Long term non-progressors, viremic and elite controllers among women infected with non-subtype B HIV-1 in Mombasa, Kenya

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ABSTRACT

Background: Studies have reported ART-naïve individuals who show no apparent disease progression despite prolonged infection (long-term non-progressors; LTNPs), or spontaneously control viral replication (HIV controllers). Few of these studies have assessed their presence among populations predominantly infected with non-subtype-B HIV-1.

Methods: We conducted data analysis of a prospective cohort of HIV-1 seropositive women in Mombasa, Kenya with estimated dates of seroconversion to determine the proportion of unique HIV-1 phenotypes. Long-term non-progression was defined as duration of infection ≥10 years without ART, characterized by majority CD4+ counts within normal range (≥500 cells/mL for LTNPs-10 and ≥600 cells/mL for LTNPs-7). HIV controllers maintained plasma viral loads (PVLs) below 2000 copies/mL (viremic controllers; VCs) or below 100 copies/mL (elite controllers; ECs).

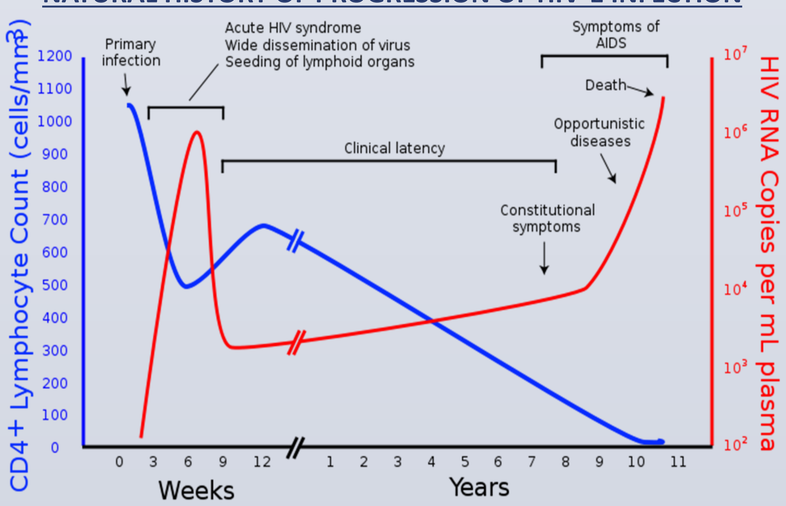
Results: There were 332 HIV-1 seroconverters between February 1993 and March 2014. Of 157 with infecting subtype data available, 121 (77%) were infected with subtype A, 20 (12.7%) subtype D, 11 (7%) subtype C, and 5 (3.1%) had inter-subtype recombinant forms. We identified 21 (6%) seroconverters with unique phenotypes. Seventeen (21%) of 83 ART-naïve women with at least 7 years of follow-up were classified as LTNP-7, while 6 (21%) of 29 women who accrued further follow-up to 10 years were classified as LTNP-10. Among women with >3 PVLs over at least 1 year of follow up post-seroconversion, we classified 7 (23%) and 1 (3%) as VCs and EC, respectively. The odds of being classified as a LTNP-7 were lower for participants who had a viral load set point higher than 4.2 log copies (OR = 0.69, 95% CI: 0.62-0.77, P <0.001) and who took longer than 168 days to achieve this set point (OR =0.73, 95% CI: 0.65-0.82, P<0.001).

Conclusion: Unique phenotypes of HIV-1 infection were identified in a population predominantly infected with non-subtype B strains of HIV-1 in Mombasa, Kenya. Long-term non-progression appears to be likely with lower viral load set point and shorter duration to achieve this.

OBJECTIVE

To determine the prevalence and characteristics of these unique HIV-1 phenotypes among women in the Mombasa Cohort; a prospective cohort study of female sex workers (FSWs) established in 1993 to characterize the incidence and correlates of HIV-1. The predominant HIV-1 subtypes previously identified in this cohort include A, C and D.

NATURAL HISTORY OF PROGRESSION OF HIV-1 INFECTION



BACKGROUND

LTNPs = ART-naïve, no apparent disease progression despite prolonged infection while **HIV controllers** = Spontaneous control over viral replication. Unique phenotypes of HIV-1 infection mainly evaluated in populations predominantly infected with subtype-B HIV-1. They form an important study group in understanding pathogenesis of natural HIV-1 infection for development of novel HIV-1 interventions including immunotherapy or a functional vaccine/cure.

METHODOLOGY

Descriptive analysis aimed at determining the presence and characteristics of these unique HIV-1 phenotypes. Study population = HIV-1 positive participants with estimated dates of seroconversion (HIV-1 seroconverters) in a prospective cohort study of FSWs in Mombasa. Study procedures included regular CD4+ lymphocyte counts (CD4+ count), plasma HIV-1 RNA/viral load (PVL). Infecting HIV-1 subtype determined by back-testing samples collected at estimated time of infection.

To estimate time of HIV-1 infection, stored plasma samples obtained during visits prior to sero-conversion were back-tested to identify any that were HIV-1 RNA positive. If one or more of these pre-seroconversion samples was positive for HIV-1 RNA, the estimated date of infection was considered to be 17 days prior to the first RNA-positive sample. If none of the pre-seroconversion samples was positive for HIV-1 RNA, the estimated date of HIV-1 infection was the mid-point between the last HIV-1-seronegative visit and the first HIV-1-seropositive visit

DEFINITION OF UNIQUE PHENOTYPES

LTNP–7

- ≥2 CD4+ counts over ≥7 years
- Majority CD4 counts ≥600 cells/mL
- No prior ART
- Non-progressive CD4+ lymphocyte pattern over time

LTNP–10

- ≥2 CD4+ counts over ≥10 years
- Majority CD4 ≥500 cells/mL
- No prior ART
- Non-progressive CD4+ lymphocyte pattern over time

Viremic Controllers

- ≥3 PVLs over ≥12 months post-seroconversion
- Majority PVL measures detectable but ≤2000 copies/mL
- No prior ART
- Pattern of virologic control over time

Elite Controllers

- ≥3 PVLs over ≥12 months post-seroconversion
- Majority PVL measures undetectable using standard assays
- No prior ART
- Pattern of virologic control over time

FINDINGS

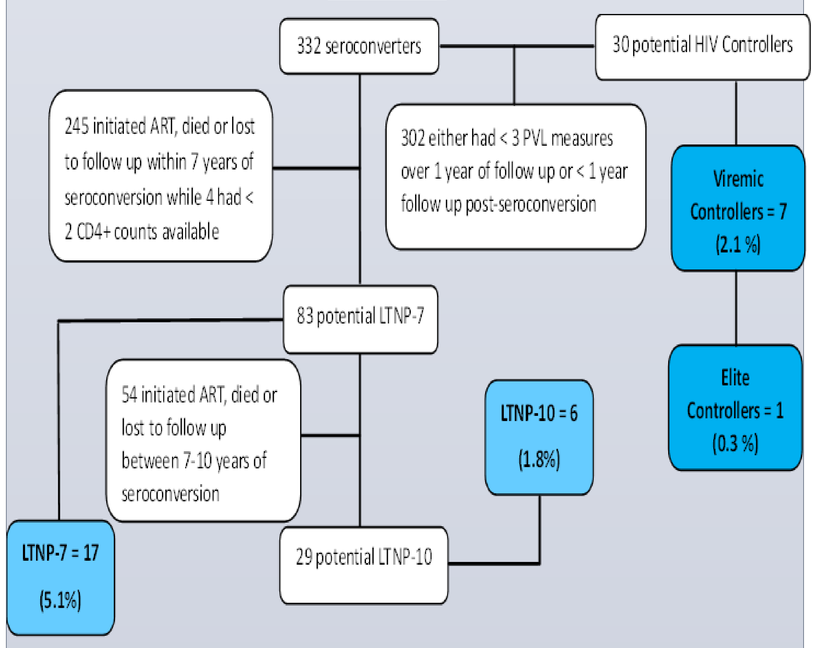


Fig. 1: Proportion of unique HIV-1 phenotypes

Fig. 2: LTNP showing progression after super-infection

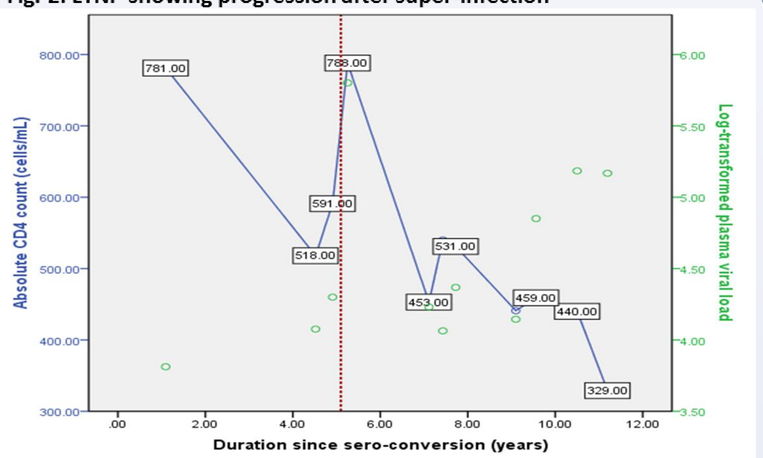
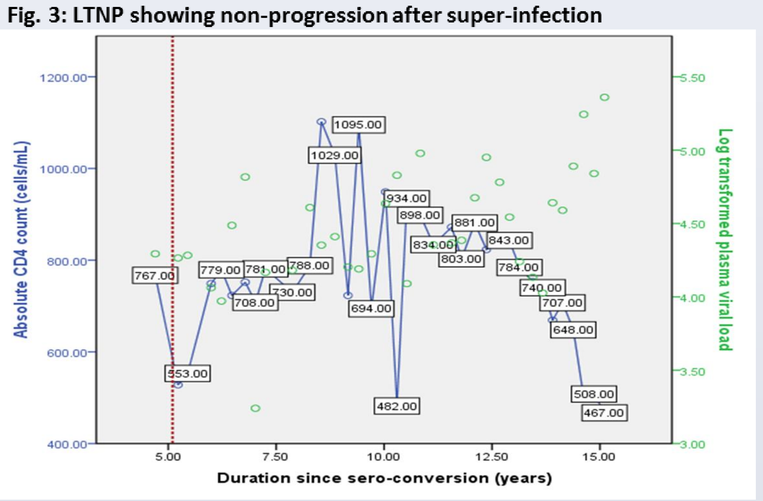


Fig. 3: LTNP showing non-progression after super-infection



Characteristic	All HIV-1 sero-converters in cohort (N=332)		Sero-converters who are not unique (N=311)		Sero-converters who are unique phenotypes (N=21)	
Demographic characteristics						
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Age at sexual debut	17	15-18	17	15-18	18	17-18
Age at sero-conversion	29	26-35	29	25-35	33	26-36
Number of live births	1	1-2	2	1-2	1	1-2
Years of education	8	7-10	8	7-10	8	7-11
Years working as sex worker	4	2-7	4	2-7	5	3-8
Behavioral characteristics						
Sexual risk practices in the week prior to sero-conversion	**N**	**%**	**N**	**%**	**N**	**%**
No intercourse	125	38	117	38	8	38
100% condom use	122	36	115	37	7	33
Unprotected intercourse	85	26	79	25	6	29
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Frequency of sexual intercourse	1	0-2	1	0-2	1	0-2
Number of sex partners	1	0-1	1	0-1	1	0-1
Laboratory characteristics						
Genital infections at SC	**N**	**%**	**N**	**%**	**N**	**%**
Herpes simplex virus type-2	285	89	267	89	18	90
Trichomoniasis	27	8	27	9	-	-
Vulvovaginal candidiasis	74	23	71	23	3	14
Bacterial vaginosis	140	43	133	44	7	33
Gonorrhea	27	8	27	9	-	-
Genital ulcer disease	10	3	10	3	-	-
Infecting HIV subtype						
Subtype A	121	77	115	77	6	75
CRF A/C	1	1	-	-	1	12.5
CRF A/D	4	3	4	3	-	-
Subtype C	11	7	11	7	-	-
Subtype D	20	12	19	13	1	12.5
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Viral load set point	4.7	4-5.3	4.7	4.1-5.3	4.2	3.3-4.8
Days to viral load set point	185	154-264	187	153-283	168	164-231

Table 1: Characteristics of different categories of HIV seroconverters

CONCLUSIONS & RECOMMENDATIONS

We identified unique HIV-1 phenotypes among women predominantly infected with non-subtype B HIV-1 who were more likely to have a lower viral load set point and took a shorter duration to achieve this. We intend to further study their immuno-genetic and epidemiologic correlates at estimated time of HIV-1 infection.

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