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Epidemic characteristics of local HIV-2 transmission across Hunan province, China

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ABSTRACT

Objective: To elucidate the epidemiological features of HIV-2 in Hunan Province, China, utilizing sequence analysis.

Methods: Thirteen individuals diagnosed with HIV-2 infection in Hunan Province, China, from 2017 to 2023 were included in this study. Amplification of HIV-2 *env* and *pol* regions was conducted, followed by Sanger sequencing. Phylogenetic and molecular transmission network analyses were performed to delineate molecular features and transmission dynamics.

Results: All 14 individuals contracted HIV-2 through heterosexual intercourse, comprising 7 males and 7 females, with a median age of 58 years. Among them, three couples (HN001 and HN013, HN010 and HN011, HN008 and HN009) were identified, along with commercial sexual activity engagement reported for subject HN004. Notably, subjects HN001, HN003, HN008, and HN010 engaged in commercial sexual activities at the same location as subject HN004. Phylogenetic analysis of the *pol* gene revealed close proximity of sequences from all subjects to reference sequences from Gambia (Sub-type A). Employing a genetic distance threshold of 1.5 %, eight out of the 14 subjects formed a molecular transmission network, with HN002 and HN004 identified as central nodes.

Conclusion: From 2017 to 2023, all HIV-2-infected individuals in Hunan Province, China, acquired the virus through identifiable routes, indicating transmission of similar HIV-2 strains among them.

1. Introduction

The Human Immunodeficiency Virus (HIV) consists of two primary types: HIV type 1 (HIV-1) and HIV type 2 (HIV-2), exhibiting genetic homology of approximately 40 % to 60 %.Globally, HIV-2 continues to be overlooked as a significant public health issue. Approximately two million individuals are known to be infected with HIV-2, with the majority residing in West Africa. (Gottlieb et al., 2018; Gottlieb et al., 2008; Menéndez-Arias and Alvarez, 2014) HIV-2 was first isolated in 1985 from sex workers and AIDS patients in West Africa before subsequently disseminating to other regions worldwide. (Clavel et al., 1986; Kanki et al., 1986; RS Gurjar et al., 2009; Valadas et al., 2009; Torian et al., 2010) Co-infections of HIV-1 and HIV-2 are prevalent in West Africa, representing 0.3 % to 1 % of all HIV infections. (Nsagha et al., 2012; Popper et al., 2000) Currently HIV-2 is divided into 7 main groups (groups A-F, H2_01_AB) (Ceccarelli et al., 2021). In comparison to HIV-1, HIV-2 exhibits weaker pathogenicity, lower transmission efficiency, and slower progression post-infection. (Kanki et al., 1994; Marlink et al., 1994; Gottlieb et al., 2002; Whittle et al., 1994; Andersson et al., 2000) Only 20 % to 30 % of individuals infected with HIV-2 ultimately progress to develop acquired immunodeficiency syndrome (AIDS). (Andersson et al., 2000; Jagodzinski et al., 2020) HIV-1 constitutes the predominant HIV epidemic in China, comprising over 10 recognized subtypes, the main subtypes being CRF07_BC and CRF01_AE (Bbosa et al., 2019). However, occurrences of HIV-2 are rare in China. The first reported case of HIV-2 infection in China occurred in 1998. Subsequent sporadic cases of imported HIV-2 infections via sexual contact have been documented in provinces including Fujian, Guangzhou, Ningxia, Hubei, Shanghai, and others. (Su et al., 2019) In 2017, two cases of local HIV-2 infection were diagnosed in Hunan Province, marking the first report of locally acquired HIV-2 cases in China. (Peng et al., 2018) Subsequent studies by Peng et al. indicated covert,

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Table 1
Primers designed in-house to amplify and sequence the gene of the HIV-2 isolate.

Primer	Sequence	Location	Fragment size(bp)	Genomic region
Outer pair				
envA	5′-GCTAGGGTTCTTGGGTTTTCTCGCGACAGCAGG-3′	7691–7723	453	*env*(GP36)
envB	5′-CAAGAGGCGTATCAGCTGGCGGATCAGGAA-3′	8415–8444		
Inner pair				
envC	5′-GGGATACTGCAGCAACAGCAACAGCTGTTG-3′	7782–7811		
envD	5′-GGGAGGGGAAGAGAATTCTGGCCTATA-3′	8265–8291		
Outer pair				
gagA	5′-AGGTTACGGCCCGGCGGAAAGAAAA-3′	603–627	708	gag
gagB	5′-CCTACTCCCTGACAGGCCGTCAGCATTTCTTC-3′	1581–1612		
Inner pair				
gagC	5′-AGTACATGTTAAAACATGTAGTATGGGC-3′	628–655		
gagD	5′-CCTTAAGCTTTTGTAGAATCTATCTACATA-3′	1437–1466		
Outer pair				
RTC	5′-ATGACAGGGGATCCCCCAArCAATATTTTTG-3′	2309–2339	995	*pol* (RT)
RT2	5′-GAAGTCCCAGTCTGGGATCCATGTCACTTGCCA-3′	3593–3526		
Inner pair				
RT3	5′-GAGGCATTAAAAGAGATCTGTGAAAAAATGG-3′	2474–2504		
RT4	5′-TCCCCAAATGACTAGTGCTTCTTTTTCCTAT-3′	3500–3529		

long-term local transmission of HIV-2 in Hunan Province. (Peng et al., 2021) Nevertheless, the molecular and epidemic characteristics of this local HIV-2 transmission in Hunan Province, China, remain unknown, necessitating comprehensive investigation to provide crucial insights for HIV-2 disease management in the nation.

2. Materials and methods

2.1. Ethics statement

The research protocol, approved by the relevant institutional review boards or independent ethics committees, was conducted in accordance with standards ensuring patient safety and welfare, adhering to Good Clinical Practices, and following the principles of the Declaration of Helsinki and its amendments.Verbal informed consent was obtained from the physicians responsible for the AIDS patients at clinical sites, and patient identities were documented with the physicians' signatures. The study and verbal consent procedure were approved by the Ethical Committee of Hunan Provincial Center for Disease Control and Prevention (ethical approval number: Hunan CDC IRB-PJ2022(022)). Informed consent was obtained from all participants.

2.2. Patients

From 2017 to 2023, all 14 patients diagnosed with HIV-2 infections were included in the study. They resided in Xiangtan City, Hunan Province, China. HIV-2 infections were confirmed using a recomLine HIV-1 & HIV-2 IgG serologic test (Mikrogen Diagnostik, Germany). Each patient provided 10 mL of peripheral blood collected in EDTA anticoagulant tubes. The blood plasma was separated within 6 h and stored at −70 °C for further analysis.

2.3. Nucleic acid extraction and PCR testing

HIV-2 RNA was extracted from plasma using QIAamp Viral RNA mini kit (Qiagen, Germany) according to the manufacturer's protocol. Approximately 453 bp *gag* gene fragment (HXB2 positions 620–1072) of the conserved region of HIV-2 virus were amplified by nested reverse transcriptase polymerase chain reaction (nested RT-PCR) with in-house primers: H1 (5′- AGAGGCTGGCAGATTGAGC-3 −3′), H2 (5′- CAAGACGGAGTTTCTCGCG-3′) and H4 (5′- TAGGAGCACTCGTCGTGGT −3′). The 1st round PCR was performed with a one-step RT PCR kit (Promega, USA) and the cycling procedure were as follows: incubation at 50 °C for 30 min, 94 °C for 5 min, 35 cycles of 94 °C for 10 s, 55 °C for 30 s, and 72 °C for 30 s, 72 °C for 7 min. The 2nd round PCR was performed using a Taq PCR Master mix (Tiangen, Beijing, China), with the procedure of: 94 °C for 5 min, 30 cycles of 94 °C for 10 s, 55 °C for 30 s, and 72 °C for 30 s, and 72 °C for 7 min. The PCR products were purified and sequenced by the General Biology System (Anhui) Co., Ltd. The sequencing result was compared with the HIV-2 *gag* gene reference sequence (http://blast.ncbi.nlm.nih.gov/Blast.cgi) by BLASTN 2.13.0+.

2.4. HIV-2 gene sequencing and sequence analysis

HIV-2 *env(*GP*36)* (HXB2: 7758 - 8795), *gag* (HXB2:790 - 2292), *pol* (integrase, INHXB2:4230 - 5096) and *pol* (reverse transcriptase, RTHXB2: 2550 - 3870) regions were amplified by using in-house designed primers (Table 1). These primers were based on HIV-2/SIVSM/SIVMAC consensus sequences. (Myers et al., 1993; Fisher et al., 2010)

Sequences were cleaned with the Chromas software version 1.62 (www.technelysium.com.au/chromas.html), and edited with BioEdit (7.0.2). The Vector NTI Suite 6 software was then employed to assemble a ContigExpress Project. Screening and tree-building analysis of aligned sequences for optimal base substitution models in a maximum-likelihood system using Mega 7.0.14, The best substitution models required for the phylogenetic tree of *pol* region, *gag* region, and gp36 were HKY+*G*, HKY+*G* + *I*, HKY+*G*. All reference sequences that underwent a BLAST search for closely related HIV-2 sequences were downloaded from the Los Alamos database. The pairwise genetic distances were calculated by the Kimura 2-parameter method using MEGA 7.0.14. The amino acid p-distance model in MEGA 7.0.14 was used to find the distance of the translated amino acid sequences. Phylogenetic trees were constructed using complete gene sequences of *env (*GP36), *gag* and *pol* that were available in the GenBank.

3. Results

3.1. Demographic characteristics

All 14 subjects were infected through heterosexual contact. 64.28 % (9/14) were either married or in sexual partnerships, with 50.00 % (7/14) being male. The age ranged from 37 to 76 years, with a median of 58 years.Four cases were diagnosed in 2017, one in 2018, three in 2019, two in 2021, one in 2022 and three in 2023 and one in 2024.

3.2. Phylogenetic analysis

Gene sequencing was performed on 14 subjects for LTR, *pol*(RT), *gag*, and *env*(GP36).

Gene distances between the *pol, gag,* and *env*(GP36) genome sequences were calculated separately in this study.

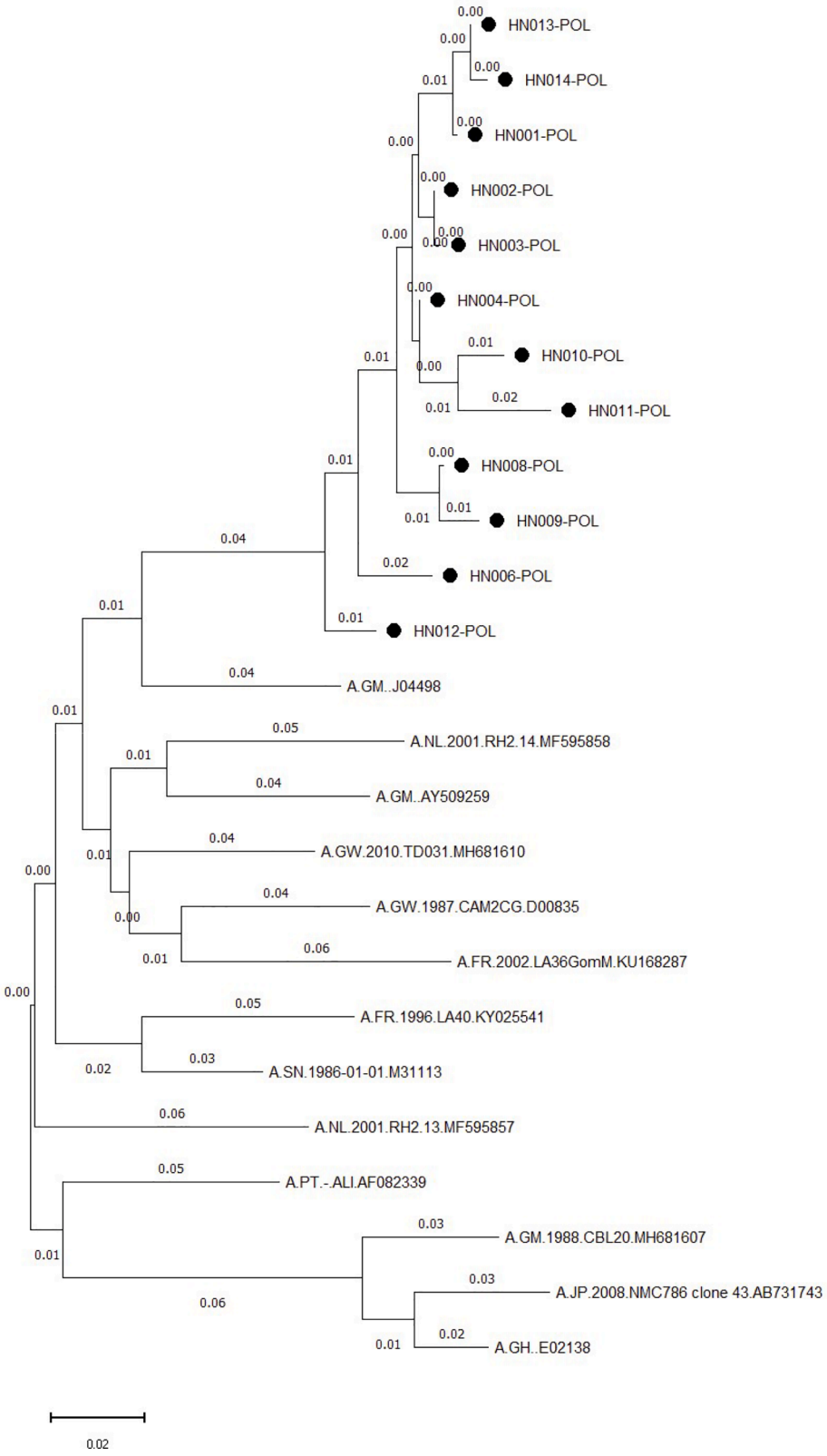

Fig. 1. Phylogenetic tree analysis of 12 HIV-2 positive infects (*pol* RT gene).

Phylogenetic analysis of the *pol* gene indicated that all samples clustered together, closely resembling the reference strain A.GM.

Using a genetic distance threshold of 1.5 %, molecular propagation network analysis revealed that eight samples were included in the network (Fig. 3).

HN002 and HN004 were identified as the core nodes of the molecular transmission network.

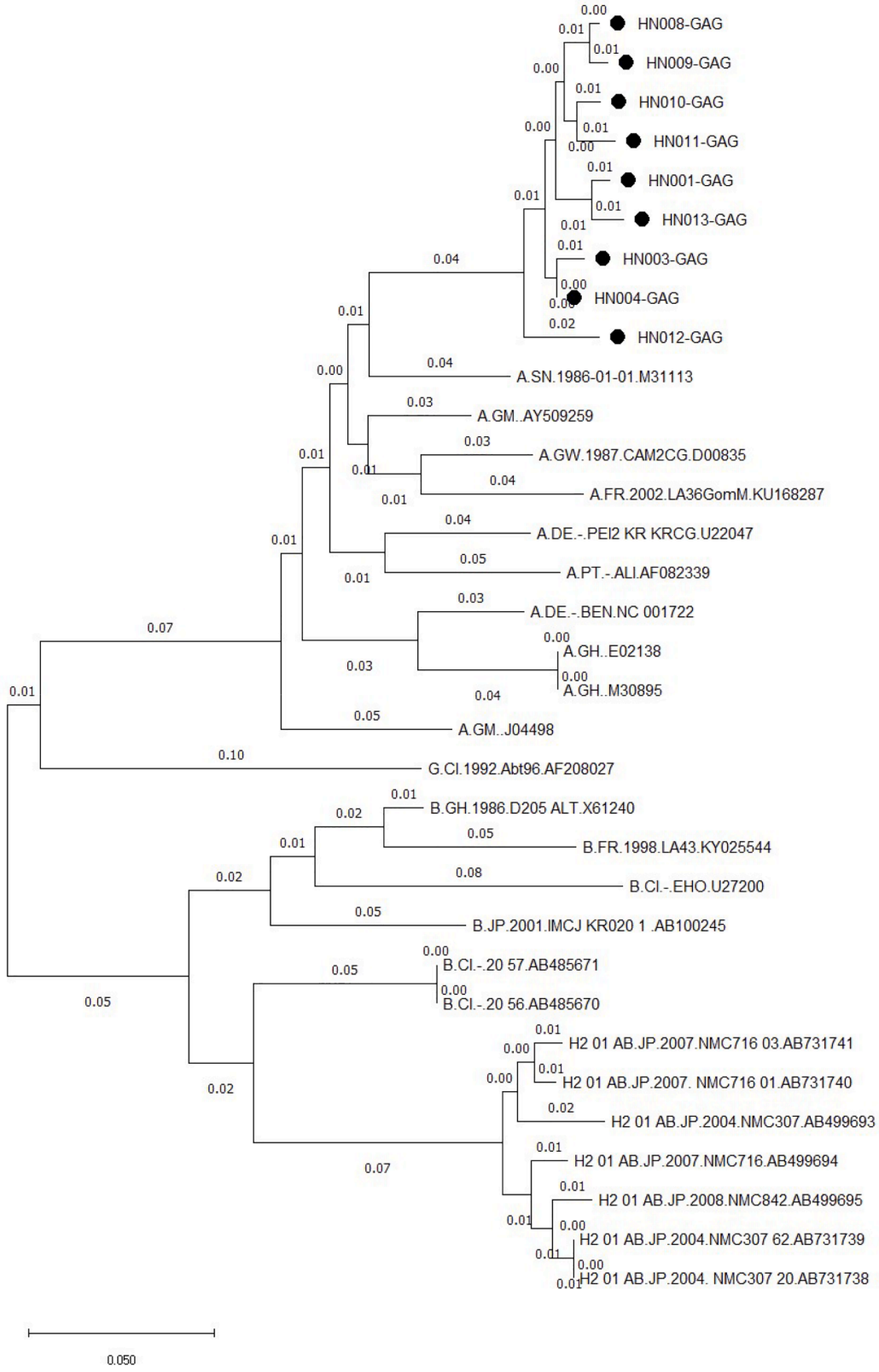

Fig. 2. Phylogenetic tree analysis of 9 HIV-2 positive infects (*gag* gene).

3.3. Phylogenetic analysis

Gene sequencing was conducted for LTR, *pol*(RT), *gag*, and *env*(GP36) genes in all 14 subjects.HIV Blast analysis of the LTR gene indicated that all samples belonged to HIV-2 strains.Amplification of *pol*(RT), *gag*, and *env*(GP36) genes was successful in 12, 9, and 5 samples, respectively. Gene distances between *pol, gag*, and *env*(GP36) genome sequences were calculated separately in this study.Results revealed that distances between *pol*(RT) genes ranged from 0.000 to 0.025, with an average of 0.015.Distances between *gag* genes ranged from 0.007 to 0.043, with an

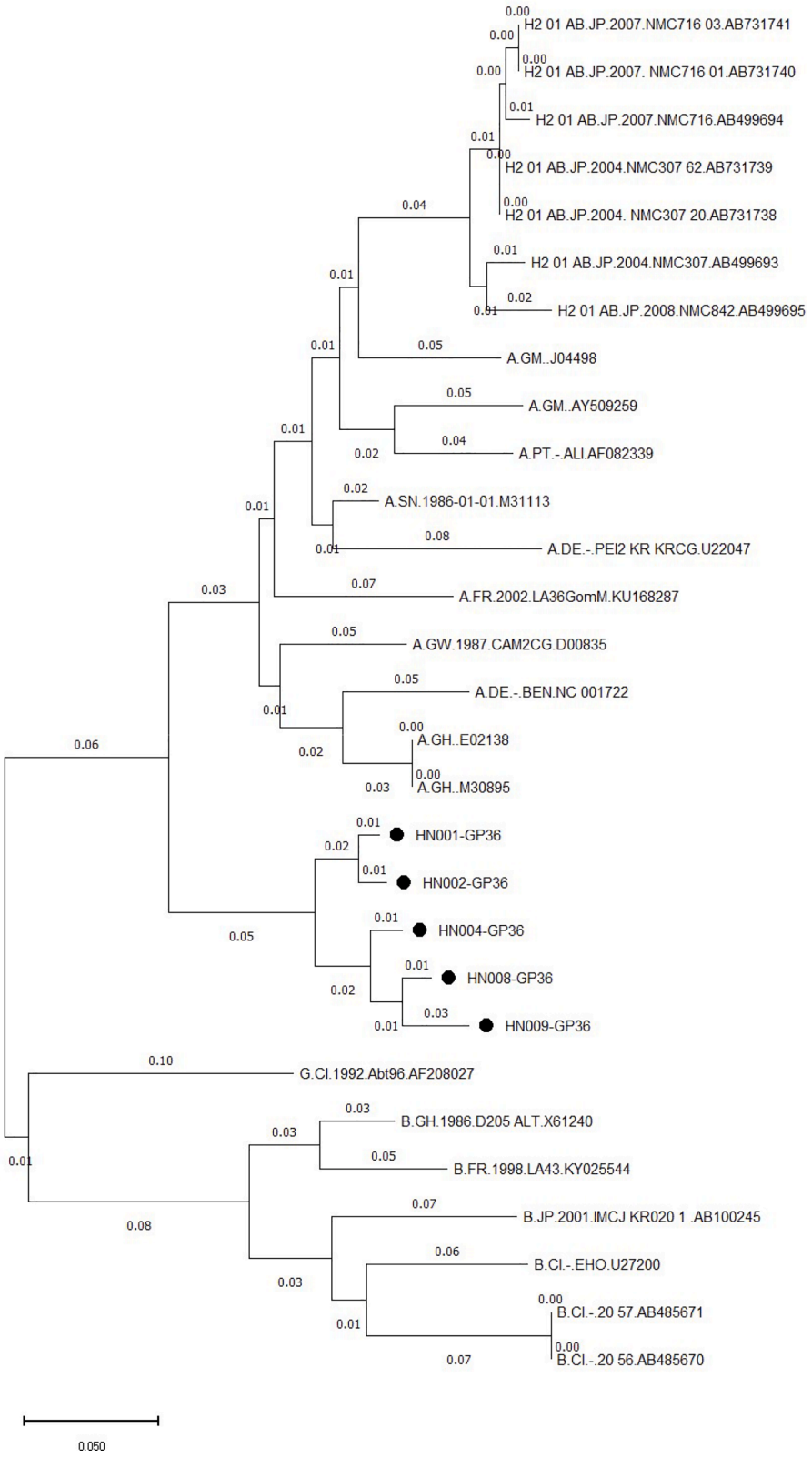

Fig. 3. Phylogenetic tree analysis of 5 HIV-2 positive infects (GP36).

average of 0.024.*env*(GP36) gene distances ranged from 0.019 to 0.072, with an average of 0.052.*env*(GP36) exhibited the highest degree of variation, followed by *pol*, with *gag* showing the least variation.

Phylogenetic analysis of the study sequences, along with reference sequences, could ascertain the classification of HIV-2 groups or detect novel groups if the sequences did not align with any established groups. The phylogenetic analysis of *pol, gag*, and GP36 genes showed that all 14 subjects were infected with HIV-2 group A and clustered with reference sequences from the Gambia (GM) and Senegal (SN) regions of West Africa. This finding was corroborated by a maximum likelihood analysis

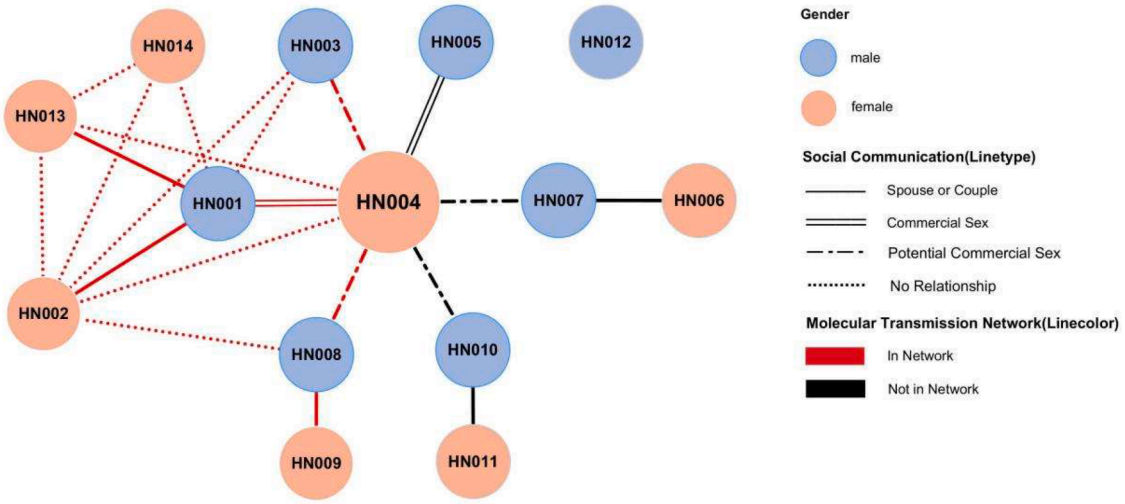

Fig. 4. Social communication and Molecular transmission network of 14 HIV-2 Infected Patients.

with a bootstrap value of 100 (Figs. 1-3).

3.4. HIV-2 molecular propagation network analysis

The phylogenetic analysis of the *pol* gene revealed that all samples formed a single cluster closely resembling the reference strain A.GM. J04498 (Human immunodeficiency virus type 2, isolate SBLISY, complete genome), prevalent in Gambia, Africa. (SR Gurjar et al., 2009) This cluster further subdivided into five smaller clusters. Among these, HN001&HN013, HN010&HN011, and HN008&HN009 represented sexual partners or couples, while HN001&HN004 and HN005&HN004 engaged in commercial sex. The contact history of HN006&HN012 remained unknown and requires further investigation (Fig. 4).Epidemiological investigation of social communication networks revealed that HN001, HN003, HN005 (no sequence available), HN007 (no sequence available), HN008, and HN010 engaged in commercial sex at the same location. Additionally, HN004 offered paid sexual services at this site, while HN002/HN013, HN006, HN009, and HN011 were spouses of HN001, HN007, HN008, and HN010, respectively. HN004 served as the central node in the social communication network.Using a genetic distance threshold of 1.5 %, the analysis of the molecular propagation network revealed that eight samples were integrated into the network (Fig. 4). HN002 and HN004 were identified as the core nodes of the molecular transmission network.

4. Discussion

The emergence of HIV-2, previously rare and mostly confined to West Africa, has now become a considerable concern, particularly in China. Despite limited reports of imported infectious diseases due to restricted overseas residency, documentation of local HIV-2 infections among Chinese nationals remains conspicuously scarce. (Franchini et al., 1989; Kumar et al., 1990) Noteworthy is the recent identification of fourteen cases of HIV-2 infection in Hunan Province spanning the period 2017–2023. Previous research has predominantly associated HIV-2 infections in China with overseas residency, emphasizing the importance of detecting local instances in Hunan Province. This revelation underscores the challenges of globalization, where international travel and migration facilitate the spread of viruses, underscoring the urgent necessity for global health collaboration and surveillance.

Phylogenetic analysis in this study unveiled that all HIV-2 cases in Hunan Province belonged to HIV-2 Group A, prevalent worldwide, particularly in regions like Africa, Portugal, Spain, France, the United Kingdom, the United States, Korea, and India, with India contributing around 95 % of Asian HIV-2 infections. (Yan et al., 1999; Chen et al., 2003) Despite their recent identification in Hunan, these cases exhibit significant genetic similarity to global HIV-2 strains, hinting at potential involvement in international transmission routes, necessitating thorough exploration of their origins and transmission pathways.

This study employed phylogenetic analysis covering *pol, gag,* and gp36 regions to elucidate the genetic characteristics of HIV-2 strains in Hunan Province. Remarkably, all strains showed tight clustering with Bootstrap values exceeding 95, suggesting a common origin of infection and robust communication among sequences. Evaluation of genetic distances across *pol*(RT), *gag*, and *env*(GP36) genes revealed varying degrees of variability, with *env*(GP36) exhibiting the highest variability, followed by *pol*(RT), and *gag* displaying the least variability. This intrinsic variability in HIV-2 underscores diverse selective pressures and evolutionary constraints among gene regions, crucial for understanding HIV-2 evolution and drug resistance mechanisms, potentially impacting biological traits and transmission dynamics, warranting further investigation.

Integration of phylogenetic tree and molecular transmission network analyses provided insights into the transmission dynamics of HIV-2 cases in Hunan Province. Initially, a social network epidemiological survey revealed that all HIV-2-infected individuals resided within the same geographic locale and contracted the infection through familial transmission. Subsequent phylogenetic analysis of the *pol* gene revealed that all 14 samples formed a coherent cluster resembling reference strains from Gambia (A.GM), implying a shared source of infection or transmission network among these cases. Significantly, a high bootstrap value of 100 in the maximum likelihood analysis reinforced the robustness of this clustering, further validating the classification of HIV-2 Group A.

Additionally, the molecular transmission network analysis unveiled that nine identified strains formed a substantial cluster, with a critical node termed HN004. Designated as a female sex worker (FSW), HN004 participated in commercial sexual activities with two male or more individuals, while the other four females were either partners or spouses of these infected males. This signifies a localized HIV-2 epidemic driven by commercial sexual interactions and transmission within partnerships, deeply rooted in the regional context. It emphasizes the pivotal role of commercial sexual activities in HIV-2 transmission, particularly within specific clusters. Moreover, HN004 emerged as a central node in the transmission network, highlighting the essential contribution of sex workers to viral dissemination. Importantly, the analysis underscores the significant involvement of commercial sex work in distinct clusters, as evidenced by the connection between individuals HN001 and HN004,

Table 2
14 patients with HIV-2 infection progress of disease and antiviral therapy.

No.	Gender	Age	Diagnostic Time	Marital Status	The baseline CD4 (cells/ml)	Social transmission network	Status
HN001	Male	57	2017	Married	131	Had intercourse with the sex workers	Refuse to follow up
HN002	Female	54	2017	Married	2527	The sexual partner of HN001	Refuse to follow up
HN003	Male	75	2017	Divorced	395	Had intercourse with the sex workers	Dead
HN004	Female	61	2017	Divorced	56	the sex workers	In treatment
HN005	Male	37	2018	Married	938	Had intercourse with the sex workers	Untreated
HN006	Female	66	2019	Married	28	The wife of HN007	In treatment
HN007	Male	69	2019	Married	204	Had intercourse with the sex workers	Dead
HN008	Female	53	2019	Divorced	186	Had intercourse with the sex workers	In treatment
HN009	Female	54	2021	Divorced	262	The sexual partner of HN008	In treatment
HN010	Male	53	2021	Married	688	Had intercourse with the sex workers	In treatment
HN011	Female	53	2022	Married	665	The sexual partner of HN001	In treatment
HN012	Male	57	2023	Married	/	/	Dead
HN013	Female	61	2023	Divorced	82	Had intercourse with the sex workers	In treatment
HN014	Female	73	2023	Married	238	/	In treatment

with HN004 identified as a key player in this transmission network. This emphasizes the substantial role of commercial sex work in driving HIV-2 transmission within specific communities, with HN004 acting as a crucial component for viral spread within the cluster. The identification of transmission clusters and pivotal nodes like HN004 carries profound implications for HIV-2 prevention and intervention strategies. A nuanced comprehension of transmission dynamics within specific networks empowers public health authorities to devise more targeted interventions, especially tailored for sex workers and their clients, as well as individuals in sexual partnerships.

This study has several notable limitations. Firstly, the sample size utilized was inadequate, potentially compromising the generalizability of findings concerning disease progression and antiviral therapy efficacy, particularly regarding local HIV-2 strains. Further investigation is necessary to confirm the representativeness of these findings. Secondly, while network analysis provides valuable insights, it highlights the complex nature of HIV-2 transmission dynamics. Uncertainties persist in the relationships and contact histories among cases, as evidenced by the unclear connection between HN012 and HN014. Additional epidemiological research is essential to comprehensively elucidate these associations. The identification of transmission clusters and pivotal nodes such as HN004 carries significant implications for HIV-2 prevention and intervention strategies (Table 2).

5. Conclusion

Between 2017 and 2023, Hunan Province recorded more than fourteen cases of HIV-2, all belonging to subtype A and interconnected, indicating a potentially persistent local prevalence. These cases primarily stemmed from local transmission, particularly through heterosexual commercial sex and intra-family contact, underscoring the urgent need for effective prevention and control measures. The increasing local prevalence resulted in three fatalities, highlighting the gravity of the situation. This research elucidates the molecular characteristics and transmission dynamics of HIV-2 in Hunan Province, providing vital insights for developing enhanced prevention strategies and understanding the local epidemic context. Future studies should prioritize enlarging sample sizes, investigating the impact of commercial sexual activities and partner relationships on HIV-2 transmission, and developing targeted public health interventions to mitigate transmission risks, especially among sex workers and their clients. These efforts are crucial for curtailing HIV-2 transmission in Hunan Province and improving the well-being of affected individuals.

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Availability of data and material

The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Xiaobai Zou: Writing – review & editing, Writing – original draft, Formal analysis. **Jianmei He:** Writing – review & editing, Funding acquisition, Formal analysis. **Xiaojun Li:** Writing – review & editing, Formal analysis. **Jun Zheng:** Investigation, Formal analysis, Data curation. **Xiaolin Su:** Investigation, Data curation. **Jie Chen:** Investigation, Formal analysis. **Xi Chen:** Writing – review & editing, Funding acquisition, Methodology, Resources.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

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