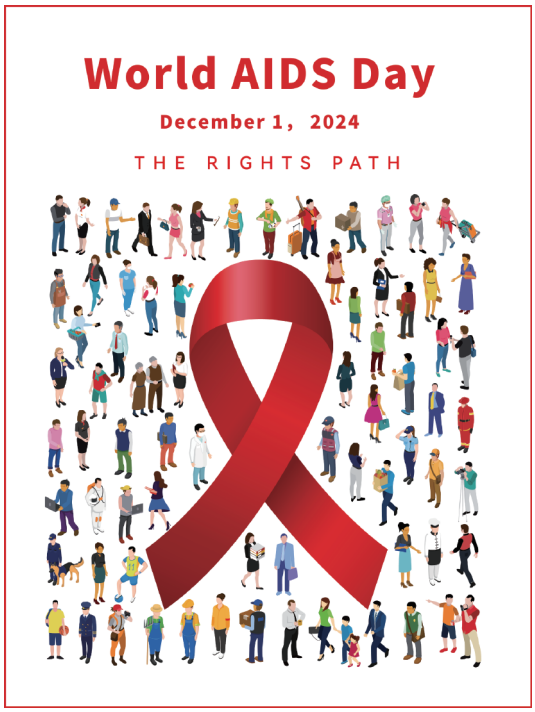
ISSN 2096-7071 (Print)
ISSN 2096-3101 (Online)
CN 10-1629/R1

CHINA CDC WEEKLY

Vol. 6 No. 48 Nov. 29, 2024

中国疾病预防控制中心周报



WORLD AIDS DAY ISSUE

Foreword

Prioritizing the People in HIV Prevention: Transforming Data into Effective Policies and Actions 1249

Vital Surveillances

Evolution of HIV Epidemic and Emerging Challenges — China, 1989–2023 1251

National and Regional Molecular Epidemiology of HIV-1 — China, 2004–2023 1257

Survival of People Living with HIV/AIDS from Pre-ART Era to Treat-all Era — China, 1985–2022 1264

Preplanned Studies

An Index–Contact Paired Data Analysis on Sexual Contact Tracing Outcomes of HIV-Infected Individuals — Yunnan Province, China, 2022–2024 1271

Methods and Applications

Study on the Technical Parameters for Estimating HIV-1 Incidence by Using a Recombinant Antigen-based Capture Enzyme Immunoassay — China 1278

ISSN 2096-7071
9 772096 707248 48>

China CDC Weekly

Cover Image: adapted from National Center for AIDS/STD Control and Prevention, China CDC, https://ncaids.chinacdc.cn/zx-zx/zxzx/202411/t20241114_302651.htm.

This week's issue was organized by Guest Editor Fan Lyu.

Foreword

Prioritizing the People in HIV Prevention: Transforming Data into Effective Policies and Actions

Fan Lyu[1,2,#]

In the contemporary landscape of global health challenges, human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) remain significant public health concerns both domestically and internationally. Recent UNAIDS estimates indicate that by the end of 2023, approximately 39.9 million people were living with HIV/AIDS globally, with 1.3 million new infections and 630,000 deaths (*1*). While current prevention and treatment strategies have contributed to a steady decline in new infections and mortality rates, we remain considerably distant from achieving the ambitious target of "ending the AIDS epidemic by 2030".

The interconnected nature of our globalized world necessitates collaborative approaches to infectious disease prevention. Since the initial diagnosis of HIV in a foreign traveler in China in 1985, the nation has witnessed nearly four decades of epidemic evolution. Currently, China's HIV-positive population exceeds 1.3 million, with annual new diagnoses consistently surpassing 100,000 (*2*). The epidemic's trajectory has shifted dramatically, from primarily affecting injecting drug users to commercial plasma donors, and subsequently to predominantly sexual transmission routes. The geographic distribution has expanded from its initial concentration in southwestern regions to encompass the majority of cities and counties nationwide (*3*). Concurrently, the viral landscape has evolved from predominant subtype B to recombinant strains, including CRF07_BC, CRF01_AE, and CRF08_BC (*4*).

Comprehensive epidemiological understanding serves as the cornerstone of effective infectious disease control. To this end, China has implemented a sophisticated epidemiological and molecular surveillance system (*5*) that has monitored HIV prevalence and evolution over four decades. This surveillance has informed the development of targeted interventions, including methadone maintenance therapy, needle exchange programs, Blood Donation Law implementation, expanded testing initiatives, and universal treatment protocols (*6*). These people-centered policies have yielded substantial results, effectively eliminating blood-borne transmission and significantly reducing both injecting drug use and mother-to-child transmission (*7*). However, the dynamic nature of the epidemic, coupled with evolving social conditions and technological capabilities, necessitates continuous policy innovation and optimization to maintain effectiveness.

China's AIDS prevention and control program currently aligns with UNAIDS's "six 95%" targets, positioning the nation to make significant contributions toward global AIDS elimination (*8*). However, several critical questions demand urgent attention: How has the epidemic pattern evolved? Given the predominant sexual transmission route among the general population, do traditional intervention strategies maintain their efficacy? Has the survival rate of HIV-infected individuals in China improved significantly under current antiviral treatment protocols? What are the evolutionary trajectories and distribution patterns of HIV strains across China? Addressing these questions is crucial for evidence-based policy formulation.

This special issue addresses these pressing questions by providing a comprehensive analysis of HIV epidemiology in China. Our findings reveal the emerging significance of non-marital and non-commercial heterosexual transmission in facilitating HIV spread within the general population. Following the expansion of eligibility criteria for free antiretroviral treatment (ART), we observed a marked improvement in survival rates among HIV-infected individuals. Furthermore, our analysis highlights an increasing prevalence of recombinant viral strains. These insights provide crucial evidence for developing targeted and scientifically grounded prevention and control policies in China.

Moving forward, it is imperative to implement integrated, multidisciplinary research approaches that combine classical epidemiological theories with advanced intelligent technologies. This integration will enable a more nuanced and comprehensive understanding of HIV epidemic patterns while facilitating a multidimensional evaluation of AIDS prevention and control strategies. Such evidence-based approaches will strengthen policy-

making processes, advancing China's AIDS prevention and control efforts to new heights while contributing substantially to global AIDS elimination and protecting population health and well-being.

doi: 10.46234/ccdcw2024.250

[#] Corresponding author: Fan Lyu, fanlv@chinaaids.cn.

[1] National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China; [2] National Key Laboratory of Intelligent Tracking and Forecasting for Infectious Diseases, National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China.

Submitted: November 19, 2024; Accepted: November 22, 2024

REFERENCES

1. UNAIDS. The path that ends AIDS: UNAIDS Global AIDS Update 2023. Geneva: Joint United Nations Programme on HIV/AIDS. 2023. https://www.unaids.org/sites/default/files/media_asset/2023-unaids-global-aids-update_en.pdf.
2. The Chinese Center for Disease Control and Prevention Sexually Transmitted Disease of AIDS Prevention and Control Center. The AIDS and STD epidemic in the second quarter of 2024 in China. Chin J AIDS STD 2024;30(9):893. http://dx.doi.org/10.13419/j.cnki.aids.2024.09.01. (In Chinese).
3. Wu ZY, Chen JF, Scott SR, McGoogan JM. History of the HIV epidemic in China. Curr HIV/AIDS Rep 2019;16(6):458 – 66. https://doi.org/10.1007/s11904-019-00471-4.
4. He X, Xing H, Ruan YH, Hong KX, Cheng CL, Hu YY, et al. A comprehensive mapping of HIV-1 genotypes in various risk groups and regions across China based on a nationwide molecular epidemiologic survey. PLoS One 2012;7(10):e47289. https://doi.org/10.1371/journal.pone.0047289.
5. Tang HL, Li DM, Qin QQ, Chen FF, Ge L, Cai Y, et al. Inheritance and development: promote the high-quality development of AIDS monitoring in China based on evidence. Chin J AIDS STD 2023;29(7):733-6. http://dx.doi.org/10.13419/j.cnki.aids.2023.07.01. (In Chinese).
6. Lyu F, Xu P. Theory and practice of evidence-based policy research on AIDS prevention and control. Beijing: People's Medical Publishing House. 2022. (In Chinese).
7. Han MJ. Analysis of HIV epidemic and prospects for prevention and control in China. Chin J AIDS STD 2023;29(3):247-50. http://dx.doi.org/10.13419/j.cnki.aids.2023.03.01. (In Chinese).
8. Lyu F, Liu ZF, Liu YF, Han MJ, Yan J. Anchor the goal, enhance capabilities, and promote the high-quality development of AIDS prevention and control. Chin J AIDS STD 2024;30(4):335-8. http://dx.doi.org/10.13419/j.cnki.aids.2024.04.01. (In Chinese).

Fan Lyu, MD, PhD
Acting Director of National Center for AIDS/STD Control and Prevention
PI of National Key Laboratory of Intelligent Tracking and Forecasting for Infectious Diseases, National Center for AIDS/STD Control and Prevention, Beijing, China.

Vital Surveillances

Evolution of HIV Epidemic and Emerging Challenges — China, 1989–2023

Chang Cai[1,2]; Houlin Tang[1,2]; Dongmin Li[1,2]; Qianqian Qin[1,2]; Fangfang Chen[1,2]; Yichen Jin[1,2]; Fan Lyu[1,2,#]

ABSTRACT

Introduction: This study aimed to provide a comprehensive analysis of the human immunodeficiency virus (HIV) epidemiological landscape in China through a historical review and current assessment.

Methods: Data were extracted from China's HIV/AIDS Comprehensive Response Information Management System (CRIMS). Transmission patterns across different phases were visualized using stacked area charts. Geographical correlations between transmission routes were analyzed using scatter plots and Pearson correlation coefficients. The extent and trends of HIV spread among the general population were evaluated using Venn diagrams and Cochran-Armitage tests.

Results: The HIV epidemic in China evolved through four distinct phases: injecting drug user (IDU) dominated (1989–1994), former plasma donor (FPD) outbreak (1995–2005), sexual transmission dominance (2006–2014), and general population spread (2015–present). A strong correlation was observed between provinces reporting high numbers of IDU cases and those with elevated heterosexual transmission (r=0.88, P<0.001). Between 2015 and 2023, 393,926 cases were identified among the general population through non-marital and non-commercial heterosexual contact (NMNCHC). The proportion of general population cases among heterosexual transmissions increased significantly from 46.2% to 55.7% (Z=42.7, P<0.001).

Conclusion: The significant spread of HIV into the general population necessitates the development of targeted prevention strategies for both high-risk and general populations to address emerging epidemiological challenges.

China maintains a highly sophisticated HIV surveillance and reporting system that enables real-time monitoring of epidemic trends. In the early 2000s, the epidemic was characterized by three distinct phases: sporadic cases (1985–1988), localized spread (1989–1994), and localized with local generalized epidemic (1995–present) (*1*). Since then, the epidemic has undergone significant transformations, including a shift in the primary transmission route from blood to sexual transmission, persistently high annual diagnosis rates, and a notable increase in the proportion of elderly cases (*2*–*3*). By the end of 2023, China reported nearly 1.3 million people living with HIV, representing a significant portion of the estimated 39.9 million cases globally (*4*).

The formulation of evidence-based strategies to advance high-quality HIV prevention and control is crucial for addressing evolving epidemic patterns both domestically and internationally (*5*). This study analyzed national surveillance data from 1989 to 2023 to provide a comprehensive historical review and current assessment of HIV epidemiology in China. Through a detailed examination of epidemic phenomena and emerging prevention challenges, this research establishes a foundation for developing future policies and strategic interventions.

METHODS

Data were extracted from the Comprehensive Response Information Management System (CRIMS) database of China, using the cumulative database as of June 2024 for cases reported between 1989 and 2023. CRIMS is a real-time online database that allows personal information updates during follow-up, which may result in discrepancies with previously published data. Although 22 cases were reported between 1985 and 1988, these were all foreigners or related to imported blood products (*6*). Therefore, this study's analysis begins in 1989, when the first indigenous case was reported.

Non-marital and non-commercial heterosexual contact (NMNCHC) refers to heterosexual behavior

between individuals who are neither married nor in a regular relationship and where no monetary or material transaction occurs. This includes sexual encounters between temporary partners and casual heterosexual contacts (*7*). NMNCHC was incorporated into the online case report form as an HIV contact history category in August 2014 (*8*).

For this study, the general population is defined as individuals without HIV-positive spouses or immediate family members who have not engaged in high-risk behaviors such as injecting drug use, male same-sex behavior, or commercial sex work (either selling or buying). These individuals' HIV exposure risk is exclusively through non-marital, non-commercial heterosexual contact.

The analysis employed descriptive statistics and stacked area charts to illustrate transmission patterns across different phases. Geographical correlations between transmission routes were examined using scatter plots and Pearson correlation coefficients. The extent and trends of HIV spread among the general population were assessed using Venn diagrams and the Cochran-Armitage test. All statistical tests were two-sided, with significance set at $P<0.05$. Analyses were conducted using Microsoft Excel (Microsoft Corp 2016, Redmond, Washington USA) and R (version 4.4.0, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Transmission Modes in Different Phases

The HIV epidemic in China can be categorized into four distinct phases based on transmission patterns. Phase 1 (1989–1994) began with the first indigenous outbreak among injecting drug users (IDUs) in 1989, accompanied by sporadic cases of heterosexual transmission. During this initial phase, 1,138 infections were reported, with 87.3% attributed to drug injection and 10.0% to heterosexual contact.

Phase 2 (1995–2005) witnessed continued growth in both injection drug use and heterosexual transmission. Additionally, infections among former plasma donors (FPD) emerged and peaked at approximately 23,000 cases following the national HIV testing campaign in 2004. Of the 82,674 total infections reported during this phase, injection drug use accounted for 35.7%, heterosexual contact for 14.4%, and plasma/blood-product donation and reception for 42.3%.

Phase 3 (2006–2014) marked a significant shift as heterosexual contact surpassed injection drug use as the predominant transmission route. This period also saw a rapid increase in homosexual transmission, while infections from plasma/blood-product donation and reception declined until elimination. Among the 533,374 reported infections during this phase, injection drug use represented 14.4%, heterosexual contact 62.8%, and homosexual contact 16.1%.

Phase 4 (2015–present) is characterized by the sustained dominance of heterosexual transmission, leading to substantial spread within the general population — a phenomenon analyzed in detail in the third section. Of the 1,131,464 infections reported during this phase, heterosexual and homosexual contact accounted for 72.0% and 25.2%, respectively (Figure 1).

Correlations in the Geographical Distribution of Different Transmission Routes

Analysis of transmission route patterns across different epidemic phases revealed that HIV spread in China was primarily driven by injecting drug use, plasma/blood donation and reception, and sexual contact (both heterosexual and homosexual). Previous research has demonstrated that multiple high-risk behaviors among infected individuals facilitated HIV transmission across different population groups (*8*).

Our geographical analysis of these four transmission routes revealed their presence across all 31 provincial-level administrative divisions (PLADs) in China. A strong positive linear correlation ($r=0.88$, $P<0.001$) emerged between the cumulative number of injection drug users and heterosexually transmitted cases at the provincial level. However, no significant correlations were observed among other transmission routes (Figure 2).

The Spread of HIV to the General Population

HIV exposure through heterosexual contact can occur through three distinct pathways: NMNCHC, commercial heterosexual contact (CHC), and contact with an HIV-positive spouse/regular partner (HSP).

Between 2015 and 2023, 787,445 individuals (97.3%) out of 808,978 cases of heterosexual HIV transmission provided detailed contact histories. Among these cases, 393,926 (50.0%) were from the general population with NMNCHC as their sole risk

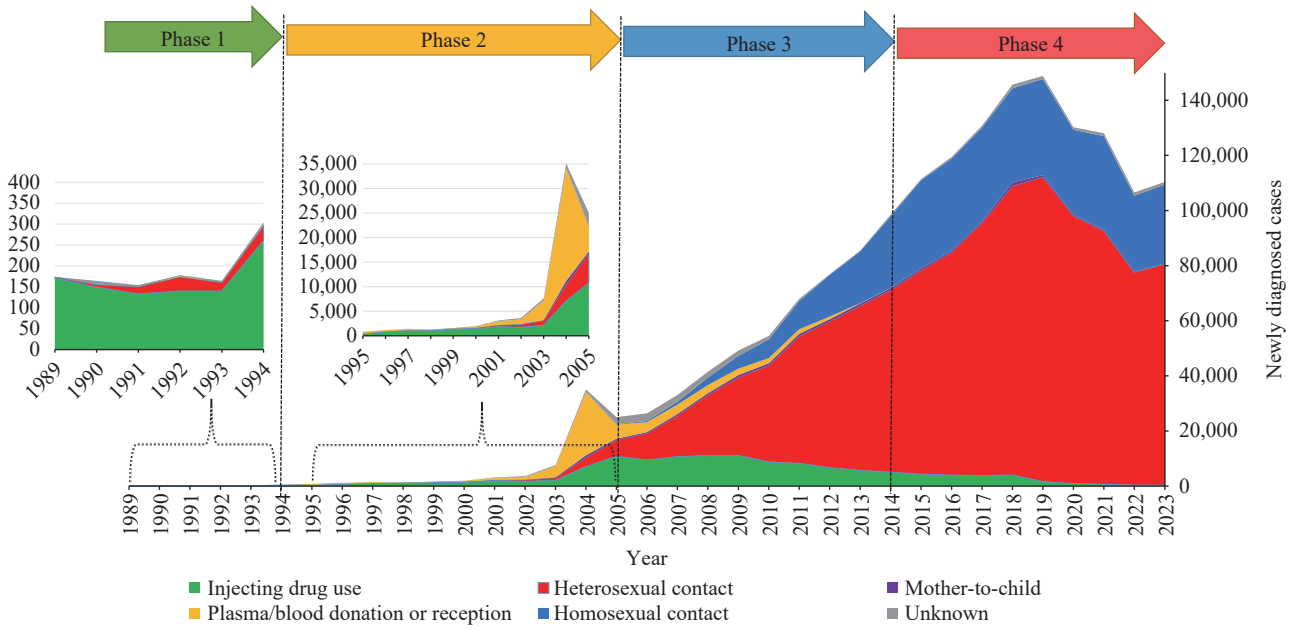


FIGURE 1. number of newly diagnosed HIV cases attributed to different transmission routes in China, 1989–2023.
Abbreviation: HIV=human immunodeficiency virus.

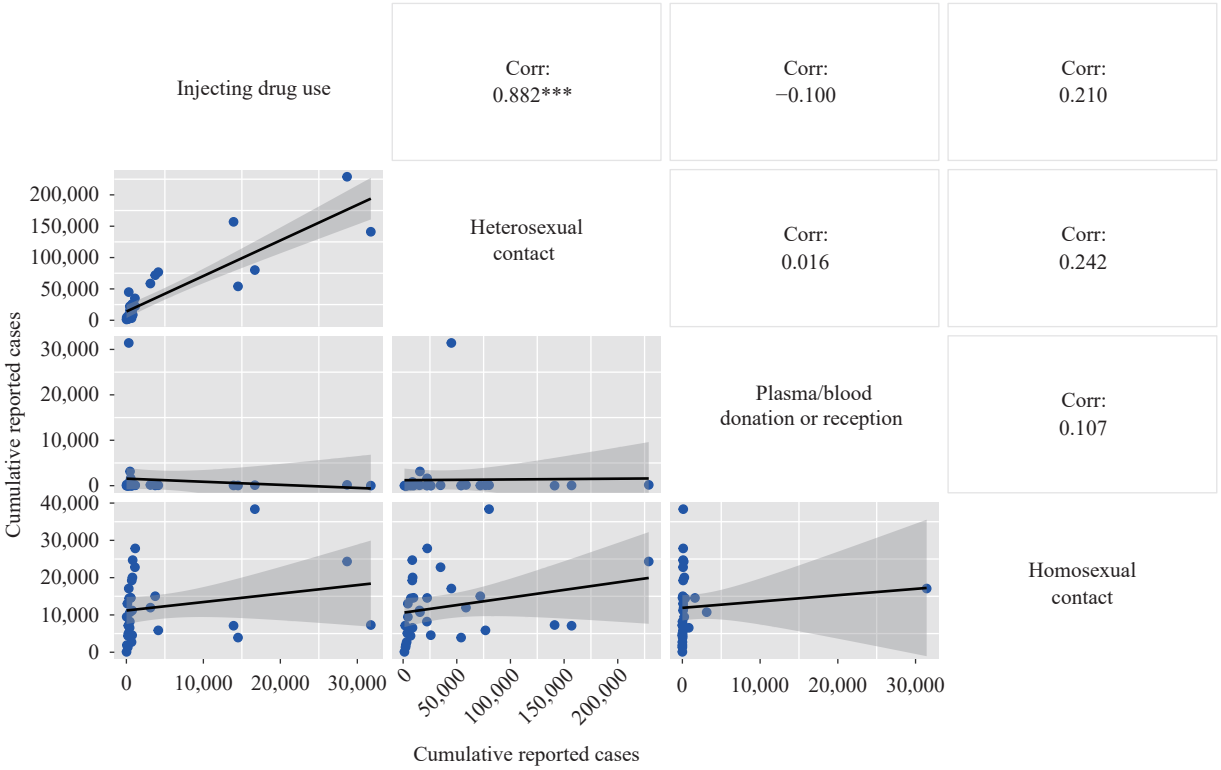


FIGURE 2. Scatter plot and correlation coefficient matrix diagram of the cumulative numbers of individuals infected with HIV through four transmission routes in 31 PLADs, by 2023.
Note: Asterisk indicates statistical significance.
Abbreviation: Corr=correlation coefficient; PLADs=provincial-level administrative divisions.

factor, 290,557 (36.9%) reported only CHC, 75,641 (9.6%) had an HSP without other non-marital heterosexual contact, and 27,321 (3.5%) reported multiple contact histories. These distributions are detailed in Table 1 and Figure 3. The proportion of general population cases among heterosexual

TABLE 1. Contact histories of individuals with heterosexual HIV transmission in China by year, 2015 –2023.

Year	Total cases	NMNCHC	CHC	HSP	Multiple contact histories
2015	72,686	33,577 (46.2)	28,259 (38.9)	8,200 (11.3)	2,650 (3.6)
2016	79,198	37,585 (47.5)	30,469 (38.5)	8,509 (10.7)	2,635 (3.3)
2017	89,593	43,609 (48.7)	33,628 (37.5)	9,055 (10.1)	3,301 (3.7)
2018	102,145	51,032 (50.0)	37,096 (36.3)	10,168 (10.0)	3,849 (3.8)
2019	107,520	52,684 (49.0)	40,371 (37.5)	10,339 (9.6)	4,126 (3.8)
2020	95,368	46,766 (49.0)	36,290 (38.1)	8,973 (9.4)	3,339 (3.5)
2021	89,218	45,925 (51.5)	32,684 (36.6)	7,781 (8.7)	2,828 (3.2)
2022	74,318	39,649 (53.4)	26,044 (35.0)	6,335 (8.5)	2,290 (3.1)
2023	77,399	43,099 (55.7)	25,716 (33.2)	6,281 (8.1)	2,303 (3.0)
Z		42.737	−23.83	−27.598	−9.4913
P		<0.001	<0.001	<0.001	<0.001

Abbreviation: NMNCHC=non-marital and non-commercial heterosexual contact; CHC=commercial heterosexual contact; HSP=HIV-positive spouse/regular partner.

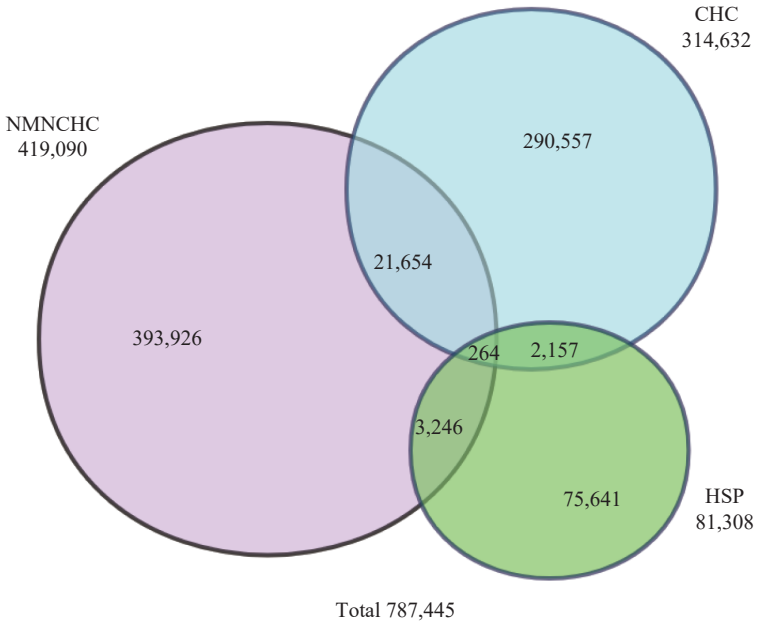


FIGURE 3. Contact histories of cumulative individuals with heterosexual HIV transmission in China, 2015–2023.
Abbreviation: NMNCHC=non-marital and non-commercial heterosexual contact; CHC=commercial heterosexual contact; HSP=HIV-positive spouse/regular partner; HIV=human immunodeficiency virus.

transmissions showed a significant upward trend, increasing from 46.2% to 55.7% (Z=42.7, *P*<0.001), while all other contact history categories exhibited declining trends, as shown in Table 1.

DISCUSSION

Based on our analysis, the HIV epidemic in China evolved through four distinct phases, each characterized by a predominant transmission mode. While detection rates and delayed diagnosis patterns varied across populations, previous research has confirmed that these variations do not invalidate our phase classification (*2*). At the provincial level, we observed a strong correlation (r=0.88, *P*<0.001) between the geographical distribution of injection drug use (prevalent in the initial phase) and heterosexual transmission (dominant in the final two phases). This correlation likely stems from HIV-infected injecting drug users being the primary source of transmission to heterosexual populations (*8*), resulting in their profound influence on subsequent heterosexual

transmission patterns. This suggests that regions with earlier epidemic emergence may experience higher rates of heterosexual transmission.

The elimination of transmission through plasma/blood donation and reception, along with the successful containment of drug injection and mother-to-child transmission, demonstrates the effectiveness of targeted interventions for well-defined populations. Traditional control strategies, such as the Blood Donation Law of 1998 and the needle exchange program initiated in 2000, effectively blocked blood-related transmission routes. The 2004 implementation of active testing campaigns targeting high-risk populations, particularly former plasma donors (*9*), successfully identified transmission sources while accounting for the marked increase in case numbers within these populations.

Sexual transmission presents unique challenges due to the large, widely distributed populations involved, making traditional identification approaches less effective. Previous research estimates that men who engage in homosexual behavior comprise approximately 1.7% of adult males (*10*), while female sex workers represent 0.19% to 0.75% of women in corresponding age groups, with male clients numbering 2.4 to 5.8 times higher (*11*–*12*). The general population engaging in non-marital and non-commercial heterosexual contact represents the largest demographic, facilitating ongoing HIV transmission from high-risk populations to the general population.

Our findings reveal significant HIV spread within the general population, with nearly 0.4 million general individuals diagnosed with HIV infection over the past 9 years, representing more than 50% of all heterosexual transmissions since 2019. This substantial infection rate through casual sexual encounters and temporary relationships reflects both evolving social norms (*13*) and improved testing accessibility. Most heterosexual transmission cases are identified through medical institutions during non-AIDS-related care, primarily due to challenges in targeted detection and low testing awareness. While expanded provider-initiated HIV testing has increased case identification, this approach often fails to detect infections promptly (*14*), potentially allowing secondary transmission before effective intervention.

The general population's heterogeneity across age, gender, occupation, and education levels poses significant challenges for developing unified health education strategies, particularly compared to more concentrated high-risk populations. Furthermore, since non-marital and non-commercial heterosexual contact typically occurs in contexts of trust or sexual impulse, a significant disconnect exists between knowledge and behavior (*15*).

This study has two primary limitations. First, the general population estimates may be inflated due to the relatively low sensitivity of non-marital and non-commercial heterosexual contact history reporting. Second, transmission route misclassification may occur due to reliance on self-reported contact histories, particularly regarding homosexual transmission potentially being misclassified as heterosexual transmission.

In conclusion, HIV has significantly penetrated the general population through heterosexual contact, necessitating the development of distinct, tailored prevention strategies for both high-risk and general populations to address these emerging challenges.

Conflicts of interest: No conflicts of interest.

Acknowledgements: The contributions of staff members at provincial, prefectural, and county-level CDC.

Funding: Supported by the National Key Research and Development Plan (Grant number 2022YFC2305201). The funding agency had no role in data collection, analysis, interpretation, or manuscript preparation.

doi: 10.46234/ccdcw2024.251

[#] Corresponding author: Fan Lyu, fanlv@chinaaids.cn.

[1] National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China; [2] National Key Laboratory of Intelligent Tracking and Forecasting for Infectious Diseases, National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China.

Submitted: October 14, 2024; Accepted: November 21, 2024

REFERENCES

1. Zheng XW. The development of epidemiological surveillance of AIDS in China. China Med News 2001;16(19):7-9. https://rs.yiigle.com/CN115399202004/831423.htm. (In Chinese).
2. Wu ZY, Chen JF, Scott SR, McGoogan JM. History of the HIV epidemic in China. Curr HIV/AIDS Rep 2019;16(6):458 – 66. https://doi.org/10.1007/s11904-019-00471-4.
3. Han MJ. Analysis of HIV epidemic and prospects for prevention and control in China. Chin J AIDS STD 2023;29(3):247-50. http://dx.doi.org/10.13419/j.cnki.aids.2023.03.01. (In Chinese).
4. The path that ends AIDS: UNAIDS Global AIDS Update 2023. https://www.unaids.org/en/resources/documents/2023/global-aids-update-2023
5. Lv F, Xu P. Theory and practice of evidence-based policy research on AIDS prevention and control. Beijing: People's Medical Publishing House. 2022. https://www.pmphmall.com/gdsdetail/646642-324239. (In Chinese).

6. Zheng XW, Zhu D, Yang GH, Zhang GY. A report on AIDS surveilance from 1985 to 1988 in China. Chin J Epidemiol 1989;10(2): 65 – 7. https://doi.org/10.3760/cma.j.issn.0254-6450.1989.02.101.
7. Dong ZL, Ma LY, Cai C, Gao GF, Lyu F. Demographic features of identified PLWHA infected through commercial and nonmarital noncommercial heterosexual contact in China from 2015 to 2018: a retrospective cross-sectional study. BMC Infect Dis 2021;21(1):71. https://doi.org/10.1186/s12879-020-05757-2.
8. Cai C, Tang HL, Qin QQ, Jin YC, Lyu F. Behavioral verification and risk factors of HIV cross-population transmission in China: analysis of national surveillance data 1989–2022. BMC Infect Dis 2024;24(1):49. https://doi.org/10.1186/s12879-023-08956-9.
9. Wu ZY, Sullivan SG, Wang Y, Rotheram-Borus MJ, Detels R. Evolution of China's response to HIV/AIDS. Lancet 2007;369(9562): 679 – 90. https://doi.org/10.1016/S0140-6736(07)60315-8.
10. Hu MG, Xu CD, Wang JF. Spatiotemporal analysis of men who have sex with men in mainland China: social app capture-recapture method. JMIR Mhealth Uhealth 2020;8(1):e14800. https://doi.org/10.2196/14800.
11. Guo W, Bao SL, Lin W, Wu GH, Zhang W, Hladik W, et al. Estimating the size of HIV key affected populations in Chongqing, China, using the network scale-up method. PLoS One 2013;8(8): e71796. https://doi.org/10.1371/journal.pone.0071796.
12. Huan XP, Bao SL, Yang HT, Xu JS, Qiu T, Zhang X, et al. The application of network scale-up method on female sex workers and clients size estimation in Taizhou city. Chin J Prev Med 2013;47(3): 233 – 7. https://doi.org/10.3760/cma.j.issn.0253-9624.2013.03.010.
13. Wu ZY. Characteristics of HIV sexually transmission and challenges for controlling the epidemic in China. Chin J Epidemiol 2018;39(6):707 – 9. https://doi.org/10.3760/cma.j.issn.0254-6450.2018.06.002.
14. Yue Q, Liu YF, Li J, Zang CP. Analysis on late HIV diagnosis among newly reported human immunodeficiency virus/acquired immunodeficiency syndrome cases between 2009 and 2017 in medical institutions. Chin J Prev Med 2018;52(12):1248 – 53. https://doi.org/10.3760/cma.j.issn.0253-9624.2018.12.011.
15. Liu H, Zhu QY, Zhang L, Liu YJ, Xu P, Yu MH, et al. HIV-related knowledge, attitude, and practices research among college students - six Chinese cities, 2021. China CDC Wkly 2022;4(47):1043 – 50. https://doi.org/10.46234/ccdcw2022.210.

Vital Surveillances

National and Regional Molecular Epidemiology of HIV-1 — China, 2004–2023

Dong Wang[1]; Yi Feng[1]; Jingjing Hao[1]; Hongping Hu[1]; Fangyuan Li[1]; Jialu Li[1]; Yuhua Ruan[1]; Lingjie Liao[1]; Jing Hu[1]; Chang Song[1]; Yiming Shao[1]; Hui Xing[1,#]

ABSTRACT

Introduction: The genetic diversity of human immunodeficiency virus (HIV)-1 subtypes significantly influences the effectiveness of diagnostic tools, antiretroviral therapy (ART), and vaccine development. This study aimed to assess the regional and national prevalence of HIV-1 subtypes and recombinants in China between 2004 and 2023 using pol gene segment analysis.

Methods: We analyzed annual HIV/AIDS reports and pol gene segment sequences from all Chinese provinces between 2004 and 2023. The distribution of HIV-1 subtypes and recombinants across China and within its regions was estimated by multiplying the proportion of each subtype, circulating recombinant form (CRF), and unique recombinant form (URF) in each province by the corresponding number of reported HIV infections.

Results: Analysis of 94,476 pol gene segments from 31 provinces revealed that CRF01_AE strain accounted for 32.1% of HIV-1 infections during 2004–2023, while CRF07_BC lineage represented 39.1%. CRF08_BC strain contributed 9.2%, followed by subtype B (8.7%) and CRF55_01B (2.4%). Other CRFs collectively comprised 6.0% of infections, while URFs and other subtypes accounted for 1.3% and 1.1%, respectively.

Conclusions: The study revealed significant regional variations and temporal changes in the proportions of HIV-1 CRFs, subtypes, and URFs across China, emphasizing the importance of continued surveillance of strain distribution patterns.

Human immunodeficiency virus type 1 (HIV-1) remains a critical global health security challenge, affecting 39.9 million people as of 2023 (*1*). While expanded access to antiretroviral therapy (ART) has effectively reduced HIV-1 transmission rates, a definitive cure remains elusive, underscoring the critical importance of developing an effective HIV-1 vaccine for pandemic eradication (*2*).

The extensive genetic heterogeneity of HIV-1 presents significant challenges for diagnostics, ART, and vaccine development (*3*). According to the Los Alamos National Laboratory (LANL), HIV-1 group M strains comprise 10 distinct subtypes, along with circulating recombinant forms (CRFs) and unique recombinant forms (URFs) that arise through subtype recombination. Contemporary vaccine development strategies encompass mosaic vaccines, polyvalent approaches, and targeting evolutionarily conserved regions within the HIV genome. However, successful design, evaluation, and implementation of HIV-1 vaccines necessitate comprehensive and precise data regarding the prevalence of HIV-1 subtypes and recombinants to ensure vaccine immunogens match the circulating strains in target populations (*4*).

Continuous surveillance of strain distribution patterns is therefore essential. Global distribution patterns of HIV-1 subtypes and recombinants have been extensively documented by Hemelaar et al. (*5*) and Williams et al. (*6*), revealing CRF strains, particularly CRF01_AE, as predominant in East and Southeast Asia. While China similarly exhibits CRF strain predominance, it demonstrates distinct prevalence patterns characterized by the co-circulation of CRF01_AE, CRF07_BC, CRF08_BC, and CRF55_01B (*7*).

In this study, we analyzed pol gene segment sequences collected across China in conjunction with provincial HIV infection reports from 2004–2023 to comprehensively assess the regional and national distribution patterns of HIV-1 subtypes and recombinants.

METHODS

Our study analyzed a comprehensive dataset of HIV-1 pol region sequences from China comprising

two distinct subsets. The first subset consisted of sequences retrieved from the Los Alamos HIV Sequence Database, while the second originated from the Division of Research on Virology and Immunology at the National Center for AIDS/STD Control and Prevention, China CDC. Following rigorous quality control measures, including the removal of duplicate sequences and those lacking provincial sampling information, we established a refined dataset of 94,476 unique pol region sequences, ensuring one sequence per infected individual.

For sequence subtyping, we employed a dual-analysis approach. Initially, sequences were processed through the HIV subtyping tool of the National Microbiology Data Center's HIV database. Concurrently, we conducted phylogenetic analysis using FastTree. To resolve any discrepancies between these methodologies, we performed additional confirmatory analysis using IQtree2.exe, ensuring accurate subtype classification.

To estimate the national and regional distribution patterns of HIV-1 subtypes, we integrated our sequence analysis with provincial HIV infection surveillance data. The proportion of each subtype, CRF, and URF within each province was multiplied by the corresponding number of reported HIV infections to calculate comprehensive distribution estimates across China's regions and time periods.

RESULT

Characteristics of the Database

Our comprehensive analysis encompassed 94,476 HIV-1 pol gene segment sequences collected across China from 2004–2023.

Analysis of the sequence database revealed CRF01_AE as the predominant strain, comprising 38.6% (36,486/94,476) of all sequences, followed closely by CRF07_BC at 33.2% (31,388/94,476). Subtype B represented 9.6% (9,080/94,476) of sequences, while CRF08_BC and CRF55_01B accounted for 7.0% (6,575/94,476) and 4.3% (4,052/94,476), respectively. Notably, the aggregate proportion of all circulating recombinant forms (CRFs) constituted a substantial 88.5% (83,595/94,476) of the total sequences (Table 1, Supplementary Table S1, available at https://weekly.chinacdc.cn/).

Distribution of HIV-1 CRFs, Subtypes, and URFs in China

This extensive dataset was systematically stratified into four distinct chronological periods: 2004–2009, 2010–2014, 2015–2019, and 2020–2023, as detailed in Table 2. During 2004–2023, CRF01_AE and CRF07_BC emerged as the predominant strains, accounting for 32.1% and 39.1% of HIV-1 infections, respectively. CRF08_BC contributed significantly at 9.2%, followed by subtype B at 8.7% and CRF55_01B at 2.4%. Additional CRFs, including CRF59_01B, CRF79_0107, CRF85_BC, and 81 other distinct recombinant forms, collectively represented 6.0% of infections. URFs constituted 1.3% of cases, while other subtypes (including A1, C, D, and nine other subtypes or sub-subtypes) accounted for the remaining 1.1%.

Temporal analysis revealed significant shifts in HIV-1 subtype distribution (Table 2 and Figure 1).

TABLE 1. Distribution of HIV-1 subtypes, circulating recombinant forms (CRFs), and unique recombinant forms (URFs) in China.

Characteristics	HIV-1 CRFs						URFs	Total recombinants	HIV-1 subtypes		
	01_AE	07_BC	08_BC	55_01B	Other	Total CRFs			B	Other	Total subtypes
Weighted (%)	32.1	39.1	9.2	2.4	6.0	88.9	1.3	90.2	8.7	1.1	9.8
Unweighted (%)	38.6	33.2	7.0	4.3	5.4	88.5	1.1	89.6	9.6	0.8	10.4

Note: CRF denotes circulating recombinant form; URF denotes unique recombinant form. Other CRFs encompass CRF02_AG, CRF03_A6B, CRF06_cpx, CRF09_cpx, CRF10_CD, CRF11_cpx, CRF12_BF, CRF13_cpx, CRF15_01B, CRF16_A2D, CRF18_cpx, CRF19_cpx, CRF22_01A1, CRF25_cpx, CRF33_01B, CRF34_01B, CRF35_A1D, CRF43_02G, CRF45_cpx, CRF51_01B, CRF52_01B, CRF53_01B, CRF54_01B, CRF56_cpx, CRF57_BC, CRF58_01B, CRF59_01B, CRF61_BC, CRF62_BC, CRF64_BC, CRF65_cpx, CRF67_01B, CRF68_01B, CRF69_01B, CRF76_01B, CRF77_cpx, CRF79_0107, CRF80_0107, CRF84_A1D, CRF85_BC, CRF87_cpx, CRF88_BC, CRF96_cpx, CRF97_01B, CRF100_01C, CRF101_01B, CRF102_0107, CRF103_01B, CRF104_0107, CRF105_0108, CRF106_cpx, CRF107_01B, CRF109_0107, CRF110_BC, CRF111_01C, CRF112_01B, CRF113_0107, CRF114_0155, CRF115_01C, CRF118_BC, CRF119_0107, CRF120_0107, CRF121_0107, CRF123_0107, CRF125_0107, CRF126_0755, CRF128_07B, CRF134_0107, CRF137_0107, CRF140_0107, CRF145_0107, CRF149_01B, CRF151_0107, CRF154_0755, CRF155_0755. Other subtypes include subtypes A1, A3, A6, C, D, F1, F2, G, and H. The unweighted row represents the actual proportions of subtypes, CRFs, and URFs in the sequence database. The weighted row presents estimated proportions based on actual sequence distributions and provincial HIV infection reports.Total CRFs is the sum of CRF01_AE, CRF07_BC, CRF08_BC, CRF55_01B, and other CRFs. Total recombinants is the sum of total CRFs and URFs. Total subtypes is the sum of subtype B and other subtypes.

TABLE 2. Spatiotemporal distribution of HIV-1 subtypes, CRFs, and URFs across four time periods.

Region/Years	HIV-1 CRFs						URFs	Total recombinants	HIV-1 subtypes		
	01_AE	07_BC	08_BC	55_01B	Other	Total CRFs			B	Other	Total subtypes
China											
2004–2009 (%)	31.0	24.8	10.0	0.6	5.0	71.4	1.7	73.1	24.7	2.2	26.9
2010–2014 (%)	41.1	35.9	6.0	2.1	5.6	90.7	0.9	91.6	7.2	1.3	8.4
2015–2019 (%)	31.4	46.1	8.4	3.0	4.4	93.4	0.9	94.3	5.0	0.7	5.7
2020–2023 (%)	27.6	42.2	11.9	3.2	9.0	94.0	1.8	95.9	3.5	0.6	4.1
Central											
2004–2009 (%)	12.8	1.8	0.3	0.1	0.4	15.4	0.1	15.5	84.3	0.2	84.5
2010–2014 (%)	44.1	20.8	1.9	4.4	3.1	74.4	0.2	74.6	25.1	0.3	25.4
2015–2019 (%)	37.1	30.0	4.4	5.7	3.2	80.3	1.1	81.4	18.1	0.5	18.6
2020–2023 (%)	30.1	37.7	5.9	3.7	8.3	85.8	1.8	87.5	11.3	1.2	12.5
East											
2004–2009 (%)	38.5	16.5	3.4	0.0	2.6	61.0	0.2	61.2	36.8	2.0	38.8
2010–2014 (%)	56.0	25.7	1.7	1.4	5.6	90.2	0.2	90.4	7.1	2.4	9.6
2015–2019 (%)	40.1	35.0	5.1	3.6	6.4	90.2	1.1	91.3	7.9	0.8	8.7
2020–2023 (%)	30.4	40.1	6.3	2.8	11.8	91.5	2.8	94.3	4.4	1.3	5.7
North											
2004–2009 (%)	35.1	9.1	1.6	0.6	0.8	47.2	0.1	47.3	52.3	0.4	52.7
2010–2014 (%)	52.1	21.7	1.1	1.1	4.4	80.3	0.3	80.6	18.7	0.7	19.4
2015–2019 (%)	52.3	29.7	0.9	2.4	6.2	91.4	0.8	92.2	7.5	0.3	7.8
2020–2023 (%)	37.3	38.7	1.0	2.2	13.1	92.3	2.7	95.0	4.9	0.0	5.0
Northeast											
2004–2009 (%)	36.4	2.1	5.3	0.3	8.2	52.2	0.0	52.2	47.2	0.6	47.8
2010–2014 (%)	71.6	9.3	0.0	0.8	5.9	87.6	0.9	88.5	9.4	2.1	11.5
2015–2019 (%)	71.5	16.9	0.5	0.8	4.1	93.8	0.3	94.1	5.5	0.4	5.9
2020–2023 (%)	48.4	29.7	0.8	1.5	10.3	90.8	2.7	93.4	5.6	1.0	6.6
Northwest											
2004–2009 (%)	0.9	93.6	0.1	0.0	0.0	94.6	0.0	94.6	5.3	0.0	5.4
2010–2014 (%)	16.1	77.9	0.1	0.4	1.0	95.5	0.3	95.8	4.2	0.0	4.2
2015–2019 (%)	15.0	74.5	0.7	2.1	3.4	95.6	0.6	96.3	3.4	0.3	3.7
2020–2023 (%)	10.8	67.6	1.9	1.6	11.7	93.6	3.7	97.3	2.0	0.7	2.7
South											
2004–2009 (%)	69.2	13.5	6.3	2.3	2.6	93.9	0.3	94.2	4.7	1.1	5.8
2010–2014 (%)	62.3	20.6	7.7	4.6	1.9	97.1	0.2	97.3	2.4	0.2	2.7
2015–2019 (%)	54.6	24.2	8.2	7.7	2.8	97.5	0.4	97.9	1.9	0.2	2.1
2020–2023 (%)	39.1	26.3	13.7	9.9	6.8	95.8	2.2	98.1	1.7	0.3	1.9
Southwest											
2004–2009 (%)	21.0	29.0	22.5	0.0	10.9	83.4	4.5	87.9	7.4	4.7	12.1
2010–2014 (%)	21.9	50.8	10.5	0.8	9.6	93.7	1.9	95.6	2.5	1.9	4.4
2015–2019 (%)	13.7	63.4	14.1	0.9	4.6	96.7	1.1	97.9	1.0	1.1	2.1
2020–2023 (%)	20.2	48.9	19.5	0.9	7.9	97.4	0.8	98.2	1.3	0.4	1.8

Note: The Northeast region comprises HLJ, JL, and LN; North includes NM, BJ, TJ, HE, and SX; East encompasses SH, JS, ZJ, AH, FJ, JX, and SD; South consists of GD, GX, and HI; Central includes HA, HB, and HN; Northwest comprises SN, GS, QH, NX, and XJ; Southwest includes CQ, SC, GZ, YN, and XZ. Data are presented as proportions of total reported HIV infections within each region and time period.

Abbreviation: HIJ=Heilongjiang; JL=Jilin; LN=Liaoning; NM=Neimenggu; BJ=Beijing; TJ=Tianjin; HE=Hebei; SX=Shanxi; SH=Shanghai; JS=Jiangsu; ZJ=Zhejiang; AH=Anhui; FJ=Fujian; JX=Jiangxi; SD=Shandong; GD=Guangdong; GX=Guangxi; HI=Hainan; HA=Henan; HB=hubei; HE=Hunan; SN=Shannxi; GS=Gansu; QH=Qinghai; NX=Ningxia; XJ=Xinjiang; CQ=Chongqing; SC=Sichuan; GZ=Guizhou; YN=Yunnan; XZ=Xizang.

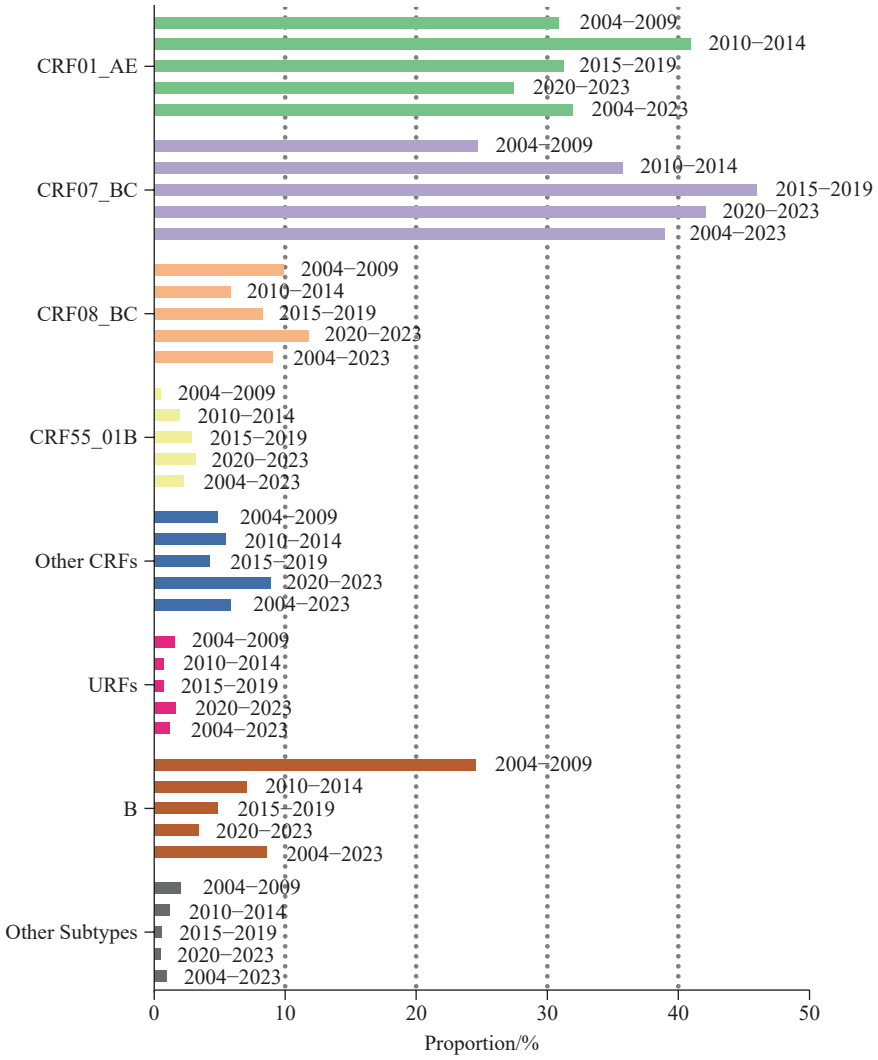


FIGURE 1. Temporal trends in the distribution of HIV-1 genetic variants in China, 2004–2023.
abbreviation: HIV-1=human immunodeficiency virus type 1.

CRF07_BC demonstrated a marked increase from 24.8% to 46.1% during 2004–2019, followed by a decline in 2020–2023. Conversely, CRF01_AE reached its peak prevalence of 41.1% during 2010-2014, subsequently showing a gradual decrease through 2015–2023. Subtype B exhibited a consistent downward trend, reaching its lowest prevalence of 3.5% in 2020–2023.

The epidemiological pattern of CRF08_BC showed initial decline followed by steady increase from 2015–2023. CRF55_01B demonstrated consistent growth throughout the study period, increasing from 0.6% to 3.2%. Other CRFs showed fluctuating patterns, reaching their highest prevalence of 9.0% during 2020–2023.

URF prevalence exhibited a complex pattern, initially decreasing through the first two time periods, stabilizing during 2010–2019, and subsequently increasing in 2020–2023. In contrast, other subtypes showed a consistent declining trend throughout the entire study period (2004–2023).

Regional Distribution of HIV-1 CRFs, Subtypes, and URFs

The proportions of HIV-1 CRFs, subtypes, and URFs exhibited distinct regional variations across China's seven geographical regions and demonstrated significant temporal changes throughout the study period (Figure 2 and Table 2).

During 2004–2009, distinct regional patterns emerged: the northeastern, northern, and eastern regions were predominantly affected by CRF01_AE and subtype B strains, collectively accounting for over 75% of infections. The southern region showed

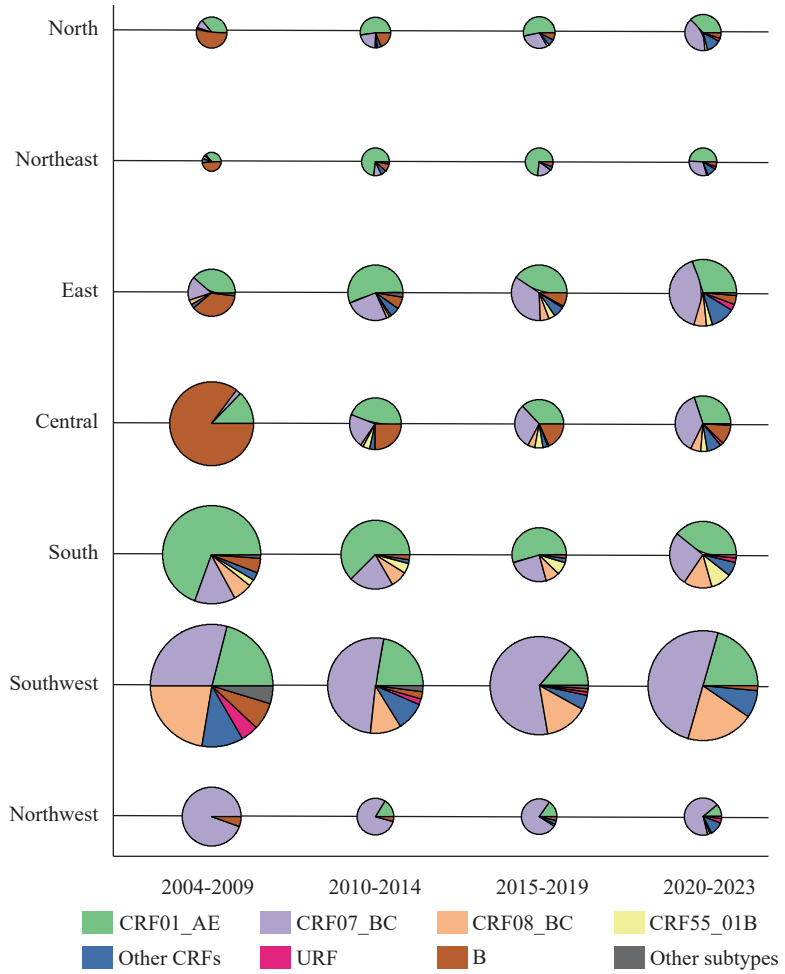


FIGURE 2. Regional Distribution and temporal evolution of HIV-1 genetic variants across China's seven regions, 2004–2009, 2010–2014, 2015–2019, and 2020–2023.

CRF01_AE dominance at 69.2%, while the central region exhibited a marked prevalence of subtype B (84.3%). The northwestern region was characterized by CRF07_BC predominance at 93.6%. The southwestern region displayed a more heterogeneous distribution, with CRF07_BC (29.0%), CRF08_BC (22.5%), and CRF01_AE (21.0%) collectively representing over 70% of infections.

A significant epidemiological shift occurred during 2020–2023, with CRF07_BC and CRF01_AE emerging as the predominant strains across all regions.

The study period revealed several notable trends: total recombinant forms showed consistent increases across six regions, with the Northeast being the sole exception. Similarly, CRF07_BC demonstrated sustained growth in all regions except the Northwest and Southwest. The 2020–2023 period was marked by regional distinctions: the Northeast showed the highest CRF01_AE prevalence (48.4%), the North recorded the highest proportion of other CRFs (13.1%), and the South maintained the highest CRF55_01B prevalence throughout the entire study period.

Central China maintained a higher proportion of subtype B infections compared to other regions throughout 2004–2023, despite its declining trend. The Northwest's epidemiological profile was dominated by CRF07_BC, which decreased from approximately 95% (2004–2009) to 67.6% (2020–2023). The Southwest consistently maintained the highest proportion of CRF08_BC infections across all four time periods.

CONCLUSIONS

This study represents the most comprehensive analysis to date of HIV-1 genetic diversity in China, encompassing 94,476 samples over a 20-year period (2004–2023). Our findings demonstrate that CRF07_BC and CRF01_AE are the predominant viral

lineages, with significant contributions from CRF08_BC, CRF55_01B, and subtype B to the overall genetic landscape. Notably, circulating recombinant forms (CRFs) account for 88.6% of all HIV-1 infections, underscoring their central role in China's HIV epidemic.

The epidemiological landscape of HIV-1 in China has undergone substantial transformation over the past decade, characterized by distinct temporal dynamics in subtype distribution. While the prevalence of CRF01_AE, CRF07_BC, and subtype B has declined, other subtypes have maintained relative stability. Conversely, CRF08_BC, CRF55_01B, URFs, and other CRFs have shown increasing prevalence. These evolutionary patterns reflect the complex interplay of multiple factors and the unique trajectory of HIV-1 transmission in China.

The early epidemic phase was marked by widespread outbreaks of subtype B strains within the BLD (*8*). Subsequent implementation of stringent blood product controls effectively reduced subtype B prevalence across central China and nationwide. Despite reintroduction into the HET population, subtype B strains have continued to show declining trends (*9*).

The epidemiological landscape has been further shaped by distinct viral lineages: CRF01_AE strains, introduced from the Golden Triangle region, have established varying prevalence patterns through multiple transmission events across different regions (*10*–*11*). CRF07_BC, originating in YN before spreading to XJ and SC, achieved particular prominence in northwestern and southwestern regions. Initially associated with IDU and HET transmission routes, a distinct CRF07_BC lineage emerged around 2005, predominantly spreading among MSM and leading to substantial increases in prevalence across central and eastern provinces (*12*).

CRF08_BC, which originated among injection drug users in Yunnan Province and was subsequently identified in Guangxi, has become a predominant strain in Southwest China (*13*). While its prevalence initially decreased due to declining injection drug use, the strain's successful transition into heterosexual transmission networks has led to a resurgence. After 2009, when sexual transmission accounted for over 90% of HIV infections in China, the epidemiological dynamics of CRF08_BC were further altered by these changing transmission patterns.

The CRF55_01B strain, which emerged in Guangdong Province, has achieved nationwide distribution primarily through China's railway infrastructure, particularly along the Beijing-Guangzhou and Beijing-Kowloon corridors. Despite its broad dissemination, this strain maintains notably higher prevalence rates in South China (*7*,*14*).

These temporal and geographical factors have collectively shaped China's complex HIV-1 epidemiological landscape, emphasizing the necessity for regionally tailored prevention and control strategies that account for these variations.

The distinct geographical distributions of HIV-1 lineages in China are significantly influenced by their biological characteristics. Research has revealed substantial differences between CRF01_AE and CRF07_BC strains, particularly in disease progression rates and X4-tropic strain prevalence. The heterogeneous biological properties of CRF01_AE lineages contribute to variable disease progression rates, subsequently affecting their transmission dynamics and distribution patterns (*15*). Studies indicate that CRF07_BC's emergence as a predominant strain in China may be attributed to its slower replication rate, which correlates with delayed disease progression (*16*). Additionally, CRF55_01B's rapid dissemination might be explained by its natural polymorphism at position V179 (*17*), associated with NVP and EFV resistance, resulting in higher viral loads and more rapid CD4 T-cell depletion during early infection (*18*).

Our comprehensive analysis of 94,476 sequences spanning 2004–2023 revealed significant geographical and sociocultural influences on HIV-1 epidemiology in China. A consistent increase in recombinant forms was observed across all regions except central China, with recombinants accounting for over 90% of infections in most regions during 2020–2023. The emergence of novel CRFs in recent years indicates ongoing recombination events, emphasizing the critical need for enhanced surveillance measures.

Several limitations warrant consideration in our study. Although some provinces initially provided limited sequence data, their relatively low HIV infection rates suggest minimal impact on the overall regional and national proportions. Additionally, our reliance on pol genome segment analysis may have resulted in an underestimation of URF prevalence.

The genetic diversity of HIV-1 subtypes significantly impacts diagnostic accuracy, ART efficacy, and vaccine development strategies. The selection of appropriate vaccine immunogen sequences presents a considerable challenge, necessitating precise alignment with circulating strains. Known variations in diagnostic efficiencies across subtypes and recombinants, coupled

with specific mutations like V179 in CRF55_01B, underscore the importance of continuous surveillance for drug-resistant mutations across all viral variants. This ongoing monitoring is crucial for optimizing both therapeutic approaches and diagnostic methodologies.

In conclusion, our study provides an essential comprehensive analysis of HIV-1 subtype and recombinant distribution patterns in China. These findings have direct implications for HIV vaccine development, diagnostic reagent selection, and ART regimen optimization. The dynamic nature of HIV-1 genetic diversity emphasizes the necessity for continued surveillance of subtype and recombinant proportions to inform and enhance public health strategies.

Conflicts of interest: No conflicts of interest.

Acknowledgements: The Division of Research on Virology and Immunology, National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention for their invaluable data support.

Funding: National Key R and D Program of China(2022YFC2305201).

doi: 10.46234/ccdcw2024.252

Corresponding author: Hui Xing, xingh@chinaaids.cn.

[1] National Center for AIDS/STD Control and Prevention (NCAIDS), Chinese Center for Disease Control and Prevention (China CDC), State Key Laboratory of Infectious Disease Prevention and Control (SKLID), Beijing, China.

Submitted: October 16, 2024; Accepted: November 14, 2024

REFERENCES

1. UNAIDS. Global AIDS update 2024，https://www.unaids.org, [2024].
2. Fauci AS. An HIV vaccine is essential for ending the HIV/AIDS pandemic. JAMA 2017;318(16):1535 – 6. https://doi.org/10.1001/jama.2017.13505.
3. Gregson J, Tang M, Ndembi N, Hamers RL, Rhee SY, Marconi VC, et al. Global epidemiology of drug resistance after failure of WHO recommended first-line regimens for adult HIV-1 infection: a multicentre retrospective cohort study. Lancet Infect Dis 2016;16(5):565 – 75. https://doi.org/10.1016/S1473-3099(15)00536-8.
4. Gaschen B, Taylor J, Yusim K, Foley B, Gao F, Lang D, et al. Diversity considerations in HIV-1 vaccine selection. Science 2002;296(5577):2354 – 60. https://doi.org/10.1126/science.1070441.
5. Hemelaar J, Elangovan R, Yun J, Dickson-Tetteh L, Fleminger I, Kirtley S, et al. Global and regional molecular epidemiology of HIV-1, 1990-2015: a systematic review, global survey, and trend analysis. Lancet Infect Dis 2019;19(2):143 – 55. https://doi.org/10.1016/S1473-3099(18)30647-9.
6. Williams A, Menon S, Crowe M, Agarwal N, Biccler J, Bbosa N, et al. Geographic and population distributions of human immunodeficiency virus (HIV)–1 and HIV-2 circulating subtypes: a systematic literature review and meta-analysis (2010–2021). J Infect Dis 2023;228(11):1583 – 91. https://doi.org/10.1093/infdis/jiad327.
7. Hao JJ, Zheng S, Gan MZ, Dong AB, Kang RH, Li MM, et al. Changing proportions of HIV-1 subtypes and transmitted drug resistance among newly diagnosed HIV/AIDS individuals - China, 2015 and 2018. China CDC Wkly 2021;3(53):1133 – 8. https://doi.org/10.46234/ccdcw2021.251.
8. Li Z, He X, Wang Z, Xing H, Li F, Yang Y, et al. Tracing the origin and history of HIV-1 subtype B′ epidemic by near full-length genome analyses. AIDS 2012;26(7):877 – 84. https://doi.org/10.1097/QAD.0b013e328351430d.
9. Li L, Sun GQ, Zhong P, Han JW, Li TY, Jia DJ, et al. HIV‐1 Thai B strain has spread out of former plasma donors into general population through sexual contact in Henan, China. J Med Virol 2016;88(4):614 – 21. https://doi.org/10.1002/jmv.24383.
10. Feng Y, He X, Hsi JH, Li F, Li XG, Wang Q, et al. The rapidly expanding CRF01_AE epidemic in China is driven by multiple lineages of HIV-1 viruses introduced in the 1990s. AIDS 2013;27(11):1793 – 802. https://doi.org/10.1097/QAD.0b013e328360db2d.
11. Wang XL, He X, Zhong P, Liu YJ, Gui T, Jia DJ, et al. Phylodynamics of major CRF01_AE epidemic clusters circulating in mainland of China. Sci Rep 2017;7(1):6330. https://doi.org/10.1038/s41598-017-06573-6.
12. Gan MZ, Zheng S, Hao JJ, Ruan YH, Liao LJ, Shao YM, et al. Spatiotemporal patterns of CRF07_BC in China: a population-based study of the HIV strain with the highest infection rates. Front Immunol 2022;13:824178. https://doi.org/10.3389/fimmu.2022.824178.
13. Feng Y, Takebe Y, Wei HM, He X, Hsi JH, Li ZP, et al. Geographic origin and evolutionary history of China's two predominant HIV-1 circulating recombinant forms, CRF07_BC and CRF08_BC. Sci Rep 2016;6:19279. https://doi.org/10.1038/srep19279.
14. Gan MZ, Zheng S, Hao JJ, Ruan YH, Liao LJ, Shao YM, et al. The prevalence of CRF55_01B among HIV-1 strain and its connection with traffic development in China. Emerg Microbes Infect 2021;10(1):256 – 65. https://doi.org/10.1080/22221751.2021.1884004.
15. Li K, Chen HH, Li JJ, Feng Y, Liang SJ, Rashid A, et al. Distinct genetic clusters in HIV-1 CRF01_AE-infected patients induced variable degrees of $CD4^+$ T-cell loss. mBio 2024;15(3):e0334923. https://doi.org/10.1128/mbio.03349-23.
16. Ma LY, Guo YF, Yuan L, Huang Y, Sun JP, Qu SL, et al. Phenotypic and genotypic characterization of human immunodeficiency virus type 1 CRF07_BC strains circulating in the Xinjiang province of China. Retrovirology 2009;6:45. https://doi.org/10.1186/1742-4690-6-45.
17. Liu YJ, Li HP, Wang XL, Han JW, Jia L, Li TY, et al. Natural presence of V179E and rising prevalence of E138G in HIV-1 reverse transcriptase in CRF55_01B viruses. Infect Genet Evol 2020;77:104098. https://doi.org/10.1016/j.meegid.2019.104098.
18. Wei L, Li H, Lv X, Zheng CL, Li GL, Yang ZR, et al. Impact of HIV-1 CRF55_01B infection on the evolution of CD4 count and plasma HIV RNA load in men who have sex with men prior to antiretroviral therapy. Retrovirology 2021;18(1):22. https://doi.org/10.1186/s12977-021-00567-z.

SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE S1. Database Composition: Distribution of HIV-1 genetic variants across 2004–2009, 2010–2014, 2015–2019, and 2020–2023.

Region/Years	HIV-1 CRFs					URF	Total CRFs	Total recombinants	HIV-1 Subtypes		Total Subtypes	*N*
	01_AE	07_BC	08_BC	55_01B	Other				B	Other		
China												
2004–2009	29.6%	22.3%	5.2%	1.3%	3.5%	0.9%	61.9%	62.8%	35.4%	1.8%	37.2%	9,488
2010–2014	44.7%	30.7%	4.5%	4.5%	4.4%	0.9%	88.8%	89.7%	9.2%	1.1%	10.3%	22,921
2015–2019	41.4%	34.1%	6.7%	5.5%	4.7%	0.9%	92.4%	93.2%	6.3%	0.5%	6.8%	43,480
2020–2023	29.2%	39.8%	11.4%	2.9%	9.2%	2.0%	92.5%	94.5%	4.8%	0.7%	5.5%	18,587
Central												
2004–2009	9.8%	1.5%	0.2%	0.0%	0.4%	0.1%	12.0%	12.0%	87.8%	0.2%	88.0%	2,225
2010–2014	51.9%	21.7%	2.4%	4.6%	2.8%	0.3%	83.4%	83.7%	16.2%	0.1%	16.3%	711
2015–2019	36.0%	29.0%	3.8%	5.6%	3.1%	1.0%	77.5%	78.4%	21.1%	0.4%	21.6%	2,662
2020–2023	29.0%	37.2%	3.9%	3.9%	7.1%	1.6%	81.0%	82.6%	16.6%	0.7%	17.4%	2,269
East												
2004–2009	35.3%	12.3%	5.0%	0.0%	3.0%	0.6%	55.6%	56.2%	41.3%	2.5%	43.8%	1,509
2010–2014	58.7%	25.6%	0.9%	1.6%	4.4%	0.2%	91.2%	91.4%	7.3%	1.3%	8.6%	2,475
2015–2019	41.5%	29.7%	4.1%	3.8%	6.8%	1.2%	85.8%	87.1%	12.4%	0.5%	12.9%	8,510
2020–2023	31.2%	40.0%	6.5%	3.4%	10.5%	2.6%	91.7%	94.3%	4.7%	1.0%	5.7%	5,298
North												
2004–2009	37.5%	15.7%	3.2%	1.2%	1.7%	0.2%	59.4%	59.6%	39.6%	0.8%	40.4%	997
2010–2014	50.7%	24.3%	1.1%	1.1%	4.0%	0.3%	81.2%	81.5%	17.9%	0.6%	18.5%	6,637
2015–2019	50.1%	30.3%	0.9%	2.5%	6.4%	0.8%	90.2%	90.9%	8.8%	0.3%	9.1%	5,536
2020–2023	37.7%	38.0%	1.3%	2.5%	13.8%	2.1%	93.3%	95.4%	4.5%	0.1%	4.6%	1,734
Northeast												
2004–2009	66.9%	4.3%	1.8%	0.6%	8.0%	0.0%	81.6%	81.6%	17.2%	1.2%	18.4%	163
2010–2014	77.7%	6.7%	0.0%	0.3%	6.1%	1.1%	90.8%	91.9%	7.0%	1.1%	8.1%	358
2015–2019	72.2%	16.6%	0.4%	0.8%	4.0%	0.2%	94.0%	94.2%	5.5%	0.3%	5.8%	1,264
2020–2023	51.3%	29.6%	0.6%	1.6%	8.8%	1.9%	92.0%	93.9%	5.3%	0.8%	6.1%	622
Northwest												
2004–2009	4.0%	85.1%	0.3%	0.0%	0.0%	0.0%	89.4%	89.4%	10.4%	0.2%	10.6%	597
2010–2014	21.4%	71.3%	0.2%	0.3%	1.1%	0.3%	94.2%	94.5%	5.5%	0.0%	5.5%	637
2015–2019	18.4%	69.1%	0.8%	2.4%	4.1%	0.8%	94.8%	95.6%	4.1%	0.3%	4.4%	1,109
2020–2023	10.5%	70.9%	1.5%	1.6%	9.9%	3.0%	94.5%	97.5%	2.0%	0.5%	2.5%	910
South												
2004–2009	53.5%	21.9%	5.6%	4.7%	3.7%	0.4%	89.5%	89.8%	8.1%	2.1%	10.2%	2,220
2010–2014	43.5%	34.2%	3.8%	9.5%	2.9%	0.4%	93.9%	94.3%	5.1%	0.6%	5.7%	8,893
2015–2019	49.5%	28.3%	6.9%	9.3%	3.1%	0.4%	97.1%	97.5%	2.3%	0.2%	2.5%	17,808
2020–2023	39.3%	33.3%	8.8%	6.0%	7.8%	2.0%	95.1%	97.1%	2.6%	0.3%	2.9%	2,490
Southwest												
2004–2009	20.1%	41.6%	14.3%	0.1%	9.4%	3.9%	85.5%	89.4%	6.5%	4.1%	10.6%	1,777
2010–2014	24.0%	34.9%	18.3%	1.0%	10.6%	4.0%	88.8%	92.7%	3.6%	3.6%	7.3%	3,210
2015–2019	12.7%	58.2%	17.7%	1.0%	5.7%	1.6%	95.3%	96.9%	1.3%	1.8%	3.1%	6,591
2020–2023	20.1%	40.3%	27.2%	0.9%	8.0%	1.2%	96.6%	97.8%	1.3%	0.9%	2.2%	5,264

Vital Surveillances

Survival of People Living with HIV/AIDS from Pre-ART Era to Treat-all Era — China, 1985–2022

Shi Wang[1]; Houlin Tang[1]; Decai Zhao[1]; Chang Cai[1]; Yichen Jin[1]; QianQian Qin[1]; Fangfang Chen[1]; Liping Fei[1]; Hehe Zhao[1]; Zhongnian Yang[1]; Fan Lyu[1,2,#]

ABSTRACT

Introduction: A comprehensive analysis of nationwide survival trends for people living with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS, PLWHA) from the initial reported case to present has not been conducted. This study evaluated the survival outcomes of PLWHA reported in China from 1985 to 2022.

Methods: We analyzed data from PLWHA recorded in the National HIV/AIDS Comprehensive Response Information Management System from 1985 to 2022. Survival rates were calculated using Kaplan-Meier curves, and factors associated with survival time were analyzed using Cox proportional hazard models.

Results: Progressive relaxation of antiretroviral therapy initiation criteria led to significant improvements in survival rates across different diagnostic periods in China. The 1-year and 5-year cumulative survival rates increased from 85.2% and 66.1% in the 1985–2003 cohort to 91.1% and 81.4% in the 2016–2022 cohort. Cox proportional hazard analysis revealed elevated mortality risks among males, individuals aged ≥65 years, those with injection drug use or other transmission routes, hospital-tested patients, and those with lower CD4 counts at diagnosis or without treatment.

Conclusions: Antiretroviral therapy has effectively reduced mortality risk among PLWHA in China. Future efforts should focus on expanding HIV testing to reduce the proportion of late diagnoses with lower CD4 counts and providing targeted, differentiated services for older populations to further decrease mortality risk among PLWHA.

Over the past 40 years, China's HIV epidemic has undergone significant evolution, with numerous preventive and control measures implemented to reduce HIV transmission and disease burden. The introduction of antiretroviral therapy (ART) has markedly improved survival outcomes among people living with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS, PLWHA) (*1*). As ART research advanced, China progressively adjusted its free ART eligibility criteria for PLWHA, modifying CD4 cell count thresholds from <200 to <350, then to ≤500 cells/μL, and finally to universal treatment regardless of CD4 count in 2004, 2008, 2014, and 2016, respectively (*2*).

Early survival studies of PLWHA in China primarily focused on specific high-risk populations, such as people who inject drugs and former plasma donors (*3-4*). With the evolution of primary transmission routes, numerous studies have examined long-term PLWHA survival in localized areas (*5*). However, comprehensive nationwide survival data spanning from the first reported case to present remains lacking. Understanding long-term survival patterns within China's complex and evolving HIV epidemic context can illuminate population-level trends in survival and mortality while identifying survival disparities among PLWHA subpopulations. In this study, we analyzed data from the National HIV/AIDS Comprehensive Response Information Management System (CRIMS) to evaluate PLWHA survival from 1985 to 2022. Our findings provide crucial insights for optimizing future HIV prevention and control strategies.

METHODS

Data were extracted from the CRIMS database, which encompasses comprehensive HIV/AIDS diagnosis, treatment, and follow-up data reported from 31 provinces in China. The study included all newly reported PLWHA in CRIMS between 1985 and 2022. After excluding 19,218 (1.1%) individuals with missing follow-up records or logical data inconsistencies, the final analysis dataset was established.

The primary outcome measure was all-cause mortality. The observation period extended from the date of HIV/AIDS diagnosis (starting point) to December 31, 2023 (endpoint). Survival time was calculated as the duration between diagnosis and either death or the follow-up endpoint. The main exposure variable was the diagnostic period cohort. Based on pivotal changes in Chinese ART standards (*2*), the study population was stratified into five cohorts by diagnosis year: 1985–2003, 2004–2007, 2008–2013, 2014–2015, and 2016–2022. The period from 1985 to 2003 was designated as the pre-ART era, preceding China's implementation of free national ART in 2004. The 2016–2022 period was classified as the treat-all era, as it marked the initiation of universal ART access regardless of CD4 counts.

The analysis incorporated socio-demographic and clinical variables including sex at birth, age at diagnosis, HIV transmission route, testing venue, CD4 count at diagnosis, and ART initiation status. CD4 counts at diagnosis were stratified into four categories: <200, 200–350, 351–499, and ≥500 cells/μL. Individuals presenting with AIDS-defining illnesses within 6 months of diagnosis were classified in the "CD4<200 or AIDS" group, while those lacking CD4 test results within this period were categorized as "unknown."

Survival trends were analyzed using Kaplan-Meier curves, stratified by diagnostic cohort and demographic factors within cohorts, including age at diagnosis, HIV transmission route, and CD4 count at diagnosis. Log-rank tests assessed between-group survival differences. Cox proportional hazard models were employed to estimate hazard ratios (*HR*s) and 95% confidence intervals (*CI*s) for evaluating the impact of diagnostic cohort, socio-demographic factors, and clinical indicators on mortality risk. To accurately assess the impact of ART policies on PLWHA survival, we conducted additional analyses on the ART-recipient subgroup using the same model framework. Statistical analyses were performed using R software (version 4.3.1, R Foundation for Statistical Computing, Vienna, Austria), with statistical significance set at $P<0.05$ using two-sided tests.

RESULTS

Among the 1,619,060 PLWHA included in this study, 433,420 deaths occurred by December 31, 2023. Analysis of survival rates across the 5 diagnostic cohorts revealed progressive improvements, with 1-year survival rates increasing from 85.2% to 91.1% and 5-year survival rates rising from 66.1% to 81.4%. The differences in survival rates across diagnostic cohorts were statistically significant ($P<0.001$) (Figure 1). Similar trends of improved survival with evolving treatment criteria were observed across age groups, HIV transmission routes, and CD4 count categories at diagnosis (Figure 2). Notably, across all diagnostic cohorts, survival rates decreased with advancing age ($P<0.001$). In post-2004 cohorts, individuals with homosexual transmission consistently demonstrated higher survival rates compared to other transmission routes ($P<0.001$). Additionally, PLWHA with higher CD4 counts at diagnosis showed significantly better survival outcomes ($P<0.001$).

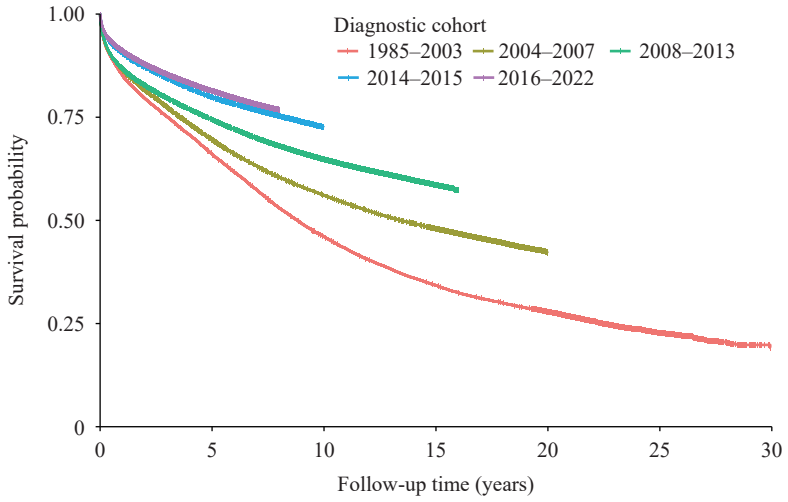


FIGURE 1. Survival time since HIV diagnosis by cohort in China, 1985–2022.
Abbreviation: HIV=human immunodeficiency virus.

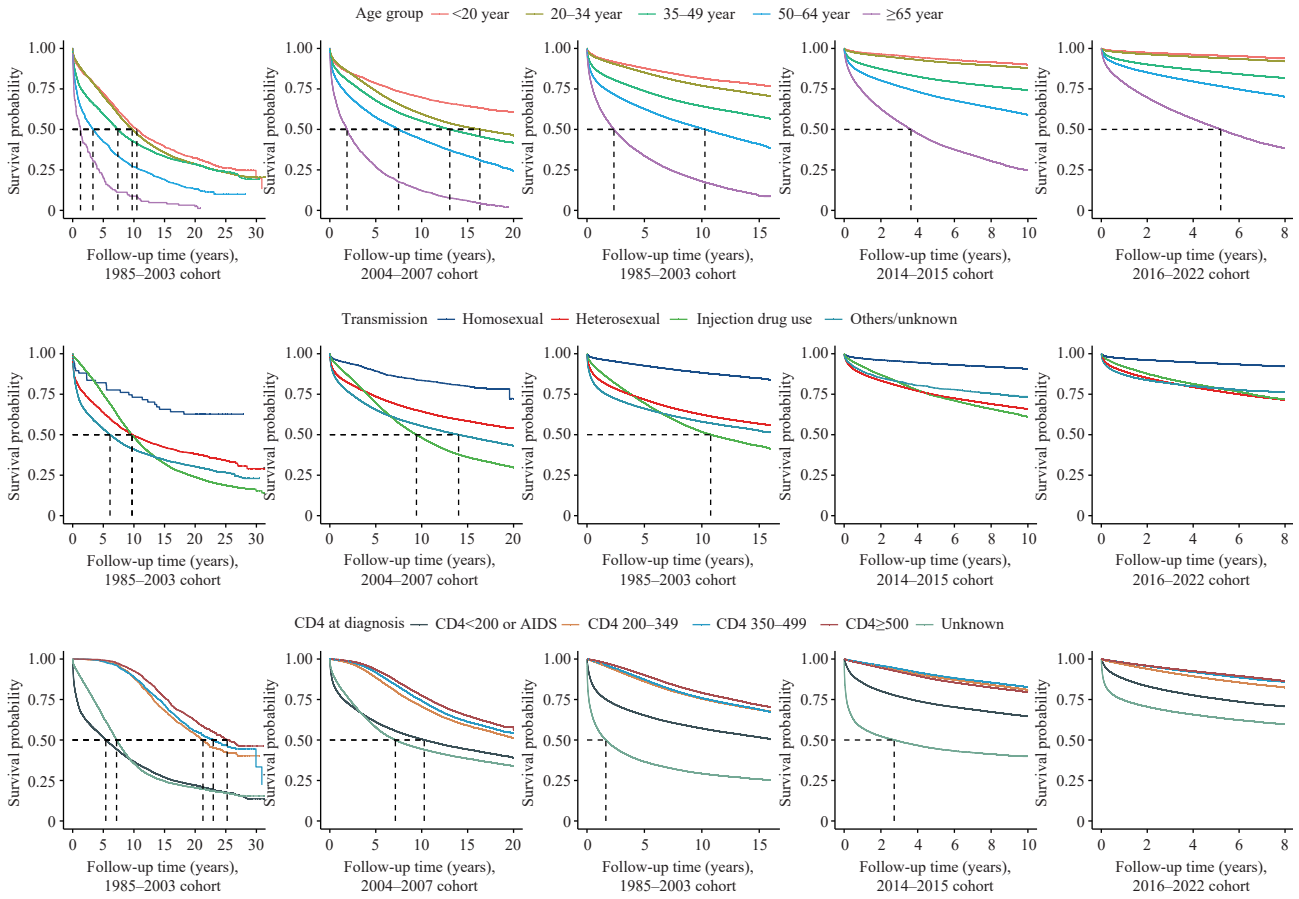


FIGURE 2. Survival time by different age group, transmission and ART initiation from pre-ART era to treat-all era in China,1985–2022.
Abbreviation: ART=antiretroviral therapy.

The Cox proportional hazard model, adjusted for age at diagnosis, sex, transmission route, venue of testing, and CD4 count at diagnosis, demonstrated progressively lower mortality risks corresponding to changes in treatment criteria (Table 1). Compared to the 2016–2022 diagnostic cohort, the adjusted *HR*s were 1.92 (95% *CI*: 1.89, 1.96), 1.75 (95% *CI*: 1.73, 1.77), 1.73 (95% *CI*: 1.72, 1.75), and 1.35 (95% *CI*: 1.34, 1.36) for the 1985–2003, 2004–2007, 2008–2013, and 2014–2015 cohorts, respectively. Analysis of ART recipients revealed a consistent reduction in mortality risk across post-2004 diagnostic cohorts. Higher mortality risks were associated with male sex, age ≥65 years, injection drug use or other transmission routes, hospital-based testing, and lower CD4 counts or AIDS at diagnosis ($P<0.05$). Subgroup analyses incorporating ART initiation as an additional adjustment factor yielded similar results, with untreated PLWHA showing consistently higher mortality risks compared to those receiving ART (Table 2).

DISCUSSION

The implementation of China's national free ART policy has significantly enhanced survival outcomes among PLWHA. Survival rates markedly improved from the pre-2003 period (1-year: 85.2%; 5-year: 66.1%) to the post-2016 era (1-year: 91.1%; 5-year: 81.4%). These outcomes position China's survival rates above those reported in Thailand (2014–2018: 1-year: 88.2%; 5-year: 75.1%) (*6*), though below those achieved in the Republic of Korea (2014–2018: 1-year: 96.8%; 5-year: 93.4%) (*7*) and Japan, where 10-year survival rates increased from 65.0% in the pre-ART era to 96.0% for those diagnosed after 2008 (*8*). These international variations likely reflect differences in healthcare infrastructure, socioeconomic conditions, and patient demographics. Notably, the near-universal ART coverage in Japanese and the Republic of Korean studies may explain their superior outcomes. Our findings align with U.S. data, showing that mortality risk during follow-up was approximately twice as high

TABLE 1. Cox proportional hazards regression models for mortality risk among people living with HIV/AIDS in China, 1985–2022 (*n*=1,619,060).

Characteristic	All people		People on ART	
	Proportion(%)	Adjusted *HR* (95% *CI*)	Proportion (%)	Adjusted *HR* (95% *CI*)
Diagnostic cohort				
1985–2003	1.5	1.92 (1.89, 1.96)[§]	0.7	1.07 (1.03, 1.11)[§]
2004–2007	7.2	1.75 (1.73, 1.77)[§]	5.8	1.21 (1.18, 1.23)[§]
2008–2013	22.8	1.73 (1.72, 1.75)[§]	21.0	1.18 (1.17, 1.19)[§]
2014–2015	12.9	1.35 (1.34, 1.36)[§]	13.2	1.11 (1.10, 1.13)[§]
2016–2022	55.6	Ref.	59.2	Ref.
Sex				
Male	75.7	1.50 (1.49, 1.51)[§]	74.9	1.55 (1.53, 1.56)[§]
Female	24.3	Ref.	25.1	Ref.
Age group, years				
<20	3.6	0.58 (0.57, 0.60)[§]	3.8	0.46 (0.44, 0.48)[§]
20–34	34.5	0.69 (0.68, 0.69)[§]	35.6	0.62 (0.61, 0.63)[§]
35–49	29.6	Ref.	29.7	Ref.
50–64	21.1	1.63 (1.62, 1.65)[§]	21.3	1.83 (1.81, 1.85)[§]
≥65	11.1	3.52 (3.49, 3.56)[§]	9.6	4.31 (4.26, 4.37)[§]
HIV transmission route				
Homosexual contact	21.4	0.42 (0.41, 0.42)[§]	23.9	0.44 (0.43, 0.45)[§]
Heterosexual contact	65.6	Ref.	65.7	Ref.
Injection drug use	7.8	2.09 (2.07, 2.11)[§]	5.8	2.16 (2.12, 2.19)[§]
Others/unknown	5.3	1.18 (1.16, 1.19)[§]	4.6	1.40 (1.37, 1.42)[§]
CD4 at diagnosis (cells/μL)				
CD4<200 or AIDS	31.9	1.87 (1.85, 1.89)[§]	32.3	2.11 (2.07, 2.15)[§]
CD4 200–349	22.4	0.99 (0.97, 1.00)[†]	24.6	1.22 (1.20, 1.24)[§]
CD4 350–499	16.8	0.99 (0.98, 1.00)	17.9	1.08 (1.06, 1.10)[§]
CD4 ≥500	14.4	Ref.	15.0	Ref.
Unknown	14.5	3.25 (3.22, 3.29)[§]	10.2	1.78 (1.75, 1.82)[§]
Venue of testing				
Hospitals	50.8	1.45 (1.44, 1.47)[§]	49.7	1.28 (1.27, 1.29)[§]
VCT clinics	26.2	Ref.	27.7	Ref.
Others	23.0	0.97 (0.96, 0.98)[§]	22.6	0.97 (0.96, 0.98)[§]

Note: Model 1: Adjusted for age group, sex, HIV transmission route, and venue of testing. Model 2: Model 1 with additional adjustment for ART initiation.
Abbreviations: *HR*=hazard ratio; *CI*=confidence interval; ART=antiretroviral therapy; HIV=human immunodeficiency virus; VCT=voluntary counseling and testing.
* Analysis excluded 81 PLWHA with missing age data.
[†] *P*<0.05.
[§] *P*<0.001.

for individuals diagnosed in the pre-ART era compared to the treat-all era (*9*).

The enhanced survival of PLWHA can be partially attributed to the declining proportion of untreated individuals. Our analysis revealed substantially higher mortality risks among untreated populations compared to those receiving ART across all diagnostic cohorts. The proportion of untreated individuals decreased markedly from 56.3% to 9.2% as ART initiation criteria were relaxed. Furthermore, survival improvements were observed even among those receiving ART, likely due to earlier treatment initiation

TABLE 2. Cox proportional hazards regression models for mortality risk of PLWHA by different diagnostic periods in China.

Characteristic	1985–2003		2004–2007		2008–2013		2014–2015		2016–2022	
	Proportion (%)	Adjusted *HR* (95% *CI*)	Proportion (%)	Adjusted *HR* (95% *CI*)	Proportion (%)	Adjusted *HR* (95% *CI*)	Proportion (%)	Adjusted *HR* (95% *CI*)	Proportion (%)	Adjusted *HR* (95% *CI*)
Sex										
Male	76.0	1.08 (1.03, 1.12)§	67.0	1.34 (1.31, 1.36)§	71.8	1.29 (1.27, 1.31)§	77.9	1.29 (1.27, 1.32)§	77.9	1.45 (1.43, 1.47)§
Female	24.0	Ref.	33.0	Ref.	28.2	Ref.	22.1	Ref.	22.1	Ref.
Age group, years										
<20	6.2	0.65 (0.61, 0.70)§	4.0	0.64 (0.61, 0.67)§	3.8	0.66 (0.63, 0.68)§	3.9	0.54 (0.50, 0.58)§	3.3	0.42 (0.40, 0.45)§
20–34	62.5	0.79 (0.76, 0.82)§	48.8	0.82 (0.80, 0.83)§	41.1	0.73 (0.72, 0.74)§	37.3	0.61 (0.59, 0.62)§	28.6	0.52 (0.51, 0.53)§
35–49	25.8	Ref.	36.5	Ref.	33.0	Ref.	30.6	Ref.	27.1	Ref.
50–64	5.0	1.66 (1.55, 1.77)§	9.0	1.54 (1.50, 1.58)§	14.8	1.55 (1.53, 1.58)§	19.0	1.61 (1.58, 1.65)§	26.2	1.52 (1.50, 1.54)§
≥65	0.5	1.72 (1.44, 2.06)§	1.8	1.76 (1.68, 1.85)§	7.2	2.05 (2.01, 2.08)§	9.1	2.41 (2.35, 2.47)§	14.7	2.51 (2.48, 2.55)§
HIV transmission route										
Homosexual contact	0.3	0.69 (0.46, 1.02)	1.6	0.56 (0.51, 0.62)§	15.8	0.49 (0.48, 0.51)§	27.8	0.49 (0.48, 0.51)§	25.3	0.54 (0.53, 0.55)§
Heterosexual contact	11.1	Ref.	28.5	Ref.	65.0	Ref.	66.6	Ref.	71.8	Ref.
Injection drug use	52.9	1.02 (0.96, 1.08)	32.2	1.33 (1.30, 1.36)§	13.8	1.34 (1.32, 1.36)§	4.5	1.52 (1.47, 1.58)§	1.7	1.50 (1.45, 1.55)§
Others/unknown	35.7	1.49 (1.41, 1.57)§	37.6	1.37 (1.34, 1.40)§	5.4	1.14 (1.11, 1.16)§	1.1	1.16 (1.06, 1.26)§	1.2	1.33 (1.27, 1.39)§
CD4 at diagnosis (cells/μL)										
CD4<200 or AIDS	35.9	3.54 (3.27, 3.83)§	39.2	2.71 (2.63, 2.79)§	32.6	2.56 (2.52, 2.61)§	30.7	2.31 (2.25, 2.37)§	30.8	2.52 (2.47, 2.58)§
CD4 200–349	6.1	1.48 (1.34, 1.64)§	9.4	1.40 (1.34, 1.45)§	18.3	1.37 (1.34, 1.40)§	22.8	1.17 (1.14, 1.21)§	26.2	1.26 (1.23, 1.29)§
CD4 350–499	5.7	1.24 (1.11, 1.37)†	10.1	1.15 (1.10, 1.19)§	19.2	1.15 (1.13, 1.17)§	18.8	1.05 (1.01, 1.08)†	16.5	1.04 (1.01, 1.06)†
CD4 ≥500	6.6	Ref.	11.5	Ref.	18.1	Ref.	19.4	Ref.	14.1	Ref.
Unknown	45.6	2.68 (2.48, 2.90)§	29.9	2.21 (2.14, 2.28)§	11.9	2.63 (2.58, 2.68)§	8.4	2.84 (2.75, 2.92)§	12.4	3.01 (2.95, 3.08)§
Venue of testing										
Hospitals	17.4	1.15 (1.09, 1.22)§	20.7	1.27 (1.24, 1.30)§	44.3	1.15 (1.14, 1.17)§	52.5	1.30 (1.27, 1.33)§	57.9	1.42 (1.40, 1.44)§
VCT clinics	11.4	Ref.	30.3	Ref.	28.6	Ref.	28.3	Ref.	24.7	Ref.
Others	71.2	0.88 (0.83, 0.92)§	49.1	0.88 (0.87, 0.90)§	27.2	0.83 (0.82, 0.84)§	19.2	0.92 (0.89, 0.95)§	17.5	0.84 (0.83, 0.86)§

Continued

Characteristic	1985–2003		2004–2007		2008–2013		2014–2015		2016–2022	
	Proportion (%)	Adjusted *HR* (95% *CI*)	Proportion (%)	Adjusted *HR* (95% *CI*)	Proportion (%)	Adjusted *HR* (95% *CI*)	Proportion (%)	Adjusted *HR* (95% *CI*)	Proportion (%)	Adjusted *HR* (95% *CI*)
ART initiation										
Treated	43.7	Ref.	68.1	Ref.	78.4	Ref.	87.5	Ref.	90.8	Ref.
Untreated	56.3	10.79 (10.35, 11.24)§	31.9	9.64 (9.46, 9.82)§	21.6	11.77 (11.62, 11.92)§	12.5	11.57 (11.34, 11.81)§	9.2	12.56 (12.42, 12.70)§

Note: The model was adjusted for age group, sex, HIV transmission route, venue of testing, and ART initiation. Ref. means reference.

Abbreviation: *HR*=hazard ratio; *CI*=confidence interval; ART=antiretroviral therapy; HIV=human immunodeficiency virus; VCT=voluntary counseling and testing.

* The analysis excluded 56 PLWHA with missing age data from the 1985–2003 cohort and 25 PLWHA with missing age data from the 2004–2007 cohort.

† $P<0.01$.

§ $P<0.001$.

following the adjustment of ART eligibility criteria.

The mortality risk for PLWHA diagnosed at age 65 or older was significantly higher compared to those diagnosed between ages 35–49. This disparity intensified over time, with the adjusted *HR* increasing from 1.72 in the 1985–2003 cohort to 2.51 in the 2016–2022 cohort. For older PLWHA receiving ART, reduced immune resilience compared to younger adults contributes to elevated mortality risk (*10*). Furthermore, older PLWHA face increased risks of comorbidities including hypertension, cardiovascular diseases, and malignancies (*11*). The convergence of HIV infection with these age-related conditions may compound disease burden. Given both the rising proportion of newly reported older PLWHA and the increased longevity of existing patients due to ART, healthcare systems must urgently develop targeted, differentiated strategies to address the unique challenges posed by an aging PLWHA population (*12*).

Despite expanded treatment criteria enabling earlier ART initiation at higher CD4 counts, a substantial proportion of patients still present with advanced disease. Our analysis revealed that patients with CD4 counts below 200 or AIDS-defining events had significantly higher mortality risk [adjusted *HR* (*AHR*)=1.87, 95% *CI*: 1.85, 1.89] compared to those with CD4 counts ≥500. Notably, 30.8% of patients in the 2016–2022 cohort presented with CD4 counts below 200 or AIDS-defining illness. Hospital-based diagnoses increased from 17.4% in the 1985–2003 cohort to 57.9% in the 2016–2022 cohort, with these patients more likely to present at advanced disease stages compared to those identified through voluntary counseling and testing (*13*). Late ART initiation is associated with persistent immunological dysfunction and increased mortality risk compared to early treatment (*14*). While rapid ART initiation and personalized clinical management can significantly reduce mortality in late presenters (*15*), early detection remains crucial. Although China's expanded HIV testing strategies show promise for improving survival through earlier diagnosis, their long-term impact requires further evaluation, particularly given the ongoing challenges in providing high-quality HIV care at the primary care level.

This study was subject to several limitations. First, there was inherent survivorship bias, as only living PLWHA have the opportunity to receive ART, which may confound our assessment of ART policy impacts on survival outcomes. Second, as the data originated

from a routine surveillance system, the collected information was inherently limited. Future research examining long-term survival of PLWHA would benefit from in-depth analyses of intrinsic factors such as comorbidities, social support networks, and medication adherence patterns.

In conclusion, China's implementation of the national free ART policy has effectively improved survival outcomes among PLWHA. Moving forward, continued expansion of HIV testing strategies is crucial to reduce the proportion of late diagnoses with lower CD4 count levels. Additionally, developing differentiated and precise services for older populations will be essential to further reduce mortality risk among PLWHA.

Conflicts of interest: No conflicts of interest.

Acknowledgments: All personnel involved in AIDS prevention, control, and data reporting activities.

Funding: Supported by the National Key Research and Development Plan (Grant number 2022YFC2305201).

doi: 10.46234/ccdcw2024.253

[#] Corresponding author: Fan Lyu, fanlv@chinaaids.cn.

[1] National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China; [2] National Key Laboratory of Intelligent Tracking and Forecasting for Infectious Diseases, National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China.

Submitted: October 15, 2024; Accepted: November 20, 2024

REFERENCES

1. Zhao Y, Wei L, Dou ZH, Zhao DC, Gan XM, Wu YS, et al. Changing mortality and patterns of death causes in HIV infected patients — China, 2013-2022. China CDC Wkly 2023;5(48):1073 – 8. https://doi.org/10.46234/ccdcw2023.201.
2. Zhang FJ, Zhao Y, Ma Y, Zhao DC, Dou ZH, Wu YS, et al. Progress and achievements of free antiretroviral treatment for AIDS in China. Chin J AIDS STD 2022;28(1):6-9. http://dx.doi.org/10.13419/j.cnki.aids.2022.01.02. (In Chinese).
3. Lai SH, Chen J, Celentano D, Page JB, Lai H, Yang JY, et al. Adoption of injection practices in heroin users in Guangxi Province, China. J Psychoact Drugs 2000;32(3):285 – 92. https://doi.org/10.1080/02791072.2000.10400451.
4. Zhang LF, Qiao XC, Nie XY, Guo XL, Mei ZQ. A retrospective cohort study on the survival of blood-borne human immunodeficiency virus cases in a county, China. Chin J Epidemiol 2004;25(11):941 – 4. https://doi.org/10.3760/j.issn:0254-6450.2004.11.006.
5. Ke SS, Fang Q, Lan JG, Qiao NN, Zhang XH, Xie CP, et al. Survival times of HIV/AIDS in different *AIDS diagnostic and treatment guidelines* from 2006 to 2020 in Liuzhou, China. BMC Public Health 2023;23(1):1745. https://doi.org/10.1186/s12889-023-15662-3.
6. Manosuthi W, Charoenpong L, Santiwarangkana C. A retrospective study of survival and risk factors for mortality among people living with HIV who received antiretroviral treatment in a resource-limited setting. AIDS Res Ther 2021;18(1):71. https://doi.org/10.1186/s12981-021-00397-1.
7. Park B, Choi Y, Kim JH, Seong H, Kim YJ, Lee M, et al. Mortality and causes of death among individuals diagnosed with human immunodeficiency virus in Korea, 2004-2018: an analysis of a nationwide population-based claims database. Int J Environ Res Public Health 2022;19(18):11788. https://doi.org/10.3390/ijerph191811788.
8. Tsuda H, Koga M, Nojima M, Senkoji T, Kubota M, Kikuchi T, et al. Changes in survival and causes of death among people living with HIV: three decades of surveys from Tokyo, one of the Asian metropolitan cities. J Infect Chemother 2021;27(7):949 – 56. https://doi.org/10.1016/j.jiac.2021.02.003.
9. Braunstein SL, Kersanske L, Torian LV, Lazar R, Harriman G. survival among new yorkers with HIV from 1981 to 2017: inequities by race/ethnicity and transmission risk persist into the post-HAART era. AIDS Behav 2022;26(1):284 – 93. https://doi.org/10.1007/s10461-021-03382-x.
10. Castillo-Rozas G, Tu SX, Luz PM, Mejia F, Sierra-Madero J, Rouzier V, et al. Clinical outcomes and risk factors for immune recovery and all-cause mortality in Latin Americans living with HIV with virological success: a retrospective cohort study. J Int AIDS Soc 2024;27(3):e26214. https://doi.org/10.1002/jia2.26214.
11. Hasse B, Ledergerber B, Furrer H, Battegay M, Hirschel B, Cavassini M, et al. Morbidity and aging in HIV-infected persons: the swiss HIV cohort study. Clin Infect Dis 2011;53(11):1130 – 9. https://doi.org/10.1093/cid/cir626.
12. Godfrey C, Vallabhaneni S, Shah MP, Grimsrud A. Providing differentiated service delivery to the ageing population of people living with HIV. J Int AIDS Soc 2022;25 Suppl 4(Suppl 4):e26002. http://dx.doi.org/10.1002/jia2.26002.
13. Zhang XJ, Wang N, Vermund SH, Zou HC, Li XH, Zhang FJ, et al. Interventions to improve the HIV continuum of care in China. Curr HIV/AIDS Rep 2019;16(6):448 – 57. https://doi.org/10.1007/s11904-019-00469-y.
14. Kitahata MM, Gange SJ, Abraham AG, Merriman B, Saag MS, Justice AC, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. N Engl J Med 2009;360(18):1815 – 26. https://doi.org/10.1056/NEJMoa0807252.
15. Kamya MR, Petersen ML, Kabami J, Ayieko J, Kwariisima D, Sang N, et al. SEARCH human immunodeficiency virus (HIV) streamlined treatment intervention reduces mortality at a population level in men with low CD4 counts. Clin Infect Dis 2021;73(7):e1938 – 45. https://doi.org/10.1093/cid/ciaa1782.

Preplanned Studies

An Index–Contact Paired Data Analysis on Sexual Contact Tracing Outcomes of HIV-Infected Individuals — Yunnan Province, China, 2022–2024

Wenjun Yan[1,&]; Junli Huo[2,&]; Xiaojing An[2,&]; Qiongli Duan[3]; Yu Han[2]; Nengmei Huang[3]; Ting Tan[4]; Zhimin Yang[2]; Jing Han[1]; Mengjie Han[1]; Yuhua Shi[2,#]; Jian Li[1,#]

Summary

What is already known about this topic?

A substantial proportion of people living with human immunodeficiency virus (PLWH) remain unaware of their infection status. Contact tracing serves as an effective public health tool for identifying human immunodeficiency virus (HIV) infections and supports progress toward achieving the 95-95-95-95 goals.

What is added by this report?

An egocentric contact tracing study conducted in Yunnan, China, between January 2022 and June 2024 enrolled 1,981 index cases, of whom 314 (15.9%) had at least 1 HIV-positive sexual contact. These index cases reported 2,171 sexual contacts, with 1,509 (69.5%) receiving HIV testing and 317 (21.0%) testing positive. Higher education levels and employment status among sexual contacts were positively associated with HIV testing uptake. HIV infection was more likely among contacts when the index case was female and identified through active HIV testing. Long-term sexual partnerships and inconsistent condom use demonstrated elevated infection risk.

What are the implications for public health practice?

The effectiveness of contact tracing outcomes is influenced by characteristics of both index cases and their sexual contacts. These factors should be incorporated into the design and implementation of sexual contact tracing programs.

Despite numerous innovative interventions, achieving the second 95 target [95% of people living with human immunodeficiency virus (PLWH) know their human immunodeficiency virus (HIV) status] set by the Joint United Nations Programme on HIV and AIDS (UNAIDS) remains challenging (*1*). In China, approximately 20% of PLWH were estimated to be unaware of their infection status in 2020 (*2*), with more than 40% of HIV-infected individuals receiving diagnoses at advanced stages of infection (*3*). This late diagnosis pattern leads to poorer clinical outcomes and impedes efforts to control HIV transmission (*4*). Contact tracing has emerged as a promising strategy for controlling the spread of infectious diseases (*5*–*7*). While previous research has primarily focused on examining associations between contact characteristics and tracing outcomes, the intimate nature of HIV transmission suggests that incorporating index case characteristics could provide crucial insights into understanding transmission networks within populations (*8*). To enhance and optimize contact tracing strategies, we conducted an egocentric contact tracing study from 2022 to 2024 in Yunnan, China. Our findings demonstrate that both index case and sexual contact characteristics significantly influence sexual contact tracing outcomes. These results suggest that interventions leveraging these facilitating factors offer promising pathways toward achieving the UNAIDS targets.

This egocentric contact tracing survey was conducted between January 2022 and June 2024 in Honghe Hani and Yi Autonomous Prefecture (Honghe Prefecture) of Yunnan Province, China. Newly diagnosed HIV-infected individuals aged 18 years or older who could provide sexual contact information were eligible and invited to participate as index cases. After providing informed consent, participants were interviewed by trained local health specialists using an anonymous questionnaire with unique identification numbers linking index cases. Interviews were conducted in private rooms where participants provided detailed information about their individual characteristics and all sexual partners with whom they had engaged in sexual intercourse. Index cases were subsequently encouraged to notify their sexual partners and refer them for HIV counseling and testing. Sexual contacts who tested HIV-positive were invited to

participate as new index cases in subsequent rounds of contact tracing. This iterative process continued until either no additional HIV-positive contacts were identified or no further sexual contacts could be traced. The study protocol was approved by the Ethics Committee of Yunnan Center for Disease Control and Prevention (Permit Number: YNCDC/QR-KJB-2021-003).

Contact tracing outcomes were classified as "successful" when at least one HIV-positive sexual partner was identified from an index HIV case. Testing modalities were categorized as either active, defined as HIV testing at a voluntary counseling and testing (VCT) clinic, or passive, which included all other identification pathways [e.g., provider-initiated testing and counseling (PITC)]. Data analysis was conducted at both index case and contact levels. At the index case level, bivariate and multivariate logistic regression analyses evaluated associations between index case characteristics and tracing outcomes. At the contact level, index–contact paired data were analyzed using multilevel logit models to assess relationships between both index case and contact factors related to HIV testing uptake and infection status among sexual contacts. All statistical analyses were performed using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA) with a significance level of 0.05.

The contact tracing process and identification of HIV infections are detailed in Supplementary Table S1 and Figure S1 (available at https://weekly.chinacdc.cn/). Among 1,981 enrolled index cases (1,925 newly reported during the study period, 54 identified from first-round contact tracing, and 2 from second-round), a total of 2,171 sexual contacts were reported, with a mean of 1.1 partners per index case (range: 1–4) and a median of 1 partner. Of these contacts, 69.5% (1,509/2,171) underwent HIV testing, with 21.0% (317/1,509) testing positive. The sexual network index (*9*) (contacts recruited per HIV-infected index case) was 0.8 (1,509/1,981). In the first round, 1,925 index cases reported 2,097 contacts, of whom 1,474 were tested and 308 were positive. Of these positive contacts, 54 participated as second-round index cases, reporting 69 contacts, with 32 tested and 9 positive. In the third round, 2 of the 9 positive contacts participated as index cases, reporting 5 contacts, of whom 3 were tested with no positive results.

The demographic profile of index cases showed a predominance of male individuals, aged 36–55 years, from ethnic minority backgrounds, with primary school education or less, who were married and employed. Notably, 85% were identified through passive testing, and approximately 35% presented with CD4 counts ≤200 cells per microliter at baseline. Sexual contacts were predominantly female (>50%), aged 36–55 years, from ethnic minorities, with primary school education or less, and employed. Most contacts were married, with approximately half engaged in non-marital, non-commercial sexual partnerships with their index case. The majority of relationships (71.9%) were of 1 year or less duration, with nearly 65% reporting sexual contact once or twice weekly in the previous 6 months. Condom use was notably low, with 65.8% reporting never using condoms during sexual encounters with their index case. Significant differences between index cases and sexual contacts were observed across gender, age, ethnicity, education, and marital status (Supplementary Table S2, available at https://weekly.chinacdc.cn/).

The success rate of tracing HIV-positive sexual contacts varied significantly by index case characteristics, with notably higher rates among female and married index cases. Additionally, index cases identified through active testing methods demonstrated superior contact tracing outcomes (Table 1).

Multivariate analysis revealed that sexual contacts of ethnic minorities, those with higher educational attainment, and employed individuals demonstrated increased likelihood of HIV testing uptake. Testing rates were notably higher among spouses and long-term partners, those in established relationships, individuals reporting frequent sexual activity, and those practicing consistent condom use. The probability of HIV infection was significantly elevated among contacts whose index case was female and identified through active testing protocols. Additionally, established relationships, particularly among spouses and long-term partners, exhibited higher infection rates compared to temporary or commercial relationships. HIV positivity was markedly increased among individuals reporting inconsistent or no condom use versus those maintaining consistent condom use practices (Table 2).

DISCUSSION

Our egocentric contact tracing study revealed a 21.0% positive detection rate, substantially higher than conventional screening methods such as PITC (0.2%) and VCT (4.2%) (*10*). This elevated efficiency in

TABLE 1. Association between sociodemographic and behavioral characteristics and sexual contact tracing outcomes among index HIV cases in Honghe Prefecture, Yunnan Province, China 2022–2024.

Characteristic	Index, *N*=1,981	Traced, *N*=314		Bivariate		Multivariate	
		n	*%**	*cOR*	*95% CI*	*aOR*	*95% CI*
Sex							
Male	1,350	116	8.6	1.0		1.0	
Female	631	198	31.4	**4.9**	**3.8, 6.3**	**4.7**	**3.6, 6.2**
Age							
18–35 years	378	46	12.2	1.0		1.0	
36–55 years	1,062	175	16.5	**1.4**	**1.0, 2.0**	1.1	0.7, 1.7
≥56 years	541	93	17.2	**1.5**	**1.0, 2.2**	1.2	0.7, 1.9
Ethnicity							
Han	728	116	15.9	1.0		1.0	
Ethnic minorities	1,253	198	15.8	1.0	0.8, 1.3	0.9	0.7, 1.2
Education							
≤Primary school	1,248	216	17.3	1.0		1.0	
Junior high school	512	70	13.7	0.8	0.6, 1.0	0.9	0.6, 1.2
≥Senior high school	221	28	12.7	0.7	0.5, 1.1	0.8	0.5, 1.4
Marital status							
Never married	506	42	8.3	1.0		1.0	
Currently married	863	175	20.3	**2.8**	**2.0, 4.0**	**1.6**	**1.1, 2.5**
Divorced or widowed	612	97	15.9	**2.1**	**1.4, 3.1**	1.1	0.7, 1.8
Occupation							
Unemployed	320	53	16.6	1.0		1.0	
Employed	1,661	261	15.7	0.9	0.7, 1.3	0.9	0.6, 1.3
Type of HIV testing							
Passive testing	1,684	222	13.2	1.0		1.0	
Active testing	297	92	31.0	**3.0**	**2.2, 3.9**	**3.1**	**2.2, 4.2**
CD4 counts at baseline (cells/microliter)							
≤200	695	92	13.2	1.0		1.0	
201–350	587	92	15.7	1.2	0.9, 1.7	1.0	0.8, 1.5
351–500	359	59	16.4	1.3	0.9, 1.8	1.0	0.7, 1.5
≥501	301	67	22.3	**1.9**	**1.3, 2.7**	1.3	0.9, 1.9
Unknown	39	4	10.3	0.7	0.3, 2.2	0.8	0.2, 2.4

Note: bolded denotes *P*<0.05.

Abbreviation: HIV=human immunodeficiency virus; *cOR*=crude odds ratio; *aOR*=adjusted odds ratio; *CI*=confidence interval.

* Refers to the efficacy of contact tracing: the probability of successfully tracing other positive cases through the index case, which is calculated as the number of index cases with HIV-positive contacts divided by total index cases.

identifying HIV infections compared to routine practices underscores the value of sexual contact tracing as a targeted intervention strategy. Our findings also highlight how the characteristics of both index cases and their sexual contacts significantly influence contact tracing outcomes, suggesting the need for these factors to be incorporated into program design.

The success of sexual contact tracing was notably influenced by specific characteristics of index cases. Female index cases demonstrated superior tracing outcomes compared to their male counterparts. This gender disparity may be attributed to male index cases often having multiple partners, potentially compromising their ability to accurately recall contact details and leading to tracing failures (*11*–*12*). Additionally, index cases identified through active HIV testing showed improved tracing results compared to those detected passively, consistent with previous

TABLE 2. HIV testing and infection among sexual contacts by sociodemographic and behavioral characteristics in Honghe Prefecture, Yunnan Province, China, 2022–2024.

Characteristic	Contacts *N*=2,171	Tested *N*=1,509 (%)*	Positive *N*=317 (%)†	Tested *vs.* untested		Positive *vs.* negative	
				cOR (95% *CI*)	*aOR* (95% *CI*)	*cOR* (95% *CI*)	*aOR* (95% *CI*)
Index							
Sex							
Male	1,487	990 (66.6)	113 (11.4)	1.0	1.0	1.0	1.0
Female	684	519 (75.9)	204 (39.3)	**1.6 (1.3, 1.9)**	1.0 (0.7, 1.5)	**5.0 (3.9, 6.5)**	**2.6 (1.3, 5.3)**
Age							
18–35 years	420	301 (71.7)	46 (15.3)	1.0	1.0	1.0	1.0
36–55 years	1,158	784 (67.7)	179 (22.8)	0.8 (0.6, 1.1)	0.8 (0.5, 1.1)	**1.6 (1.1, 2.3)**	0.7 (0.4, 1.4)
≥56 years	593	424 (71.5)	92 (21.7)	1.0 (0.8, 1.3)	1.0 (0.7, 1.6)	**1.5 (1.0, 2.3)**	0.7 (0.3, 1.5)
Ethnicity							
Han	795	548 (68.9)	116 (21.2)	1.0	1.0	1.0	1.0
Ethnic minorities	1,376	961 (69.8)	201 (20.9)	1.0 (0.9, 1.3)	0.8 (0.6, 1.0)	1.0 (0.8, 1.3)	0.7 (0.5, 1.1)
Education							
≤Primary school	1,364	954 (69.9)	221 (23.2)	1.0	1.0	1.0	1.0
Junior high school	561	388 (69.2)	70 (18.0)	1.0 (0.8, 1.2)	1.0 (0.8, 1.3)	0.7 (0.5, 1.0)	0.9 (0.6, 1.5)
≥Senior high school	246	167 (67.9)	26 (15.6)	0.9 (0.7, 1.2)	0.9 (0.6, 1.4)	0.6 (0.4, 1.0)	0.6 (0.3, 1.2)
Marital status							
Never married	554	368 (66.4)	38 (10.3)	1.0	1.0	1.0	1.0
Currently married	948	691 (72.9)	181 (26.2)	**1.4 (1.1, 1.7)**	1.0 (0.8, 1.4)	**3.1 (2.1, 4.5)**	0.7 (0.4, 1.3)
Divorced or widowed	669	450 (67.3)	98 (21.8)	1.0 (0.8, 1.3)	1.0 (0.7, 1.4)	**2.4 (1.6, 3.6)**	1.0 (0.6, 2.0)
Occupation							
Unemployed	349	238 (68.2)	52 (21.9)	1.0	1.0	1.0	1.0
Employed	1,822	1,271 (69.8)	265 (20.9)	1.1 (0.8, 1.4)	1.1 (0.8, 1.5)	0.9 (0.7, 1.3)	0.7 (0.4, 1.2)
Type of HIV testing							
Passive testing	1,841	1,267 (68.8)	223 (17.6)	1.0	1.0	1.0	1.0
Active testing	330	242 (73.3)	94 (38.8)	1.2 (1.0, 1.6)	1.1 (0.8, 1.4)	**3.0 (2.2, 4.0)**	**3.1 (2.0, 4.8)**
CD4 counts at baseline (cells/microliter)							
≤200	760	515 (67.8)	89 (17.3)	1.0	1.0	1.0	1.0
201–350	634	431 (68.0)	92 (21.4)	1.0 (0.8, 1.3)	0.9 (0.7, 1.2)	1.3 (0.9, 1.8)	1.1 (0.7, 1.8)
351–500	402	291 (72.4)	62 (21.3)	1.2 (1.0, 1.6)	1.2 (0.9, 1.6)	1.3 (0.9, 1.9)	1.1 (0.7, 1.8)
≥501	333	244 (73.3)	70 (28.7)	1.3 (1.0, 1.7)	1.1 (0.8, 1.5)	**1.9 (1.3, 2.8)**	1.2 (0.7, 2.1)
Unknown	42	28 (66.7)	4 (14.3)	1.0 (0.5, 1.8)	0.9 (0.4, 1.9)	0.8 (0.3, 2.4)	1.2 (0.3, 5.4)
Contacts							
Sex of contacts							
Female	1,327	894 (67.4)	106 (11.9)	1.0	1.0	1.0	1.0
Male	844	615 (72.9)	211 (34.3)	**1.3 (1.0, 1.6)**	0.9 (0.6, 1.3)	**3.9 (2.8, 5.5)**	1.7 (0.7, 4.4)
Age of contacts							
<18 years	19	14 (73.7)	2 (14.3)	1.0	1.0	1.0	1.0
18–35 years	809	526 (65.0)	71 (13.5)	0.7 (0.2, 1.9)	0.7 (0.2, 2.3)	0.9 (0.2, 4.7)	0.6 (0.1, 4.8)
36–55 years	1,089	776 (71.3)	170 (21.9)	0.9 (0.3, 2.5)	1.1 (0.3, 3.7)	1.7 (0.3, 8.3)	0.6 (0.1, 4.9)
≥56 years	254	193 (76.0)	74 (38.3)	1.1 (0.4, 3.3)	1.0 (0.3, 3.7)	3.7 (0.7, 18.7)	0.6 (0.1, 5.2)

Continued

Characteristic	Contacts *N*=2,171	Tested *N*=1,509 (%)*	Positive *N*=317 (%)†	Tested *vs.* untested		Positive *vs.* negative	
				cOR (95% *CI*)	*aOR* (95% *CI*)	*cOR* (95% *CI*)	*aOR* (95% *CI*)
Ethnicity of contacts							
Han	1,030	653 (63.4)	128 (19.6)	1.0	1.0	1.0	1.0
Ethnic minorities	1,141	856 (75.0)	189 (22.1)	**1.7 (1.4, 2.1)**	**1.8 (1.4, 2.4)**	1.2 (0.9, 1.5)	1.1 (0.7, 1.8)
Education of contacts							
≤Primary school	1,432	980 (68.4)	211 (21.5)	1.0	1.0	1.0	1.0
Junior high school	592	423 (71.5)	84 (19.9)	1.2 (0.9, 1.4)	**1.6 (1.2, 2.1)**	0.9 (0.7, 1.2)	0.9 (0.5, 1.4)
≥Senior high school	147	106 (72.1)	22 (20.8)	1.2 (0.8, 1.8)	**2.2 (1.3, 3.9)**	1.0 (0.6, 1.6)	0.9 (0.4, 2.1)
Marital status of contacts							
Never married	651	427 (65.6)	48 (11.2)	1.0	1.0	1.0	1.0
Currently married	775	582 (75.1)	185 (31.8)	**1.6 (1.3, 2.0)**	0.8 (0.6, 1.2)	**3.7 (2.6, 5.3)**	1.2 (0.6, 2.4)
Divorced or widowed	745	500 (67.1)	84 (16.8)	1.1 (0.9, 1.3)	0.9 (0.7, 1.2)	**1.6 (1.1, 2.4)**	1.5 (0.8, 2.9)
Occupation of contacts							
Unemployed	309	159 (51.5)	29 (18.2)	1.0	1.0	1.0	1.0
Employed	1,862	1350 (72.5)	288 (21.3)	**2.5 (1.9, 3.2)**	**2.3 (1.7, 3.2)**	1.2 (0.7, 2.0)	0.8 (0.4, 1.8)
Type of sexual relationship with index case							
Commercial sexual partnership	681	400 (58.7)	25 (6.3)	1.0	1.0	1.0	1.0
Spouse or long-term sexual partnership	375	358 (95.5)	185 (51.7)	**14.8 (8.8, 24.8)**	**12.7 (6.8, 23.6)**	**16.0 (10.0, 25.7)**	**2.3 (1.1, 4.6)**
Non-marital and non-commercial sexual partnership	1,115	751 (67.4)	107 (14.3)	**1.4 (1.2, 1.8)**	1.1 (0.8, 1.4)	**2.5 (1.6, 4.0)**	0.8 (0.4, 1.6)
Duration of sexual relationship with index case							
≤1 years	1,560	1,004 (64.4)	76 (7.6)	1.0	1.0	1.0	1.0
1–3 years	200	159 (79.5)	57 (35.9)	**2.1 (1.5, 3.1)**	**1.6 (1.0, 2.4)**	**6.8 (4.5, 10.3)**	**5.4 (3.2, 9.3)**
>3 years	411	346 (84.2)	184 (53.2)	**2.9 (2.2, 3.9)**	0.9 (0.6, 1.4)	**13.9 (10.0, 19.2)**	**7.1 (4.2, 12.2)**
Frequency of sexual behavior with index case in the past 6 months							
<once a week	554	327 (59.0)	48 (14.7)	1.0	1.0	1.0	1.0
1–2 times a week	1,379	985 (71.4)	225 (22.8)	**1.7 (1.4, 2.1)**	**1.6 (1.3, 2.1)**	**1.7 (1.2, 2.5)**	1.5 (0.9, 2.4)
≥3 times a week	238	197 (82.8)	44 (22.3)	**3.3 (2.3, 4.9)**	**3.3 (2.1, 5.1)**	**1.7 (1.0, 2.7)**	1.7 (0.8, 3.4)
Frequency of condom use with index case in the past 6 months							
Never	1,428	980 (68.6)	229 (23.4)	1.0	1.0	**20.3 (6.1, 68.0)**	**31.1 (7.6, 128.0)**
Inconsistently	506	326 (64.4)	85 (26.1)	0.8 (0.7, 1.0)	0.8 (0.6, 1.0)	**23.5 (6.9, 80.0)**	**31.9 (7.6, 133.7)**
Consistently	237	203 (85.7)	3 (1.5)	**2.7 (1.9, 4.0)**	**3.9 (2.5, 5.9)**	1.0	1.0

Note: bolded denotes $P<0.05$.
Abbreviation: HIV= human immunodeficiency virus; *cOR*= crude odds ratio; *aOR*= adjusted odds ratio; *CI*=confidence interval.
* Refers to HIV testing rate: the number of contacts tested for HIV as a percentage of total contacts.
† Refers to HIV positivity rate: the number of contacts tested positive as a percentage of total contacts tested for HIV.

research (*13*). This pattern likely reflects the heightened health awareness among individuals who proactively seek HIV testing through VCT clinics. These findings emphasize that the characteristics of index HIV cases are crucial considerations in optimizing contact tracing strategies.

Our index-contact paired data analysis revealed that HIV testing uptake among contacts was primarily influenced by the contacts' characteristics. Sexual contacts with higher educational attainment and employment status demonstrated increased testing rates, likely attributable to enhanced health literacy (*14*). Relationship dynamics played a crucial role, with long-term and stable partners showing higher testing

rates compared to commercial partners, aligning with previous findings in China (*9*). This pattern underscores the efficiency of contact tracing strategies, particularly among these high-risk populations. Moreover, frequent sexual activity and consistent condom use were positively associated with HIV testing rates, suggesting that individuals who engage in regular sexual activity while practicing safe sex may have a heightened awareness of HIV risk and greater motivation to know their status. These findings emphasize that improving accessibility and acceptability of HIV testing services could significantly enhance screening uptake (*15*).

The likelihood of HIV infection among sexual contacts was influenced by both contact characteristics and index case factors. Contacts had higher infection rates when their index case was female and identified through active testing protocols. Long-term and stable partnerships also demonstrated elevated infection risks. The higher detection rate among partners of female index cases may be attributed to women typically having fewer sexual contacts, though further research is needed to elucidate the underlying mechanisms. The prevalence of inconsistent condom use emerged as a significant factor in HIV transmission between partners. Evidence suggests that comprehensive intervention programs integrating condom promotion with testing services yield superior outcomes compared to isolated health education initiatives (*16*). These integrated approaches are fundamental to advancing both HIV prevention and testing outcomes.

This study has several important limitations that warrant consideration. First, as the research was conducted in a single prefecture of Yunnan Province, the generalizability of our findings to other regions remains uncertain. Second, the use of convenience sampling may have introduced selection bias, potentially limiting the representativeness of our study population. Third, the reliance on index cases to provide information about their sexual contacts may have introduced information bias through recall errors, social desirability bias, or deliberate omission of contact details.

Despite these methodological constraints, our findings provide compelling evidence for the feasibility and effectiveness of contact tracing as a strategy for identifying HIV infections. The results illuminate critical factors that could enhance sexual contact tracing outcomes. Future research should build upon these findings by developing and evaluating targeted strategies that address both index cases and their sexual partners simultaneously.

Acknowledgements: The authors would like to thank all participants who so willingly gave their time to provide the study data. This work was supported by National Natural Science Foundation of China (Grant Number: 72164040). The funder had no role in study design, data collection, data analysis, and the decision to publish or preparation of the manuscript.

Conflicts of interest: The authors declare that there is no potential conflict of interest.

doi: 10.46234/ccdcw2024.254

[#] Corresponding authors: Jian Li, jli@chinaaids.cn; Yuhua Shi, shiyuhua@yncdc.cn.

[1] National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China; [2] Yunnan Center for Disease Control and Prevention, Kunming City, Yunnan Province, China; [3] Center for Disease Control and Prevention in Honghe Hani and Yi Autonomous Prefecture, Mengzi, Yunnan Province, China; [4] Kunming Medical University, Kunming City, Yunnan Province, China.
[&] Joint first authors.

Submitted: August 20, 2024; Accepted: October 20, 2024

REFERENCES

1. Global HIV Statistics. Global HIV & AIDS statistics — fact sheet. 2024. https://www.unaids.org/en/resources/fact-sheet. [2024-8-1].
2. Zhao Y, Han MJ, Ma Y, Li DM. Progress towards the 90-90-90 targets for controlling HIV — China, 2018. China CDC Wkly 2019;1(1):5 – 7. https://doi.org/10.46234/ccdcw2019.003.
3. Sun CQ, Li JJ, Liu XY, Zhang Z, Qiu T, Hu HY, et al. HIV/AIDS late presentation and its associated factors in China from 2010 to 2020: a systematic review and meta-analysis. AIDS Res Ther 2021;18(1):96. https://doi.org/10.1186/s12981-021-00415-2.
4. Waters L, Sabin CA. Late HIV presentation: epidemiology, clinical implications and management. Expert Rev Anti Infect Ther 2011;9 (10):877 – 89. https://doi.org/10.1586/eri.11.106.
5. Oh MK, Boker JR, Genuardi FJ, Cloud GA, Reynolds J, Hodgens JB. Sexual contact tracing outcome in adolescent chlamydial and gonococcal cervicitis cases. J Adolesc Health 1996;18(1):4 – 9. https://doi.org/10.1016/1054-139X(95)00109-6.
6. Christie TKS, Kendall P. The science of partner notification: a review of the available evidence. BC Med J 2003;45(3):124-7. https://bcmj.org/articles/science-partner-notification-review-available-evidence.
7. Centers for Disease Control and Prevention. Current trends partner notification for preventing human immunodeficiency virus (HIV) infection -- Colorado, Idaho, South Carolina, Virginia. 2001. https://www.cdc.gov/mmwr/preview/mmwrhtml/00000042.htm. [2024-7-28].
8. Klovdahl AS. Social networks and the spread of infectious diseases: the AIDS example. Soc Sci Med 1985;21(11):1203 – 16. https://doi.org/10.1016/0277-9536(85)90269-2.
9. Lin HJ, He N, Ding YY, Qiu DH, Zhu WM, Liu X, et al. Tracing sexual contacts of HIV-infected individuals in a rural prefecture, Eastern China. BMC Public Health 2012;12:533. https://doi.org/10.1186/1471-2458-12-533.
10. Han Y, An XJ, Ma YL, Huo JL, Zhang XB, Yang ZM, et al. Exploration and practice of HIV contact tracing strategy in Yunnan Province. Chin J AIDS STD 2022;28(7):852-4. http://dx.doi.org/10.13419/j.cnki.aids.2022.07.23. (In Chinese).
11. Maierhofer CN, Powers KA, Matoga MM, Chen JS, Jere E, Massa C, et

al. Characterizing network-based HIV testing interventions to guide HIV testing and contact tracing at STI clinics in Lilongwe, Malawi. J Acquir Immune Defic Syndr 2023;94(2):151 – 9. https://doi.org/10.1097/QAI.0000000000003240.
12. Parish WL, Laumann EO, Mojola SA. Sexual behavior in China: trends and comparisons. Popul Dev Rev 2007;33(4):729 – 56. https://doi.org/10.1111/j.1728-4457.2007.00195.x.
13. Hong H, Zhang DD, Jiang HB, Shi HB, Tan SW, Gu WZ, et al. HIV infection and related factors of traceability efficiency among sex partners of HIV positive men who have sex with men. Chin J Epidemiol 2021;42(12):2100 – 5. https://doi.org/10.3760/cma.j.cn112338-20210811-00632.
14. Wawrzyniak AJ, Ownby RL, McCoy K, Waldrop-Valverde D. Health literacy: impact on the health of HIV-infected individuals. Curr HIV/AIDS Rep 2013;10(4):295 – 304. https://doi.org/10.1007/s11904-013-0178-4.
15. Sundararajan R, Ponticiello M, Nansera D, Jeremiah K, Muyindike W. Interventions to increase HIV testing uptake in global settings. Curr HIV/AIDS Rep 2022;19(3):184 – 93. https://doi.org/10.1007/s11904-022-00602-4.
16. Chow EPF, Tung K, Tucker JD, Muessig KE, Su S, Zhang XH, et al. Behavioral interventions improve condom use and HIV testing uptake among female sex workers in China: a systematic review and meta-analysis. AIDS Patient Care STDS 2015;29(8):454 – 60. https://doi.org/10.1089/apc.2015.0043.

SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE S1. Rounds of tracing of sexual contacts for index HIV cases in Honghe Prefecture, Yunnan Province, China, 2022–2024.

The process of contact tracing	First round	Second round	Third round	Total
Number of index HIV cases	1,925	54	2	1,981
Number and proportion (%) of index HIV cases traced at least one sexual contact tested positive*	305 (15.8)	9 (16.7)	0 (0)	314 (15.9)
Number of sexual contacts reported by index cases	2,097	69	5	2,171
Number and proportion (%) of sexual contacts received HIV testing†	1,474 (70.3)	32 (46.4)	3 (60.0)	1,509 (69.5)
Number and proportion (%) of sexual contacts tested HIV positive§	308 (20.9)	9 (28.1)	0 (0)	317 (21.0)

Abbreviation: HIV=human immunodeficiency virus.
* Contact tracing efficacy: proportion of index cases that led to identification of at least one HIV-positive contact, calculated as the number of index cases with HIV-positive contacts divided by total index cases.
† HIV testing uptake: proportion of contacts who received HIV testing, calculated as the number of contacts tested divided by total contacts.
§ HIV positivity rate: proportion of tested contacts who were HIV-positive, calculated as the number of contacts testing positive divided by total contacts tested.

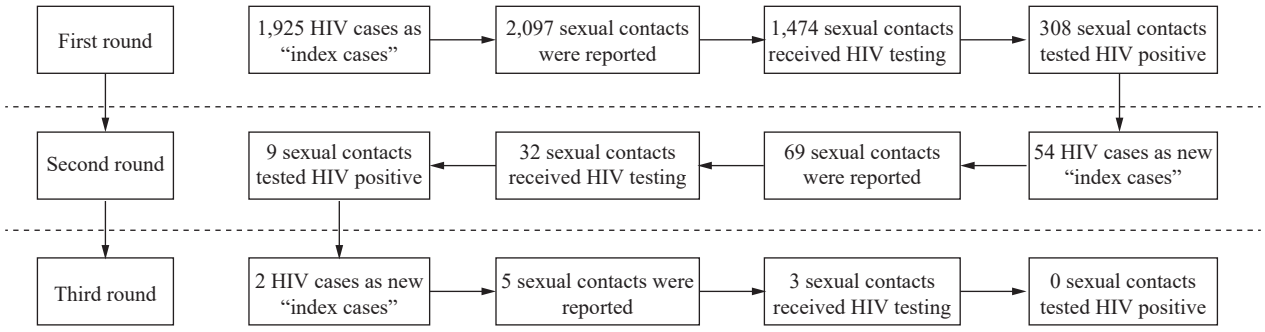
SUPPLEMENTARY TABLE S2. Sociodemographic and behavioral characteristics of index HIV cases and sexual contacts in Honghe Prefecture, Yunnan Province, China, 2022–2024.

Characteristic	Index *N*=1,981		Contacts *N*=2,171		χ^2/F	*P*
	n	%	*n*	%		
Sex					185.827	<0.001
Male	1,350	68.2	844	38.9		
Female	631	31.8	1,327	61.1		
Age*					919.34	<0.001
Mean (SD)	47.1	12.9	40.4	12.0		
<18 years	0	0.0	19	0.8		
18–35 years	378	19.1	809	37.3		
36–55 years	1,062	53.6	1,089	50.2		
≥56 years	541	27.3	254	11.7		
Ethnicity					83.544	<0.001
Han	728	36.8	1,030	47.4		
Ethnic minorities	1,253	63.3	1,141	52.6		
Education					35.679	<0.001
≤Primary school	1,248	63.0	1,432	66.0		
Junior high school	512	25.8	592	27.3		
≥Senior high school	221	11.2	147	6.7		
Marital status					42.486	<0.001
Never married	506	25.5	651	30.0		
Currently married	863	43.6	775	35.7		
Divorced or widowed	612	30.9	745	34.3		
Occupation					3.638	0.057
Unemployed	320	16.2	309	14.2		
Employed	1,661	83.8	1,862	85.8		
Type of HIV testing						
Passive testing	1,684	85.0				
Active testing	297	15.0				

Continued

Characteristic	Index N=1,981		Contacts N=2,171		χ^2/F	P
	n	%	n	%		
CD4 counts at baseline (cells/microliter)						
≤200	695	35.1				
201–350	587	29.6				
351–500	359	18.1				
≥501	301	15.2				
Unknown	39	2.0				
Type of sexual relationship with index case						
Spouse or long-term sexual partnership			375	17.3		
Commercial sexual partnership			681	31.4		
Non-marital and non-commercial sexual partnership			1,115	51.3		
Duration of sexual relationship with index case						
≤1 year			1,560	71.9		
1–3 years			200	9.2		
>3 years			411	18.9		
Frequency of sexual behavior with index case in the past 6 months						
<once a week			554	25.5		
1–2 times a week			1,379	63.5		
≥3 times a week			238	11.0		
Frequency of condom use with index case in the past 6 months						
Never			1,428	65.8		
Inconsistently			506	23.3		
Consistently			237	10.9		

Abbreviation: HIV=human immunodeficiency virus; SD=standard deviation.
* Chi-square analysis was not feasible due to zero-frequency cells. Age disparity between groups was alternatively analyzed using survey regression procedures ("proc surveyreg").



SUPPLEMENTARY FIGURE S1. Process flowchart of HIV contact tracing and case identification.
Abbreviation: HIV=human immunodeficiency virus

Methods and Applications

Study on the Technical Parameters for Estimating HIV-1 Incidence by Using a Recombinant Antigen-based Capture Enzyme Immunoassay — China

Wenli Liang[1,&]; Jibao Wang[2,&]; Hongxia Yan[3,&]; Xinhui Zhang[4]; Dorjiwangmo [5]; Dongmin Li[1]; Xing Duan[2]; Hao Wu[3]; Yinyin Wang[6]; Li Bai[7]; Jian Sun[5]; Mengjie Han[1]; Yikui Wang[2]; Bin Su[3]; Min Wang[8]; Tashibazong [5]; Wenge Xing[1]; Cui Zhang[1]; Ruijuan Qiao[7,#]; Maofeng Qiu[1,#]

ABSTRACT

Introduction: A novel recombinant antigen-based capture enzyme immunoassay (RAg-CEIA) was optimized and used to determine technical parameters for estimating human immunodeficiency virus type 1 (HIV-1) incidence in China.

Methods: We employed orthogonal experimental design to optimize RAg-CEIA by adjusting raw material dilution ratios. The assay was used to measure normalized optical density (ODn) values in 171 longitudinal plasma specimens from 51 HIV-1 seroconverting individuals, plotted against estimated days post-seroconversion. We determined the optimal ODn threshold value for differentiating recent from long-term infections and calculated the mean duration of recent infection (MDRI) for incidence estimation. The false recent rate (FRR) was determined using 481 HIV-1 antibody-positive specimens with infection durations exceeding twice the MDRI.

Results: Optimal RAg-CEIA parameters were established with a raw material dilution ratio of 1/12 for calibrator preparation and an enzyme conjugate titer of 1:1200. ODn values demonstrated consistent temporal increases across HIV-1 seroconverting individuals, though with notable kinetic heterogeneity in individual responses. The optimal ODn threshold value of 0.8 for distinguishing recent from long-term infections corresponded to an MDRI of 205 days and an FRR of 4.78%.

Conclusions: The optimized RAg-CEIA effectively differentiates recent from long-term HIV-1 infections at the population level, enabling reliable HIV-1 incidence estimation in China.

Laboratory detection of recent human immunodeficiency virus type 1 (HIV-1) infection remains a critical challenge in HIV-1 surveillance and control efforts. Among commercially available assays, two predominant methods are the HIV-1 BED capture enzyme immunoassay (BED-CEIA) and limiting antigen avidity enzyme immunoassay (LAg-Avidity EIA) (*1*–*2*). BED-CEIA operates by measuring the progressive increase in HIV-1-specific immunoglobulin G (IgG) proportion relative to total IgG during the first two years post-seroconversion. It utilizes a branched peptide incorporating gp41 immunodominant sequences from HIV-1 subtypes B, E, and D, enabling consistent detection across various viral subtypes (*1*). LAg-Avidity EIA, conversely, measures the increasing antibody-antigen binding strength that develops over time following infection (*2*–*4*). This assay employs rIDR-M, a multi-subtype recombinant protein encompassing the immunodominant region (IDR) of HIV-1 (group M) gp41, which offers advantages in large-scale production (*2*). While BED-CEIA demonstrates superior operational stability, it exhibits a higher false recent rate (FRR) compared to LAg-Avidity EIA (*5*). To combine the advantageous features of both assays — namely, BED-CEIA's operational stability and LAg-Avidity EIA's convenient antigen preparation and lower FRR — we developed a recombinant antigen-based capture enzyme immunoassay (RAg-CEIA). This novel assay incorporates a modified HIV-1 recombinant antigen conjugated with horseradish peroxidase (HRP), replacing the branched peptide and streptavidin-labeled HRP components of BED-CEIA. The novel antigen maintains the core structure of rIDR-M from LAg-Avidity EIA but features strategic modifications: the His tag is relocated to the C-terminus, while a linker and hydrophilic Trx fusion tag are added to the N-terminus, enabling HRP labeling (*6*). However, further optimization is required to ensure data comparability with BED-CEIA results.

This study aims to optimize RAg-CEIA and establish technical parameters for HIV-1 incidence estimation in China.

METHODS

Specimens

This study utilized 668 HIV-1 antibody-positive plasma specimens and 1 HIV-1 negative plasma specimen, categorized as follows: 1) One large-volume HIV-1 antibody-positive plasma specimen and one large-volume HIV-1 negative plasma specimen were used to prepare the calibrator (CAL), high positive control (HPC), low positive control (LPC), and negative control (NC). 2) 15 HIV-1 antibody-positive plasma specimens with known normalized optical density (ODn) values from BED-CEIA were employed for RAg-CEIA optimization. 3) 171 longitudinal plasma specimens from 51 HIV-1 seroconverting individuals were analyzed to determine the optimal ODn threshold value for recent/long-term infection classification and to calculate the mean duration of recent infection (MDRI). They comprised 81 specimens (31 individuals) from a man who have sex with men (MSM) cohort in Beijing Municipality and 90 specimens (20 individuals) from a routine HIV-1 testing cohort in Yunnan Province. Inclusion criteria specified an interval of less than 60 days between the last negative and first positive HIV-1 antibody test results, absence of acquired immune deficiency syndrome (AIDS), and no prior antiretroviral treatment (*1*). 4) 481 HIV-1 antibody-positive plasma specimens collected across five provinces (Beijing, Yunnan, Guizhou, Gansu, and Xizang) were used to calculate the FRR. These specimens met the criteria of non-AIDS status, no antiretroviral treatment history, and infection duration exceeding twice the MDRI (*7*).

Experimental Process

The RAg-CEIA protocol followed previously established procedures (*6*). Briefly, specimen preparation involved adding 500μL of specimen diluent (3% bovine serum albumin, fraction V, in wash buffer containing 0.1% Triton X-100 in phosphate buffer solution; pH 7.2) to titer tubes arranged in an 8×12 rack. Subsequently, 5μL of NC, CAL, LPC, HPC, or test specimens were added and thoroughly mixed via pipetting. 100μL of each mixture was transferred to wells of a 96-well microplate pre-coated with goat anti-human IgG antibody. The microplate underwent incubation at 37 ℃ (±1℃) for 1 h, followed by 5 wash cycles. After adding 100μL of enzyme conjugate per well, the plate was incubated for 30 minutes at 37 ℃ (±1℃) and washed again. Color development was initiated by adding 100μL of tetramethylbenzidine (TMB) substrate, followed by 30-minute incubation at 37 ℃ (±1℃) in darkness. The reaction was terminated with 100 μL of 1 N H_2SO_4, and optical density (OD) measurements were taken at 450 nm with 630 nm reference wavelength. Controls and specimens were tested in triplicate or duplicate, with ODn values calculated as the ratio of median OD to median CAL OD.

Assay Optimization

RAg-CEIA optimization employed orthogonal experimental design to determine optimal parameters for the CAL dilution ratio and enzyme conjugate (HIV-1 recombinant antigen labeled with HRP) titer. The optimization targeted two primary objectives: 1) achieving linear correlation between RAg-CEIA and BED-CEIA ODn values for 15 HIV-1 antibody-positive specimens with BED-CEIA ODn values of 0.6-1.0, and 2) establishing a CAL OD value of approximately 0.8. The CAL, HPC, and LPC were prepared by diluting heat-inactivated HIV-1 antibody-positive plasma in heat-inactivated HIV-1 negative plasma, while the enzyme conjugate was diluted in specimen diluent.

Data Analysis

ODn values were obtained from 171 longitudinal plasma specimens using optimized RAg-CEIA. A comprehensive database was established incorporating specimen background information and corresponding RAg-CEIA ODn values. The estimated days post-seroconversion were calculated using the midpoint between the last negative and first positive HIV-1 antibody test results (*1*). ODn values were plotted against estimated days post-seroconversion, and the optimal threshold ODn value for recent/long-term infection classification and MDRI were determined using the R package inctools (version 4.4.1; R Foundation for Statistical Computing, Vienna, Austria) (*7*). The FRR was calculated from 481 HIV-1 antibody-positive plasma specimens as the percentage of specimens incorrectly classified as recent infections (*7*).

RESULTS

Assay Optimization and Quality Control

The orthogonal experimental analysis revealed optimal parameters for the RAg-CEIA: a raw material dilution ratio of 1/12 for calibrator preparation and an enzyme conjugate titer of 1:1,200. Consequently, the dilution ratios for HPC and LPC preparation were established at 1/6 and 1/24, respectively. The assay demonstrated excellent operational stability, with coefficients of variation (CVs) for both OD and ODn values of CAL, LPC, and HPC consistently below 10% (Table 1).

ODn Kinetics Measured by RAg-CEIA Among 51 Seroconverting Individuals

Analysis of ODn values, which reflect the ratio of HIV-1-specific IgG to total IgG, demonstrated a consistent temporal increase across nearly all subjects. Notable heterogeneity was observed in individual immune responses. While ODn values exhibited relatively tight clustering during early seroconversion, the distribution progressively widened over time (Figure 1).

Technical Parameters for Estimating HIV-1 Incidence in China

Optimal sensitivity and specificity were achieved at an ODn threshold value of 0.8 for distinguishing between recent and long-term infections, corresponding to an MDRI of 205 days [95% confidence interval (*CI*): 176, 242 days]. Using this threshold, specimens with ODn≤0.8 were classified as recent HIV-1 infections, while those above this value were designated as long-term infections. In the analysis of 481 HIV-1 antibody-positive plasma specimens, 23 samples were misclassified as recent infections by RAg-CEIA, yielding an FRR of 4.78% (95% *CI*: 3.05%, 7.09%).

DISCUSSION

Current technological limitations and individual immunological variations constrain the utility of existing HIV-1 recent infection detection assays. These assays primarily serve to classify recent versus long-term HIV-1 infections and estimate HIV-1 incidence at the population level, rather than providing definitive individual diagnoses.

RAg-CEIA represents an innovative assay that successfully combines the superior operational stability of BED-CEIA with the advantages of LAg-Avidity EIA, namely convenient antigen preparation and reduced FRR. Our validation demonstrates excellent experimental stability, with CVs below 10% for both OD and ODn values across controls CAL, LPC and HPC. The assay achieves an MDRI of 205 days and an FRR of 4.78% for HIV-1 incidence estimation in China, showing marked improvement over the BED-CEIA's FRR of 6.85% in Chinese populations (*8*). Since MDRI and FRR are crucial determinants of HIV-1 incidence estimation accuracy, and these parameters are influenced by HIV-1 subtypes and population-specific immune responses, it is essential to establish region-specific MDRI and FRR values before implementing any assay in new geographical areas (*7*).

International studies have documented substantial variation in MDRI values across HIV-1 subtypes for both BED-CEIA and LAg-Avidity EIA. BED-CEIA's MDRI ranges from 127 days (Thai AE) to 236 days (subtypes AG, AD), with an overall MDRI of 197 days (95% *CI*: 173, 220 days). LAg-Avidity EIA shows similar variability, with MDRI values spanning 109 days (subtype A&D) to 152 days (subtype C) and an overall MDRI of 130 days (95% *CI*: 118, 142 days) (*9*–*10*). In China, field applications of these assays yield overall MDRIs of 168 days and 130 days, respectively (*8*). Our MDRI calculations for RAg-CEIA utilized specimens from both an MSM cohort in Beijing and a routine HIV-1 testing cohort in Yunnan

TABLE 1. Mean, SD, and CV of OD and ODn values of the controls from 14 runs.

Controls	OD		ODn	
	Mean±SD	CV (%)	Mean±SD	CV (%)
NC	0.036±0.010	28.1	0.048±0.014	30.4
CAL	0.751±0.062	8.2	1	0
LPC	0.522±0.077	4.4	0.695±0.055	3.6
HPC	1.486±0.103	7.0	1.983±0.124	6.2

Abbreviation: SD=standard deviation; CV=coefficient of variation; OD=optical density; ODn=normalized optical density; NC=negative control; CAL=calibrator; LPC=low positive control; HPC=high positive control.

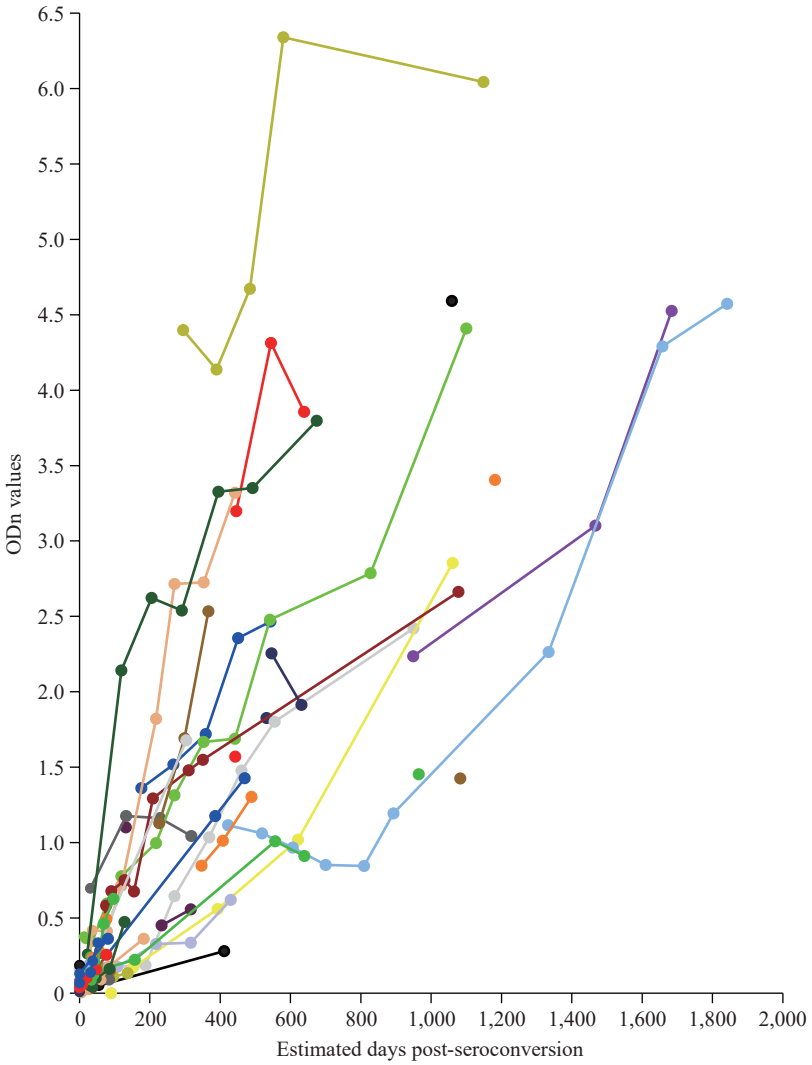


FIGURE 1. ODn kinetics measured by RAg-CEIA among 51 seroconverting individuals from 2 cohorts. Each color of line and dot represents an individual with sequential specimens collected over days post-seroconversion and each dot represents a specimen. ODn values reflecting the ratio of HIV-1-specific IgG to total IgG increased in almost all individuals over time. There was heterogeneity among individual responses.
Abbreviations: ODn=normalized optical density; RAg-CEIA=recombinant antigen-based capture enzyme immunoassay; HIV-1=human immunodeficiency virus type 1; IgG=immunoglobulin G.

(*11–12*), providing representative coverage of China's predominant HIV-1 subtypes. The fourth national HIV molecular epidemic survey revealed that CRF07_BC (41.3%), CRF01_AE (32.7%), and CRF08_BC (11.3%) account for 85.3% of HIV-1 infections in China (*13*). This limited subtype diversity suggests minimal impact of genetic variability on MDRI calculations when estimating population-level HIV-1 incidence.

The limitations of this study are the relatively small specimen pool used for calculating incidence estimation parameters and only the overall MDRI is obtained. These constraints stem from China's policy of immediate antiretroviral treatment upon HIV-1 diagnosis, which significantly restricts the availability of longitudinal plasma specimens from both seroconverting individuals and those with long-term infections.

Conflicts of interest: No conflicts of interest.

Funding: Supported by the National Science and Technology Major Project of the 13th Five-year Plan (grants 2017ZX10201101-002-003 and 2018ZX10721102-003-002).

doi: 10.46234/ccdcw2024.255

[#] Corresponding authors: Maofeng Qiu, qiumf@chinaaids.cn; Ruijuan Qiao, qiaoruijuan@outlook.com.

[1] National Key Laboratory of Intelligent Tracking and Forecasting for Infectious Diseases, National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China; [2] Department of AIDS/STD Control and Prevention, Dehong Center for Disease Control and Prevention, Mangshi County, Dehong Dai and Jingpo Autonomous Prefecture, Yunnan Province, China; [3] Beijing Key Laboratory for HIV/AIDS Research, Beijing Youan Hospital, Capital Medical University, Beijing, China; [4] Institute of Infectious Diseases Prevention and Treatment, Guizhou Provincial Center for Disease Control and Prevention, Guiyang City, Guizhou Province, China; [5] Department of AIDS Control and Prevention, Xizang Autonomous Region Center for Disease Control and Prevention, Lhasa City, Xizang Autonomous Region, China; [6] Experimental Center, Guizhou Provincial Center for Disease Control and Prevention, Guiyang City, Guizhou Province, China; [7] Department of AIDS Control and Prevention, Gansu Provincial Center for Disease Control and Prevention, Lanzhou City, Gansu Province, China; [8] Laboratory Department, Liupanshui Center for Disease Control and Prevention, Liupanshui City, Guizhou Province, China.
[&] Joint first authors.

Submitted: November 04, 2024; Accepted: November 20, 2024

REFERENCES

1. Parekh BS, Kennedy MS, Dobbs T, Pau CP, Byers R, Green T, et al. Quantitative detection of increasing HIV type 1 antibodies after seroconversion: a simple assay for detecting recent HIV infection and estimating incidence. AIDS Res Hum Retroviruses 2002;18(4):295 – 307. https://doi.org/10.1089/088922202753472874.
2. Duong YT, Qiu MF, De AK, Jackson K, Dobbs T, Kim AA, et al. Detection of recent HIV-1 infection using a new limiting-antigen avidity assay: potential for HIV-1 incidence estimates and avidity maturation studies. PLoS One 2012;7(3):e33328. https://doi.org/10.1371/journal.pone.0033328.
3. Persaud D, Gay H, Ziemniak C, Chen YH, Piatak Jr M, Chun TW, et al. Absence of detectable HIV-1 viremia after treatment cessation in an infant. N Engl J Med 2013;369(19):1828 – 35. https://doi.org/10.1056/NEJMoa1302976.
4. WHO. Global guidance on criteria and processes for validation: elimination of mother-to-child transmission of HIV, syphilis and hepatitis B virus. 2022. https://www.who.int/publications/i/item/9789240039360. [2023-12-1]
5. Dobbs T, Liu X, Anderson R, Nkengasong J, Parekh BS. A comprehensive evaluation of the proficiency testing program for the HIV-1 BED incidence assay. J Clin Microbiol 2011;49(10):3470 – 3. https://doi.org/10.1128/jcm.01122-11.
6. Di Y, Meng TT, Jing YY, Liu XW, Duan LJ, Jiang Y, et al. Development of a recombinant antigen for capture enzyme immunoassay to detect recent HIV-1 infection. Chin J AIDS STD 2019;25(6):552 – 5,558. https://doi.org/10.13419/j.cnki.aids.2019.06.02.
7. UNAIDS, WHO. Using recency assays for HIV surveillance — 2022 technical guidance. 2023. https://www.unaids.org/en/resources/documents/2023/using-recency-assays-HIV-surveillance. [2023-12-1]
8. Chinese Center for Disease Control and Prevention. National guideline for detection of HIV/AIDS. 2015. https://ncaids.chinacdc.cn/fzyw_10256/jsgf/201608/t20160810_133524.htm. (In Chinese). [2023-12-1]
9. Parekh BS, Hanson DL, Hargrove J, Branson B, Green T, Dobbs T, et al. Determination of mean recency period for estimation of HIV type 1 incidence with the BED-capture EIA in persons infected with diverse subtypes. AIDS Res Hum Retroviruses 2011;27(3):265 – 73. https://doi.org/10.1089/aid.2010.0159.
10. Duong YT, Kassanjee R, Welte A, Morgan M, De A, Dobbs T, et al. Recalibration of the limiting antigen avidity EIA to determine mean duration of recent infection in divergent HIV-1 subtypes. PLoS One 2015;10(2):e0114947. https://doi.org/10.1371/journal.pone.0114947.
11. Huang XJ, Chen H, Li W, Li HY, Jin X, Perelson AS, et al. Precise determination of time to reach viral load set point after acute HIV-1 infection. J Acquir Immune Defic Syndr 2012;61(4):448 – 54. https://doi.org/10.1097/QAI.0b013e31827146e0.
12. He N, Duan S, Ding YY, Rou KM, McGoogan JM, Jia MH, et al. Antiretroviral therapy reduces HIV transmission in discordant couples in rural Yunnan, China. PLoS One 2013;8(11):e77981. https://doi.org/10.1371/journal.pone.0077981.
13. Zhong P. Progress in research and practice of molecular epidemiology of HIV-1. Electron J Emerging Infect Dis 2019;4(3):137 – 44. https://doi.org/10.19871/j.cnki.xfcrbzz.2019.03.003.

Youth Editorial Board

Indexed by Science Citation Index Expanded (SCIE), Social Sciences Citation Index (SSCI), PubMed Central (PMC), Scopus, Chinese Scientific and Technical Papers and Citations, and Chinese Science Citation Database (CSCD)

The inauguration of *China CDC Weekly* is in part supported by Project for Enhancing International Impact of China STM Journals Category D (PIIJ2-D-04-(2018)) of China Association for Science and Technology (CAST).

CCDC weekly

Vol. 6 No. 48 Nov. 29, 2024

Responsible Authority
National Disease Control and Prevention Administration

Sponsor
Chinese Center for Disease Control and Prevention

Editing and Publishing
China CDC Weekly Editorial Office
No.155 Changbai Road, Changping District, Beijing, China
Tel: 86-10-63150501, 63150701
Email: weekly@chinacdc.cn

CSSN
ISSN 2096-7071 (Print)
ISSN 2096-3101 (Online)
CN 10-1629/R1