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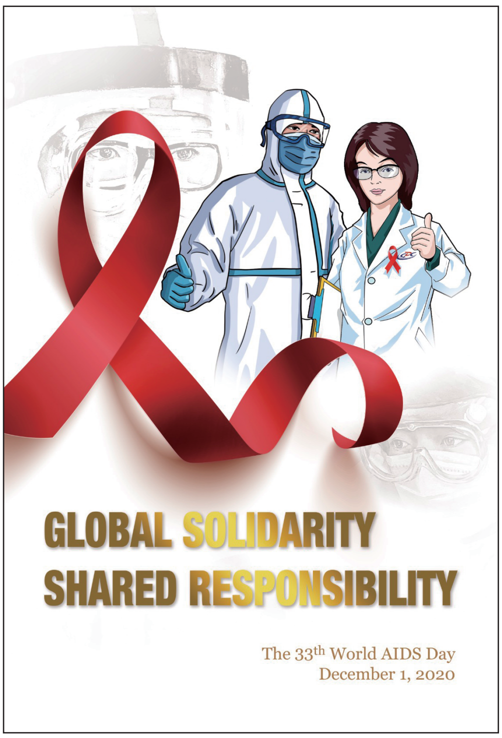

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Preplanned Studies

Epidemiological Characteristics of Newly-Reported HIV Cases Among Youth Aged 15−24 Years — China, 2010−2019

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Summary

What is already known about this topic?

An estimated 1,400 new cases of human immunodeficiency virus (HIV) occur every day among youths globally. However, HIV distribution among youth aged 15–24 years in China has not been researched extensively.

What is added by this report?

Between 2010 and 2019, a total of 141,557 HIV cases among the group aged 15–24 years were reported in China with a male to female ratio at 4.07∶1. The main route of HIV transmission was unprotected sex among men who have sex with men (MSM), and heterosexual transmission for females.

What are the implications for public health practice?

Effective HIV control and prevention measures need to target youth aged 15–24 years, especially among MSM. Sexual health education and HIV prevention should start from primary and secondary school levels.

The estimated number of people living with human immunodeficiency virus (HIV) has grown to 38 million globally by the end of 2019. About 1,400 new HIV infections occur every day (*1*–*2*) among the group aged 15–24 years, which the United Nations (UN) defines as ‘youths’ (*3*). Youths face a higher risk of HIV infection due to their increased sexual activity and related risky behaviors (*4*). In China, all new diagnoses of HIV infections are required to be reported to the HIV/AIDS Comprehensive Response Information Management System (CRIMS). This study described the epidemiological characteristics of newly reported HIV cases among the 15–24 age group between 2010 and 2019. The data were extracted from CRIMS on December 31, 2019. Newly reported HIV cases from the 15–24 age group during 2010–2019 were selected from the mainland of China. HIV case records include demographic characteristics, area of reporting, route of HIV infection, diagnosis site, etc. The spatial distribution was described in terms of reporting areas and provincial-level administrative divisions (PLADs). A total of 141,557 HIV cases from the 15–24 age group were reported from 2010 to 2019 in China. The annual numbers showed an upward trend between 2010 and 2015 and remained stable from 2016 to 2019 with a male-to-female ratio at 4.07∶1, and the route of HIV infection was mainly homosexual transmission among men who have sex with men (MSM). The results show that between 2010 and 2019, the number of HIV diagnoses among youth aged 15–24 in 2010 and 2019 were 9,373 and 15,790, respectively, with an average annual increase of 6.0%. The average annual increase was 10.0% for males (Table 1).

An estimated 80.3% of reported HIV cases were males. The male-to-female ratio was 4.07∶1, and there was an increasing trend year over year. Over the past decade starting 2010, the average age for the overall population, males, and females were 22.2±3.34 years, 22.2±3.29 years, and 22.1±3.51 years, respectively. An estimated 78.9% of reported cases were in the 20–24 age group. The proportions of reported cases aged 15–19 increased from 15.7% in 2010 to 24% in 2019, while decreasing from 84.3% in 2010 to 76% in 2019 for those aged 20–24. The reported cases over the past decade were mainly of Han ethnicity (79.4%). The proportion of students among reported cases increased from 8.5% in 2010 to 21.7% in 2019. Over the past decade starting from 2010, Sichuan Province accounted for the highest number over the study period. There were increases in the proportions of reported cases in eastern (Shanghai, Zhejiang, Jiangsu, Anhui, Jiangxi, Fujian, and Shandong) and central (Henan, Hubei, Hunan) China, while decreases were found in southwestern [Chongqing, Sichuan, Guizhou, Yunnan, Xizang (Tibet)] China, which was the region that comprised the highest proportion in 2019. Males diagnosed with HIV were mainly distributed in southwestern, eastern, and central China, and the top 5 PLADs with the highest number of reported cases in 2019 were Sichuan, Guangdong, Hunan, Jiangsu, and Henan. Females were mainly distributed in southwe-

TABLE 1. Demographic characteristics of reported cases of HIV aged 15–24 years in China: 2010–2019 [n(%)].

Demographic characteristics	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Sex										
Male	5,841(62.3)	6,917(67.2)	8,222(71.9)	9,944(77.5)	12,624(82.0)	14,412(84.9)	14,226(85.1)	13,842(84.9)	13,881(84.4)	13,717(86.9)
Female	3,532(37.7)	3,382(32.8)	3,210(28.1)	2,885(22.5)	2,769(18.0)	2,574(15.1)	2,484(14.9)	2,465(15.1)	2,557(15.6)	2,073(13.1)
Sex ratio (male∶female)	1.65	2.05	2.56	3.45	4.60	5.60	5.73	5.62	5.43	6.62
Age group										
15–19	1,472(15.7)	1,783(17.3)	2,190(19.2)	2,527(19.7)	3,267(21.2)	3,776(22.2)	3,706(22.2)	3,694(22.6)	3,716(22.6)	3,790(24.0)
20–24	7,901(84.3)	8,516(82.7)	9,242(80.8)	10,302(80.3)	12,126(78.8)	13,210(77.8)	13,004(77.8)	12,613(77.4)	12,722(77.4)	12,000(76.0)
Ethnicity										
Han	6,100(65.1)	7,245(70.4)	8,605(75.3)	10,009(78.0)	12,661(82.4)	14,151(83.3)	13,913(83.3)	13,394(82.1)	13,124(79.8)	13,137(83.2)
Other groups	3,273(34.9)	3,054(29.6)	2,827(24.7)	2,820(22.0)	2,732(17.6)	2,835(16.7)	2,797(16.7)	2,913(17.9)	3,314(20.2)	2,653(16.8)
Transmission route										
Homosexual transmission	2,404(25.6)	3,334(32.4)	4,721(41.3)	5,906(46.0)	8,418(54.7)	9,978(58.7)	9,842(58.9)	9,440(57.9)	9,362(57.0)	96,46(61.1)
Heterosexual transmission	4,676(50.0)	5,265(51.1)	5,593(48.9)	6,014(46.9)	6,131(39.8)	6,424(37.8)	6,307(37.7)	6,311(38.7)	6,546(39.8)	5,872(37.2)
Others	2,293(24.4)	1,700(16.5)	1,118(9.8)	909(7.1)	844(5.5)	584(3.4)	5,61(3.4)	556(3.4)	530(3.2)	272(1.7)
Regional distribution										
East	1,315(16.1)	1,518(17.2)	1,952(19.5)	2,185(19.3)	2,889(21.2)	3,212(21.8)	3,113(21.6)	3,004(21.5)	3,057(21.7)	2,932(22.0)
South	1,564(16.7)	1,625(15.8)	1,648(14.4)	1,752(13.6)	2,076(13.5)	2,395(14.1)	2,323(13.9)	2,273(13.9)	2,337(14.2)	2,370(15.0)
Central	720(7.7)	866(8.4)	1,025(8.9)	1,242(9.7)	1,566(10.2)	1,835(10.8)	1,810(10.8)	1,820(11.2)	1,939(11.8)	2,099(13.3)
Southwest	3,900(41.6)	4,012(38.9)	3,828(33.5)	4,221(32.9)	4,489(29.1)	4,665(27.5)	4,671(28.0)	4,536(27.8)	4,841(29.5)	4,139(26.2)
Others	1,874(17.9)	2,278(19.7)	2,979(23.7)	3,429(24.5)	4,373(26.0)	4,879(25.8)	4,793(25.8)	4,674(25.6)	4,264(22.8)	4,250(23.5)

Notes: 1. The data outside the brackets are the number of people, and the data in parentheses are the vertical composition ratio; The sex ratio is the ratio of men to women. 2. East includes Shanghai, Zhejiang, Jiangsu, Anhui, Jiangxi, Fujian and Shandong; South includes Guangdong, Guangxi, Hainan; Central includes Henan, Hubei, Hunan; Southwest includes Chongqing, Sichuan, Guizhou, Yunnan, Xizang (Tibet).

stern, northwestern (Shaanxi, Gansu, Qinghai, Xinjiang, Ningxia), and southern (Guangdong, Guangxi, Hainan) China, and the top 5 PLADs with the highest number of reported cases in 2019 were Sichuan, Yunnan, Xinjiang, Guangdong, and Guizhou (Table1).

Among newly reported HIV cases between 2010 and 2019 among youth aged 15–24 years, the proportions of blood or plasma transfusion and injection drug use transmission decreased annually. Sexual transmission was the main route of HIV infection and the proportion of homosexual contact transmission showed an upward trend in 2010–2015 and remained stable after that (Table 1). Homosexual transmission was the main route of HIV infection among males, and heterosexual transmission was the main route of HIV infection among females (Table 2).

DISCUSSION

Youth aged 15–24 years are at a critical stage in their development and protecting them from disease is a major task. Results from the study showed that the number of newly reported HIV cases among the 15–24 age group increased initially and then gradually stabilized during the 2010–2019 period. Although increases have occurred in recent years, epidemiological characteristics were more complicated and included imbalanced sex ratio and regional distribution, increased proportion of homosexual transmission, and increasing proportion of reported cases of 15–19 age group.

Although 78.9% of reported cases were among the group aged 20–24 years, their high-risk sexual behaviors might occur earlier. It was reported that the average age of first sexual experience of adolescents was 15.9 years old and a large proportion of adolescent men who have sex with men (AMSM) aged 15–19 years were already engaged in multiple HIV-related risk behaviors (*5–6*). Results from the study indicated that the proportion of reported cases of the 15–19 age group also increased year over year and may be related to the earlier age of sexual behavior. Early sexual behavior leads to prolonged exposure to HIV infection, which increases the risk of HIV infection (*7*). This also indicated the need to start HIV prevention education at the primary and secondary school levels. More comprehensive training on safe sex behaviors targeting middle school students should be strengthened and initiated to reduce high-risk sexual behaviors.

Previous studies have shown that the new HIV infection rate of young MSM (15–24 years old) in China is at a high level (*8*). This study showed that the reported HIV cases among the 15–24 age group are mainly among males transmitting primarily through unprotected homosexual intercourse, and this trend is increasing annually. Unlike in the past, MSM have access to a diverse range of information, and the Internet and online social media platforms have enabled increases in anonymous or near-anonymous sex (*9*). The increase of HIV infections among young students in China in recent years was mainly caused by unprotected sex among males (*10*). The trends in this group indicate that this public health challenge deserves greater attention from the government and relevant departments.

This study was subject to some limitations. First, the proportion of males reporting homosexual transmission may be underreported due to fear of social discrimination. Second, the increase in the number of

TABLE 2. Routes of transmission of reported cases of HIV by males and females aged 15–24 years in China: 2010–2019 [n(%)].

Year	Male			Female	
	Homosexual transmission	Heterosexual transmission	Others	Heterosexual transmission	Others
2010	2,404(41.1)	1,681(28.8)	1,756(30.1)	2,995(84.8)	537(15.2)
2011	3,334(48.2)	2,221(32.1)	1,362(19.7)	3,044(90.0)	338(10.0)
2012	4,721(57.4)	2,629(32.0)	872(10.6)	2,964(92.3)	246(7.7)
2013	5,906(59.4)	3,288(33.1)	750(7.5)	2,726(94.5)	159(5.5)
2014	8,417(66.7)	3,526(27.9)	681(5.4)	2,605(94.1)	164(5.9)
2015	9,978(69.2)	3,965(27.5)	469(3.3)	2,459(95.5)	115(4.5)
2016	9,842(69.2)	3,932(27.6)	452(3.2)	2,375(95.6)	109(4.4)
2017	9,440(68.2)	3,964(28.6)	438(3.2)	2,347(95.2)	118(4.8)
2018	9,362(67.4)	4,087(29.5)	432(3.1)	2,459(96.2)	98(3.8)
2019	9,646(70.3)	3,856(28.1)	215(1.6)	2,016(97.3)	57(2.8)

reported HIV cases over the 10-year period beginning in 2010 may be related to improvements in HIV testing capacity. The development of the surveillance system, therefore, may lead to a capturing a higher proportion of newly-diagnosed HIV cases in China.

The number of newly reported HIV cases from 2010 to 2019 among Chinese youth aged 15–24 years increased initially and then gradually stabilized, and the infections were mainly caused by unprotected sex among males. The proportion of reported cases in the 15–19 age group has increased year over year. As a next step sexual health education and HIV prevention should be strengthened for primary and secondary school students, while online social media platforms should be better utilized to carry out comprehensive prevention and treatment for young MSMs.

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Preplanned Studies

A Pilot Program of Pre-Exposure and Post-Exposure Prophylaxis Promotion among Men Who Have Sex with Men — 7 Study Sites, China, 2018–2019

Xiaofang Wang[1]; Jie Xu[1,#]; Zunyou Wu[1]

Summary

What is already known on this topic?

Pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) had been proved to be effective in HIV prevention among men who have sex with men (MSM) internationally. Use of either PrEP or PEP was found to be limited among Chinese MSM. Relatively little data was reported in China.

What is added by this report?

Our program indicated that PEP was more acceptable than PrEP among MSM in China. Drugs of lower cost and related knowledge dissemination could increase PrEP and PEP uptake among MSM in China.

What are the implications for public health practice?

PrEP and PEP are likely to contribute significantly to human immunodeficiency virus (HIV) prevention in China.

Human immunodeficiency virus (HIV) prevalence among men who have sex with men (MSM) continues to rise globally (*1*), and China has faced the same epidemic. Pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) are innovative strategies that have been proven to be effective in HIV prevention among MSM (*2*). However, the strategies have not been implemented nationwide in China. From October 2018 to September 2019, a pilot program was conducted to establish a delivery mode of PrEP/PEP services and inform the development of national PrEP/PEP guidelines. This pilot program established PrEP and PEP services targeting MSM in seven sites in China. Data such as the number of MSM taking PrEP/PEP and the number of follow-up for PrEP/PEP users were collected. In the pilot program, MSM users of PrEP or PEP were limited. There were more MSM taking PEP than those who were taking PrEP. The high costs of drugs were the main barrier for MSM who met the criteria of PrEP or PEP uptake but chose not to take it. Follow-up rates were low for both PrEP and PEP users. PrEP and PEP knowledge dissemination should be strengthened among MSM. Generic low-cost drugs for PrEP and PEP may increase the availability and acceptability of these drugs in controlling the HIV epidemic.

This pilot program was implemented from October 2018 to September 2019 in 7 sites including the following areas: Beijing Municipality, Tianjin Municipality, Harbin City of Heilongjiang Province, Changsha City of Hunan Province, Nanning City of Guangxi Zhuang Autonomous Region, Kunming City of Yunnan Province, and Guiyang City and Zunyi City (site covered both cities) of Guizhou Province. Each site set up 1–2 PrEP/PEP clinics for implementing the program. Information of the program was disseminated through online advertising posted in mobile phone applications, instant messaging chat rooms, and other websites known to be frequently used in the Chinese MSM community. The program was also promoted at China CDC voluntary counseling and testing clinics and by peer referral from community-based organizations.

Participant eligibility criteria for PrEP/PEP uptake included the following: 1) being biologically male; 2) being 18 years or older; 3) having had at least one sexual contact with another male in the past; 4) being tested HIV negative; and 5) being at risk of HIV infection, which could mean that the individuals in the past six months have had multiple male sex partners or sexually transmitted diseases, have been involved in commercial sex, or have had male sex partners who have used club drugs or who have infected with HIV. In addition, potential PEP users must have been exposed to HIV within the last 72 hours.

At PrEP/PEP clinics, participants received counseling and risk assessment of HIV infection. If assessed to be at risk of HIV infection, they would be tested for HIV, syphilis, Hepatitis B, and serum creatinine. Those tested as HIV negative would sign a written informed consent form and received a prescription from doctors at clinics. The first follow-up was one month after the first visit at clinics, and the following follow-ups took place every three months. At each follow-up, participants received the same testing as the first visit and a prescription. With the prescription, they could purchase drugs at hospitals or pharmacies. PrEP users took drugs on a daily basis or sex-event driven basis, and PEP users took drugs every day for 28 days (*3*–*4*).

Data on the PrEP/PEP users' demographic characteristics, HIV-risk assessments, test results, drug prescriptions, and follow-ups were collected by clinic medical staff and recorded using Microsoft Excel 2010. Data were reported to local CDCs and the national program team every month. Data analysis was performed in SPSS (version 17.0, SPSS Inc, Chicago, IL, USA).

Among 417 MSM who consulted staff about PrEP and met PrEP uptake criteria, 65.2% (272/417) chose to take PrEP. Around 98.2% (267/272) of the MSM taking PrEP were located in Beijing. Among 900 MSM who consulted about PEP and met PEP uptake criteria, 83.7% (753/900) chose to take PEP. The MSM taking PEP were mainly located in Tianjin (22.7%, 171/753), Guizhou (20.2%, 152/753), and Guangxi (22.6%, 170/753) (Table 1). Main reasons for not taking PrEP or PEP were high drug costs and concerns of side effects.

Most PrEP (59.6%) or PEP (53.5%) users were in the 25–35 age group. A total of 68.5% (185/272) of PrEP users and 42.2% (318/753) of PEP users attended the first follow-up. Older MSM in both groups were more likely to attend the first follow-up than young MSM (Table 2). Around 10.0% (27/272) and 20.2% (152/753) of MSM attended the second follow-up for PrEP and PEP, respectively. No MSM attended the third or later follow-ups.

DISCUSSION

No real-world tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) regiment PrEP uptake data in China has been reported, although the first related study is being conducted (*5*). Our pilot program found that many MSM took PrEP and PEP services in the seven study sites in less than one year, which indicated relatively high demand of PrEP/PEP services among MSM. However, high costs of the drugs made MSM consulting staff for PrEP or PEP but ultimately deciding not to use the drugs. Around 98% (267/272) of the MSM taking PrEP were located in Beijing, which was likely due to a research study providing free PrEP drugs for MSM in Beijing. As of November 2020, PrEP drugs cost around 1,980 RMB (approximately 300 USD) per month and PEP costs 3,980 RMB (approximately 570 USD) per time. Some sites reported that some MSM inquired about PrEP or PEP and associated costs at clinics but chose to purchase generic drugs of much lower price from Thailand or India. Therefore, generic drugs of lower price would likely increase the availability and acceptability of the regiment. The other main barrier reported by MSM was that they were concerned about

TABLE 1. Pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP) taken among men who have sex with men in the 7 study sites, China, 2018–2019.

Study site	PrEP			PEP		
	Number inquiring about drugs, n (%)	Number of taking, n (%)	Main reasons for not taking	Number inquiring about drugs, n (%)	Number of taking, n (%)	Main reasons for not taking
Beijing	327(78.4)	267(98.2)	Side effects, bone mineral density	55(6.1)	32(4.2)	Side effects
Tianjin	69(16.6)	0(0)	High cost, side effects	218(24.2)	171(22.7)	High cost, side effects
Kunming, Yunnan	0(0)	0(0)		118(13.1)	115(15.3)	High cost
Guiyang and Zunyi, Guizhou	8(1.9)	0(0)	High cost	184(20.5)	152(20.2)	High cost
Nanning, Guangxi	4(1.0)	4(1.5)		173(19.2)	170(22.6)	high cost
Changsha, Hunan	9(2.1)	1(0.3)	High cost, side effects	146(16.2)	107(14.2)	
Harbin, Heilongjiang	0(0)	0(0)	No pilot for PrEP	6(0.7)	6(0.8)	
Total	417(100.0)	272(100.0)	High cost, side effects	900(100.0)	753(100.0)	High cost

TABLE 2. Attendance of first follow-up at one month after taking pre-exposure prophylaxis or post-exposure prophylaxis among men who have sex with men in the 7 study sites, China, 2018–2019.

Age	Total, n (%)	Attending first follow-up		*p* value*	OR (95% CI)
		Yes, n (%)	No, n (%)		
PrEP					
18–24 years	37(13.6)	19(51.4)	18(48.6)	0.011	0.33(0.14–0.77)
25–35 years	162(59.6)	112(69.1)	50(30.9)	0.284	0.71(0.37–1.34)
≥36 years	71(26.1)	54(76.1)	17(23.9)		
Total	270(100.0)	185(68.5)	85(31.5)		
PEP					
18–24 years	204(27.1)	65(31.9)	139(68.1)	0.001	0.47(0.31–0.74)
25–35 years	403(53.5)	181(44.9)	222(55.1)	0.326	0.83(0.57–1.21)
≥36 years	145(19.3)	72(49.7)	73(50.3)		
Total	752(100.0)	318(42.3)	434(57.7)		

Abreviation: PrEP=Pre-exposure prophylaxis; PEP=Post-exposure prophylaxis; OR=odds ratio; 95% CI=95% confidence interval.
* *p* values were calculated using uni-variate logistic regression, setting the independent value of age as a categorical variable.

side effects of the drugs, which was in accordance with previous studies (*6*). This implies that the safety of PrEP/PEP drugs should be highlighted during PrEP and PEP knowledge dissemination in the future.

Most PrEP or PEP users were between 25–35 years old, likely because MSM of this age group were generally more sexually active than other MSM. Follow-up rates were generally low, but rates were much lower among PEP users than PrEP users, which was likely due to PEP users not needing to come back for further prescription drugs while PrEP users often must return for this reason. Given the importance of follow-ups, factors contributing to low follow-up rates need further study. Also, PrEP/PEP clinic doctors, local CDC staff, and community-based organization (CBO) staff who work with MSM should prioritize increasing PrEP/PEP follow-up rate.

This report on the pilot program was subject to some limitations. First, there was limited data for analyzing factors for PrEP or PEP usage, which should be further explored in future studies. Second, the MSM in the program were not representative. Third, as no free drugs were provided in the program, limited numbers of MSM took PrEP outside of Beijing. Hence, there was no relative data in other areas of China or abroad to draw comparisons for our conclusions. However, the program still demonstrated some real needs of MSM in these study sites.

In conclusion, both PrEP and PEP services were acceptable among MSM in China. Current high cost of original drugs limit their uptake. To scale up the services, the cost of original drugs should be reduced or generic drugs of lower cost should be produced. To ensure adherence to the strategy, CBOs should also be involved to coordinate with hospitals.

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Preplanned Studies

Epidemiological Characteristics of Newly Diagnosed Cases of HIV through Injection Drug Use — China, 2012–2019

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Summary

What is already known about this topic?

The annual rates of newly diagnosed cases of human immunodeficiency virus (HIV) are increasing in China, yet the annual number of newly diagnosed cases of HIV infected through injection drug use (IDU) is decreasing.

What is added by this report?

Newly diagnosed cases of HIV infected through IDU in China from 2012 to 2019 show decreases year over year, but the risk of new infections through injecting drugs still exists.

What are the implications for public health practice?

This study highlighted that new HIV infections through IDU continue to be at a low level. However, individuals that are newly diagnosed as HIV-positive through IDU need to have their baseline CD4 T+ lymphocytes (CD4) cell counts monitored and have their sources of infections traced.

The human immunodeficiency virus (HIV) epidemic in China remains interspersed nationwide but is highly concentrated in some regions and in some high-risk populations (*1*). The rate of newly diagnosed cases of HIV have rapidly increased, and HIV is still been a major public health challenge in China (*2*). From 2012 to 2019, a total of 942,705 cases of HIV in individuals aged 15 years or above were newly diagnosed and recorded in the Chinese HIV/AIDS Comprehensive Response Information Management System (CRIMS), and the number of newly diagnosed HIV infections increased year over year. Of them, 42,242 HIV cases were infected via injection drug use (IDU) and the annual number of newly diagnosed HIV infections via IDU decreased. The variables in the analysis of the CRIMS database included demographic characteristics (gender, date of birth, current address code, nationality, marital status, education level, occupation, etc.), infection route, source of sample, date of diagnosis, date of verification, and baseline CD4 T+ lymphocytes (CD4) cell counts. Age was calculated by the difference between the date of diagnosis and the date of birth. CD4 cell count was a major indicator of HIV infection disease progression. Baseline CD4 cell counts were greater than or equal to 500 cells/mm^3, which meant that the HIV infection time was less than two years (less than two years (*3*) and was designated as the standard of new infection. Data processing and analyses were conducted using SAS software (version 9.4; SAS Institute; Cary, NC).

From January 1, 2012 to December 31, 2019, there were 42,242 newly diagnosed cases of HIV in individuals aged 15 years and above who were infected via IDU, accounting for 4.5% of the total newly diagnosed cases of HIV in this period, and the proportion showed decreases year over year (χ^2=12780.98, p<0.001) (Table 1).

Of the 42,242 newly diagnosed cases of HIV infected via IDU during 2012–2019, 85.5% of individuals were males, 61.1% had at most a primary school education or were illiterate, 40.6% were married and living with partners, 60.3% were of non-Han ethnicities, 50.2% were farmers, and 46.3% were diagnosed from detention centers. The major age group was 25–44 years old, accounting for 76% of newly diagnosed cases of HIV infected via IDU (Table 2). For educational levels based on age groups,

TABLE 1. Number and proportion of newly diagnosed cases of HIV infected via injection drug use (IDU) — China, 2012–2019.

Year of diagnosis	Newly diagnosed case of HIV*	Newly diagnosed cases HIV infected via IDU*	Proportion (%)
2012	81,567	8,242	10.1
2013	89,236	6,952	7.8
2014	102,649	6,213	6.1
2015	114,656	5,010	4.4
2016	123,809	4,987	4.0
2017	133,713	4,585	3.4
2018	146,772	4,423	3.0
2019	150,303	1,830	1.2
Total	942,705	42,242	4.5

* Individuals aged 15 years and over.

TABLE 2. Demographic characteristics of newly diagnosed cases of HIV infected via injection drug use — China, 2012–2019.

Characteristics	2012	2013	2014	2015	2016	2017	2018	2019	Total
Gender									
Male	7,101(86.2)	5,976(86.0)	5,350(86.1)	4,245(84.7)	4,253(85.3)	3,813(83.2)	3,818(86.3)	1,545(84.4)	36,101(85.5)
Female	1,141(13.8)	976(14.0)	863(13.9)	765(15.3)	734(14.7)	772(16.8)	605(13.7)	285(15.6)	6,141(14.5)
Age group (years)									
15–24	978(11.9)	856(12.3)	687(11.1)	495(9.9)	437(8.8)	399(8.7)	361(8.2)	107(5.8)	4,320(10.2)
25–34	3,429(41.6)	2,888(41.5)	2,596(41.8)	2,019(40.3)	2,040(40.9)	1,736(37.9)	1,619(36.6)	566(30.9)	16,893(40.0)
35–44	3,089(37.5)	2,520(36.2)	2,242(36.1)	1,803(36.0)	1,738(34.9)	1,599(34.9)	1,591(36.0)	636(34.8)	15,218(36.0)
45–54	647(7.9)	602(8.7)	601(9.7)	618(12.3)	700(14.0)	751(16.4)	720(16.3)	415(22.7)	5,054(12.0)
55–	99(1.2)	86(1.2)	87(1.4)	75(1.5)	72(1.4)	100(2.2)	132(3.0)	106(5.8)	757(1.8)
Marital status									
Married, or living with partner	3,192(38.7)	2,578(37.1)	2,338(37.6)	1,904(38.0)	2,106(42.2)	2,179(47.5)	2,184(49.4)	660(36.1)	17,141(40.6)
Single	3,340(40.5)	2,859(41.1)	2,497(40.2)	1,930(38.5)	1,815(36.4)	1,420(31.0)	1,306(29.5)	685(37.4)	15,852(37.5)
Divorced, or widowed	1,390(16.9)	1,323(19.0)	1,178(19.0)	1,070(21.4)	941(18.9)	901(19.7)	792(17.9)	471(25.7)	8,066(19.1)
Unknown	320(3.9)	192(2.8)	200(3.2)	106(2.1)	125(2.5)	85(1.9)	141(3.2)	14(0.8)	1,183(2.8)
Education									
College and above	84(1.0)	60(0.9)	68(1.1)	86(1.7)	74(1.5)	80(1.7)	89(2.0)	83(4.5)	624(1.5)
High school or technical secondary school	516(6.3)	433(6.2)	431(6.9)	294(5.9)	293(5.9)	285(6.2)	234(5.3)	155(8.5)	2,641(6.3)
Junior high school	2,968(36.0)	2,330(33.5)	1,892(30.5)	1,668(33.3)	1,462(29.3)	1,223(26.7)	998(22.6)	641(35.0)	13,182(31.2)
Primary school	2,983(36.2)	2,472(35.6)	2,349(37.8)	1,684(33.6)	1,705(34.2)	1,462(31.9)	1,545(34.9)	579(31.6)	14,779(35.0)
Illiterate	1,691(20.5)	1,657(23.8)	1,473(23.7)	1,278(25.5)	1,453(29.1)	1,535(33.5)	1,557(35.2)	372(20.3)	11,016(26.1)
Ethnicity									
Han	3,623(44.0)	2,758(39.7)	2,451(39.4)	2,128(42.5)	1,942(38.9)	1,619(35.3)	1,373(31.0)	885(48.4)	16,779(39.7)
Other	4,619(56.0)	4,194(60.3)	3,762(60.6)	2,882(57.5)	3,045(61.1)	2,966(64.7)	3,050(69.0)	945(51.6)	25,463(60.3)
Occupation									
Farmer or rural laborer	3,570(43.3)	3,530(50.8)	2,954(47.5)	2,413(48.2)	2,567(51.5)	2,500(54.5)	2,763(62.5)	907(49.6)	21,204(50.2)
Housekeeping service or unemployment	2,596(31.5)	2,156(31.0)	2,138(34.4)	1,597(31.9)	1,468(29.4)	1,207(26.3)	989(22.4)	562(30.7)	12,713(30.1)
Other	1,648(20.0)	772(11.1)	749(12.1)	692(13.8)	659(13.2)	734(16.0)	565(12.8)	315(17.2)	6,134(14.5)
Unknown	428(5.2)	494(7.1)	372(6.0)	308(6.1)	293(5.9)	144(3.1)	106(2.4)	46(2.5)	2,191(5.2)
Site of diagnosis									
Voluntary counseling and testing centers	1,414(17.2)	1,175(16.9)	879(14.1)	647(12.9)	794(15.9)	641(14.0)	318(7.2)	226(12.3)	6,094(14.4)
Hospital	2,187(26.5)	1,935(27.8)	1,749(28.2)	1,399(27.9)	1,451(29.1)	1,316(28.7)	720(16.3)	516(28.2)	11,273(26.7)
Detention center	3,853(46.7)	3,271(47.1)	2,990(48.1)	2,408(48.1)	2,438(48.9)	2,081(45.4)	1,661(37.6)	850(46.4)	19,552(46.3)
Other	637(7.7)	421(6.1)	531(8.5)	503(10.0)	271(5.4)	517(11.3)	1,680(38.0)	228(12.5)	4,788(11.3)

67.8% and 68.5% of individuals aged 15–24 years and 25–34 years had education levels below primary school, respectively.

Of the newly diagnosed cases of HIV infected through IDU in 2012–2019, 28.0% of individuals had baseline CD4 cell counts greater than or equal to 500 cells/mm^3, but this figure decreased year over year from 2012 to 2019 (χ^2=186.60, p<0.001) (Figure 1). During the same period, 17.8% of the newly diagnosed cases of HIV infected not through IDU had baseline CD4 cell counts greater than or equal to 500 cells/mm^3.

DISCUSSION

In the past 30 years, the main mode of transmission of HIV in China has changed drastically as the primary route of transmission has changed from IDU to sexual transmission. The prevention and control of the HIV epidemic in drug users has achieved great successes as the annual incidence of HIV among drug users participating in methadone maintenance treatment (MMT) has reached zero and HIV prevalence of among drug users has decreased year over year, which suggests that the control of the HIV epidemic among drug users has been largely successful (*4*). During the study period of 2012–2019, only 4.5% of newly diagnosed cases of HIV were infected via IDU, and this proportion dropped from 10.1% in 2012 to 1.2% in 2019. During this same period, the results of sentinel surveillance of drug users in China also showed decreases in the HIV antibody positive rate (*5*). In 2012, the HIV antibody positive rate in the sentinel surveillance of drug users was 3.9% (*6*), and it was 2.4% in 2019 (*7*).

The main demographic characteristics of newly diagnosed cases of HIV infected via IDU indicated that most individuals were males, had low levels of education, were of non-Han ethnicity, and were farmers. The results indicating that the educational level of not completing primary school in individuals aged 15–24 years (67.8%) and 25–34 years (68.5%) indicated that HIV prevention efforts for these populations were likely difficult and that traditional methods to disseminate health knowledge or provide health information may prove suboptimal for these populations.

During 2012–2019, the annual number of newly diagnosed cases of HIV infected via IDU was decreasing year over year, but 28.0% of individuals had baseline CD4 cell counts greater than or equal to 500 cells/mm^3, which indicated that these individuals may have been infected within the past two years and that HIV transmission via IDU has not been completely eliminated and that the risk of transmission still exists. MMT has played an important role in reducing the incidence of HIV among injection drug users (*8*), and the incidence of HIV among outpatients of MMT clinics in China decreased from 0.2/100 person-years in 2012 to 0.02/100 person-years in 2019. However, newly diagnosed cases of HIV infected via IDU with the first CD4 cell counts exceeding

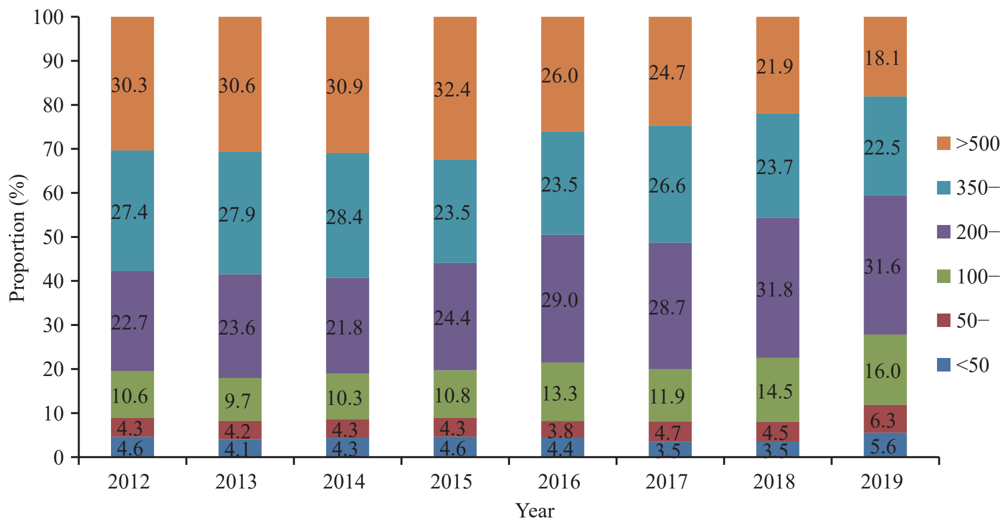

FIGURE 1. Proportion of baseline CD4 cell counts in newly diagnosed cases of HIV infected via injection drug use (IDU) — China, 2012–2019.

500 cells/mm^3 were mainly from the detention centers, which indicated that these individuals were possibly arrested and diagnosed in the detention centers due to drug abuse.

This study was subject to some limitations. First, the analysis was based on newly diagnosed cases of HIV infected via IDU and was likely influenced by the scope of HIV testing and by recording methodology. Second, determining the true sources of infection for the cases was unlikely to be definitive. Further case tracing and molecular transmission network analysis can help determine these sources of infection with greater certainty and better inform targeted interventions to reduce the risk of HIV transmission via IDU.

Conflict of Interests: The authors declare no competing interests.

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Vital Surveillance

Tuberculosis/HIV Coinfection and Treatment Trends — China, 2015−2019

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ABSTRACT

Introduction: New data has become available on the implementation of tuberculosis/human immunodeficiency virus (TB/HIV) two-way screening and anti-TB treatment for TB/HIV coinfected patients in China from 2015 to 2019, which can be used to propose key strategies for further TB/HIV prevention and treatment.

Methods: The report on TB/HIV coinfection in the mainland of China from 2015 to 2019 was collected to compare the annual trend and the rate of geographical distribution.

Results: From 2015 to 2019, the proportion of TB screening using chest x-ray or sputum examination among HIV-positive people increased from 79.8% to 88.0% (p<0.01). The proportion ranged from 40.7% to 97.1% among various provincial-level administrative divisions (PLADs), with a median of 87.3%. TB prevalence among HIV-positive people decreased from 1.1% to 0.8% (p<0.01) over the 5 years. The proportion of HIV testing among TB patients increased from 46.0% to 64.0% (p<0.01). The prevalence of HIV among TB patients increased from 0.8% to 1.1% (p<0.01). The success rate of anti-TB treatment for TB/HIV patients was 87.6%, and the primary reason for unsuccessful treatment were death (5.3%) and other reason such as availability of only basic treatment options (5.0%).

Conclusions and Implications for Public Health Practice: TB/HIV two-way screening in China improved significantly during the 5-year period, however there were large regional differences and gaps in target HIV-screening rates among TB patients, suggesting that two-way screening in some PLADs and the HIV screening among TB patients should be strengthened. Early diagnosis, early treatment, and treatment management of TB/HIV patients should also be strengthened.

INTRODUCTION

Tuberculosis (TB) and human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) are both chronic infectious diseases that present major public health challenges globally. Together, TB and HIV can lead to coinfections that promote the severity of symptoms and likelihood of fatality and present an even greater challenge to the global health community. TB is the most common opportunistic infection and the most important cause of death for HIV/AIDS patients. In the absence of effective prevention and control measures, it can account for 1/3 of the total deaths of HIV/AIDS patients. At the same time, the immunosuppressive state of HIV/AIDS patients puts them at greater risk of TB infection, up to 19 times higher than individuals not affected by HIV (*1*). In 2018, there were 10 million cases of TB in the world, 8.6% of which were comorbid with HIV; 1,451,000 TB patients died, of which 251,000 (17.3%) were HIV positive (*2*). China is one of the 30 countries with a high burden of TB, ranking third in the world in terms of annual incidence and also one of the 30 countries with a high burden of TB/HIV coinfection. In 2018, an estimated 18,000 new TB/HIV coinfections occurred (*2*). Earlier detection, earlier diagnosis, and earlier anti-TB and anti-retroviral therapy are effective measures to reduce the number of deaths of TB/HIV patients. Therefore, two-way screening, i.e. routine TB screening for HIV patients and HIV testing for TB patients, should be implemented to find TB/HIV coinfection as early as possible (*3*).

METHODS

Each year, a formatted report on TB/HIV coinfection is required to be submitted to China CDC by 31 provincial-level administrative divisions (PLADs) in mainland China. Information in the report includes two-way screening and treatment outcomes of TB/HIV patients, of which the data quality is supervised by China CDC. Data in this study were collected from the reports from 2015 to 2019, aggregated in Excel, and verified for logical errors.

The rates were compared using tables and a chi-squared test and further analyzed using a Cochran-Armitage test for trend (α=0.05) using SAS (version 9.4, SAS Institute). Data in various PLADs was presented as a spatial distribution using ArcGIS 10.6 (Esri Institute).

RESULTS

During 2015–2019, a total of 3,771,942 HIV/AIDS patients were registered and under supervision, 659,676 of whom were newly diagnosed and 3,112,266 were previously documented (Table 1). Among them, 3,540,831 (93.9%) underwent TB screening using symptom query, including 618,197 (93.7%) among newly diagnosed patients and 2,922,634 (93.9%) among existing patients (χ^2=35.89, p<0.01). In the past 5 years, the proportion of patients undergoing TB screening using symptom query decreased from 94.2% to 92.7% (z=–17.94, p<0.01) among newly diagnosed patients and increased from 93.1% to 93.9% (z=15.53, p<0.01) among existing patients. In total, 3,216,466 (85.3%) underwent TB screening using chest x-ray or sputum examination, including 572,544 (86.8%) among newly diagnosed patients and 2,643,922 (85.0%) among existing patients (χ^2=1467.49, p<0.01). In the 5 years, the proportion undergoing chest x-ray or sputum examination increased from 82.9% to 89.0% (z=32.40, p<0.01) among newly diagnosed HIV/AIDS patients and increased from 79.0% to 87.8% (z=160.90, p<0.01) among existing patients. Among the HIV/AIDS patients underwent TB screening using any method, 28,694 (0.9%) were diagnosed as TB, including 11,514 (2.0%) among the newly diagnosed patients and 17,180 (0.6%) among existing patients (χ^2=9863.31, p<0.01). From 2015 to 2019, TB detection rate among the newly diagnosed HIV/AIDS patients decreased from 2.1% to 1.9% (z=–2.69, p<0.01) and decreased from 0.9% to 0.6% (z=–17.88, p<0.01) among existing patients.

Among the 31 PLADs, proportion of TB screening using symptom query ranged 40.7%–99.2%, with a median of 94.2%, and 28 (90.3%) of the PLADs achieved rates ≥90%. Regions with lower proportions of TB screening were mainly in central and western parts of the country (Figure 1A). Prevalence of TB among the HIV/AIDS patients ranged from 0.2%–5.2%, with a median of 0.7%, and 7 (22.6%) of

TABLE 1. TB screening among HIV-positive patients in China, 2015–2019 [n(%)].

Category	Year	HIV-positive	Symptom screening	Chest or sputum testing	TB-positive
Newly diagnosed	2015	112,264	105,788 (94.2)	93,098 (82.9)	1,981 (2.1)
	2016	120,428	113,706 (94.4)	103,073 (85.6)	1,972 (1.9)
	2017	133,541	125,106 (93.7)	116,665 (87.4)	2,410 (2.1)
	2018	145,122	136,144 (93.8)	127,725 (88.0)	2,706 (2.1)
	2019	148,321	137,453 (92.7)	131,983 (89.0)	2,445 (1.9)
	Subtotal	659,676	618,197 (93.7)	572,544 (86.8)	11,514 (2.0)
Follow-up	2015	440,307	409,899 (93.1)	347,645 (79.0)	3,078 (0.9)
	2016	524,594	494,264 (94.2)	431,394 (82.2)	2,954 (0.7)
	2017	625,097	585,167 (93.6)	521,625 (83.4)	3,192 (0.6)
	2018	702,018	663,259 (94.5)	622,815 (88.7)	3,924 (0.6)
	2019	820,250	770,045 (93.9)	720,443 (87.8)	4,032 (0.6)
	Subtotal	3,112,266	2,922,634 (93.9)	2,643,922 (85.0)	17,180 (0.6)
Total HIV	2015	552,571	515,687 (93.3)	440,743 (79.8)	5,059 (1.1)
	2016	645,022	607,970 (94.3)	534,467 (82.9)	4,926 (0.9)
	2017	758,638	710,273 (93.6)	638,290 (84.1)	5,602 (0.9)
	2018	847,140	799,403 (94.4)	750,540 (88.6)	6,630 (0.9)
	2019	968,571	907,498 (93.7)	852,426 (88.0)	6,477 (0.8)
	Subtotal	3,771,942	3,540,831 (93.9)	3,216,466 (85.3)	28,694 (0.9)

the PLADs had TB prevalence among the HIV/AIDS patients over 1%, including Tibet (5.2%), Qinghai (4.2%), Guangxi (2.2%), Beijing (2.2%), Jiangxi (1.6%), Gansu (1.2%), and Guizhou (1.1%).

From 2015 to 2019, a total of 3,865,549 TB patients were registered in mainland China, among whom 13,446 (0.3%) knew their HIV positive status at the time of diagnosis (Table 2). The proportion of knowing their HIV positive status increased from 0.3% to 0.5% (z=30.87, p<0.01) during the 5-year period. During the same period of time, in total, 2,126,518 (55.0%) TB patients underwent HIV testing, with the proportion increasing from 46.0% to 64.0% (z=252.40, p<0.01). Among TB patients that underwent HIV testing at diagnosis, the HIV positive rate was 0.3%, increasing from 0.2% (z=3.09, p<0.01). Overall, 19,023 (0.9%) of TB patients were found to be positive, including those previously who previously knew their status, with the number increasing over 70%, and the proportion increasing from 0.8% to 1.1% (z=16.29, p<0.01) in the 5-year period.

Among the 31 PLADs, the proportion of HIV testing among TB patients ranged 8.9%–94.8%, with a median of 52.3% (Figure 1B). Among TB patients that underwent HIV screening, the overall HIV positive proportion ranged 0.1%–2.4%, with a median

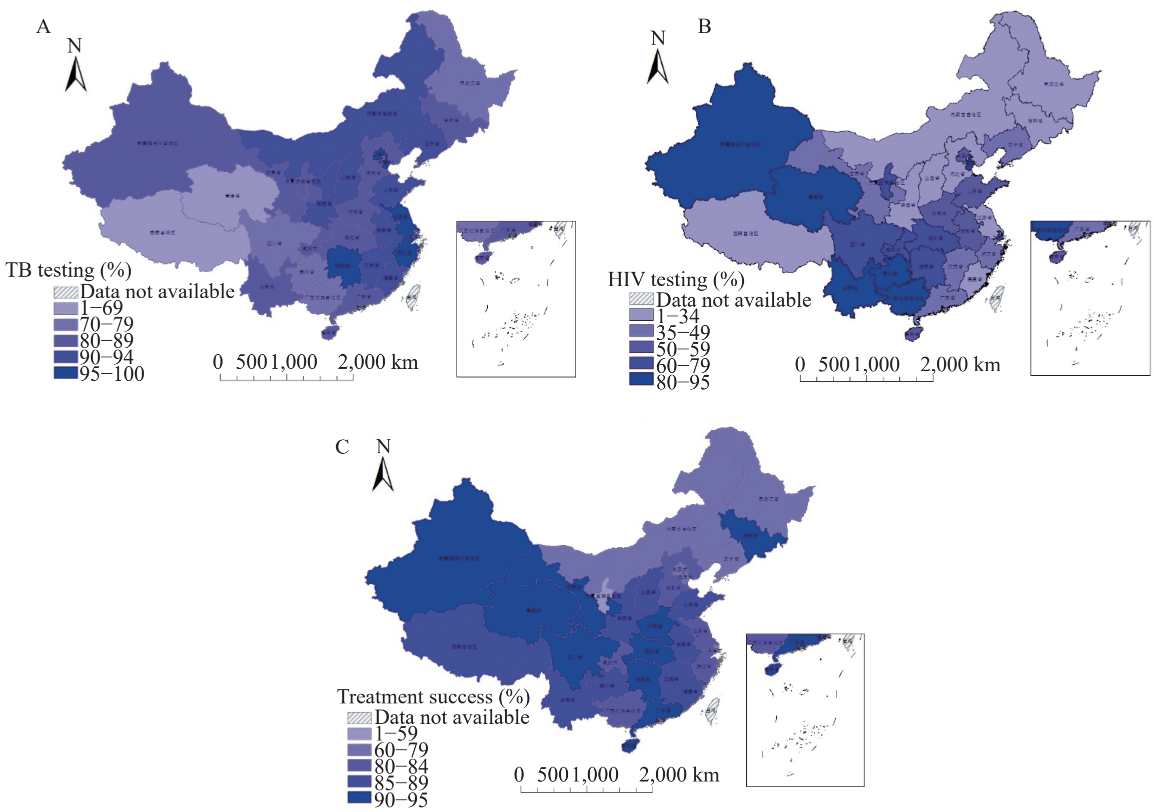

FIGURE 1. Geographical distribution of TB/HIV double screening and anti-TB treatment outcomes for TB/HIV patients in China, 2015–2019. (A) TB screening among HIV/AIDS patients. (B) HIV testing among TB patients. (C) Anti-TB treatment for TB/HIV patients.

TABLE 2. HIV screening among TB patients in China, 2015–2019 [n(%)].

Year	TB registered individual	Known HIV-positive status	Underwent HIV testing	Newly detection HIV-positive status	HIV-positive
2015	798,098	2,041 (0.3)	366,984 (46.0)	894 (2.4)	2,935 (0.8)
2016	771,841	2,081 (0.3)	394,099 (51.1)	1,013 (2.6)	3,094 (0.8)
2017	774,706	2,330 (0.3)	420,875 (54.3)	1,050 (2.5)	3,380 (0.8)
2018	790,182	3,196 (0.4)	477,255 (60.4)	1,372 (2.9)	4,568 (1.0)
2019	730,722	3,798 (0.5)	467,305 (64.0)	1,248 (2.7)	5,046 (1.1)
Total	3,865,549	13,446 (0.3)	2,126,518 (55.0)	5,577 (2.6)	19,023 (0.9)

of 0.5%; 5 (16.1%) PLADs had proportions of HIV-positivity of ≥1%, including Sichuan (2.4%), Guangxi (2.4%), Fujian (1.8%), Chongqing (1.5%), and Yunnan (1.2%).

During 2014–2018, 30,849 TB/HIV patients were registered and enrolled in anti-TB treatment program, of whom 27,033 (87.6%) were successfully treated. For patients with different categories of TB (including resistance to various drugs), the success rates of anti-TB treatment were statistically different (χ^2=510.96, p<0.01). Patients with smear negative pulmonary TB had the highest success rate (89.6%), and those with extra-pulmonary TB had the lowest success rate (69.1%). Death (5.4%), either from non-TB or TB, accounted for the highest proportion unsuccessfully treated patients, followed by other reasons (5.0% including response refusal), lost to follow-up (1.2%), and treatment failure (0.8%).

In the 31 PLADs, rates of anti-TB treatment success among TB/HIV patients ranged 53.3%–95.1% with a median of 86.4%; 10 (32.3%) PLADs achieved success rates of ≥90%, but 7 (22.6%) had rates of <80%.

DISCUSSION

This study examined the trends of TB/HIV coinfections in China from 2015 to 2019 and found that significant challenges still remained. The burden posed by TB/HIV coinfections increased by nearly 75% during this period. While the proportion of HIV patients receiving TB screening via chest x-ray or sputum examination increased from 79.8% to 88.0% during this period, this proportion still remains below the strategic requirements and are especially prominent in central and western China, suggesting a suboptimal allocation of resources in active TB case finding among people living with HIV. Furthermore, HIV screening amongst TB patients improved from 46% to 64%, which still does not meet the 100% target proposed by the End TB Strategy. TB prevalence among newly-diagnosed HIV patients was 2.0%, which was higher than 0.6% prevalence among existing HIV patients, indicating that earlier TB screening is crucial for HIV/AIDS. Outcomes of anti-TB therapy for TB/HIV patients also showed no improvements in this period.

Due to the implementation of a modern TB control strategy, the global TB pandemic is declining (*2*). The World Health Organization (WHO) put forward the ambitious goal of ending TB by 2035, and the management of TB/HIV coinfected patients is a major component of this effort (*4*). The results of this analysis showed that from 2015 to 2019, the number of TB patients registered in China decreased at a rate of 2.2% per year but the total number of HIV/TB patients were increasing. As HIV-positive people are at higher-risk of TB infection, the continuous rise of the HIV epidemic is posing a severe challenge for TB control in China.

Implementing two-way screening is an important strategy for the early active detection of TB/HIV coinfected patients. China has set forth a target of 90% TB screening rate among HIV/AIDS patients (*3*). The results of this analysis showed that the proportion of HIV positive people undergoing TB screening based on symptoms, chest x-ray, or sputum has increased in the five year period, indicating that the cooperation between TB and HIV control institutions has gradually strengthened. In addition, areas with low TB screening rates were mainly concentrated in the central and western PLADs, which were also areas with comparatively high TB incidence. The next step should be to optimize the allocation of resources and promote active case finding of TB among HIV-positive individuals in central and western China.

Recording HIV status for all TB patients is key component of the WHO's End TB Strategy (*2*). In terms of geographical distribution, the proportion of TB patients having underwent HIV screening was higher in most areas of the southwest, but lower in some north PLADs. However, voluntary HIV counseling and testing carried out among TB patients may meet more resistance due to lack of HIV awareness, fear of HIV, a sense shame, and other reasons (*5*–*7*). In a cross-sectional study of Peru, the HIV screening rate among TB patients was 61.8% in routine procedures, and this rate increased to 76.1% after extra interventions by researchers (*5*). From 2011 to 2013, the HIV screening rate among TB patients in Hefei Province increased from 40.2% to 53.5%, which was likely due to the extensive mobilization of TB patients to TB designated hospital (*7*). Our study suggested that in the areas with low HIV screening rates, it was necessary to fully integrate local TB control facilities, improve the awareness of patients on HIV, and include HIV testing into routine TB testing projects.

Compared with the TB detection rate among HIV positive patients, the HIV positive rate among TB patients was lower with only 0.3% of TB patients testing positive for. In addition, the HIV positive rate of all TB patients was 0.9% overall. According to a systematic review conducted in mainland China before 2010, this proportion was close to the result of HIV infection rate of TB patients, 0.9% (0.6%–1.4%) (*8*). A meta-analysis of foreign studies shows that the prevalence of TB/HIV coinfection was 2.9%–72.3%, of which 25.2% were HIV positive from TB screening, and the highest rate among African countries is 31.3% (*9*). A meta-analysis of studies in sub Saharan Africa showed that the overall HIV prevalence among TB patients was 31.8% (95% CI: 27.8–36.1) (*10*). Globally, prevalence of HIV among TB patients was 11% (*2*).

Although the overall HIV prevalence among TB patients in China was lower than that of some other countries, the HIV positive rate increased from 0.8% to 1.1% during the study period, and the prevalence in some areas was far higher than that of the whole country. For example, Urumqi City in Xinjiang reported that the HIV positive rate among TB patients in 2007–2015 was 8.3% (*11*). The results indicate that the HIV prevalence among TB patients is increasing in China, and it is necessary to pay more attention to HIV screening among TB patients.

Overall success rate of anti-TB treatment for TB/HIV patients in 2014–2018 cohort was 87.6%, which was higher than the global level of 75% in 2018 (*2*). However, in some areas with a high burden of TB/HIV, the success rate of treatment was far lower than the national level. Delays in the diagnosis of TB/HIV patients was an important risk factor in the failure of treatment, which was mainly due to the imperfect linkage mechanism between the disease control institution and the treatment institutions (*12*). At a country scale, however, more research is needed to uncover the main reasons for unfavorable outcomes of anti-TB treatment among TB/HIV patients. From this current study, the rising rates of mortality and unsuccessful basic treatment among TB/HIV patients is a major concern and should be targeted. The next step should be to enhance the cooperation and linkage mechanisms between TB and HIV prevention and control institutions to ensure earlier detection of TB/HIV patients and earlier treatment.

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Perspectives

China CDC's HIV/AIDS Vaccine Efforts, from Basic Research to Clinical Studies

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After nearly 40 years of research and control efforts, much progress has been made to accomplish the most significant achievements in antiviral drug development and cocktail therapy that has transformed the human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) treatment regiment from having the highest mortality into a manageable chronic disease like hypertension or diabetes. The control goals for AIDS established by the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) set a target of treating 30 million HIV/AIDS patients by the end of 2020 (*1*). However, more work is needed to achieve the prevention goal set at 2020 of having less than a half million new HIV infections since there were still 1.7 million new HIV infections by the end of 2019 (*2*).

Close to 80 million people have been estimated to be infected by HIV since it was first detected in 1981, and roughly half have died. The global AIDS pandemic has been characterized by a fast mutating virus [at least 10 times faster than the coronavirus disease 2019 (COVID-19) virus] that has a relatively long incubation time (7 to 8 years for AIDS compared to 7 to 14 days for COVID-19) and largely heterogenous distribution amongst various countries (from over 30% to less than 0.1%) due to the diversity of human behaviors. There is no silver bullet to control HIV/AIDS and comprehensive strategy and measures are always needed. However, it is believed that an effective HIV vaccine will provide a useful tool to achieve full control of HIV/AIDS.

All conventional vaccine procedures and modern techniques have been applied to HIV vaccine research in the past 3 decades. After over 300 HIV vaccine clinical trials have been conducted, no vaccine candidate nor clear path to success remains in sight. Historically, the major hurdle in vaccine development has not been making the vaccine itself, but rather finding the right pathogen causing the disease, especially for emerging diseases, since traditional vaccines can be produced by following traditional vaccine procedures of killing or attenuating the original pathogens or taking the genetic vaccine procedure of using the immunogens and getting rid of the toxic parts of the pathogen.

However, the above conventional vaccine technologies work well only for the diseases of category A pathogens, but not for category B pathogens, a term I named. The major difference between the two rely on if the pathogen can induce protective immunity in humans during natural infection (category A) or not (category B). The key to success for category A vaccines are due to evolution, in which the human immune system is strong enough to control the pathogen as demonstrated by many asymptomatic infections and self-limiting disease courses such as in hepatitis B virus or even COVID-19 virus infections (Figure 1) (*3*). Therefore, category A vaccines are nature-born vaccines and gifts from evolution. The most rapidly made category A vaccine is the swine influenza vaccine in 2009. It only took the Chinese pharmaceutical companies less than 100 days from receiving the virus strains from the WHO to manufacturing the vaccine, conducting clinical trials, and receiving Chinese Food and Drug Administration (China FDA) licensing to administer the vaccines to Chinese people to successfully control the 2009 H1N1 epidemic. The COVID-19 vaccine is another fast produced and licensed vaccine in 2020.

Unfortunately, the HIV pathogen falls into category B, which do not induce enough protective immunity in the course of human natural infection. So far, not a single virus-free sera convertor with HIV has ever been found. The biggest barrier to a successful HIV vaccine is to empower the ineffective human immune system to evolve to defend us against HIV infection. While there is no need for sophisticated vaccine design or to understand the mechanism of immune protection against category A pathogen infection, we must discover novel approaches other than the conventional vaccines procedures to catch up with evolution.

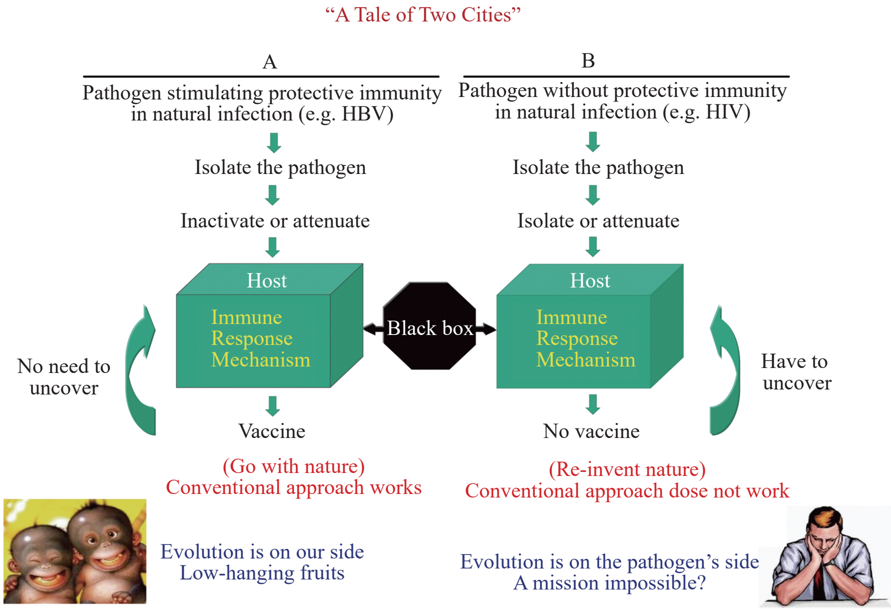

FIGURE 1. Different research designs and approach for two vaccine typeesigns and approach for two vaccine types.

Therefore, HIV vaccine research at the China CDC is based on the hypothesis that one can only induce protective immunity by either redesigning the HIV immunogen or modulating the host immune response to control the HIV infection. To test our hypothesis, we developed 4 working strategies: 1) systematically screening the circulating HIV-1 strains to identify the predominant vaccine strain (*4–5*); 2) learning for protective immunity from the world's first lentivirus vaccine (HIV belong to lentiviruses), the equine infectious anemia virus (EIAV) vaccine, to shed light how to design an HIV vaccine (*6–7*); 3) improving HIV vaccine immunogenicity by redesigning conserved regions and utilizing novel immunization protocols (*8*); and 4) using replication competent viral vectors to stimulate balanced immune responses with both antibody and T cell responses against HIV.

Following these strategies, we selected the most predominant HIV-1 clade, the CRF07 B'/C HIV-1 as the vaccine strain, which was independently confirmed as one of the best HIV vaccine candidates by US scientists (*9*). We chose the replication competent Tiantan vaccinia (TV), the Chinese smallpox vaccine strain, as the vaccine vector due to its strong immunogenicity and good safety records in smallpox eradication campaigns (*10*). In collaboration with scientists who developed the EIAV vaccine, we found that the broader T cells and neutralizing antibody (nAb) responses are related to the protection of the EIAV vaccine (*11*). The key amino acids in the conserved region of the envelope glycoprotein (env) of HIV-1 was genetically modified according to learning from the mutated env structure of the EIAV vaccine strain, aiming at improving its immunogenicity. The nAb induced by the modified HIV env can neutralize multiple strains from both HIV-1 B and B'/C viruses with broader neutralizing profiles compared with wide type HIV-1 env (Figure 2) (*12*).

We developed both DNA and recombinant TV (rTV) vaccine candidates expressing HIV-1 CRF 07 gag, pol, and env genes in collaboration with China's National Vaccine and Serum Institute (*13–14*). In preclinical testing, the two vaccines used in a priming (DNA vaccine) and boost (rTV) regiment could stimulate strong HIV1-specific cellular and humoral immune responses in small animals and monkeys. Those monkeys immunized with vaccine could resist infection when challenged with chimeric simian immunodeficiency virus (SHIV) containing homologous HIV1 gp120 (*15*).

After being approved by China FDA, we conducted Phase I clinical trials with DNA priming (at 0, 4, and 8 weeks) and rTV vaccine boost (at week 16) in 48 healthy volunteers in collaboration with Peking Union Medical College Hospital (ChiCTR-TRC-100128). The vaccines were well tolerated, and no severe adverse events were reported. Both antibody (100%) and T cell (over 60%) responses against HIV-1 were detected in subjects with DNA vaccine priming and rTV vaccine boost. The T cell responses in the vaccines were multifunctional (IL2/IFN-g/TNF-α) with stronger responses to CD4 cells than to CD8 cells (*16*).

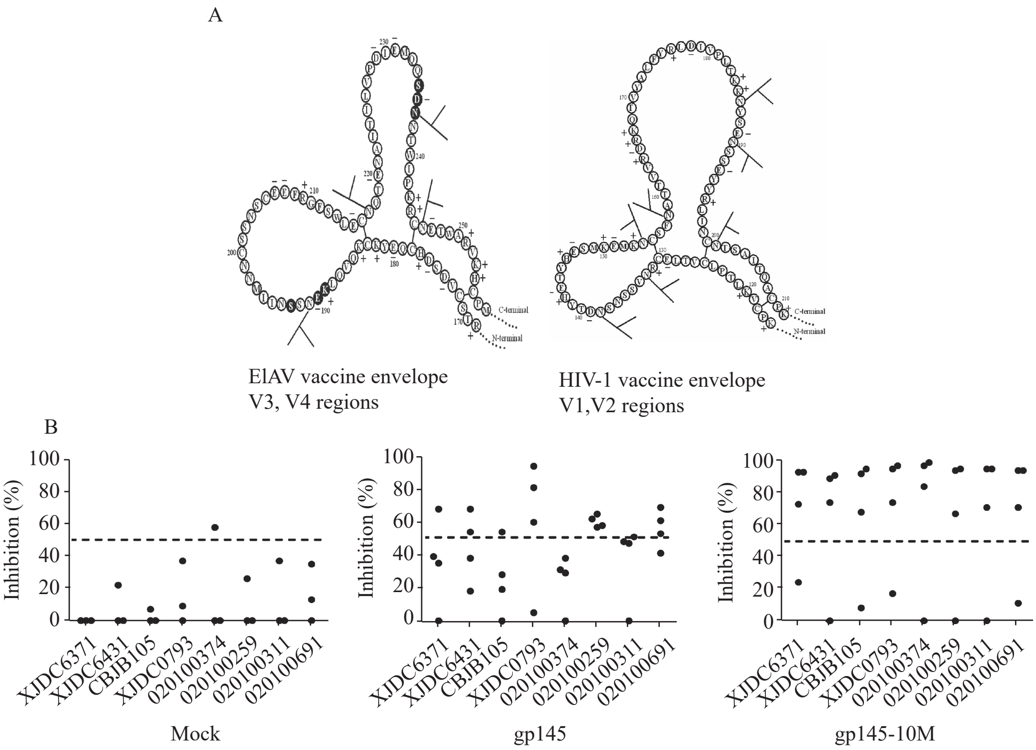

FIGURE 2. The introduced mutations and improved immunogenicity of the modified HIV envelope based on the envelope structure of EIAV vaccine strain. A. Schematic envelope structure of the EIAV D510 and the HIV-1 CN54. The left figure shows the EIAV V3, V4 regions; the right figure shows the HIV-1 V1, V2 regions. N-Glycosylation sites are shown as branched lines. B. Comparative inhibition of HIV-1 infection by sera collected at Week 16 from mock-, gp145- and gp145-10M-immunized guinea pigs. The neutralizing experiment was conducted by using a panel of clinical HIV-1 isolates from PBMCs in TZM-bl cell assays. The dotted line in the figure indicates the 50% inhibition rate.

We conducted the first Phase II clinical trial of the vaccines with priming boost regiment on 150 volunteers in collaboration with Beijing Youan Hospital. The vaccines were well tolerated with no serious adverse events (SAE) by all volunteers and again induced strong HIV-1 specific antibody (100%) responses and good T cell responses (over 60%). The vaccines could also induce good antibody to V1V2 loop but not much neutralizing antibody responses. To stimulate better neutralizing antibody responses, we discussed with the US National Institute of Allergy and Infectious Diseases (NIAID) and signed a memorandum of understanding (MOU) to conduct a Sino-US collaborative clinical trial of combining our DNA/rTV vaccines with the gp145 trimer vaccine in China (*17*).

While waiting for NIAID to finish the Phase I clinical trial of the gp145 vaccine in the US, we started the second Phase II DNA/rTV vaccine trial with a second rTV boost in order to stimulate stronger and longer lasting neutralizing antibody and T cell responses. The second Phase II clinical trial were conducted in 150 volunteers in two hospitals in Beijing and Hangzhou in a multicenter clinical trial format in preparation for future Phase IIb/III multicenter clinical trials of both the China CDC vaccines and the Sino-US joint vaccine trials. All vaccine injections were concluded in the second Phase II clinical trial. We are currently working closely with the HIV Vaccine Trials Network (HVTN) leadership group and NIAID to prepare the Investigational New Drug (IND) application to the China FDA for the joint Sino-US DNA/rTV/gp145 vaccine trials. We hope the joint Sino-US HIV vaccine clinical trial could be initiated in 2021 as an international collaborative effort to progress the global HIV vaccine programs.

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