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Young MSM Population Is Changing HIV Epidemic Pattern in Northeast China: a Seven-year Cross-sectional Study

Qing-Hai Li
Harbin Medical University
Jia-Ye Wang
Harbin Medical University
Si-Yu Liu
Harbin Medical University
Xiao-Xiao Liu
Harbin Medical University
Zi-Yan Tang
Harbin Medical University
Dong-Ming Li
Harbin Medical University
Fu-Xiang Wang (wangfuxiang999@hotmail.com)
The Third People's Hospital of Shenzhen
Xiao-Hong Chen
Harbin Medical University
Shu-Lin Liu
Harbin Medical University

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Abstract

Background: Human immunodeficiency virus type 1 (HIV-1) epidemic in China is featured by geographical diversity of epidemic patterns. Understanding the characteristics of regional HIV epidemic allows carrying out targeted prevention and control measures. However, in some regions of Northeast China, current HIV-1 epidemic feature is largely unknown.

Methods: Information of 1006 newly diagnosed HIV-1 infected participants were collected before antiretroviral therapy during 2010-2016 in Harbin city of Northeast China. HIV-1 genotype was identified based on the viral *gag* and *env* genes. Comparison analyses were made among different participant groups and sampling time periods to understand HIV-1 epidemic trend. Multivariable logistic regression was used to evaluate the factors associated with immune status of participants.

Results: Homosexual contact among men who have sex with men (MSM) was the main transmission route and CRF01_AE was the most dominant HIV-1 genotype. Newly diagnosed cases were getting younger, which was mainly due to the continuous increase in the proportion of young cases (aged < 30 years) among CRF01_AE-infected individuals, especially the CRF01_AE-infected MSM. The proportion of cases with good immune status (CD4 count > 500 cells/μl) continued to increase, and younger in age, HIV-1 infection via homosexual contact among MSM and infection by non-CRF01_AE genotype were positive factors for the good immune outcome.

Conclusions: Young MSM have become a new vulnerable group for HIV-1 transmission in Northeast China. This group is changing local HIV-1 epidemic pattern. Measures for preventing and controlling HIV-1 infection among this population are urgently needed in the future.

Introduction

Human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) epidemic in China becomes increasingly severe and complicated. By the end of 2018, the reported absolute number of Chinese people living with HIV-1 was approximately 0.89 million, but the real number was estimated at more than 1.25 million [1]. One big challenge for HIV/AIDS control is the geographical and temporal diversity of epidemic patterns throughout the whole country. In the past twenty years, HIV/AIDS epidemic pattern has obviously changed, including regional distribution, transmission route, age composition and dominant virus genotypes [2–4]. For the regions with high HIV-1 incidence such as southwest provinces Yunnan and Guangxi, the features of HIV/AIDS epidemic have been described extensively [4–6]. However, for the regions where HIV-1 incidence is relative low but annually reported case number rises rapidly, such as Heilongjiang, the current situation of HIV/AIDS epidemic is largely unknown.

Heilongjiang, one province in Northeast China, lies on the border between China and Russia. Since first HIV-1 infection was identified in 1993, annually reported HIV-1 diagnoses in Heilongjiang continued to increase slowly until the year 2008 when an expansion of HIV-1 infection among men who have sex with men (MSM) occurred. Since then, newly diagnosed HIV/AIDS cases rapidly increased yearly, and

homosexual contact among MSM became dominant route of HIV-1 transmission in this province [7]. The dominant HIV-1 genotype circulating in Heilongjiang has also changed, from subtype B to circulating recombinant form 01_AE (CRF01_AE) during 2009-2012 [8–12]. However, these sporadic studies were conducted before the year 2013 and mostly based on small sample sizes, making them hard to understand the current epidemic trend of HIV/AIDS, especially the trend of HIV-1 molecular epidemiology, in this region. In this study, we made a seven-year cross-sectional analysis on more than one thousand new HIV-1 diagnoses in Heilongjiang province, reported new features and trends of HIV-1 epidemic in this northeast region of China. Our data highlighted the critical role of young MSM on the change of HIV-1 epidemic pattern in Northeast China.

Methods

The study participants and information collection

A total of 1006 participants who were newly diagnosed as HIV-1 infection from January 2010 to December 2016 in the Fourth Affiliated Hospital of Harbin Medical University were enrolled. The peripheral blood was sampled immediately after diagnoses and before antiretroviral therapy (ART). The information including sex, age, the way to acquire HIV-1 and peripheral blood CD4 positive T cell count (hereafter referred to as CD4 count) at diagnosis were collected and analyzed.

HIV-1 Genotyping

For each participant, 5 ml of whole peripheral blood was collected, and then plasma separation and HIV-1 genotyping were done. HIV-1 *gag* p17-p24 and *env* C2-C4 genes were obtained from plasma samples and genotype was determined by the cluster distribution of genes in neighbor-joining trees constructed using MEGA 6.06 software as previously described [13].

Genbank accession numbers of nucleotide sequences

The nucleotide sequences identified in this study were submitted to GenBank with accession numbers of MK702086-MK702931 for *gag* p17-p24 genes and MK702932-MK703795 for *env* C2-C4 genes.

Statistical analyses

Sampling times were divided into three periods: 2010-2011, 2012-2014, and 2015-2016. Participants were divided into four age groups: the young (< 30 years old), thirties (30-39 years old), forties (40-49 years old) and the old (≥ 50 years old). According to the CD4 counts, participants were also divided into four CD4 groups: CD4hi (> 500 cells/μl), CD4subhi (351-500 cells/μl), CD4sublo (200-350 cells/μl) and CD4lo (< 200 cells/μl).

Kruskall-Wallis test was used for comparison of the quantitative variables across groups. Chi-square test and Fisher's exact test were used for comparison of qualitative variables across multiple groups and two groups, respectively. Multivariable logistic regression was used to evaluate the factors associated with immune status of participants. Data analyses were performed by GraphPad Prism version 8.3.0

(GraphPad Software, Inc, La Jolla, CA). The *P* value less than 0.05 was considered as significant unless otherwise specified.

Results

Basic information of the participants

Among 1006 participants, 93.7% were male. Median age was 35 years old (interquartile range, IQR, 29-45), and median CD4 count was 384 cells/μl (IQR 214-490). Totally, 23.9% of cases had CD4 counts more than 500 cells/μl (CD4hi cases), indicating good immune state; and 22.5% of cases had CD4 counts less than 200 cells/μl (CD4lo cases), indicating immunodeficiency status. Sexual contact was the dominant route of HIV-1 acquirement, responsible for 85.7% of all cases and 98.6% of cases with known ways of HIV-1 acquirement, including 667 MSM and 195 heterosexually transmitted cases (Table 1). CRF01_AE was the predominant HIV-1 genotype (accounting for 62.5% of new diagnoses), followed by subtype B (16.5%) and 07&08&C (13.0%, including CRF07_BC, CRF08_BC and subtype C). Subtype A and unique recombinant form (URF) infections were also identified (Table 1 and Additional file 1: Figure S1).

Table 1
Basic characteristic of the participants in this study

	Total (n = 1006)	Sampling year			χ^2	P value
		2010-2011 (n = 140)	2012-2014 (n = 299)	2015-2016 (n = 567)		
Sex					1.09	0.5794
Male	943 (93.7)	134 (95.7)	279 (93.3)	530 (93.5)	1.09	0.5794
Female	63 (6.3)	6 (4.3)	20 (6.7)	37 (6.5)	1.09	0.5794
Age (years old)					**18.04**	**0.0061**
<30	275 (27.3)	23 (16.4)	86 (28.8)	166 (29.3)	**9.77**	**0.0076**
30-39	349 (34.7)	52 (37.1)	94 (31.4)	203 (35.8)	2.08	0.3540
40-49	215 (21.4)	37 (26.4)	57 (19.1)	121 (21.3)	3.08	0.2145
≥50	167 (16.6)	28 (20.0)	62 (20.7)	77 (13.6)	8.60	0.0136
CD4 count (cells/μl)					**12.95**	**0.0438**
<200	227 (22.5)	29 (20.7)	69 (23.1)	129 (22.8)	0.33	0.8477
200-350	194 (19.3)	35 (25.0)	63 (21.1)	96 (16.9)	5.57	0.0618
351-500	345 (34.3)	53 (37.9)	105 (35.1)	187 (33.0)	1.31	0.5187
>500	240 (23.9)	23 (16.4)	62 (20.7)	155 (27.3)	**9.64**	**0.0081**
Risk group					**39.87**	**< 0.0001**
MSM	667 (66.3)	82 (58.6)	199 (66.6)	386 (68.1)	4.55	0.1026
Heterosexual	195 (19.4)	37 (26.4)	64 (21.4)	94 (16.6)	8.08	0.0176
Others	12 (1.2)	8 (5.7)	2 (0.7)	2 (0.4)	**28.38**	**< 0.0001**
Unknown	132 (13.1)	13 (9.3)	34 (11.4)	85 (15.0)	4.35	0.1137
HIV-1 Genotype					**31.19**	**0.0001**
CRF01_AE	629 (62.5)	75 (53.6)	198 (66.2)	356 (62.8)	6.55	0.0378

Abbreviations: 07&08&C, virus that had a genotype of CRF07_BC, CRF08_BC or subtype C; MSM, men who have sex with men; NA: not applicable; Others, other risk groups including 8 cases of former plasma donors, 3 cases of injection drug users and 1 case of mother-to-child infection; URF, unique recombinant form.

Data were shown as number (%). The comparisons of the proportions of groups among three sampling time periods were done by Chi-square test with $P < 0.05$ as significant. The Post hoc multiple comparisons were done with $P < 0.0125$ as significant.

	Total (n = 1006)	Sampling year			χ^2	P value
		2010-2011 (n = 140)	2012-2014 (n = 299)	2015-2016 (n = 567)		
Subtype B	166 (16.5)	42 (30.0)	48 (16.1)	76 (13.4)	**22.51**	**< 0.0001**
07&08&C	131 (13.0)	18 (12.9)	36 (12.0)	77 (13.6)	0.41	0.8131
Subtype A	7 (0.7)	0 (0.0)	1 (0.3)	6 (1.1)	NA	NA
URF	73 (7.3)	5 (3.6)	16 (5.4)	52 (9.2)	7.53	0.0232

Abbreviations: 07&08&C, virus that had a genotype of CRF07_BC, CRF08_BC or subtype C; MSM, men who have sex with men; NA: not applicable; Others, other risk groups including 8 cases of former plasma donors, 3 cases of injection drug users and 1 case of mother-to-child infection; URF, unique recombinant form.

Data were shown as number (%). The comparisons of the proportions of groups among three sampling time periods were done by Chi-square test with $P < 0.05$ as significant. The Post hoc multiple comparisons were done with $P < 0.0125$ as significant.

Newly diagnosed cases were getting younger and cases with good immune status were getting increased

During 2010-2016, median age decreased from 39 (interquartile range, IQR 32-46) years old to 34 (IQR 28-44) years olds (Fig. 1A and Additional file 2: Table S1), and proportion of young cases (aged < 30 years) rose from 16.4–29.3% (Table 1). Especially, proportion of cases aged 15-24 years increased from 5.0% (7/140) to 11.5% (65/567, $P = 0.0277$). These data indicated a younger trend of newly diagnosed HIV-1 cases. The median CD4 count did not show significant change among the three time periods (Fig. 1B and Additional file 2: Table S2), but interestingly, proportion of CD4hi cases gradually increased from 16.4–27.3% (Table 1), suggesting a fast increase in cases with good immune status.

Young cases exhibited better immune status

Median CD4 count of the young cases (418, IQR 301-517) was higher than that of the forties (380, IQR 169-478) and the old (289, IQR 174-426) (Fig. 1C). The proportion of CD4hi cases decreased from 29.8% (82/275) in the young group to 15.6% (26/167, $P = 0.0009$) in the old group, while the proportion of CD4lo cases increased from 16.4% (45/275) in the young group to 28.1% (47/167, $P = 0.0037$) in the old group (Fig. 1D). On the other hand, the median age of CD4hi cases (34, IQR 27-42) was lower than that of CD4lo (38, IQR 31-47) or CD4sublo (37, IQR 30-50) cases (Fig. 1E). The proportion of young cases increased from 19.8% (45/227) in the CD4lo group to 34.2% (82/240, $P = 0.0006$) in the CD4hi group, and the proportion of old cases decreased from 20.7% (47/227) to 10.8% (26/240, $P = 0.0048$) (Fig. 1F). These results implied that young cases showed better immune status than the old ones and increase of the young cases might contribute to the improvement of overall immune state of HIV-1-infected cases.

Increase of young MSM cases was associated with the younger trend of HIV-1 infections

Median age of the MSM cases (34, IQR 28-44) was lower than that of heterosexuals (37, IQR 31-47) and the “unknown” cases (42, IQR 31-50) who could not articulate the way to acquire HIV-1 (Fig. 2A). During the three sampling time periods, median age of MSM decreased from 37 (IQR 31-45) years old to 34 (IQR 27-42) years old, and proportion of young MSM rose from 20.7% (17/82) to 32.1% (124/386, $P = 0.0467$) (Fig. 2B and 2C). But these variables in heterosexuals or “unknown” cases did not exhibit obvious change (Additional file 2: Table S1, S3 and S4). For all the participants, proportion of MSM in young cases (74.2%, 204/275) was higher than that in the forties (58.1%, 125/215, $P = 0.0002$) and in the old cases (56.3%, 94/167, $P = 0.0002$). These data indicated that the increase of young MSM cases made a substantial contribution to the younger trend of new HIV-1 diagnoses.

Increase of CD4hi MSM cases was associated with the overall immune status of HIV-1 infected cases

Median CD4 counts in MSM, heterosexuals and “unknown” cases were similar and did not show obvious change among the three periods (Fig. 2D and 2E and Additional file 2: Table S2). But, for HIV-1 infected MSM, the proportion of CD4hi cases increased from 15.9% (13/82) to 28.8% (111/386, $P = 0.0186$) (Fig. 2F), suggesting the expansion of MSM cases with good immune status. No significant change on the proportion of any CD4 group in heterosexuals or “unknown” cases was observed during the study period (Additional file 2: Tables S3 and S4). In addition, 68.3% (164/240) of CD4hi cases in this study acquired HIV-1 via homosexual contact with MSM. These results implied that expansion of CD4hi MSM cases made the major contribution to the increased proportion of CD4hi cases in this region.

Increase of CRF01_AE-infected young MSM made a critical contribution to the younger trend of new HIV-1 diagnoses

There was no difference on the median ages of cases infected by different HIV-1 genotypes (Fig. 3A). But for CRF01_AE infected cases, the median age decreased from 38 (IQR 33-46) years old to 34 (IQR 28-43) years old during the three periods, and the proportion of young cases rapidly increased from 9.3% (7/75) to 30.9% (110/356, $P < 0.0001$) (Fig. 3B and 3C and Additional file 2: Table S1). For subtype B and 07&08&C infected cases, the median age did not show significant variation during these time periods (Additional file 2: Table S1).

Among all the young cases enrolled in this study, 62.9% (173/275) were infected by CRF01_AE genotype; and among these young CRF01_AE infected cases, 76.9% (133/173) were MSM, i.e. nearly half (133/275) of young cases were CRF01_AE-infected MSM. During this study interval, young case proportion in CRF01_AE-infected MSM rose rapidly from 26.1% (6/23) in 2010-2011 to 51.2% (85/166, $P = 0.0269$) in 2015-2016. There was no difference on the median ages of MSM cases infected by different HIV-1 genotypes (Fig. 3D). But similar with the situation in CRF01_AE infections, the median age of CRF01_AE-infected MSM decreased from 36 (IQR 32-44) years old to 33 (IQR 27-41, $P = 0.0336$) years old (Fig. 3E), and the proportion of young cases increased from 13.6% (6/44) to 34.0% (85/250, $P = 0.0074$) (Fig. 3F). These data indicated that the continuous increase of young CRF01_AE-infected cases, especially young MSM, played a critical role in the younger trend of new HIV-1 diagnoses.

Multiple HIV-1 genotypes co-contributed to the increased proportion of CD4hi cases

Subsequently, we wanted to know whether a special genotype made substantial contribution to the increase of CD4hi cases in new infections. As shown in Fig. 3G, the participants infected by 07&08&C (460, IQR 352-594) and URF (456, IQR 368.5-549) had much higher median CD4 counts than those infected by CRF01_AE (361, IQR 178-456) or subtype B (385.5, IQR 206-533) (Fig. 3G). As expected, the proportion of CD4hi cases in 07&08&C (42.7%, 56/131) and URF (38.4%, 28/73) infections were also higher than that in CRF01_AE (16.5%, 104/629) and subtype B (29.5%, 49/166) infections (Fig. 3H). But, the median CD4 count or the composition proportion of CD4 groups in any genotype group did not exhibit significant change over the three time periods (Additional file 2: Tables S2 and S5). These data indicated participants infected by different HIV-1 genotypes tended to be living in distinct immunological states, but based on the current data, the increased proportion of CD4hi cases could not be explained by the infection of one special HIV-1 genotype.

Younger in age, homosexual contact with MSM and non-CRF01_AE infection were positive factors for good immune status

In order to find the underlying factors associated with the increase of CD4hi cases, we constructed a multivariable logistic regression equation using CD4 count more than 500 cells/μl (CD4hi) as the positive outcome. As shown in Table 2, age was a negative factor for the CD4hi outcome. Compared to female, male had much lower odds of being CD4hi case. But, compared to heterosexuals, MSM had higher odds of being CD4hi case. Relative to CRF01_AE infection, subtype B, 07&08&C or URF infection had higher odds of being CD4hi case. These date indicated younger in age, HIV-1 acquirement via homosexual contact among MSM and infection of non-CRF01_AE virus were positive factors for being CD4hi cases.

Table 2
Factors associated with being CD4hi case of sexually infected participants (*n* = 862)

Factor	Group	OR (95% CI)	*P* value
Age		0.97 (0.96-0.99)	0.0013
Sex	Female *	1	
	Male	0.33 (0.15-0.70)	0.0042
Risk group	Heterosexual *	1	
	MSM	1.62 (1.00-2.62)	0.0482
Genotype	CRF01_AE *	1	
	Subtype B	1.87 (1.20-2.92)	0.0061
	07&08&C	3.57 (2.31-5.53)	< 0.0001
	URF	2.94 (1.69-5.10)	0.0001

Abbreviations: 07&08&C, virus that had a genotype of CRF07_BC, CRF08_BC or subtype C; CI, confidence interval; MSM, men who have sex with men; OR, odds ratio; URF, unique recombinant form.

*, reference group.

Discussion

HIV-1 epidemic in China is featured by the highly geographical and temporal diversity of epidemic patterns throughout the whole country. This study was the first cross-sectional molecular epidemiological research with large sample size in Heilongjiang of Northeast China. Large sample size allowed us to preliminarily understand the HIV-1 epidemiological features and trends in different high-risk populations, age groups and in the individuals infected by different genotype infections or in different immune status and thus to more comprehensively understand HIV-1 epidemic in Northeast China.

The first finding in the present study was that male-male sexual contact among MSM was the major route of HIV-1 transmission and CRF01_AE was the dominant HIV-1 genotype during 2010-2016. Unlike the situation in some European and American countries where HIV-1 epidemic initiated among MSM, few cases were reported among Chinese MSM until the year 2005. HIV-1 prevalence among MSM rapidly increased, from 1.4% in 2005 to 8% in 2015. Since 2010, MSM population has become the highest-risk group for HIV-1 transmission in China [4]. The HIV-1 epidemic in Chinese MSM unevenly distributes across provinces and regions, highly concentrating in municipalities, provincial capitals or cities with large population sizes and fast economic growth, such as Beijing, Shanghai, Guangzhou [14].

Harbin is the capital of Heilongjiang province, one of three economic centers in Northeast China as well as one of cities that were affected by the first wave of HIV-1 expansion among MSM during 2006-2008

[14]. HIV-1 prevalence among MSM population in Harbin rapidly increased from 1.0–9.5% between 2006 and 2011 [15, 16]. Our previous studies demonstrated that MSM became the highest-risk group for HIV-1 infection in Heilongjiang province during 2009-2012, accounting for 57.9% and 69.0% of new diagnoses in 2009-2010 and 2011-2012, respectively [7]. In this study, we found MSM cases accounted for 66.3% of all new diagnoses during 2010-2016, consistent with our previous studies [7, 11], indicating the samples collected in this study were representative of HIV-1 infections in Heilongjiang. The proportion of MSM cases in Harbin was also similar with the cities in where HIV-1-infected Chinese MSM concentrate, such as Jilin (another northeast province), Beijing [17] and Shanghai [18]. Importantly, although the annual new diagnoses continued to increase, the MSM proportion remained stable during this study interval, suggesting a stably growing period of HIV-1 infected MSM during 2010-2016 and the increasing risk of HIV-1 acquirement and transmission among MSM population in this city of Northeast China.

CRF01_AE genotype accounts for only 5% of global HIV-1 infections, and concentrates in Southeast Asia and China [19, 20]. In 1990s, CRF01_AE virus was introduced into China and rapidly spread throughout the whole country. Since 2007, CRF01_AE has become the most prevalent genotype in China except the northwest region. In Northeast China, more than half of HIV-1 infections were caused by CRF01_AE genotype [21]. Several sporadic studies provided limited epidemiological feature of HIV-1 genotype in Harbin city. Our previous studies reported that subtype B was the main genotype in 1997-2000 and in 2007 [8, 9] and that CRF01_AE surpassed subtype B and became the dominant genotype in 2011-2012 [11]. In the present study, we found since 2010, CRF01_AE had become the main genotype in this region, and continued to dominate HIV-1 genotype during 2010-2016. Similar with the situation of HIV-1 infected MSM, the proportion of CRF01_AE cases in annual new diagnoses kept relatively stable (53.6%-66.2%), suggesting CRF01_AE epidemic in Harbin has also reached to a stably growing period. Furthermore, in the present study, near 70% of CRF01_AE infected participants acquired HIV-1 via male-male sexual contact, higher than the national average level (approximately 58%) [22], supporting the observation that CRF01_AE viruses (clusters 4 and 5) epidemic in Northeast China mainly concentrated in MSM population [12, 23, 24]. Recent studies demonstrated CRF01_AE cluster 4 has had a longer growth stage (> 10 years) than the other clusters [25] but is just in the very early stage of its epidemic in Northeast China [26]. It was also found that CRF01_AE cluster 4 (rather than cluster 5) infection among Chinese MSM was associated with fast decline of CD4 count and poor immune recovery under combination ART outside of Northeast China [27, 28]. However, the pathogenic feature of CRF01_AE clusters in Northeast China is unknown, which will be one interesting issue in our future studies.

The second finding of this study was that new HIV-1 diagnoses exhibited a younger trend in this seven-year study interval, which was mainly attributed to the rapid expansion of CRF01_AE-infected young MSM. In 2005-2008, the clustering hotspots of Chinese young people living with HIV/AIDS (15-24 years old) mainly distributed within heterosexuals and intravenous drug users in southwest provinces. After 2008, new hotspots among MSM in central and northeast provinces emerged. On the national scale, new HIV-1 cases aged 15-24 years increased by an annual average of 35% during 2011-2015 [29]. For Harbin city, HIV/AIDS cases aged 15-24 years increased about 5-fold between 2005 and 2012 [30]. This study found the proportion of new diagnoses aged < 30 years and aged 15-24 years rapidly rose from 16.4%

and 5.0–29.3% and 11.5% during 2010-2016, respectively, implying that young people have become a new vulnerable group of HIV-1 infection in Northeast China. More concerns should be put on this population in future.

CRF01_AE infections accounted for 64.3% (429/667) of newly diagnosed MSM in Harbin, slightly higher than the national level (57.36%) reported in a meta-analytic integration of 66 molecular epidemiological studies conducted during 2008-2016 [22]. A study on HIV-1 infected MSM from 13 Chinese provinces indicated the proportion of CRF01_AE cases aged 16-25 years decreased from 55.4–43.5% between 2009 and 2014 [31]. However, in the present study, both of the proportions of CRF01_AE cases aged < 30 years and aged 15-24 years among HIV-1 infected MSM quickly increased approximately three times during 2010-2016 (13.6–34.0% and 4.5–13.6%, respectively), suggesting a rapid-expansion period of CRF01_AE-infected young MSM cases in Harbin city. The measures for HIV-1 prevention and control targeting young MSM population should be strengthened.

The third finding was that proportion of new HIV-1 diagnoses with fine immune status (CD4hi cases) significantly increased in Harbin, and age, sexual transmission mode of HIV-1 infection and virus genotype were associated with the immune status of HIV-1 infected participants. The overall improved immune status could be partially explained by the scale-up of HIV testing in China. It was reported that between 2009 and 2018, the total person-times of HIV testing increased from 55.6 million to more than 240 million in China [3], which allowed finding out more cases at the early stage of the disease. Young people seem to be more likely to know their HIV-1 status. Compared with old people, young MSM had a higher HIV-1 incidence and a higher prevalence of HIV-1 recent infection [32]. These studies support our finding that both younger in age and HIV-1 infection among MSM were positive factors associated with being CD4hi cases. However, it is worth noting that recently infected HIV-1 cases are usually highly infectious because of their high viral load, but they mainly remain undetected [33]. And, young MSM exhibited a higher prevalence of high-risk behaviors (recreational drug use, unprotected anal intercourse and concurrent multiple sex partnerships) than old MSM [32]. Therefore, recently infected young MSM will speed up HIV-1 transmission and secondary infection within MSM population. We speculate that the rapid increase of cases with high CD4 count in young MSM would continue to be an important feature of HIV-1 epidemic in Northeast China in following years.

HIV-1 genotype was identified as another factor associated with immune status of participants in this study. Several cohort studies in China have demonstrated that HIV-1 genotype was the independent variable associated with disease progression. CRF01_AE infection is commonly associated to lower baseline CD4 count, more rapid CD4 count decline and faster progression to immunodeficiency than non-CRF01_AE infection in China [34–36]. Consistent with the above findings, in this study, relative to non-CRF01_AE infection, CRF01_AE infection in Harbin had significantly lower odds of being CD4hi case.

In this study, 07&08&C infected cases kept stable increase during 2010-2016 (Table 1). More importantly, the risk group and age compositions of 07&08&C and CRF01_AE infected cases were quite similar (data not shown), suggesting the co-circulation of CRF01_AE and 07&08&C strains in similar population in

Harbin. Extensive studies have demonstrated CRF07_BC infection exhibits a slow disease progression [34]. Consistent with this, our data indicated both median CD4 count and the proportion of CD4hi cases in 07&08&C cases were much higher than those in CRF01_AE cases. The weaker pathogenicity of 07&08&C virus might make potential contribution to the increase of CD4hi cases. This was supported by our data from logistic regression analysis that relative to CRF01_AE infection, 07&08&C infection had higher odds of being CD4hi case. More importantly, the co-circulation of CRF01_AE and 07&08&C strains in Northeast China would augment the potential recombination between these viruses and subsequently promote the emergence of new recombinant HIV-1 forms [12], leading to new and larger burden on the prevention and control of HIV-1 in China.

One more evidence for the overall improved immune status of the participants in Harbin city was also observed in this study. As shown in Table 1, the proportion of “late diagnoses” (CD4 count < 200 cells/μl at diagnoses) in newly identified HIV-1 cases ranged from 20.7–23.1% in Harbin during 2010-2016, much lower than the national level (35.5%-41.8%) in 2010-2014 [37] and the provincial level of Heilongjiang in 1993-2012 (28.6%-38.4%) [7]. This may be due to the high availability of HIV testing in China and people's higher pursuit of health and life quality.

There were several limitations in this study. First, although we had made great efforts to collect samples from clinical monitoring sites, the sample size in early time period (2010-2011) was still small (n = 140). Therefore, in some statistical analyses, differences among groups or subgroups may be underestimated. Even so, several important findings were yielded. We believe that using a larger sample size will further confirm our findings. Second, in this study, we hypothesized that the incubation period and the interval between infection and diagnosis were same in different age groups, high-risk populations and HIV-1 genotype infected groups. Although this is generally true for most HIV-1 infected people, there might be some exceptions. Third, HIV-1 genotyping based on *gag* and *env* gene regions might introduce some bias. Further analyses based on the near full-length genome of HIV-1 will be required in future, but considerable labor and financial resources will be required at same time. Despite these limitations, we still believe our work could provide several clues for further research and HIV/AIDS control in Northeast China.

Conclusions

During 2010-2016, MSM was the highest-risk population for new HIV-1 diagnoses in Harbin of Heilongjiang province and CRF01_AE was the top dominant genotype circulating in this region. This study also reported two new features of HIV-1 epidemic in Northeast China. One was new HIV-1 diagnoses exhibited a younger trend, which was mainly due to the rapid increase in CRF01_AE-infected young MSM. The second was the participants with fine immune status (CD4 count > 500 cells/μl) increased quickly, which was positively associated with younger in age, HIV-1 acquirement via homosexual among MSM and non-CRF01_AE infection. These features highlighted young people especially young MSM as the new vulnerable population for HIV-1 transmission in Northeast China and the importance of development of intervention measures targeting this population.

Abbreviations

MSM, men who have sex with men; CRF, circulating recombinant form; 07&08&C, virus that had a genotype of CRF07_BC, CRF08_BC or subtype C; URF, unique recombinant form; IQR, interquartile range; CI, confidence interval; OR, odds ratio.

Declarations

Acknowledgements

Not applicable.

Authors' contributions

F.-X.W. and S.-L.L. conceived the experiments; F.-X.W. and Q.-H.L. designed the experiments; Q.-H.L., J.-Y.W. and X.-H.C. S.-Y.L. performed the experiments; J.-Y.W., X.-X.L., Z.-Y.T. and D.-M.L. analyzed the data; F.-X.W., S.-L.L. and Q.-H.L. wrote the paper.

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Availability of data and materials

Datasets used and analyzed during the current study may be available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Fourth Affiliated Hospital of Harbin Medical University ([2015]KT003). The informed consent was obtained from each participant.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

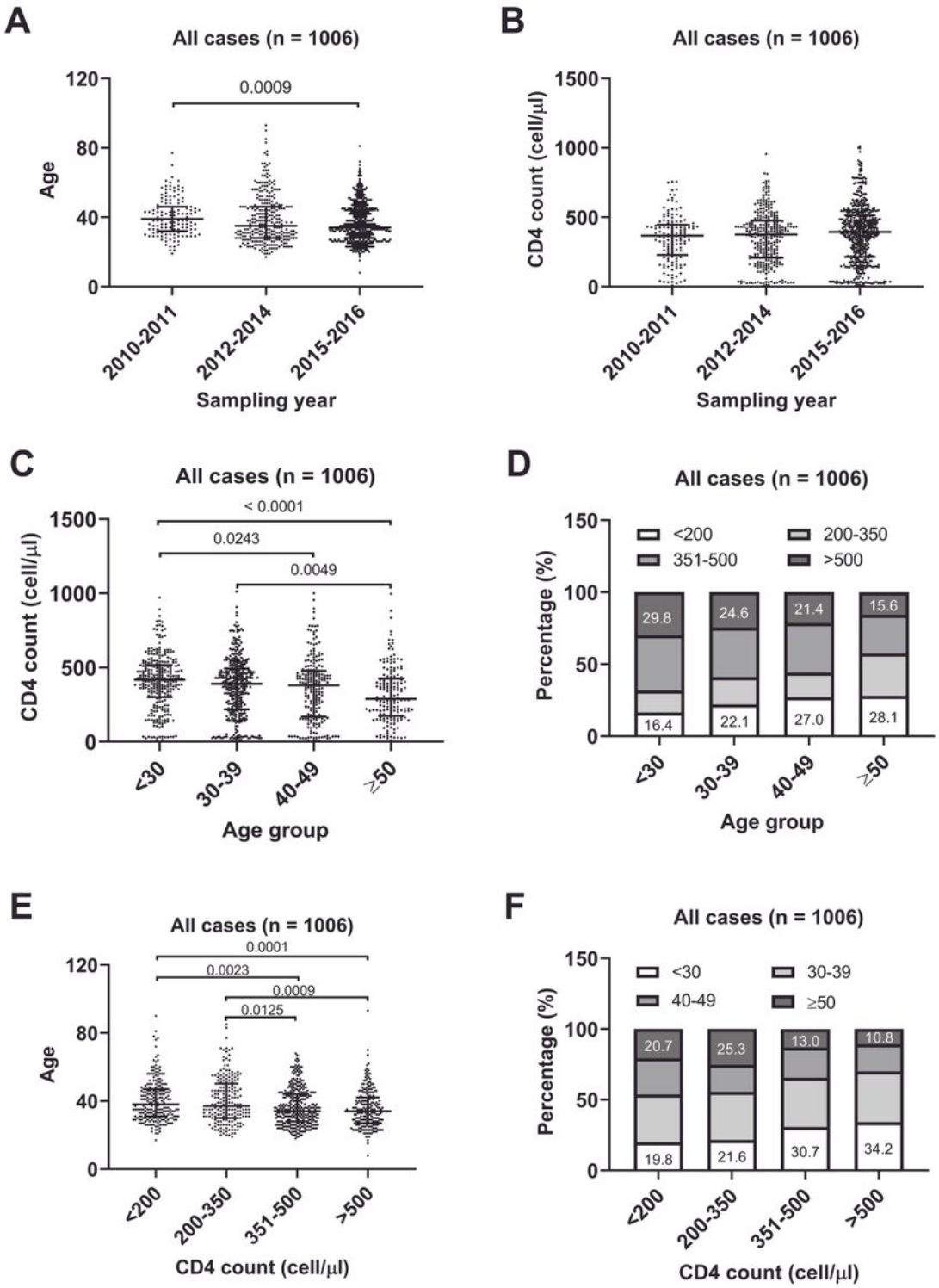

Figure 1

Comparison analyses on age and CD4 count information from all the participants. A-B, age and CD4 count in three sampling periods. C-D, CD4 count and the composition proportion of CD4 groups in four age groups. E-F, age and the composition proportion of age groups in four CD4 count groups. Data in A-C and E were shown as median with interquartile range. Comparison across groups was done by Kruskall-Wallis test. Data in D and F were shown as composition proportion.

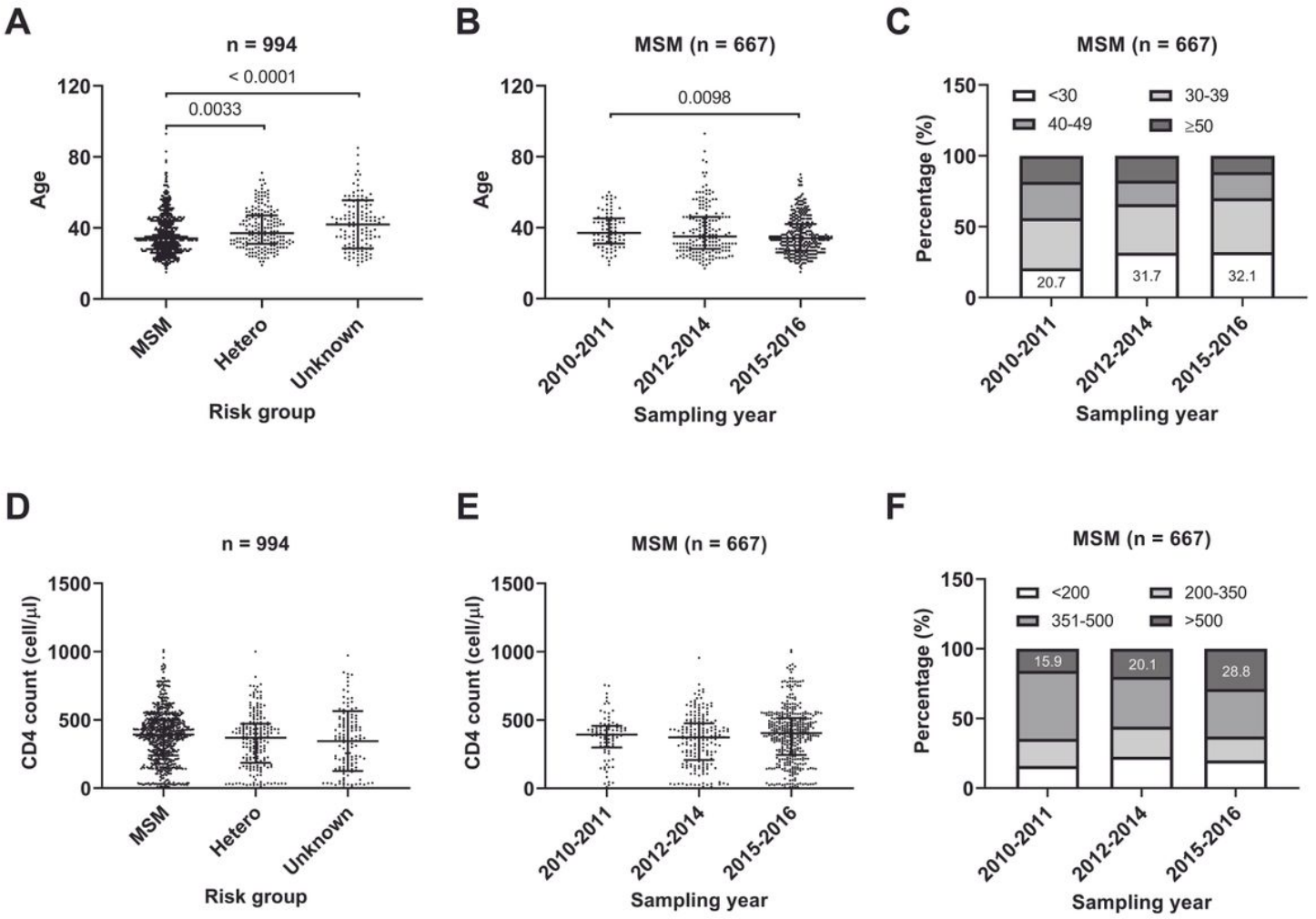

Figure 2

Comparison analyses on age and CD4 count among risk groups of HIV-1 infection and sampling periods. A, age in risk groups. B-C, age of MSM and composition proportion of age groups in three sampling periods. D, CD4 count in risk groups. E-F, CD4 count of MSM and composition proportion of CD4 count groups in three sampling periods. Data in A-B and D-E were shown as median with interquartile range. Comparison across groups was done by Kruskall-Wallis test. Data in C and F were shown as composition proportion. Abbreviations: Hetero, heterosexuals; MSM, men who have sex with men; Unknown, the cases whose route to HIV-1 acquirement were unknown.

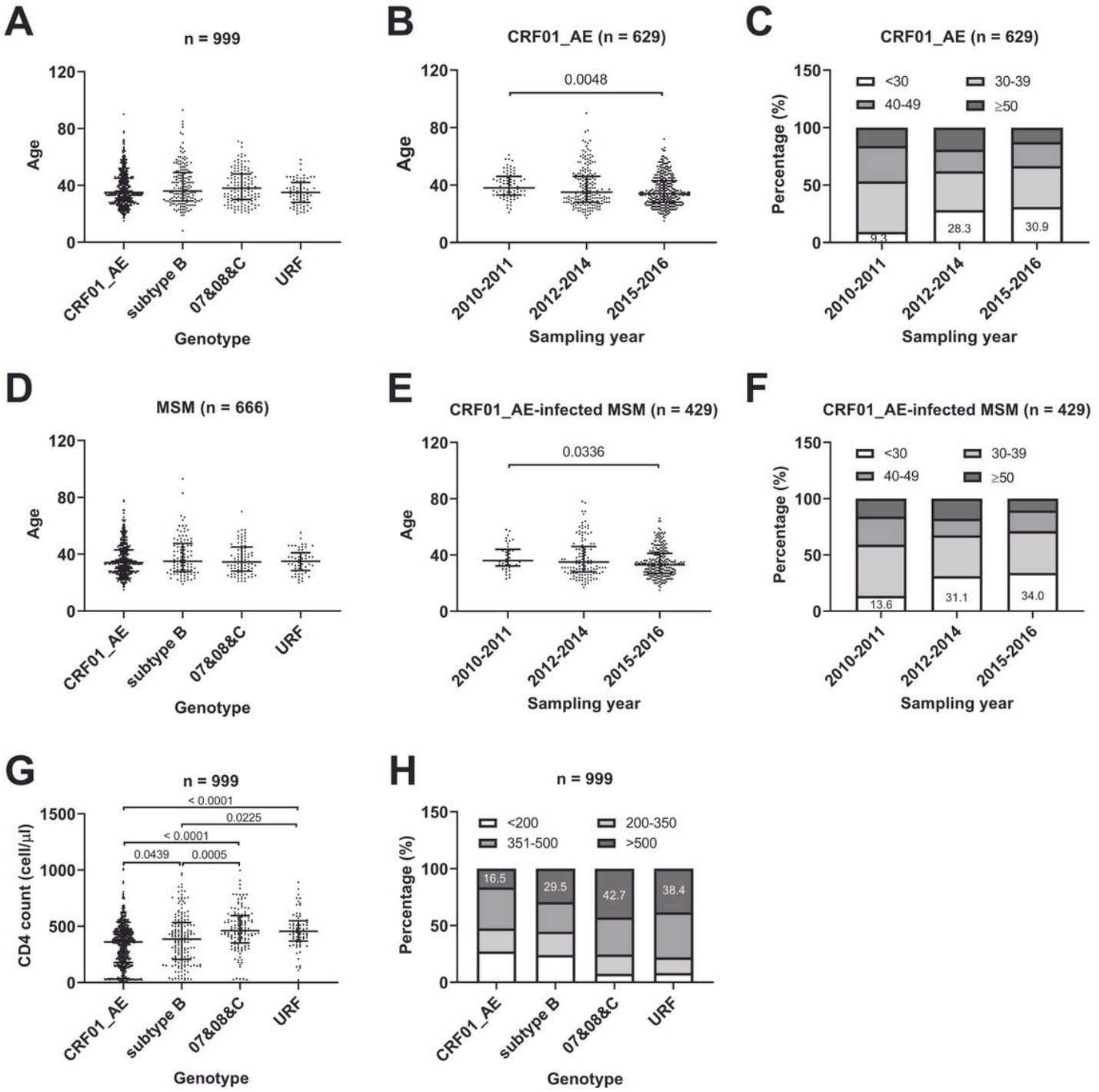

Figure 3

Comparison analyses on age and CD4 count among cases infected by different HIV-1 genotypes and in sampling periods. A, age in cases infected by different HIV-1 genotypes; B-C, age of CRF01_AE infected cases and composition proportion of age groups in three sampling periods. D, age of MSM cases infected by different genotypes. E-F, age of CRF01_AE infected MSM and composition proportion of age groups in three sampling periods. G-H, CD4 count and composition proportion of CD4 count groups in cases infected by different genotypes. Data in A-B, D-E and G were shown as median with interquartile

range. Comparison across groups was done by Kruskall-Wallis test. Data in C, F and H were shown as composition proportion. Abbreviations: 07&08&C, virus that had a genotype of CRF07_BC, CRF08_BC or subtype C; MSM, men who have sex with men; Hetero, heterosexuals; URF, unique recombinant form.

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