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Letter

Identification of a novel HIV-1 circulating recombinant form (CRF161_0107) from CRF01_AE-C5 lineage among men who have sex with men in southwestern China

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Dear Editor,

The ongoing emergence of circulating recombinant forms (CRFs) of HIV-1 was recently reported among men who have sex with men (MSM) in China (Xiao et al., 2025; Xing et al., 2024). HIV-1's global diversity is classified into four groups: M (Major, causing the pandemic), O (Outlier), N, and P. Group M, the most prevalent, is subdivided into subtypes (A–D, F–H and J–L). Recombinant viruses formed between subtypes are classified as either stable CRFs spreading in populations or unique recombinant forms (URFs). HIV-1 recombination significantly complicates HIV genetics and has the capacity to directly alter key viral properties, including replication fitness, pathogenicity, and drug resistance profiles (Cheng et al., 2022; Nora et al., 2007). As the HIV-1 epidemic in China has developed, CRF07_BC and CRF01_AE have emerged as the predominant circulating strains nationwide (Liu et al., 2023). In Yunnan Province, CRF08_BC and CRF07_BC were the two most prevalent strains in the general population, whereas CRF07_BC and CRF01_AE were the primary strains among MSM. This epidemiological situation has driven the emergence of recombinants between CRF07_BC and CRF01_AE in recent years. Since the identification of the first CRF01_AE/CRF07_BC recombinant (CRF79_0107) in 2017, 21 distinct recombinant strains of CRF_0107 have been reported. Consequently, CRF_0107 has become the most diverse CRF type in China. Of these, at least 14 were first identified among MSM and 5 have been detected in both MSM and heterosexuals. In this study, we identified a new CRF formed by the recombination of CRF01_AE and CRF07_BC in MSM. We named this new CRF CRF161_0107. These emerging CRFs will provide a paradigm for further research into the recombination patterns of CRF01_AE and CRF07_BC.

The HIV/AIDS epidemic in Yunnan Province first emerged among injecting drug users (IDUs) in border regions, before gradually spreading to populations who contracted the virus through sexual transmission (Lu et al., 2008). After 2006, sexual transmission became the main route of transmission (Jia et al., 2010). Recently, over 98% of newly reported cases have been attributed to sexual transmission, with the majority of these being due to heterosexual transmission. A previous molecular epidemiological study of HIV-1 among MSM in Kunming City, Yunnan Province, showed that three samples could not be classified into known subtypes or CRFs, but were found to be in the same evolutionary clade. This suggested that they might represent a new CRF. To further clarify this possibility, the samples were analyzed and characterized. Plasma samples were collected from three HIV-1-infected MSM individuals (19KMM070, 18KMM039, and 20M100) in Yunnan Province in 2018, 2019 and 2020, respectively. Their demographic characteristics are shown in Supplementary Table S1. There was no epidemiological link between the cases. Written informed consent for sample collection and subsequent analysis was obtained from all participants. This study was approved by the Ethical Review Committee of Yunnan Provincial Center for Disease Control and Prevention. Near-full-length genome (NFLG) sequences were amplified using nested PCR and Sanger sequencing, as in a previous study. The NFLG sequences spanned from the 5′ long terminal repeat (LTR) to the 3′ LTR and were 8415 bp (660–9068 on HXB2), 8759 bp (638–9368 on HXB2) and 8730 bp (760–9513 on HXB2) long, respectively. The sequences were submitted to GenBank under the accession numbers PV741253–PV741255. Phylogenetic analysis was conducted using MEGA 11. Recombination analyses were conducted using Simplot v3.5.1 and the Recombinant Identification Program (RIP, https://www.hiv.lanl.gov/content/sequence/RIP/RIP.html). Bayesian evolutionary analyses were performed using BEAST v1.10.4. The uncorrelated lognormal relaxed molecular clock was used in combination with the Bayesian skyline coalescent tree priors under the GTR + I + G4

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nucleotide substitution model. Each Bayesian Markov chain Monte Carlo (MCMC) analysis was run for 100 million generations and sampled every 10,000 generations. The reference sequences were obtained by a BLAST search with CRF01_AE and CRF07_BC subregions in HIV-1 database. Additionally, standard reference sequences representing different evolutionary branches of the same genotype were supplemented. The datasets were listed in Supplementary Table S2.

Phylogenetic analysis of NFLG sequences revealed that the three isolates formed a distinct monophyletic clade with a bootstrap value of 100%, genetically segregated from all known subtypes and CRFs (Fig. 1A).

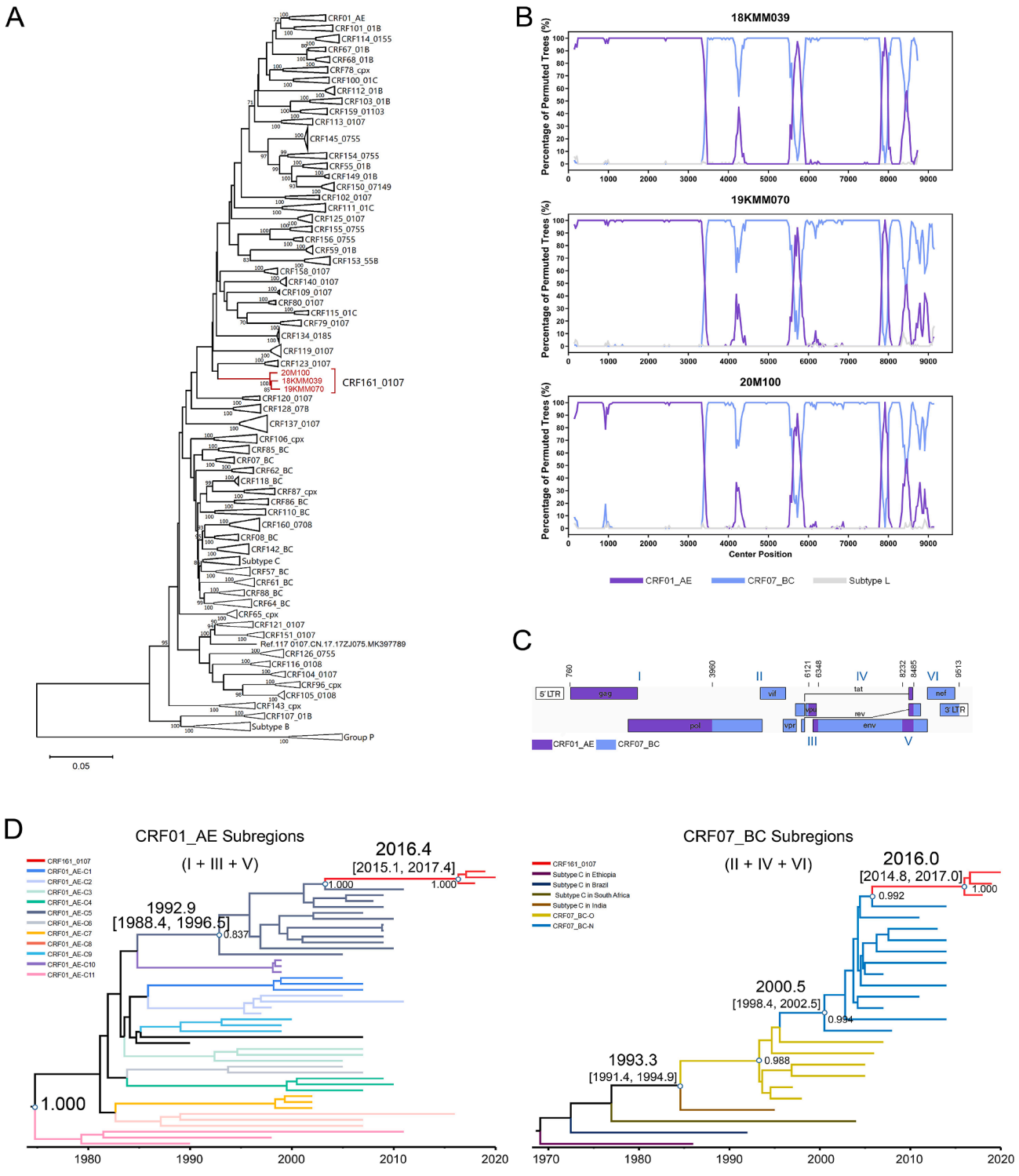

Fig. 1. Phylogenetic and recombinant analyses based on the near full-length genome sequences. **A** A neighbour-joining phylogenetic tree was constructed using the reference sequences of HIV-1 CRFs identified in China. The sequences of CRF161_0107 are highlighted in red. Values on the branches represent the percentage of 1000 bootstrap replicates, and the scale bar indicates 5% nucleotide sequence divergence. **B** Bootscanning analysis of the candidate CRF. Conditions used for this analysis: Window: 300 bp, step: 30 bp, GapStrip: on, replicates: 100, Kimura (2-parameter), T/t: 2.0. The CRF01_AE reference group included GQ477441, GU564221 and U54771. The CRF07_BC reference group included EF368372, EF368370 and AF286230. The Subtype L reference group included MN271384, AF286236 and AF457101. **C** Genomic structure of CRF161_0107. The mosaic map was generated using the Recombinant HIV-1 Drawing Tool. **D** The maximum clade credibility (MCC) trees of combined CRF01_AE segments (I + III + V) and combined CRF07_BC segments (II + IV + VI).

Recombination mapping via RIP and Bootscanning analyses further demonstrated a consistent mosaic architecture comprising alternating CRF01_AE and CRF07_BC segments (Fig. 1B). Five breakpoints partitioned the genome into six subregions (HXB2 coordinates): I_{CRF01_AE} (760–3959), II_{CRF07_BC} (3960–6120), III_{CRF01_AE} (6121–6347), IV_{CRF07_BC} (6348–8231), V_{CRF01_AE} (8232–8484) and VI_{CRF07_BC} (8485–9513) (Fig. 1C). Subregional phylogenetic trees confirmed that the CRF01_AE-derived segments (I, III and V) clustered with the reference CRF01_AE sequences and that the CRF07_BC-derived segments (II, IV and VI) grouped with the CRF07_BC lineages (Supplementary Fig. S1). This genetic composition, combined with the absence of epidemiological linkage among the isolates, fulfilled the criteria for designating a novel CRF: CRF161_0107.

To trace the origins of CRF161_0107, Bayesian evolutionary analyses were applied to concatenated segments: CRF01_AE (I + III + V) and CRF07_BC (II + IV + VI) (Fig. 1D). Maximum clade credibility (MCC) trees revealed that the time of the most recent common ancestor (tMRCA) for the concatenated CRF01_AE segments was 2016.4 (95% highest probability density (HPD): 2015.1–2017.4), while the tMRCA for the concatenated CRF07_BC segments was 2016.0 (95% HPD: 2014.8–2017.0). These estimates suggest that CRF161_0107 probably emerged around 2016. The evolutionary analysis also showed that the CRF01_AE components primarily originated from the CRF01_AE-C5 lineage, while the CRF07_BC components mainly descended from the CRF07_BC-N lineage. According to the reports, CRF_0107 primarily emerged among MSM between 2010 and 2018. This may be related to the rapid dissemination of CRF07_BC during this period, due to its enhanced transmissibility and reduced virulence (Cheng et al., 2022). CRF161_0107 emerged more recently. Bayesian evolutionary analyses revealed that the tMRCA of its two parental segments was remarkably similar (CRF01_AE: 2016.4 vs. CRF07_BC: 2016.0), enhancing the accuracy of estimates of their generation time.

Previous research has indicated that CRF01_AE can be divided into 11 lineages (Wang et al., 2024). Of these, the C4 and C5 clades were most prevalent among MSM. Furthermore, the CRF07_BC strain diverged into two lineages: the original CRF07_BC-O lineage, which is primarily associated with IDUs and heterosexual transmission, and the newer CRF07_BC-N lineage, which evolved from CRF07_BC-O and mainly circulates among MSM (Wang et al., 2024). According to cross-sectional surveys conducted in Yunnan Province in 2015 and 2018 (Chen et al., 2019; Yang et al., 2025), the CRF01_AE-C4 lineage and CRF01_AE-C5 lineage accounted for 46.6% and 3.4%, respectively. Furthermore, two-thirds of the CRF01_AE-C5 lineage infections were among individuals with non-local household registrations. This suggested that CRF01_AE-C5 had a low prevalence in Yunnan Province and was likely introduced through cross-regional transmission among specific populations. Meanwhile, the CRF07_BC-O and CRF07_BC-N lineages accounted for 55.6% and 44.4%, respectively, indicating that both lineages were circulating locally. As with most CRF_0107 strains found in MSM, the CRF07_BC segments of CRF161_0107 originated from the CRF07_BC-N lineage. However, unlike the CRF151_0107 and CRF158_0107 previously identified among MSM in Yunnan, whose CRF01_AE segments derived from the CRF01_AE-C4 lineage, the CRF01_AE segments of CRF161_0107 originated from the CRF01_AE-C5 lineage. CRF01_AE-C5 primarily circulated in northern China, whereas CRF01_AE-C4 spread nationwide in China (Li et al., 2017). CRF01_AE-C5-derived CRF_0107 is more prevalent in northern provinces. For example, CRF136_0107 was found in Heilongjiang Province and CRF163_0107 in Liaoning Province (Zhang et al., 2023; Xing et al., 2024). Furthermore, CRF01_AE-C5 has recently been reported to be involved in third-generation recombination among MSM in northern China (Li et al., 2025). Thus, the recombinant origin of CRF161_0107 suggests that the mobility among MSM may facilitate cross-regional HIV-1 transmission, and contribute to increased viral recombination.

CRF01_AE and CRF07_BC are two strains with completely different biological characteristics. CRF01_AE infection is associated with a faster rate of $CD4^+$ T cell loss and shorter overall survival, which may be attributed to a multifactorial mechanism. Notably, a significantly higher proportion of CRF01_AE viruses were predicted to use CXCR4 as a co-receptor (Li et al., 2014). In contrast, CRF07_BC is associated with slower disease progression, a lower viral load and less immune system destruction than CRF01_AE (Cheng et al., 2022). Thus, different modes of recombination could produce recombinant strains with different characteristics (Burke, 1997). The selection of viral co-receptors is associated with the *env* gene, particularly gp120. Of the 21 reported CRF_0107, 15 have gp120 mainly derived from CRF07_BC, including CRF161_0107. This may enable them to inherit the low virulence and high transmissibility properties of CRF07_BC, however, this requires further validation.

In this study, we identified and characterized a novel HIV-1 CRF (CRF161_0107) among MSM in Yunnan Province, China. This CRF emerged from a recombination event between CRF01_AE-C5 and CRF07_BC-N around 2016. These findings emphasize the ongoing dynamic evolution of HIV-1 through recombination in key populations. The identification of novel CRFs highlights the necessity for sustained molecular surveillance to track emerging recombinant strains, elucidate their transmission dynamics, and assess potential impacts on pathogenesis or treatment efficacy. Furthermore, this study emphasizes the urgent need to strengthen targeted interventions among MSM in China to control the spread of both novel and established HIV variants.

FOOTNOTES

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.virs.2026.03.008.

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