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Prevalence and Treatment Impact of HIV-1 Intersubtype Recombinants in Uganda

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Background

- HIV-1 can be group into subtypes based on nucleotide sequence similarity (A, B, C, D, F, G, H, I, J, K). Intersubtype recombination is known to occur, leading to recombinant forms (eg. AG)
- Few epidemiological and clinical outcome data exist for HIV-1 intersubtype recombinants in rural African communities.
- **Study Objective:** To estimate prevalence, examine time trends, and test for clinical correlates and outcomes associated with infections with intersubtype recombination HIV-1 in Mbarara, Uganda, where HIV-1 subtypes A1 and D co-circulate.

Methods

- **Patient cohort:** n=504 treatment-naïve individuals infected with mainly subtype A1 and D HIV-1 (according to *prrt*) were enrolled between 2005-2010 in the Mbarara-based UARTO cohort who then received PI or NNRTI-containing regimens and were monitored until 2013 (up to 7.5 years).
- **Sequencing approach:** Near-full-genome HIV-1 RNA population Sanger sequence data was collected using nested PCR targeting *gag* to *nef* as five amplicons which covered *gag* to protease(*pr*) (HXB2 coordinate 680-2724), *pr* to reverse transcriptase(*rt*) (2011-3798), *rt* to *vpu* (3626-5980), *vpr* to GP120 (5549-7760) and GP41 to *nef* (7652-9610).
- **Data Analysis:** Subtypes were inferred by Los Alamos RIP 3.0. Phylogenetic analysis was performed using a maximum-likelihood tree. "Non-recombinants" and "recombinants" infections were compared in terms of pre-therapy viral load, CD4 count, post-therapy time to virologic suppression, virologic rebound, first CD4 rise above baseline and sustained CD4 recovery.

Results

Table 1. Prevalence of HIV-1 recombinants varied depending on the genomic region examined (n=504).

Genomic Region	% Recombinants Detected
gag	15% (n=479)
pol (prrt)	10% (n=486)
pol (int)	8% (n=464)
vif	10% (n=458)
vpr	2% (n=387)
vpu	9% (n=456)
GP120	8% (n=277)
GP41	18% (n=485)
nef	4% (n=476)

Table 2. Of the 200 Ugandan patients who had sequence data for all genomic regions, prevalence of intersubtype recombination was high (46%).

Pan-genomic Subtype	% Prevalence (n=200)
A1	32%
D	19%
C	3%
G	<1%
Any Recombinants	46%*

* The most frequently observed recombinant was A1-D (25%). Other combinations were A1-C, A1-G, C-A1, C-D, D-A1, D-C, D-G (one breakpoint) and A1-C-D, A1-D-C, A1-D-G, D-A1-C, D-A1-G (two breakpoints). Stratification by year shows no temporal trend (p=0.7, Chi-square test for trend).

Figure 1. Phylogenetic analysis of the 200 near-full-genome sequences showed that recombinants did not share a common ancestor, suggesting multiple recombination events.

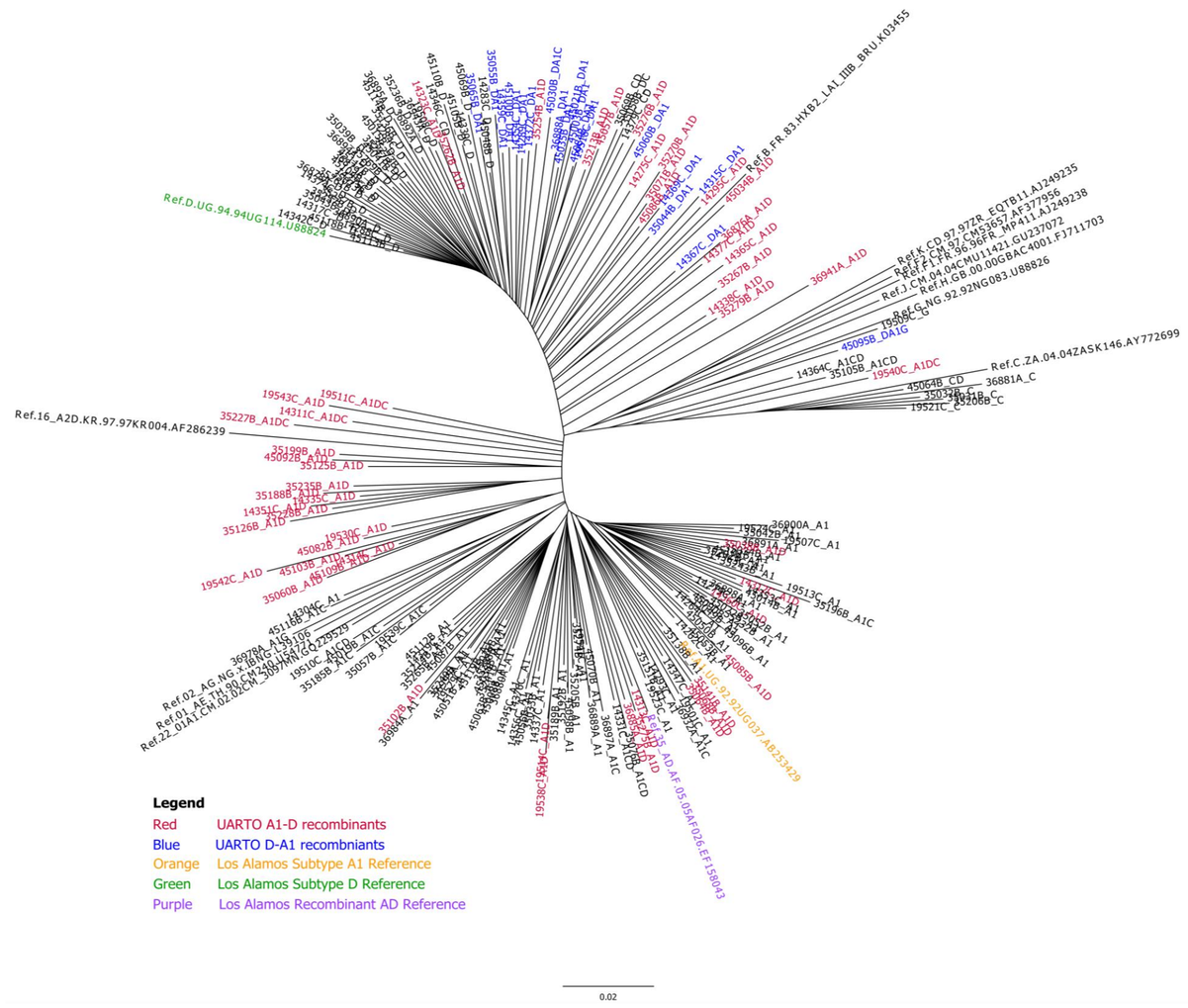
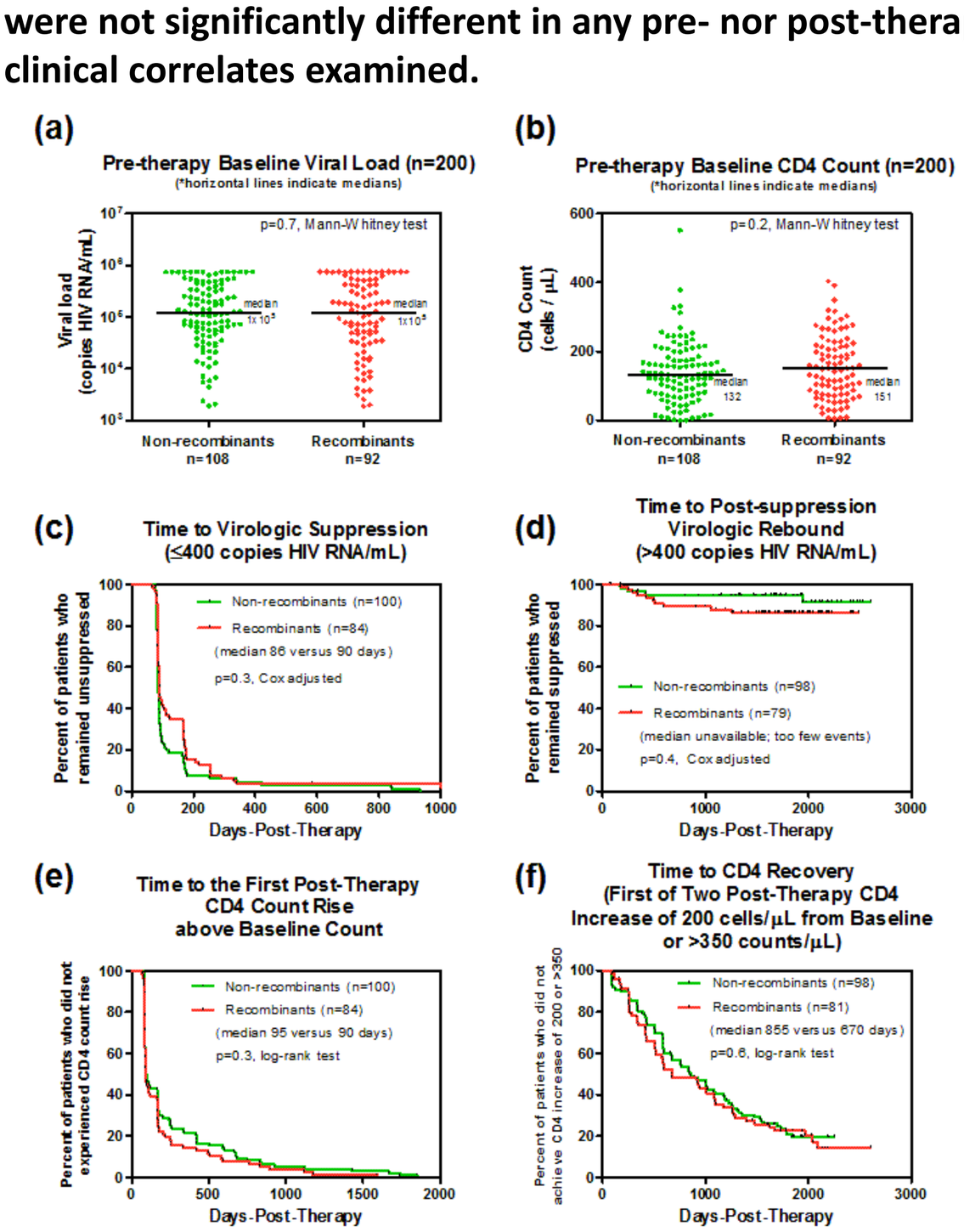


Figure 2. Non-recombinant versus recombinants infections were not significantly different in any pre- nor post-therapy clinical correlates examined.



Conclusion

Intersubtype recombination is highly prevalent (46%) in a Ugandan cohort where subtype A1 and D cocirculate if the entire HIV-1 genome was considered, but was not associated with laboratory markers of untreated HIV infection nor laboratory outcomes after initiation of antiretroviral therapy.

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