605 (539-718)	<0.0001	<0.0001
Minimum, Maximum	562 to 1290	417 to 1294	500 to 1396		
Viral Load (Copies/ml)					
< 400	N/A	6/8 (75)	5/65 (7.7)	N/A	<0.0001
Mean (SD)	N/A	1.8 (0.7)	3.9 (0.7)	N/A	<0.0001
Median (IQR)	N/A	1.5 (1.3-2.5)	4.1 (3.8-4.3)	N/A	<0.0001
Minimum, Maximum	N/A	1.3 to 2.9	1.7 to 5.2		

For viral load, n=8 for EC and 65 for CP;

Table 2b: Behavioural and clinical characteristics (excluding males)

Time-dependent CD4 count and $\log_{10}$ viral load for each group were plotted using the loess curve. The CD4 decline rate as well as the $\log_{10}$ viral load increase were determined using fixed effects modeling where month of visit formed the covariate. Among LTNPs, we stratified their last viral load into the groups 50-399, 400-2 000, 2 001-10 000 and > 10 000 copies/ml and determined their distribution. All statistical analysis was conducted using SAS Enterprise Guide 7.1 (SAS Institute, Cary, NC) using the SAS/STAT procedures SAS PROC FREQ and SAS PROC MIXED.

Results

In this study, of 24 LTNP's identified and followed up for a median of 8.3 years (IQR: 7.1-9.3) - nine had total follow up of seven years, three of eight years, and 12 of ≥ nine years; of 15 EC's followed for a median of 2.5 years (IQR: 0.54-4.18), six were followed up for between six and twelve months, two for two years, three for three years, two for four years, one for five years and one for 8.5 years; of the 109 CP's followed up for a median of 6.9 years (IQR: 5.0-7.5), 14 were followed up for two to four years, 20 for five years, 49 for six to seven years and 26 for ≥ eight years.

The majority (at least 80% in each group) of all participants were women. Median ages (IQR) were 36.4 years (IQR: 34-39.7), 36.2 years (IQR: 33.2-41.0) and 36.2 years (32.4-41.1) for LTNP, ECs and CPs respectively (table 1). Alcohol use self-reported by ECs (40%) was significantly lower than in that self-reported by CPs (67.9% p=0.045). LTNPs also had a trend to lower alcohol use than CPs. Condom use with a regular partner among LTNPs (58.3% vs 60.2%, p=0.99) and ECs (80.0% vs 60.2%, p=0.244) relative to CPs was similar but higher among ECs.

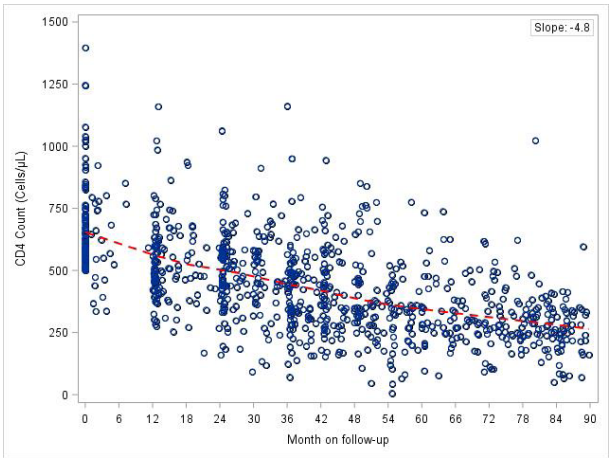

Figure 1a: CD4 count during follow-up for CPs

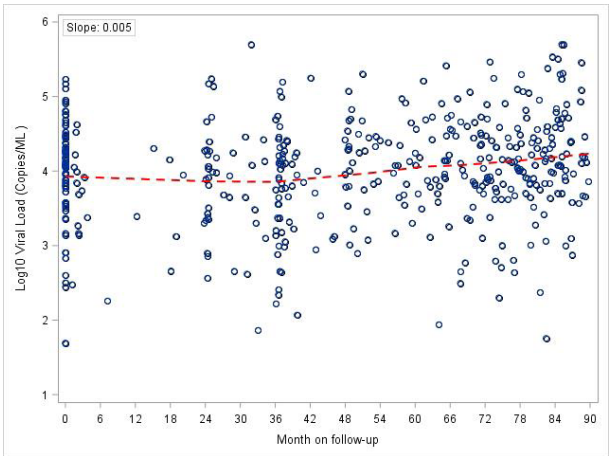

Figure 1b: Log_{10} viral load during follow-up for CPs

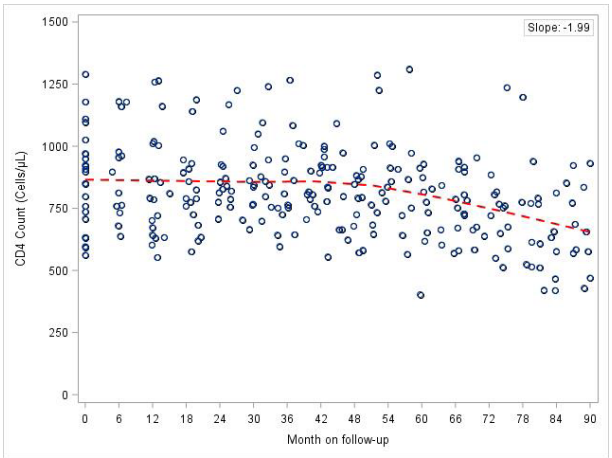

Figure 1c: CD4 count during follow-up for LTNPs

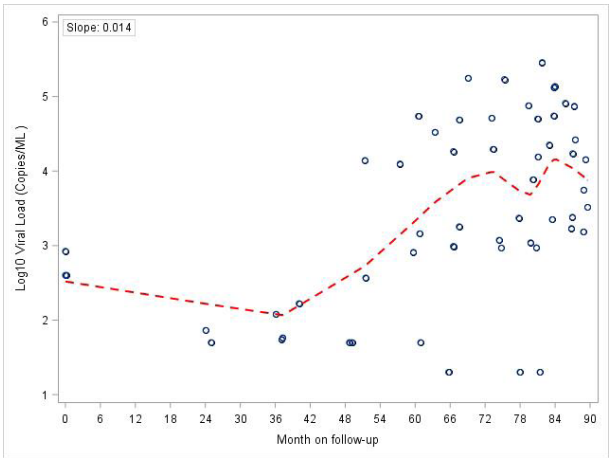

Figure 1d: Log_{10} viral load during follow-up for LTNPs

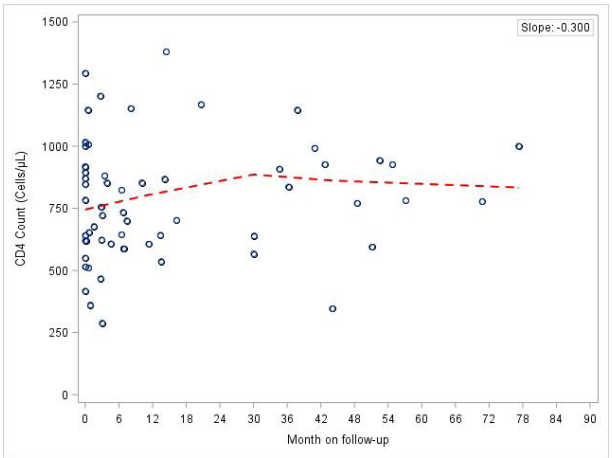

Figure 1e: CD4 count during follow-up for ECs

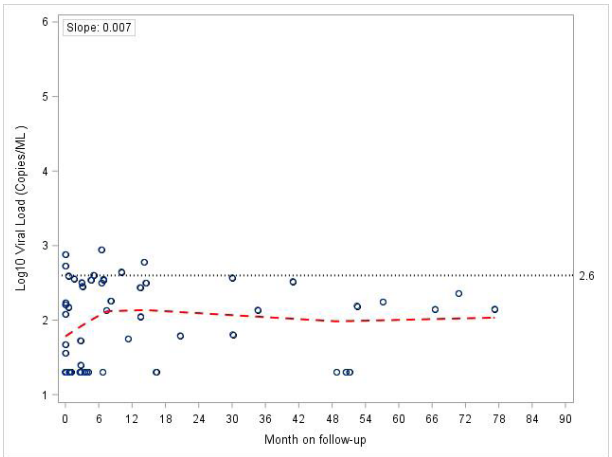

Figure 1f: Log_{10} viral load during follow-up for ECs

Figure 1: Graphs show the CD4 count and log_{10} viral load trajectories and their slopes during follow-up for CPs, LTNPs and ECs

At their baseline visit, LTNPs were more likely to be overweight or obese relative to CPs (83.3% vs. 56.5%, p=0.019) and median BMI of LTNPs was significantly larger than that of CPs (31.9 vs 25.5, p=0.0014). However, the proportion of overweight and obese ECs was similar to CPs (53.3% vs. 56.5%, p=0.789) and median BMI were almost the same.

LTNP's had significantly higher median CD4 counts on study entry (897: IQR 708-971 vs. 607: IQR 547-713; p<0.001) than CP's. Slopes of CD4 decline in LTNPs, ECs and CPs were -1.99 (95% CI: -2.6,-1.3) cells/mm^3 per month, +0.76 (95% CI: -2.6,4.1) cells/mm^3 per month and -4.8 (95% CI: -5.1,-4.6) cells/mm^3 per month, respectively (Figure 1: Graphs show the CD4 count and $\log_{10}$ viral load trajectories and their slopes during follow-up for CPs, LTNPs and ECs). However, the LTNP slopes appeared biphasic with initial period of stable CD4 count for approximately four years followed by a decline of -5.6 (95% CI: -7.6,-3.7) cells/mm^3. At the final study visit when a CD4 count was measured, median CD4 counts in LTNPs was 561 (IQR: 450.5-705), in ECs 639 (IQR: 567-908) and in CPs 205 (IQR: 156-266).

The median $\log_{10}$ viral load of LTNPs and CPs was similar (4.2 IQR: 3.5-4.7 vs 4.4 IQR: 4.1-4.9; p=0.1644) whereas unsurprisingly, ECs had a significantly lower median VL than CPs (2.2 IQR: 2.01-2.5 vs 4.4 IQR: 4.1-4.9; p<0.0001). Slopes of HIV $\log_{10}$ viral load per month for all groups were close to zero; LTNP's, EC's, CP's were 0.014 (95% CI: 0.006,0.022), 0.0051 (95% CI: -0.0047,0.016) and 0.005 (95% CI: 0.003,0.006), respectively (Figure 1). The majority of LTNPs (13/24) were able to maintain CD4 count above 500 cells/mm^3 despite VL of greater than 10,000 copies/ml.

Discussion

This observational study reports the characteristics of a relatively large cohort of HIV-infected adults, primarily women, with the LTNP and EC controller phenotypes from sub-Saharan Africa whose CD4 counts were all >500 cells/mm^3 at baseline. Although we were unable to adjust for potential confounders, our data suggests that phenotypic responses to HIV infection may be influenced by alcohol use and that BMI may be an indicator of HIV progression, even when CD4 counts are high. However, we are unable to show a cause effect relationship between these variables with currently available data.

More than three quarters of LTNPs in our study were classified as overweight or obese compared to just above half of the CPs. A study in Miami showed similar slower CD4 decline rates among overweight females than those that were underweight (25). Our findings are similar to US studies in the pre-HAART era [26-28] which reported slower CD4 decline rates in individuals with a higher BMI. Studies hypothesize that the protective mechanism against CD4 cell decline is due to higher fat mass in females resulting in increased levels of leptin, which may enhance CD4 cell proliferation (29,30). Data from South African cohorts suggests that in HIV-infected individuals, higher BMI protects against mortality and incident TB [31,32]. BMI in ECs were similar to CPs likely due to high immune activation in ECs, which might contribute to a catabolic state due to Tryptophan catabolism as it may in progressors [33,34].

Multiple reports suggest that women are diagnosed at higher CD4 counts than men, in the absence of ART, their CD4 declines are slower, and their responses to treatment are better [35,36]. This is likely due to females seeking healthcare earlier than males, the immunoregulatory effects of female hormones and better adherence to ART [37-39]. However as described by Hunt et al the improved CD4 recovery during ART in several prior published studies is unlikely to be explained by better ART adherence alone as many of them conditioned upon stably undetectable plasma HIV RNA levels [40].

Alcohol use was self-reported in a higher proportion of the LTNP group than in the other two groups. This finding is consistent with a Spanish study [41] which reported higher alcohol intake in LTNPs than progressors, the authors suggest reverse causality - to self-reported reduced alcohol intake in the progressor group as their health deteriorated. Prior reports linking alcohol intake and progression of HIV are mixed [42-44]. Heavy alcohol consumption has been reported to accelerate HIV progression in ART-naïve individuals [45]. Potential mechanisms for this effect are postulated to be a direct toxic effect on bone marrow causing lymphopenia, gastrointestinal inflammation and T cell immunosenescence [46].

Limitations include differences in calendar time of recruitment of all CPs and most LTNPs compared to the ECs who primarily were identified at routine HIV testing services several years after the LTNPs and CPs were recruited, resulting in possible bias and also shorter follow up time. We were unable to assess smoking, alcohol use and BMI at the end of the study as participants were included from multiple cohorts with different data endpoints. A selection bias might contribute to the relationship observed between alcohol use and clinical progression. It is possible that heavy alcohol users only sought clinical care when their clinical progression was more advanced compared to the other 2 groups. We are also unable to accurately attribute the impact of alcohol use on disease progression. Furthermore, no data was available on the level of alcohol or hazardous drinking. The LTNP group appear to be more highly educated and have higher income which could imply better socioeconomic status and may explain the higher BMI than the other groups. However, due to low numbers in the LTNP group we have omitted p-values and we are unable to draw conclusions on these variables. Furthermore, we acknowledge that the 3 groups are unbalanced in numbers making it difficult to draw direct conclusions.

The criteria used to identify our EC group is not as stringent as some other studies in terms of viral load and duration of follow-up due to the lack of availability of more sensitive HIV viral load assays at the time that this study was conducted.

Over the past few years there have been massive improvements in policy and access for initiation of ART. Moreover, LTNPs did not have as frequent VL assays early in their follow up. Although we defined LTNPs using a shorter follow-up duration compared to prior similar studies from Europe and USA, a large number of LTNPs had longer follow up than the study definitions required. The limited geographical region of the study sites reduces the generalizability of the study but a substantial number of these rare controller phenotypes were identified and included at a time of transition from initial low CD4 threshold-based ART initiation to universal test and treat. We have found it almost impossible to continue to identify and recruit adults with controller phenotypes as virtually all adults identified with HIV infection are almost immediately initiated on ART without a viral load being done before initiation.

This study was designed to highlight differences between the exceedingly rare two controller phenotypes (LTNPs and ECs) and those whose phenotype is by far the more usual. We primarily identified these groups to create a repository of specimens to study host immune and genetic markers associated with HIV-1 control [47,48]. It is notable that the majority of LTNP had VL stably >10 000 cells/mm^3 which may be a similar phenotype to the natural hosts of SIV where the continuous viral replication is not associated with immunopathology. CD4+ T cells in blood, lymph nodes and gut manifest no or little increase of cell-death by apoptosis [49]. This study was designed to highlight differences among the 3 groups and was not intended to be compared to novel studies that focused on genetic and viral host factors. It does however provide insight on behavioural and clinical characteristics that may contribute to HIV disease progression/stagnation and provides a platform to explore these factors with more advanced research techniques.

Conclusion

BMI in the overweight and obese range could possibly be an indicator of HIV non-progression whereas alcohol consumption could be related to a faster CD4 decline in HIV-infected individuals. The underlying mechanisms of either are not clear but similar relationships have been shown in different populations. These findings highlight the importance of considering the effect of nutrition on the rate of progression of HIV especially in less affluent communities in rural regions of South Africa where ART is not always available.

Declarations

• Ethics approval and consent to participate:
Ethical approval for all studies used in this analysis was granted by the Wits Human Research Ethics Committee. Written informed consent was obtained from each participant prior to initiating any screening procedures.

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