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Overrepresentation of Injection Drug Use Route of Infection Among Human Immunodeficiency Virus Long-term Nonprogressors: A Nationwide, Retrospective Cohort Study in China, 1989–2016

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Background. Why some persons living with human immunodeficiency virus (HIV) (PLWH) progress quickly and others remain "healthy" for a decade or more without treatment remains a fundamental question of HIV pathology. We aimed to assess the epidemiological characteristics of HIV long-term nonprogressors (LTNPs) based on a cohort of PLWH in China observed between 1989 and 2016.

Methods. We conducted a nationwide, retrospective cohort study among Chinese PLWH with HIV diagnosed before 1 January 2008. Records were extracted from China's national HIV/AIDS database on 30 June 2016. LTNPs were defined as those with AIDS-free, antiretroviral therapy–naive survival, with CD4 cell counts consistently ≥500/μL for ≥8 years after diagnosis. Prevalence was calculated, characteristics were described, and determinants were assessed by means of logistic regression. Potential sources of bias were also investigated.

Results. Our cohort included 89 201 participants, of whom 1749 (2.0%) were categorized as LTNPs. The injection drug use (IDU) route of infection was reported by 70.7% of LTNPs, compared with only 37.1% of non-LTNPs. The odds of LTNP status were greater among those infected via IDU (adjusted odds ratio [95% confidence interval], 2.28 [1.94–2.68]) and with HIV diagnosed in settings with large populations of persons who inject drugs (1.75 [1.51–2.02] for detention centers, 1.61 [1.39–1.87] for Yunnan, 1.94 [1.62–2.31] for Guangdong, and 2.90 [2.09–4.02] for Xinjiang).

Conclusions. Overrepresentation of the IDU route of infection among LTNPs is a surprising finding worthy of further study, and this newly defined cohort may be particularly well suited to exploration of the molecular biological mechanisms underlying HIV long-term nonprogression.

Keywords. CD4 cell count; HIV slow progression; injection drug use; long-term nonprogression; opioids.

In the absence of treatment, progression from acute human immunodeficiency virus (HIV) infection to AIDS tends to occur within about a decade [1]. However, a small proportion of persons living with HIV (PLWH) experience notably slower progression, maintaining high numbers of $CD4^+$ T lymphocytes (CD4 cell counts) over a protracted period without the aid of antiretroviral therapy (ART). Individuals exhibiting this infrequent phenotype are commonly referred to as long-term nonprogressors (LTNPs) [2–5]. Because of variability in the definition of LTNPs [5], estimation of the prevalence of this rare phenotype has been challenging [6], but it is generally thought to be <5% [7–10].

Thus far, a preponderance of studies has been conducted in individual LTNPs or in very small LTNP cohorts in high-income settings, such as Australia [11], Canada [12], France [7, 10], Italy [13], Spain [14], the United Kingdom [9], and the United States [8, 15], where HIV-1 subtype B is predominant [16]. Therefore, although LTNPs may hold important clues to mechanisms underlying the pathophysiology of HIV, which may aid in developing new treatment or prevention strategies (eg, finding new target epitopes for neutralizing antibodies or antiviral agents [17]), current evidence is limited by small samples in unique settings where host and viral genetics are relatively lacking in diversity.

Thus, we sought to investigate LTNPs in China, a large, ethnically diverse, middle-income country, where HIV genomic variability is very high [18]. To do this, we took advantage of China's

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National HIV/AIDS Comprehensive Response Information Management System (CRIMS), which has tracked every individual with a diagnosis of HIV infection in the entire country since 1985 [19].

METHODS

Design and Setting

We conducted a nationwide, retrospective cohort study in China to investigate long-term nonprogression of HIV disease among Chinese persons with HIV diagnosed before 1 January 2008. Data were extracted on 30 June 2016, so all participants were followed up for ≥8 years. None were excluded owing to loss to follow-up. Rather, all meeting study eligibility criteria were included regardless of the duration since the most recent follow-up visit. Figure 1 shows the design of our study.

Data Source

We used data extracted from CRIMS, a real-time, web-based information system managed by the National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention. As described elsewhere [19], CRIMS contains records for all individuals with an HIV diagnosis in China; there are no missing or duplicate cases because reporting is mandatory and records are linked to national identification numbers. Records contain contact and demographic information, testing and baseline clinical information, patient-reported route of infection, dates and details of all follow-up visits, and other health-related information (eg, coinfections and comorbid conditions), as well as dates and causes of death. However, CRIMS does have some important limitations that must be noted. For example, CRIMS records do not contain estimated dates of infection or seroconversion. Therefore, PLWH often have already had HIV infection for some years at the time of diagnosis. Indeed, a recent study in China found a median duration of infection of 6.3 years before diagnosis [20]. This means that, in China, an individual with CD4 cell counts consistently ≥500/μL without ART for >8 years, has probably been infected for even longer and remained "healthy." Moreover, it was common during our study period for persons with newly diagnosed HIV with CD4 cell counts above the 200/μL, 350/μL, and 500/μL thresholds to remain untreated for some time [21]. Although clinical guidelines specified that CD4 cell count should be evaluated annually regardless of treatment status [22], this evaluation has been inconsistent and infrequent in practice, resulting in many CRIMS records containing few CD4 cell count results. Finally, clinical guidelines in China do not allow viral load (VL) testing until ≥6 months after ART initiation and only annually thereafter [22]. Hence, no VL data are available for any patient before ART initiation, and—as with CD4 cell counts—VL testing has been inconsistent and infrequent, and records contain few results. Moreover, aside from rare drug resistance test results, viral subtype and sequence data are not available.

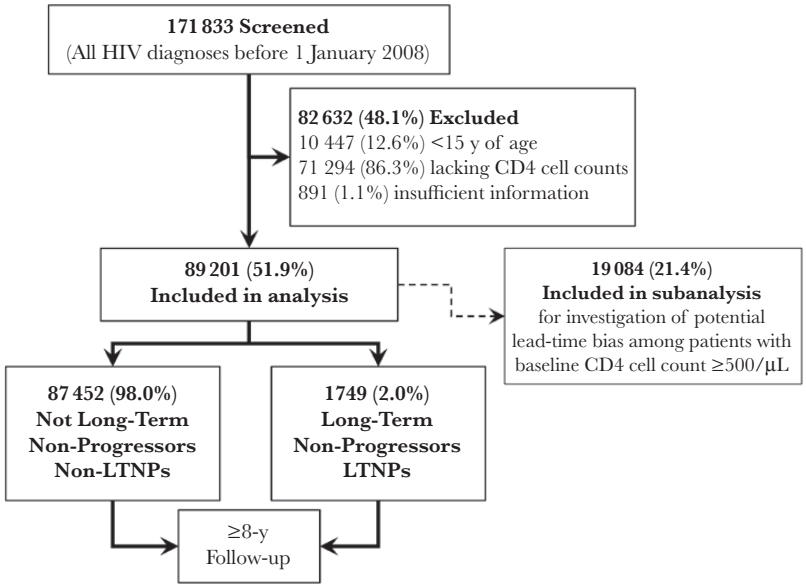

Figure 1. Development of the study cohort. All persons living with human immunodeficiency virus (HIV) in China who had a date of HIV diagnosis before 1 January 2008 were screened for study eligibility. A total of 89 201 (59.1%) were included in the analysis and categorized by their long-term nonprogressor (LTNP) status. A total of 1749 LTNPs were found, for a prevalence of 2.0%. All 89 201 study participants were followed up until records were extracted on 30 June 2016, for ≥8 years or until death. To investigate potential lead-time bias caused by earlier diagnosis in some individuals than in others, a subanalysis was conducted among only those in the cohort with baseline CD4 cell counts ≥500/μL.

Cohort Development

Development of the study cohort is shown in Figure 1. All CRIMS records with a date of HIV diagnosis before 1 January 2008 were screened for study eligibility. Two inclusion criteria were applied: ≥15 years of age at HIV diagnosis (ie, age cutoff for adulthood according to China's HIV clinical guidelines [22]) and CD4 cell counts. Records were excluded if they did not contain enough information to categorize participants by LTNP status. All eligible records were extracted on 30 June 2016, which was 8 years after the latest possible diagnosis date.

Development of the Study Definition of LTNPs

Although a recent systematic review by Gurdasani et al [5] found 159 unique definitions of HIV LTNPs in the literature, the common theme was that LTNPs remain asymptomatic with no AIDS-defining illness for a prolonged time (ie, the period of nonprogression) while retaining a high CD4 cell count (ie, the CD4 cell count threshold) in the absence of ART, although LTNPs may start ART or develop symptoms, progress to AIDS, or die after the period of nonprogression has been completed and still be considered LTNPs. However, the length of the nonprogression period and the level of the CD4 cell count threshold vary, and our data source has some important limitations that required consideration.

We examined definitions used in similar published studies. For example, Madec et al [7] used >8 years with CD4 cell counts >500/μL and Grabar et al [10] used ≥8 years with CD4 cell counts ≥500/μL, whereas Okulicz et al [8] used both ≥7 years and ≥10 years with CD4 cell counts ≥500/μL, and Mandalia et al [9] used ≥7 years and the stability of the slope of multiple CD4 cell counts. Most definitions captured in the review by Gurdasani et al [5] used a 10-year nonprogression period and a CD4 cell count threshold of 500/μL. Therefore, we too selected the ≥500/μL threshold but chose a somewhat shorter ≥8-year nonprogression period for our study, because HIV in China is often diagnosed late, a median of 6.3 years after infection [20].

We then put this into context with the data we had available to us in CRIMS, thereby defining the 2 major components of our LTNP definition. The first was duration of nonprogression ≥8 years. To meet this criterion, CRIMS records were required to demonstrate a ≥8-year survival period after the date of diagnosis (which was before 1 January 2008) with (1) no HIV/AIDS symptoms or AIDS-defining illness and (2) no ART. After 8 years, evidence of ART, symptoms, AIDS, or death did not cause records to be excluded from categorization as LTNPs.

The second component was CD4 cell count ≥500/μL. To meet this criterion, CRIMS records were required to contain (1) ≥2 CD4 cell counts ≥500/μL and none <500/μL during the ≥8-year nonprogression period after the date of diagnosis, (2) ≥1 CD4 cell count ≥500/μL after the ≥8-year nonprogression period was completed, and (3) a ≥1-year time interval between first ever and last (or most recent) CD4 cell count ≥500/μL.

To illustrate this definition, we present 7 hypothetical scenarios in Figure 2. Scenarios 1–4 describe generalized patients categorized as non-LTNPs for failure to meet ≥1 component of the LTNP study definition. Scenarios 5–7 illustrate generalized patients categorized as LTNPs. Because scenarios 1–4 (non-LTNPs) may have had a smaller chance of being categorized as LTNPs simply owing to later diagnosis, we also investigated the possibility of lead-time bias in our cohort.

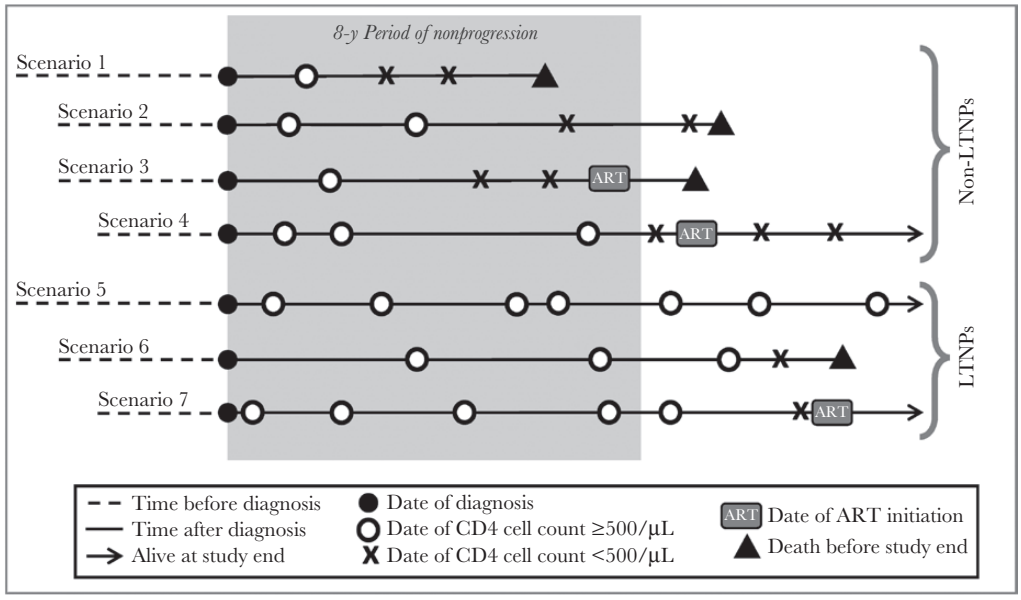

Figure 2. Illustration of the study definition of long-term nonprogressors (LTNPs). Abbreviation: ART, antiretroviral therapy.

Data Analysis

Categorical variables are presented as numbers and percentages, and prevalence comparisons were conducted using χ^2 test, with 1 category for each variable used as a reference. Continuous variables are presented as median with interquartile range (IQR) but not compared for statistical test. Missing data were categorized as unknown but still included in the analyses. Observed time was calculated from the date of diagnosis to study end or death and expressed in person-years (PYs). Factors associated with LTNP status were investigated using univariable and multivariable logistic regression with results reported as odds ratios and 95% confidence intervals (CIs). Because of potential for lead-time bias—participants with HIV diagnosed earlier may have had a greater chance of being categorized as LTNPs—we repeated the logistic regression analysis using only the subset of participants with baseline CD4 cell counts ≥500/μL. In addition, because of the potential for confounding bias owing to some key variables being related, we conducted 4 crossover stratified analyses using binary logistic regression, with LTNP status as the dichotomous dependent variable. All analyses were conducted using SPSS software (version 24.0; IBM).

Ethics

The protocol was approved by the institutional review board of the National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention. Informed consent was not required because all individuals with HIV diagnosed in China sign written informed consent at diagnosis, allowing future use of their deidentified data for epidemiological studies.

RESULTS

As shown in Figure 1, a total of 171 833 CRIMS records were screened, and a total of 89 201 (51.9%) participants were included in our cohort. Among the 82 632 who were excluded, 10 447 (12.6%) were <15 years of age, 71 294 (86.3%) lacked CD4 cell count results, and 891 (1.1%) had insufficient information in their records to categorize them as LTNPs or non-LTNPs.

Characteristics of study participants are presented in Table 1. At baseline (diagnosis), most participants were aged 25–34 years (43.6%) or ≥35 years (42.3%), male (68.0%), of Han ethnicity (73.8%), and married (52.6%). A majority had junior high school education or less (junior high, 43.4%, primary school or less, 40.8%) and worked as farmers (54.4%). The most frequent HIV infection routes were injection drug use (IDU; 37.8%) and heterosexual contact (33.4%). Most have HIV diagnosed at voluntary counseling and testing locations (28.6%) or detention centers (23.0%), in Yunnan (24.9%) or Henan (20.4%), and between 2005 and 2008 (70.3%). Most had baseline CD4 cell counts <500/μL (≤199/μL, 32.0%; 200–349/μL, 25.1%; 350–499/μL, 21.5%).

A total of 1749 participants (of 89 201) met the definition of LTNPs, for an overall, nationwide LTNP prevalence of 2.0%. The prevalence of LTNP status was higher among those who were aged 15–24 (3.8%) or 25–34 (2.5%) years, male (2.4%), ethnic Uygur (5.1%), never married (3.1%), and had homemaker/unemployed (3.0%) or service industry worker (2.9%) as their occupation. LTNP status was also more prevalent among participants with an IDU infection route (3.7%) and diagnosis in detention centers (4.0%), in Yunnan (2.5%), Guangdong (3.9%), and Xinjiang (5.0%), and in the 1990–2004 period (3.3%). The median (IQR) observed time for non-LTNPs was 8.8 (7.1–10.7) PYs and for LTNPs was a higher but comparable 11.0 (9.7–13.0) PYs (Table 1).

Results of our investigation into factors associated with LTNP status are presented in Table 2. After adjustment for confounding, we found greater odds of LTNP status among participants who were younger (adjusted odds ratio [AOR] [95% CI] vs age ≥35 years, 1.90 [1.66–2.17] for age 25–34 years and 3.34 [2.87–3.88] for age 15–24 years), had an IDU route of infection (vs heterosexual contact, 2.28 [1.94–2.68]), had HIV diagnosed in a detention center (vs a voluntary counseling and testing location, 1.75 [1.51–2.02]), a blood donation station (1.84 [1.41–2.39]), or as a part of a special investigation (1.61 [1.32–1.96]), and in Yunnan (vs other provinces, 1.61 [1.39–1.87]), Guangxi (1.46 [1.21–1.77]), Guangdong (1.94 [1.62–2.31]), or Xinjiang (2.90 [2.09–4.02]). The odds of LTNP status were lower for those of minority ethnicities other than Uygur (AOR [95% CI] vs Han, 0.66 [.57–.76]) and for those with heterosexual contact as their infection route (vs heterosexual contact, 0.45 [.25–.80]). When diagnosis location was left out of the model, the odds of LTNP status were greater for those of Uygur ethnicity (AOR [95% CI] vs Han, 1.84 [1.59–2.12]).

Results of the subanalysis that included only participants with baseline CD4 cell counts ≥500/μL are presented in Table 3. After adjusting for confounding, we found greater odds of LTNP status among those who were younger (AOR [95% CI], 1.56 [1.36–1.79] for age 25–34: years and 2.28 [1.94–2.67] for age 15–24 years), had IDU (2.12 [1.79–2.50]) or blood products (1.61 [1.14–2.28]) as their infection route, had HIV diagnosed in a detention center (1.60 [1.38–1.86]), in a blood donation station (1.66 [1.26–2.19]), or as a part of a special investigation (1.52 [1.24–1.88]), and in Yunnan (1.52 [1.31–1.78]), Guangxi (2.05 [1.68–2.49]), Guangdong (2.26 [1.87–2.73]), or Xinjiang (2.95 [2.08–4.18]). The odds of LTNP status were lower among other ethnicities (AOR [95% CI], 0.60 [.52–.70]) and those with homosexual contact as the infection route (0.45 [.25–.80]). When diagnosis location was left out of the model, the odds of LTNP status among those who reported their route of infection as blood products was no longer significantly elevated (AOR [95% CI], 0.91 [.71–1.17]).

Results of binary logistic regression analyses are presented in Tables 4–7. Among those with Uygur ethnicity, those with an IDU infection route had greater odds of LTNP status (AOR [95% CI], 2.18 [1.58–3.03]). However, among those with all other

Table 1. Characteristics of Study Participants in the Nationwide Cohort (China, 1989–2016) and Prevalence of Long-term Nonprogressor (LTNP) and Non-LTNP Status

Characteristic	All Participants, No. (Column %)[a]	Participants, No. (Row %)[a]		*P* Value[b]
		Non-LTNPs	LTNPs	
Total sample	89 201 (100.0)	87 452 (98.0)	1749 (2.0)	…
Baseline characteristics				
Age group, y				
≥35	37 750 (42.3)	37 416 (99.1)	334 (0.9)	… (Ref)
25–34	38 933 (43.6)	37 997 (97.6)	936 (2.5)	<.001
15–24	12 518 (14.0)	12 039 (96.2)	479 (3.8)	<.001
Sex				
Female	28 523 (32.0)	28 195 (98.9)	328 (1.1)	… (Ref)
Male	60 678 (68.0)	59 257 (97.7)	1421 (2.4)	<.001
Ethnicity				
Han	65 849 (73.8)	64 693 (98.2)	1156 (1.8)	… (Ref)
Uygur	5319 (6.0)	5048 (94.9)	271 (5.1)	<.001
Other[c]	15 741 (17.6)	15 476 (98.3)	265 (1.7)	.5
Unknown	2292 (2.6)	2235 (97.5)	57 (2.5)	<.001
Marital status				
Married	46 943 (52.6)	46 340 (98.7)	603 (1.3)	… (Ref)
Never married	22 405 (25.1)	21 713 (96.9)	692 (3.1)	<.001
Divorced/widowed	17 686 (19.8)	17 332 (98.0)	354 (2.0)	<.001
Unknown	2167 (2.4)	2067 (95.4)	100 (4.6)	<.001
Education				
Primary school or less	36 352 (40.8)	35 698 (98.2)	654 (1.8)	… (Ref)
Junior high school	38 754 (43.4)	37 921 (97.9)	833 (2.1)	.001
Senior high school or more	10 836 (12.1)	10 681 (98.6)	155 (1.4)	.01
Unknown	3259 (3.7)	3152 (96.7)	107 (3.3)	<.001
Occupation				
Farmer	48 521 (54.4)	47 836 (98.6)	685 (1.4)	… (Ref)
Homemaker/unemployed	18 108 (20.3)	17 563 (97.0)	545 (3.0)	<.001
Service industry worker	4237 (4.7)	4114 (97.1)	123 (2.9)	<.001
Laborer	3910 (4.4)	3825 (97.8)	85 (2.2)	<.001
Government employee	3056 (3.4)	3025 (99.0)	31 (1.0)	.07
Other[d]	6457 (7.2)	6329 (98.0)	128 (2.0)	<.001
Unknown	4912 (5.5)	4760 (96.9)	152 (3.1)	<.001
Route of infection				
Heterosexual contact	29 809 (33.4)	29 518 (99.0)	291 (1.0)	… (Ref)
Injection drug use	33 715 (37.8)	32 478 (96.3)	1237 (3.7)	<.001
Blood products[e]	19 626 (22.0)	19 484 (99.3)	142 (0.7)	.003
Homosexual contact	2572 (2.9)	2559 (99.5)	13 (0.5)	.02
Unknown	3479 (3.9)	3413 (98.1)	66 (1.9)	<.001
Type of diagnosis site				
VCT location	25 540 (28.6)	25 219 (98.7)	321 (1.3)	… (Ref)
Detention center	20 511 (23.0)	19 690 (96.0)	821 (4.0)	.03
Hospital/clinic	16 067 (18.0)	15 903 (99.0)	164 (1.0)	<.001
Blood donation station	8474 (9.5)	8382 (98.9)	92 (1.1)	.21
Investigation	7795 (8.7)	7635 (97.9)	160 (2.1)	<.001
Spouse/sex partner test	4278 (4.8)	4239 (99.1)	39 (0.9)	.06
Other[f]	6536 (7.3)	6384 (97.7)	152 (2.3)	<.001
Location of diagnosis site				
Other[g]	24 656 (27.6)	24 352 (98.8)	304 (1.2)	… (Ref)
Yunnan	22 246 (24.9)	21 700 (97.5)	546 (2.5)	<.001
Henan	18 165 (20.4)	18 036 (99.3)	129 (0.7)	<.001
Guangxi	11 334 (12.7)	11 130 (98.2)	204 (1.8)	<.001
Guangdong	6587 (7.4)	6330 (96.1)	257 (3.9)	<.001
Xinjiang	6213 (7.0)	5904 (95.0)	309 (5.0)	<.001

Table 1. Continued

Characteristic	All Participants, No. (Column %)[a]	Participants, No. (Row %)[a]		*P* Value[b]
		Non-LTNPs	LTNPs	
Year of diagnosis				
1990–2004	26 464 (29.7)	25 584 (96.7)	880 (3.3)	… (Ref)
2005–2008	62 737 (70.3)	61 868 (98.6)	869 (1.4)	<.001
Baseline CD4 cell count				
≤199/μL	28 559 (32.0)	28 559 (100)	0 (0.0)	…
200–349/μL	22 393 (25.1)	22 393 (100)	0 (0.0)	…
350–499/μL	19 165 (21.5)	19 165 (100)	0 (0.0)	…
≥500/μL	19 084 (21.4)	17 335 (90.8)	1749 (9.2)	…
Median (IQR), cells/μL	306 (152–468)	301 (149–456)	738 (611–896)	…
Follow-up characteristics				
Observation time, PYs				
All participants				
Median (IQR)	8.9 (7.2–10.7)	8.8 (7.1–10.7)	11.0 (9.7–13.0)	…
Range	0.1–26.5	0.1–26.5	8.0–23.6	…
Participants with baseline CD4 cell count ≥500/μL				
Median (IQR)	9.0 (7.9–10.8)	8.9 (7.8–10.5)	11.0 (9.7–13.0)	…
Range	0.1–23.6	0.1–20.0	8.0–23.6	…
Median participant CD4 cell count, cells/μL				
Median (IQR)	289 (151–430)	284 (147–420)	732 (612–826)	…
Range	2–1980	2–1980	504–1670	…

Abbreviations: IQR, interquartile range; LTNPs, long-term nonprogressors; PYs, person-years; Ref, reference category; VCT, voluntary counseling and testing.

[a]Data represent no. (%) of participants unless otherwise specified.

[b]Categorical variables were compared between categories using χ^2 tests.

[c]The "Other" category for the ethnicity variable includes the remaining 49 minority ethnicities recognized by the Chinese Government.

[d]The "Other" category for the occupation variable includes all other occupations as well as students.

[e]The "Blood products" category encompasses infection via either blood product donation or receipt.

[f]The "Other" category for the type of diagnosis site variable includes enlisted physical, exit and entry physical, premarital, occupational exposure, and entertainment place examinations.

[g]The "Other" category for the location of diagnosis site variable includes the remaining 27 provinces in China.

ethnicities, those with IDU infection route also had greater odds of LTNP status (AOR [95% CI], 3.97 [3.45–4.57]; Table 4). Among those with an IDU infection route, those of Uygur ethnicity had greater odds of LTNP status (AOR [95% CI], 1.75 [1.50–2.04]), and among those with other infection routes, those of Uygur ethnicity also had greater odds of LTNP status (3.44 [2.55–4.66]) (Table 5). Among participants in all 3 age groups, those with IDU infection route had greater odds of LTNP status (AOR [95% CI], 3.64 [2.90–4.57] for age 15–24 years, 3.33 [2.77–4.01] for age 25–34 years, and 4.26 [3.17–5.74] for age ≥35 years), as did those of Uygur ethnicity (2.19 [1.72–6.67] for age 15–24 years, 2.23 [1.86–2.69] for age 25–34 years, and 3.25 [2.23–4.75] for age ≥35 years) (Table 6). Finally, among participants with HIV diagnosed in 1990–2004 or in 2005–2008, the odds of LTNP status were greater among those with an IDU infection route (AOR [95% CI], 3.27 [2.54–4.22] for diagnosis in 1990–2004 and 2.85 [2.44–3.33] for diagnosis in 2005–2008) and those of Uygur ethnicity (5.33 [4.40–6.46] for diagnosis in 1990–2004 and 2.28 [1.87–2.78] for diagnosis in 2005–2008) (Table 7).

DISCUSSION

The present study represents the first-ever establishment of a large nationwide cohort of LTNPs in China—an ethnically diverse middle-income country where HIV genetic diversity is substantial [18]. We found that persons who reported their route of infection as IDU were overrepresented among this Chinese LTNP cohort at 70.7% (1237 of 1749), compared with 37.3% (32 478 of 87 452) among non-LTNPs. In multivariable analyses, the IDU infection route was associated with >2-fold higher odds of LTNP status. Moreover, HIV diagnosis in settings where persons who inject drugs (PWID) were more concentrated—detention centers [23], and Yunnan, Guangxi, Guangdong, or Xinjiang provinces [24]—was also associated with greater odds of LTNP status.

These results were unexpected, because an extensive literature documents epidemiological, clinical, in vivo, and in vitro evidence of opioids acting as an accelerator of HIV pathogenesis owing to negative effects on host immune function [25–32]. We found only 1 small study in Sweden documenting slower HIV disease progression among PWID [33]. A more recent, larger study in Hubei, China, found similar results [34]. However, in both studies, the comparison group was not non-PWID. Rather, it was men who have sex with men (MSM) [33, 34]. In China, where non-B subtype viral strains are dominant, different subtypes and circulating recombinant forms (CRFs; eg, CRF01_AE, CRF07_BC, and CRF08_BC) are known to vary in prevalence among the different key populations owing

Table 2. Factors Associated with Long-term Nonprogressor Status: Results of Univariable and Multivariable Logistic Regression Analyses in a Nationwide Cohort (China, 1989–2016)

Variable	Odds Ratio (95% Confidence Interval)		
	Unadjusted	Adjusted[a]	Adjusted[b]
Age group, y			
≥35	1.00	1.00	1.00
25–34	2.76 (2.43–3.13)	1.94 (1.70–2.21)	1.90 (1.66–2.17)
15–24	4.46 (3.87–5.13)	3.38 (2.91–3.93)	3.34 (2.87–3.88)
Sex			
Female	1.00	1.00	1.00
Male	2.06 (1.83–2.33)	1.26 (1.10–1.44)	1.23 (1.07–1.41)
Ethnicity			
Han	1.00	1.00	1.00
Uygur	3.00 (2.62–3.44)	1.84 (1.59–2.12)	0.97 (.70–1.34)
Other	0.96 (.84–1.10)	0.64 (.56–.74)	0.66 (.57–.76)
Unknown	1.43 (1.09–1.87)	1.25 (.90–1.72)	1.16 (.83–1.62)
Route of infection			
Heterosexual contact	1.00	1.00	1.00
Injection drug use	3.86 (3.40–4.39)	2.41 (2.05–2.83)	2.28 (1.94–2.68)
Blood products	0.74 (.60–.90)	0.79 (.62–1.00)	1.03 (.75–1.43)
Homosexual contact	0.52 (.30–.90)	0.35 (.20–.61)	0.45 (.25–.80)
Unknown	1.96 (1.50–2.57)	1.45 (1.06–2.00)	1.37 (.99–1.90)
Type of diagnosis site			
VCT location	1.00	1.00	1.00
Detention center	3.28 (2.88–3.73)	1.74 (1.51–2.01)	1.75 (1.51–2.02)
Hospital/clinic	0.81 (.67–.98)	0.94 (.77–1.14)	0.95 (.78–1.15)
Blood donation station	0.86 (.68–1.09)	1.77 (1.36–2.29)	1.84 (1.41–2.39)
Investigation	1.65 (1.36–1.99)	1.67 (1.37–2.03)	1.61 (1.32–1.96)
Spouse/sex partner test	0.72 (.52–1.01)	1.16 (.82–1.65)	1.27 (.90–1.81)
Other	1.87 (1.54–2.27)	1.30 (1.06–1.58)	1.25 (1.03–1.53)
Location of diagnosis			
Other	1.00	…	1.00
Yunnan	2.02 (1.75–2.32)	…	1.61 (1.39–1.87)
Henan	0.57 (.47–.70)	…	1.06 (.78–1.44)
Guangxi	1.47 (1.23–1.76)	…	1.46 (1.21–1.77)
Guangdong	3.25 (2.75–3.85)	…	1.94 (1.62–2.31)
Xinjiang	4.19 (3.57–4.92)	…	2.90 (2.09–4.02)

Abbreviation: VCT, voluntary counseling and testing.

[a]Model included all shown variables except location of diagnosis.

[b]Model included all shown variables.

to their relative abundance in sexual and needle-sharing networks [35–38]. Thus, it is possible that our finding of overrepresentation of the IDU infection route among LTNPs in China may be related to viral genetic factors. This idea is further bolstered by the observation that MSM had lower odds of being LTNPs.

We found that LTNPs in our cohort were roughly 80% more likely to have been diagnosed in a detention center, and 50%–190% more likely to have had HIV diagnosed in Yunnan, Guangxi, Guangdong, and Xinjiang. These findings make sense in the China context, because confinement of drug users in detention centers has been common practice for several decades [39], and because China's HIV epidemic among drug users is well known to have originated in Yunnan and expanded over drug trafficking routes to Guangxi, Guangdong, and Xinjiang [24]. Recent HIV genomic studies have revealed the chronology and geography of the spread of unique variants of the virus that mirror the expansion of China's HIV epidemic among drug users and are distinct from HIV genetic variants more common in other risk groups (eg, MSM) [35–38]. We believe that these findings also suggest the influence of viral factors in our cohort that require further investigation.

In the present study, we have largely focused on a first-time, epidemiological characterization of this cohort. To this end, we have found, for example, that younger age and Uygur ethnicity were associated with greater odds of LTNP status, whereas other minority groups had lesser odds. Although 1 study in the United States has found an association between LTNP status and ethnicity [8], other studies have found no such association [4, 9, 13]. The notable association between Uygur ethnicity and greater odds of LTNP status may be

Table 3. Investigation of Potential Lead-Time Bias: Results of Univariate and Multivariate Logistic Regression Analyses Among Those With Baseline CD4 Cell Counts ≥500/μL in a Nationwide Cohort (China, 1989–2016)

	Odds Ratio (95% Confidence Interval)		
Variable	Unadjusted	Adjusted[a]	Adjusted[b]
Age group, y			
≥35	1.00	1.00	1.00
25–34	1.99 (1.75–2.26)	1.60 (1.40–1.84)	1.56 (1.36–1.79)
15–24	2.51 (2.17–2.90)	2.32 (1.98–2.72)	2.28 (1.94–2.67)
Sex			
Female	1.00	1.00	1.00
Male	1.95 (1.73–2.21)	1.31 (1.14–1.51)	1.28 (1.11–1.48)
Ethnicity			
Han	1.00	1.00	1.00
Uygur	1.85 (1.60–2.13)	1.36 (1.17–1.58)	0.73 (.51–1.04)
Other	0.78 (.68–.90)	0.56 (.49–.65)	0.60 (.52–.70)
Unknown	1.43 (1.07–1.89)	1.44 (1.01–2.07)	1.24 (.86–1.79)
Route of infection			
Heterosexual contact	1.00	1.00	1.00
Injection drug use	3.07 (2.69–3.50)	2.30 (1.95–2.71)	2.12 (1.79–2.50)
Blood products	0.88 (.72–1.08)	0.91 (.71–1.17)	1.61 (1.14–2.28)
Homosexual contact	0.49 (.28–.85)	0.35 (.20–.62)	0.45 (.25–.80)
Unknown	1.86 (1.41–2.46)	1.33 (.94–1.88)	1.25 (.88–1.78)
Type of diagnosis site			
VCT location	1.00	1.00	1.00
Detention center	2.58 (2.25–2.96)	1.63 (1.41–1.88)	1.60 (1.38–1.86)
Hospital/clinic	1.01 (.83–1.22)	1.19 (.97–1.45)	1.14 (.93–1.40)
Blood donation station	0.89 (.70–1.13)	1.61 (1.22–2.12)	1.66 (1.26–2.19)
Investigation	1.41 (1.16–1.72)	1.50 (1.22–1.84)	1.52 (1.24–1.88)
Spouse/sex partner test	0.71 (.50–.99)	1.17 (.82–1.68)	1.37 (.96–1.97)
Other	1.35 (1.10–1.65)	1.13 (.92–1.39)	1.11 (.90–1.37)
Location of diagnosis			
Other	1.00	…	1.00
Yunnan	1.63 (1.41–1.88)	…	1.52 (1.31–1.78)
Henan	0.61 (.49–.75)	…	0.74 (.53–1.02)
Guangxi	2.12 (1.76–2.55)	…	2.05 (1.68–2.49)
Guangdong	3.39 (2.84–4.05)	…	2.26 (1.87–2.73)
Xinjiang	2.81 (2.37–3.32)	…	2.95 (2.08–4.18)

Abbreviation: VCT: voluntary counseling and testing.

[a]Model included all shown variables except location of diagnosis.

[b]Model included all shown variables.

explained, at least in part, by a study comparing the CD4 cell counts of healthy adults of the Uygur minority group and ethnic Han Chinese, which found that those of Uygur ethnicity have significantly higher normal CD4 cell counts [40].

Although our finding of a 2.0% prevalence for the LTNP phenotype is below that reported by some, such as Madec et al [7] in France and Okulicz et al [8] in the United States, it is well above that reported by others, including Mandalia et al [9] in

Table 4. Investigation of Potential Confounding Bias: Results of Binary Logistic Regression Evaluating Ethnicity Versus Route of Infection in a Nationwide Cohort (China, 1989–2016)

	Uygur			All Other Ethnicities		
Route of Infection	Participants, No. (%)	OR (95% CI)	*P* Value	Participants, No. (%)	OR (95% CI)	*P* Value
Heterosexual contact	45 (2.9)	1.00	…	246 (0.9)	1.00	…
Injection drug use	222 (6.2)	2.18 (1.58–3.03)	<.001	1015 (3.4)	3.97 (3.45–4.57)	<.001
Blood products	0 (0.0)	…	…	142 (0.7)	0.83 (.67–1.02)	.08
Homosexual contact	0 (0.0)	…	…	13 (0.5)	0.58 (.33–1.01)	.06
Unknown	4 (2.0)	0.67 (.24–1.90)	.46	62 (1.9)	2.20 (1.66–2.91)	<.001

Abbreviations: CI, confidence interval; OR, odds ratio.

Table 5. Investigation of Potential Confounding Bias: Results of Binary Logistic Regression Evaluating Route of Infection Versus Ethnicity in a Nationwide Cohort (China, 1989–2016)

	Injection Drug Use			All Other Routes		
Ethnicity	Participants, No. (%)	OR (CI)	*P* Value	Participants, No. (%)	OR (CI)	*P* Value
Han	786 (3.6)	1.00	…	370 (0.8)	1.00	…
Uygur	222 (6.2)	1.75 (1.50–2.04)	<.001	49 (2.8)	3.44 (2.55–4.66)	<.001
Other	15 (3.9)	0.71 (.61–.83)	<.001	42 (2.2)	0.81 (.60–1.08)	.16
Unknown	786 (3.6)	1.07 (.64–1.81)	.79	370 (0.8)	2.67 (1.94–3.69)	<.001

Abbreviations: CI, confidence interval; OR, odds ratio.

the United Kingdom. However, it is likely that differences in prevalence are attributable, at least in part, to varying definitions of LTNPs and study design, and as such, these differences may not represent meaningful interpopulation variability [5, 6]. Nevertheless, the study of this rare phenotype is important because discovery of variations in host and viral factors associated with long-term nonprogression of HIV infection further our understanding of HIV biology and could be invaluable to the development of next-generation prevention and treatment strategies [1–6, 17].

The large size and nationwide scope of our cohort were important strengths of our study. However, results should be interpreted with caution, because our study had several important limitations. First, our data source had some crucial limitations, described in the Methods. Second, the retrospective cohort design precluded any examination of causality. Third, because the route of HIV infection variable relied partly on self-reporting by patients at time of diagnosis (infection route is also verified by epidemiologists during routine case investigation), social desirability and recall bias may have led to misclassification of participants and therefore overrepresentation or underrepresentation of exposures.

Fourth, we did not have access to the dates, or even estimated dates, of infection or seroconversion and had to rely on dates of diagnosis instead. Although it is likely that LTNP prevalence was underestimated as a result, because the seroconversion date always preceded the diagnosis date, this may have also caused some lead-time bias because PLWH with earlier diagnoses may have had increased opportunity to be categorized as LTNPs. However, we found that median follow-up time was similar between LTNPs and non-LTNPs (11.0 vs 8.8 PYs) and between those reporting the IDU infection route and those reporting all other routes (8.9 [IQR, 6.9–10.8] vs 8.8 [7.5–10.7] PYs; data not shown). Furthermore, when we conducted the subanalysis using only those with HIV diagnosed "early" (ie, when the baseline CD4 cell count was still ≥500/μL), our finding of overrepresentation of the IDU route of infection among LTNPs and greater odds of LTNP status among those who reported IDU as their infection route did not change. Finally, the interrelatedness of several variables examined (eg, most persons in China of Uygur ethnicity live in Xinjiang province) may have caused some confounding bias. However, when we conducted the crossover stratified analyses using binary logistic regression, we found that the IDU route of infection was a robust predictor of LTNP status.

In conclusion, we provide a first-ever characterization of a nationwide cohort of 1749 LTNP in China who have remained

Table 6. Investigation of Potential Confounding Bias: Results of Binary Logistic Regression Evaluating Age Versus Route of Infection and Ethnicity in a Nationwide Cohort (China, 1989–2016)

	Participants Aged 15–24 y			Participants Aged 25–34 y			Participants Aged ≥35 y		
Route of Infection and Ethnicity	No. (%)	OR (CI)	*P* Value	No. (%)	OR (CI)	*P* Value	No. (%)	OR (CI)	*P* Value
Route of infection									
Heterosexual contact	97 (1.8)	1.00	…	135 (1.1)	1.00	…	59 (0.5)	1.00	…
Injection drug use	359 (6.4)	3.64 (2.90–4.57)	<.001	705 (3.6)	3.33 (2.77–4.01)	<.001	173 (2.0)	4.26 (3.17–5.74)	<.001
Blood products	3 (0.8)	0.45 (.14–1.41)	.17	64 (1.3)	1.16 (.86–1.57)	.32	75 (0.5)	1.11 (.79–1.56)	.55
Homosexual contact	4 (0.5)	0.28 (.10–.76)	.01	9 (0.9)	0.79 (.40–1.55)	.49	0 (0.0)	…	…
Unknown	16 (2.9)	1.60 (.94–2.74)	.09	23 (1.5)	1.33 (.85–2.07)	.21	27 (2.0)	4.21 (2.66–6.67)	<.001
Ethnicity									
Han	286 (3.8)	1.00	…	616 (2.3)	1.00	…	254 (0.8)	1.00	…
Uygur	94 (7.9)	2.19 (1.72–6.67)	<.001	146 (5.0)	2.23 (1.86–2.69)	<.001	31 (2.6)	3.25 (2.23–4.75)	<.001
Other	83 (2.4)	0.63 (.49–.81)	<.001	150 (1.9)	0.82 (.69–.99)	.04	32 (0.7)	0.90 (.62–1.30)	.58
Unknown	16 (4.5)	1.20 (.72–2.01)	.48	24 (2.1)	0.93 (.61–1.40)	.71	17 (2.1)	2.64 (1.61–4.33)	<.001

Abbreviations: CI, confidence interval; OR, odds ratio.

Table 7. Investigation of Potential Confounding Bias: Results of Binary Logistic Regression Evaluating Year of Diagnosis Versus Route of Infection and Ethnicity in a Nationwide Cohort (China, 1989–2016)

	Participants With HIV Diagnosis in 1990–2004			Participants With HIV Diagnosis in 2005–2008		
Route of Infection and Ethnicity	No. (%)	OR (CI)	*P* Value	No. (%)	OR (CI)	*P* Value
Route of infection						
Heterosexual contact	67 (2.2)	1.00	…	224 (0.8)	1.00	…
Injection drug use	678 (6.9)	3.27 (2.54–4.22)	<.001	559 (2.3)	2.85 (2.44–3.33)	<.001
Blood products	115 (0.9)	0.40 (.29–.54)	<.001	27 (0.4)	0.49 (.33–.73)	<.001
Homosexual contact	3 (3.6)	1.67 (.51–5.41)	.40	10 (0.4)	0.48 (.25–.90)	.023
Unknown	17 (4.0)	1.85 (1.07–3.17)	.03	49 (1.6)	1.93 (1.42–2.64)	<.001
Ethnicity						
Han	566 (2.6)	1.00	…	590 (1.3)	1.00	…
Uygur	147 (12.5)	5.33 (4.40–6.46)	<.001	124 (3.0)	2.28 (1.87–2.78)	<.001
Other	162 (4.6)	1.80 (1.50–2.15)	<.001	103 (0.8)	0.63 (.51–.78)	<.001
Unknown	5 (2.9)	1.10 (.45–2.69)	.84	52 (2.5)	1.86 (1.40–2.48)	<.001

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio.

AIDS-free for ≥8 years without treatment. Our finding of overrepresentation of the IDU route of infection among LTNPs, while seemingly contradicting a large literature that supports opioids as an accelerator of HIV disease progression, makes sense in light of the spatiotemporal development of China's HIV epidemic among PWID and suggests that perhaps a unique genetic characteristic of the viral strains circulating among the PWID population in China could be a driver of long-term nonprogression. However, both viral and host factors are known to play a role in determining the rate of HIV disease progression. Nevertheless, this unique cohort of LTNPs in a setting where viral genetic diversity is very high warrants further study because it could point to new paths toward the advancement of HIV treatment and prevention.

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