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Computational and molecular analysis of HIV release by 'Viral Protein-U' at the time of pregnancy

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Introduction: The so-called accessory genes of HIV have recently been found to be of significance with roles in viral replication and pathogenesis. The trans-membrane viral protein U of HIV causes CD4 down-regulation and is also involved in release of the virus (as a counter protein to overcome the host restriction by tetherin). The present study was carried out to determine the genetic characteristics of the trans-membrane and cytoplasmic domain of the vpu protein of HIV during pregnancy. In addition we also studied BST-2 m-RNA expression at the time of pregnancy and post-partum (preliminary results).

Materials and Methods: Blood samples were obtained from 53 HIV sero-positive patients (28 from antenatal risk group; 22 from other risk groups; 3 samples post partum). Amplification of *vpu* gene was followed by sequencing. Sequence analysis was performed with the help of MEGA and Bioedit. Homology modeling using Swift Modeler was used to construct models from the deduced amino acid sequences. VMD (Visual Molecular Dynamics) version 1.9 was used to understand the molecular features of the membrane protein. Phylogenetic analysis based on sequence and structural homology was carried out. Sequence variability was also determined using Entropy tool from Los Alamos Database. I-Mutant 2.0 and Membrane Protein Explorer were used to study the effect of mutations, stability and hydrophobicity of the trans-membrane protein. The mRNA expression levels of BST-2 were examined using Real Time PCR.

Results: Significant decrease in sequence variability in the pregnant risk group was observed. Phylogenetic results confirmed that our isolates belonged to subtype C. Multiple structural alignments of sequences from antenatal risk group revealed increased entropy in the trans-membrane domain, whereas the cytoplasmic domain was much conserved. Structural homology based on *Qres* values indicated a higher structural similarity in the trans-membrane region as compared to the cytoplasmic domain. The post partum group exhibited mRNA expression of BST-2, in contrast to its absence in other risk groups.

Conclusions: Pregnancy being an interferon depressed physiology, vpu doesn't have to put much effort to antagonize tetherin. It maintains a significantly conserved amino acid sequence with the trans-membrane domain being comparatively more variable than the cytoplasmic domain, but none of the variations in the amino acid sequence of the trans-membrane region alter the protein structurally and therefore allows an optimum viral extrication. The host restriction protein BST-2 is able to counteract for the action of vpu post-partum. The expression seems to coincide with the beginning of the interferon induced physiology i.e. labor and post partum, a host strategy to control virus release and alleviate the possibility of virus transmission at the time of delivery when the fetus is in contact with maternal secretions, and also during breastfeeding.