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3rd International AIDS Society Conference on **HIV** Pathogenesis and Treatment

Rio de Janeiro - July 24 - 27, 2005

HETEROSEXUAL TRANSMISSION OF HIV — LESSONS FROM DISCORDANT COUPLES

IAS Conf HIV Pathog Treat 2005 Jul 24-27;3rd: Abstract No. MoOa0401

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INTRODUCTION: Our goals are to define unique properties of transmitted viruses relative to the quasispecies in the chronically infected partner by analyzing transmission pairs from African discordant couple cohorts.

METHODS: HIV *env* gene sequences were PCR amplified from PBMC DNA and plasma of recent seroconverting or p24+ve individuals and their partners. Phylogenetic analyses and neutralization assays on functional *env* clones were performed.

RESULTS: In 12/12 epidemiologically-linked heterosexual transmission pairs a single virus appeared to establish infection since all of the recipient variants emanated from a single branch of the donor phylogenetic tree. In contrast, in five epidemiologically unlinked cases where STD prevalence was higher, one recipient harbored a diverse virus quasispecies, indicating transmission of multiple variants from a single donor, and a second was infected with two entirely different HIV-1 strains. Newly transmitted viruses from linked pairs exhibited (i) shorter length and fewer N-linked glycosylation sites in the gp120 V1-V4 region, (ii) limited sequence divergence as evidenced by short branch lengths in maximum likelihood analyses, and (iii) greater sensitivity to neutralization by donor plasma relative to the quasispecies in the infecting partner. Sequence divergence and V1-V4 length both showed a significant correlation with neutralization sensitivity to linked donor plasma. A signature algorithm was applied to identify specific residues that could be associated with neutralization escape. Residues located in the flanking regions of V1 and V3, C2, and the N-terminal region of V4, were associated with neutralization escape, but a concentration of residues was located in the region C-terminal to V3,

previously shown by Gaschen et al. to be under significant selective pressure in subtype C HIV-1.

CONCLUSIONS: These results argue that a majority of new infections in this cohort is initiated by a single virus and that changes in the "silent" face of the subtype-C gp120 can dramatically influence neutralization sensitivity.

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