Poster Session Number: P-B1

Transmission Networks of HIV-1 Subtype B, CRF01_AE and CRF51_01B Among Men Who Have Sex with Men (MSM) in Singapore

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Introduction

Previous study had confirmed that men who have sex with men (MSM) and heterosexual in Singapore were commonly infected with HIV-1 subtype B and CRF01_AE, respectively[1,2]. In addition, recent study reported an emergence of a novel HIV-1 CRF51_01B lineage among MSM in Singapore[3]. Despite the important impact attributed to HIV-1 subtype B, CRF01_AE and CRF51_01B, the evolutionary history, population dynamics and pattern of transmission networks of these genotypes remain unexplored. In present study, transmission network is defined as a network consisting of at least three isolates from individuals[4] of the same geographical (i.e country) origin[5] and a phylogenetic clade supported by bootstrap value of more than 90% and Bayesian posterior probability of 1.0 at the tree node[5-7]. Here, we elucidated the phylodynamic profile of HIV-1 subtype B, CRF01_AE and the recently characterized CRF51_01B strains circulating among the MSM population in Singapore.

Methodology

1. n = 105 treatment-naïve MSM were recruited from Singapore Communicable Disease Centre (CDC)
2. Sequencing of HIV-1 *protease* gene (HXB2: 2239-2629), gp120 (HXB2: 6942-7577) and gp41 (HXB2: 7803-8276) of the *env* gene.
3. Neighbor-joining tree and maximum likelihood
4. Maximum clade credibility and estimation of divergence time[8]

Results and Discussion

In present cohort study, 89 (37 subtype B, 40 CRF01_AE and 12 CRF51_01B) interpretable protease sequences, 54 (16 subtype B, 29 CRF01_AE and 9 CRF51_01B) gp120 and 96 (43 subtype B, 42 CRF01_AE and 11 CRF51_01B) gp41 of *env* gene were analyzed and substantial clustering patterns were observed (protease region: 64%, gp120 region: 70.4% and gp41 region: 62.5%). Phylogenetic reconstruction uncovered four monophyletic transmission networks, two each within subtype B lineages (B.1 and B.2) that surged around late 1990s to early 2000s and CRF01_AE (AE.1 and AE.2), diverged in early 2000s.

Results and Discussion (continued)

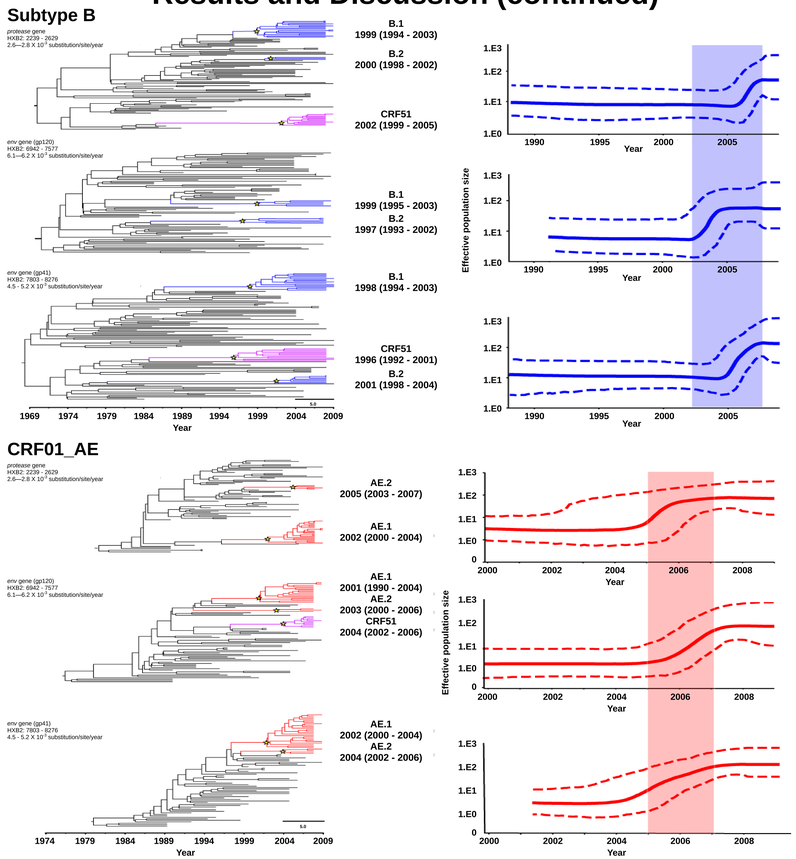


Figure 1. Bayesian's MCC trees of protease gene (HXB2: 2239 - 2629, 390bp), gp120 (HXB2: 6942 – 7577, 636bp) and gp41 (HXB2: 7803 – 8276, 474bp) of *env* gene from Singapore MSM sequence data collected between February 2008 and August 2009 are shown, with Singapore HIV-1 subtype B branches in blue, CRF01_AE in red, CRF51_01B in purple and reference sequences in black branches. Of note, CRF51_01B is a recombinant involving subtype B in protease and gp41 of *env* gene, and CRF01_AE in gp120. Five monophyletic transmission networks (two each within subtype B and CRF01_AE and one within CRF51_01B lineages) of different sizes (involving 3 – 23 MSM subjects, supported by posterior probability measure of 1.0) were observed. Bayesian coalescent analysis estimated that the emergence of multiple sub-epidemic networks occurred between 1995 and 2005, contributed largely by subtype B and later by CRF01_AE

Results and Discussion (continued)

In addition, one monophyletic transmission network was observed within CRF51_01B lineage (denoted CRF51), a recently described recombinant, involving subtype B in protease and gp41, and CRF01_AE in gp120 of *env* gene. The divergence time for CRF51_01B was estimated around 2002, 2004 and 1996 in *protease* gene, gp120 and gp41 of *env* gene, respectively, suggesting the occurrence of at least two recombination events involving subtype B of different evolutionary background. Estimation of the divergence times for each node revealed that the median interval between transmission events within these networks were short (less than 1 year): 0.9 years in subtype B, 0.75 years in CRF01_AE and 0.65 years in CRF51_01B, which indicate an ongoing active HIV-1 transmission and suggest possible epidemic expansion due to high-risk sexual behavior among MSM population[9-11]. The identification of viral transmission networks suggests that HIV-1 subtype B and CRF01_AE were introduced into the MSM population in Singapore through at least five sub-epidemics, which occurred between 1995 and 2005, corroborating with findings reported in Western Europe[7, 10-11] and Malaysia[12]. Since present study only involved subject recruited between 2008 and 2009, we believe a study spanning a longer period may improve the resolution of HIV-1 genomic diversity and transmission dynamic within MSM network in Singapore.

Conclusion

1. Identification of HIV-1 transmission networks suggests that subtype B and CRF01_AE lineages were introduced into MSM population in Singapore through active spread of multiple sub-epidemics.
2. From the perspective of public health, sexual networks within the MSM population could serve as an important factor in onward HIV-1 transmission, thus it could functions as the core entry point for the delivery of intervention strategies.
3. In addition, genealogical estimates suggested that the novel CRF51_01B lineages were likely to be generated through a series of recombination events involving CRF01_AE and multiple subtype B ancestors of different evolutionary history.
4. Present study highlights the importance of understanding of HIV-1 transmission behavior in assisting the outbreak risk assessment and disease expansion, therefore enabling preventive measures targeting onward disease transmission.

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Acknowledgement

Malaysia Ministry of Higher Education High Impact Research (HIR) grant (H-500001-00-A000012-000001)

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