Preplanned Studies

Temporal Trends of Clinical Characteristics and Treatments in People Living with HIV at the Initiation of Antiretroviral Therapy — Beijing Municipality, China, 2010–2020

Jinjuan Zhang[1,2,&]; Mengge Zhou[3,4,&]; Peicheng Wang[4]; Duoduo Wang[1,2]; Yuanqi Mi[5]; Jufen Liu[1,2,#]; Feng Cheng[4,#]

Summary

What is already known about this topic?

Antiretroviral therapy (ART) eligibility criteria and treatment regimens were updated in national guidelines. However, whether treatment was timely and followed guidelines was under-assessed.

What is added by this report?

Among 22,591 people living with human immunodeficiency virus (PLWH) who initiated ART in Beijing between 2010 and 2020, the time from diagnosis to initiating ART decreased, the clinical condition of PLWH improved, and ART regimens changed in accordance with guidelines.

What are the implications for public health practice?

Over the past decade, improvements in clinical status have been observed among PLWH; however, a proportion of PLWH remain who started ART late. Early linkage to human immunodeficiency virus (HIV) care should be further improved.

With the improvement in efficacy and reduction of side effects from antiretroviral therapy (ART), mounting evidence supports the early initiation of ART regardless of CD4 cell counts (*1–2*). In 2018, all people living with human immunodeficiency virus (PLWH) were recommended to receive ART in China (*3–4*). However, whether treatment is timely and following the updated guidelines has been under-assessed. Based on clinical data from Beijing Center for Disease Prevention and Control, the time from diagnosis to ART initiation, yearly proportion of CD4 cell counts, and ART regimens at initial treatment were analyzed among PLWH between 2010 and 2020. The median days from diagnosis of human immunodeficiency virus (HIV) to initiating ART decreased from 91 days in 2011 to 14 days from 2018 to 2020. The proportion of patients with CD4 ≤ 200 cells/mm^3 peaked at 67.1% in 2010 and then

decreased with time, leveling off at approximately 25%–30% from 2017 onward. The proportion of PLWH taking a single-tablet regimen (EVG/c/FTC/TAF) significantly increased from 2.2% in 2019 to 18.3% in 2020. Although improvements have been observed in the clinical status of treatment-naïve PLWH in China in recent years, nearly one-third of PLWH still started ART late, indicating that health education should be strengthened for high-risk groups and early diagnosis should be promoted for them. For those who have been diagnosed with HIV infection, early linkage to HIV care for PLWH should be further improved.

Data used in the current study were from a surveillance system that collects clinical data of PLWH receiving ART with long-term follow-up care in the STD/AIDS Prevention and Treatment Institute, Beijing CDC in Beijing, China. Clinicians in four hospitals in Beijing designated for HIV treatment (Peking Union Medical College Hospital, Beijing You'an Hospital, Beijing Ditan Hospital, and 302 Military Hospital of China) reported data on the platform. All PLWH who were treatment-naïve and initiated therapy in one of the above hospitals between January 1, 2010 and December 31, 2020 were included in our analysis. A total of 23,714 HIV-infected adults who started ART in Beijing, China were enrolled in the current study. After excluding those without CD4 count measurement at HIV diagnosis (*n*=965) and those aged 18 years or younger (*n*=158), 22,591 remaining cases were included in this study.

The time from diagnosis to initiating ART was defined as the number of days between HIV-reactive screening results and the receipt of HIV treatment. Temporal trends of the time from diagnosis to ART were described by year. Further subgroup analysis was performed by stratified age groups (19–29 years, 30–44 years, 45–59 years, and 60 years or older), sex, and infection route [men who have sex with men (MSM), heterosexual sex, injection drug uses (IDU),

and other (blood transfusion, mother-to-child transfusion, and unknown)]. CD4 cell count was stratified into four groups, ≤200 cells/mm^3, 200–349 cells/mm^3, 350–499 cells/mm^3, and ≥500 cells/mm^3 according to the ART-eligible policy in the guidelines for China. CD4 threshold adjusted with guideline updating, "late ART initiation" was defined as the CD4 cell count <200 cells/mm^3, at WHO stage 3 or 4, or having a clinical AIDS diagnosis prior to ART initiation. The prescription for an ART regimen at the first visit was directly obtained from the database.

Continuous variables with a normal distribution were presented as mean (standard deviation) and differences between groups were compared using one-way analysis of variance (ANOVA). Continuous variables with a skewed distribution were presented as median [interquartile range (IQR)] and compared using the Kruskal–Wallis test. Categorical variables were presented as numbers (percentages) and compared using the chi-square test or Cochran-Armitage trend test. Two-tailed P values less than 0.05 were considered statistically significant. Statistical analyses were performed with Stata version 16 (StataCorp LLC, College Station, Texas, USA).

Of the 22,591 PLWH within the current study, the median age was 31 years (IQR: 26–39 years), 95.5% were men, 68.2% were single, and 82.0% were MSM. The median CD4 count was 291.2 cells/mm^3 (IQR: 177.0–410.4). The median number of days from diagnosis to initial ART was 28 days (IQR: 13.0–103.0) (Supplementary Table S1, available in https://weekly.chinacdc.cn/).

The median days from diagnosis to initiating ART dramatically decreased from 91 (IQR: 33–471) days in 2011 to approximately 14 days from 2018 to 2020 (P for trend <0.001, Figure 1A). Trend analysis of this time interval by sex and age group showed a significant decline over time (Figure 1B and 1C, P for trend <0.001), especially in women (decreased by 94.1%, from 261.5 to 15.5 days) and PLWH aged 19 to 29 years (decreased by 89.6%, from 134 to 14 days). However, the median days from diagnosis to ART among PLWH who were IDU remained longer than that of other transmission routes, although without statistical significance, fluctuating between 127 and 992 days from 2010 to 2020, with a high of 780 days in 2020 (Figure 1D, P=0.333; P for trend 0.959). The proportion of PLWH with CD4 ≥500 cells/mm^3 was only 0.8% in 2010 but increased to 17% and stabilized from 2016 to 2020 (P for trend <0.001). On the contrary, the proportion of PLWH with CD4 ≤200 cells/mm^3 decreased from 67.1% in 2010 to ranging from 25% to 30% between 2016 and 2020 (Figure 2). The proportion of late ART initiation for PLWH declined from 52.5% in 2010 to 30.1% in 2020.

The most frequently used regimens of initial ART included EFV+3TC+TDF (76.0%), EFV+3TC+AZT (11.1%), LPV/r+3TC+TDF (3.0%), NVP+3TC+AZT (2.1%), and EVG/c/FTC/TAF (1.5%), accounting for 93.4% of all regimens from 2010 to 2020. Five of the most frequently used regimens for each year are shown in Figure 3. EFV+3TC+TDF was the predominantly used regimen, although its proportion declined from 2015. The proportion of EFV+3TC+AZT dropped from 43.6% in 2010 to only 1% in 2018. The use of NVP+3TC+AZT declined from 22.2% in 2010 to 0.3% in 2015. The use of EFV+3TC+d4T and NVP+3TC+d4T both decreased since 2010 (15.3% in 2010 to 1.0% in 2013; 14.7% in 2010 to 2.4% in 2012, respectively). However, the proportion of EVG/c/FTC/TAF significantly increased from 2.2% in 2019 to 18.3% in 2020.

DISCUSSION

Based on an 11-year surveillance study among PLWH in Beijing, China, we observed that the time from diagnosis to initiating ART has been substantially shortened, the condition of PLWH at the start of ART has been improved, and regularly prescribed ART regimens have constantly changed with the updated guidelines over the past decade.

Due to the concerted international effort to combat HIV, there has been a worldwide reduction in the time between HIV diagnosis and initiation of ART. In our study, we observed a significant decrease in the median days from HIV diagnosis to ART initiation for all PLWH, dropping from nearly 90 days in 2010 to 14 days in 2018, representing a reduction of 85%.Similarly, the time interval decreased from 660 days in 2013 to 15 days in 2019 in the African Cohort Study (AFRICOS) (5); from 418 days in 2011 to 77 days in 2015 in Australia (6), and from 69 days in 2005 to 6 days in 2018 according to the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) in the United States (7). Similar results were observed in Yunnan Province where the time from HIV diagnosis to ART initiation dropped from 1,776 days in 2004 to 27 days in 2016 (8). These results indicate an encouraging improvement in early ART initiation in China and
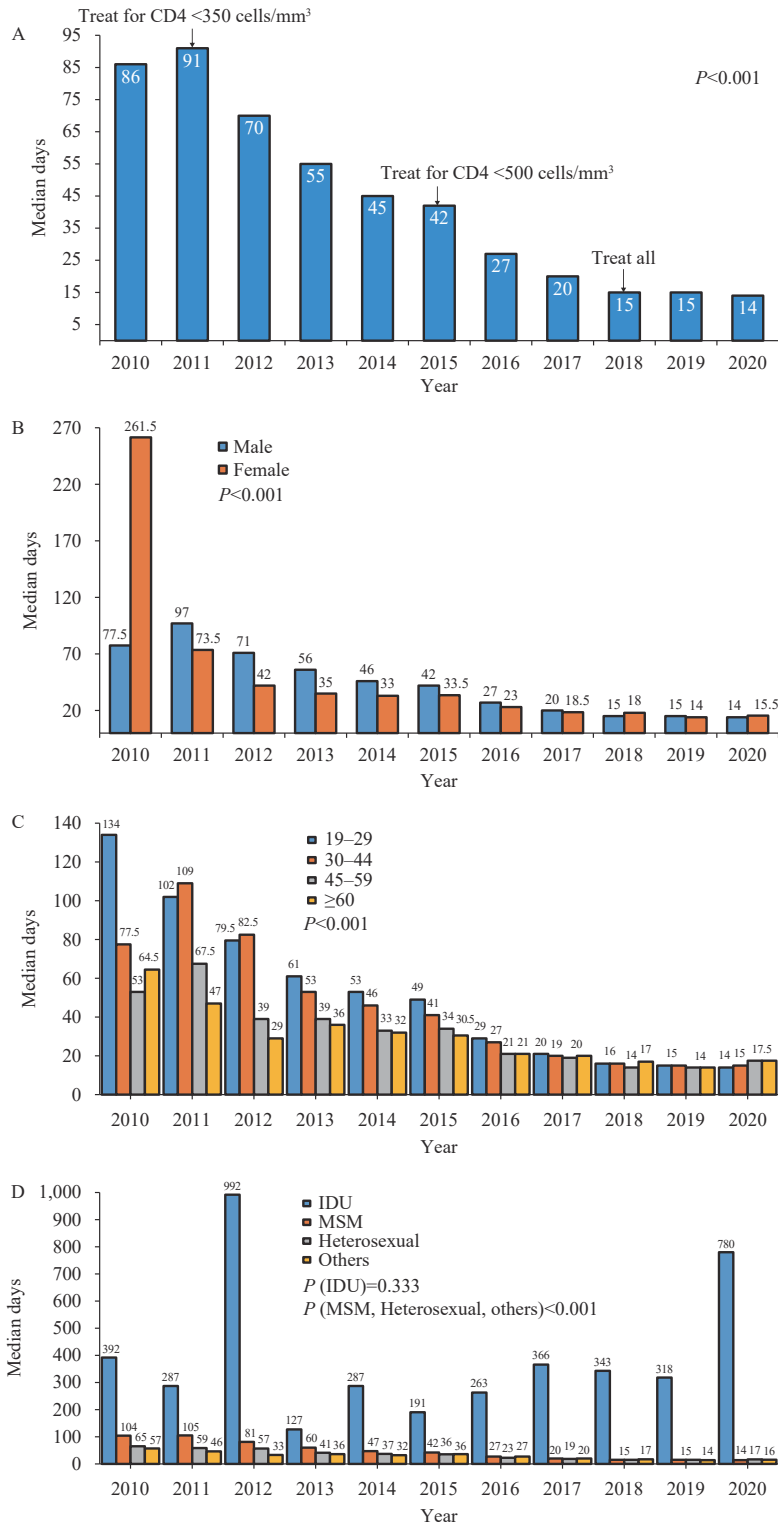
FIGURE 1. Median days from HIV diagnosis to initiating ART among PLWH in total sample and subgroups in Beijing, 2010–2020. (A) Median days from HIV diagnosis to initiating ART among PLWH in Beijing 2010–2020. (B) Median days from HIV diagnosis to initiating ART among PLWH in Beijing by sex, 2010–2020. (C) Median days from HIV diagnosis to initiating ART among PLWH in Beijing by age, 2010–2020. (D) Median days from HIV diagnosis to initiating ART among PLWH in Beijing by route of infection, 2010–2020.

Abbreviation: ART=antiretroviral therapy; HIV=human immunodeficiency virus; PLWH=people living with HIV; MSM=men who have sex with men; IDU=injection drug users.
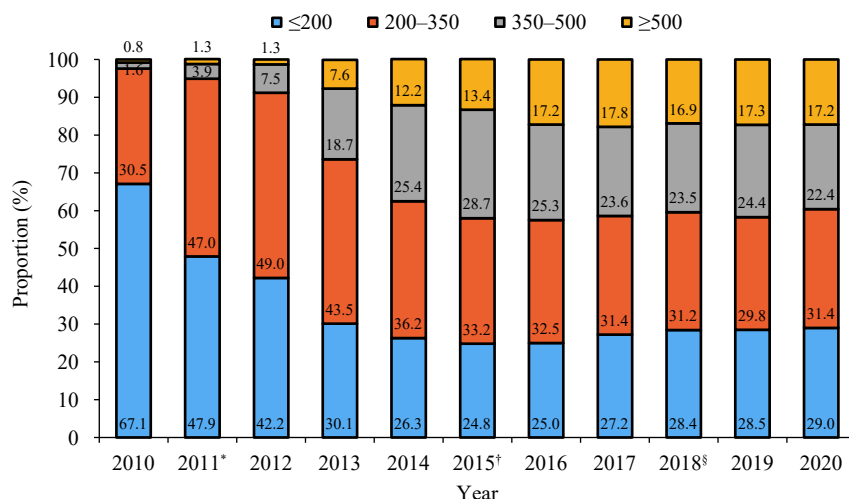
FIGURE 2. Proportion of CD4+ cell counts (stratified) among PLWH at initial treatment in Beijing, 2010–2020.
Abbreviation: PLWH=people living with human immunodeficiency virus.
* ART was recommended for PLWH whose CD4 <350 cells/mm³ in the national guideline in 2011.
† ART was recommended for PLWH whose CD4 <500 cells/mm³ in the national guideline in 2015.
§ ART was recommended for all PLWH regardless of CD4 cell counts in the national guideline in 2018.
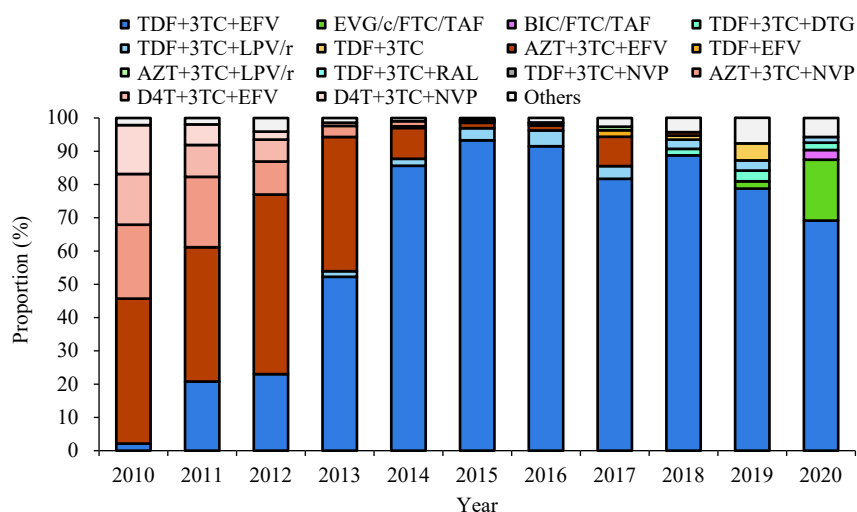

FIGURE 3. Trend of top five most commonly prescribed initial ART regimens for each year among PLWH in Beijing, 2010–2020.
Abbreviation: ART=antiretroviral therapy; PLWH=people living with human immunodeficiency virus.

worldwide with evolving clinical guidelines and supportive strategies.

However, the median number of days from diagnosis to ART still remained long in persons with intravenous drug use (PWID) in 2020, exceeding two years in Beijing, which was much longer than the 60 days reported in Yunnan in 2016 (9). Although PWID only accounted for a small proportion in this study, a large number of PWID may fear going to the hospital for ART due to criminalization and stigmatization of IDU. Therefore, it is necessary to take certain measures to identify this group of patients and provide them

with targeted assistance, such as joint administration of ART and opioid substitution therapy.

In addition to shortening the median days from HIV diagnosis to ART initiation, we also found continuous improvement in the clinical status of HIV-infected individuals at initial treatment over the past 10 years. An increase in the proportion of PLWH with CD4 cell count >500 cells/mm³ at ART initiation was observed from 2010 to 2020, from less than 1% in 2010 to more than 17% in 2020, which was higher than the 8.5% in 2014 and 14% in 2016–2019 reported in China's National Free Antiretroviral

Therapy Program. This may be owing to the treatment guideline being updated to adopt the strategy of "treat all" in China. China has made great progress in HIV control in recent decades, with the scaling up of HIV testing and treatment. However, it is remarkable that, in the era of "treat all", about one-third of PLWH still initiated ART late in 2020, which was much higher than the 21% in Canada in 2012 (9), indicating that health education should be strengthened for high-risk groups and early diagnosis should be promoted for them. For those who have been diagnosed with HIV infection, follow-up should be strengthened and early treatment should be urged.

EFV+3TC+TDF was the most commonly prescribed regimen during our study period, although its proportion declined from 2015, likely due to its status as the first-line recommended regimen in the national treatment guidelines since 2011. NVP+3TC+AZT declined and only accounted for 0.3% in 2015; this was the first-line recommended regimen in 2005 in China, but it became an alternative regimen in 2011 due to its hepatotoxicity (10).

Reducing the pill burden with the use of a single-tablet regimen (first recommended as the first-line regimen in the Chinese guideline in 2018) has been shown to improve adherence to ART. Consequently, the proportion of PLWH using single-tablet regimens significantly increased and accounted for nearly one-fifth in 2020, reflecting the influence of national guideline recommendations on clinical practice. To a certain extent, ART has become more effective and easier to take.

Our study has some limitations. First, the data were obtained during clinical care and were not primarily for research purposes; thus, some important variables, such as CD4 cell counts at HIV diagnosis, were not collected. Second, we included PLWH who were initiating ART, which may have missed undiagnosed and untreated PLWH; thus, the burden of HIV may have been underreported. Third, the HIV epidemic in China is diverse and complex. The data in this study were all collected from hospitals in Beijing; therefore, generalization of the research results is limited. In addition, as we did not have data on HIV collected in 2021 and 2022, we could not symmetrically evaluate the impact of the COVID-19 pandemic on HIV care in Beijing. Future studies will be conducted with more sufficient data.

In conclusion, notable improvements in clinical condition were observed in initial ART among HIV-infected adults in Beijing between 2010 and 2020,

which may be attributed to the continuous evolution of national strategies. However, there was a substantial number of PLWH starting ART late, indicating that health education should be strengthened for high-risk groups and early diagnosis should be promoted for them. For those who have been diagnosed with HIV infection, early linkage to HIV care for PLWH should be further improved. In addition, although the time from diagnosis to treatment was shortened, it remained long in PWID. For public health practitioners, health education and intervention regarding HIV diagnosis and treatment should be further strengthened according to different characteristics in certain regions. Current ART treatment patterns highlight the high uptake of guideline-recommended ART regimens among treatment-naïve individuals initiating ART. It is foreseeable that the single-tablet regimen will be more widely used in PLWH.

Corresponding authors: Jufen Liu, liujufen@bjmu.edu.cn; Feng Cheng, fcheng@mail.tsinghua.edu.cn.

1 Institute of Reproductive and Child Health/National Health Commission Key Laboratory of Reproductive Health, Peking University, Beijing Municipality, China; 2 Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing Municipality, China; 3 Department of Epidemiology and Biostatistics, Institute of Basic Medical Sciences Chinese Academy of Medical Sciences, School of Basic Medicine Peking Union Medical College, Beijing Municipality, China; 4 School of Medicine, Tsinghua University, Beijing Municipality, China; 5 Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, USA.
& Joint first authors.

REFERENCES

1. Farel CE, Dennis AM. Why everyone (almost) with HIV needs to be on treatment: a review of the critical data. Infect Dis Clin North Am 2019;33(3):663 – 79. http://dx.doi.org/10.1016/j.idc.2019.05.002.
2. Maina EK, Bonney EY, Bukusi EA, Sedegah M, Lartey M, Ampofo WK. CD4+ T cell counts in initiation of antiretroviral therapy in HIV infected asymptomatic individuals; controversies and inconsistencies. Immunol Lett 2015;168(2):279 – 84. http://dx.doi.org/10.1016/j.imlet.2015.10.005.
3. Ejigu Y, Magnus JH, Sundby J, Magnus M. Health outcomes of asymptomatic HIV-infected pregnant women initiating antiretroviral therapy at different baseline CD4 counts in ethiopia. Int J Infect Dis 2019;82:89 – 95. http://dx.doi.org/10.1016/j.ijid.2019.02.019.
4. The INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med 2015;373(9):795 – 807. http://dx.doi.org/10.1056/NEJMoa1506816.
5. Esber AL, Coakley P, Ake JA, Bahemana E, Adamu Y, Kiweewa F, et al. Decreasing time to antiretroviral therapy initiation after HIV diagnosis in a clinic-based observational cohort study in four African countries. J Int AIDS Soc 2020;23(2):e25446. http://dx.doi.org/10.1002/jia2.25446.

6. Medland NA, Chow EPF, McMahon JH, Elliott JH, Hoy JF, Fairley CK. Time from HIV diagnosis to commencement of antiretroviral therapy as an indicator to supplement the HIV cascade: dramatic fall from 2011 to 2015. PLoS One 2017;12(5):e0177634. http://dx.doi.org/10.1371/journal.pone.0177634.

7. Lee JS, Humes EA, Hogan BC, Buchacz K, Eron Jr JJ, Gill MJ, et al. CD4 count at entry into care and at antiretroviral therapy prescription among adults with human immunodeficiency virus in the United States, 2005-2018. Clin Infect Dis 2021;73(7):e2334 – 7. http://dx.doi.org/10.1093/cid/ciaa1904.

8. Xu JF, Sönnerborg A, Gao LM, Wang PC, Bouey JZH, Cheng F. Delayed treatment for people living with HIV in China, 2004-2016: an analysis of an observational cohort. Int J Environ Res Public Health 2020;17(5):1809. http://dx.doi.org/10.3390/ijerph17051809.

9. Lourenço L, Samji H, Nohpal A, Chau W, Colley G, Lepik K, et al. Declines in highly active antiretroviral therapy initiation at CD4 cell counts ≤ 200 cells/μL and the contribution of diagnosis of HIV at CD4 cell counts ≤ 200 cells/μL in British Columbia, Canada. HIV Med 2015;16(6):337 – 45. http://dx.doi.org/10.1111/hiv.12212.

10. Zhang XQ. Anti-retroviral drugs: current state and development in the next decade. Acta Pharm Sin B 2018;8(2):131 – 6. http://dx.doi.org/10.1016/j.apsb.2018.01.012.

SUPPLEMENTARY TABLE S1. Baseline characteristics of study population, Beijing, 2010–2020.

Variable (*n*=22,591)	N (%)
Age, median (IQR), years	31 (26.0–39.0)
Men	21,563 (95.5)
Marital status	
Married or living with partner	5,591 (24.8)
Single	15,403 (68.2)
Widowed, divorced, or separated	1,340 (6.0)
Unknown	257 (1.1)
Routes of HIV transmission	
MSM	18,531 (82.0)
Heterosexual	2,245 (9.9)
IDU	160 (0.7)
Others*	1,655 (7.4)
Coinfections	
HBsAg positive[†]	966 (5.2)
Anti-HCV positive[§]	362 (2.0)
OIs	658 (2.9)
CD4 cell counts, median (IQR), cells/mm^3	291.2 (177.0–410.4)
CD8 cell counts, median (IQR), cells/mm^3	951 (656–1,329)
CD4/CD8 ratio	0.3 (0.2, 0.4)
Time from diagnosis to initial ART, median (IQR), days	28.0 (13.0–103.0)
WHO clinical stages at diagnosis	
Stage Ⅰ	17,471 (77.3)
Stage Ⅱ	2,517 (11.1)
Stage Ⅲ	1,229 (5.4)
Stage Ⅳ	1,374 (6.1)
Proportion of CD4 cell counts, cells/mm^3	
≤200	6,608 (29.3)
200–349	7,808 (34.6)
350–499	5,065 (22.4)
≥500	3,110 (13.8)
VL, median (IQR), log$_{10}$ copies/mL	4.5 (3.9–5.0)
Year of ART initiation	
2010	374 (1.7)
2011	775 (3.4)
2012	1,199 (5.3)
2013	1,772 (7.8)
2014	2,475 (11.0)
2015	3,054 (13.5)
2016	3,231 (14.3)
2017	3,131 (13.9)
2018	2,804 (12.4)
2019	2,214 (9.8)
2020	1,562 (6.9)

Abbreviation: MSM=men who have sex with men; IDU=intravenous drug use; OIs=opportunistic infections; ART=antiretroviral therapy; IQR=interquartile range; VL=viral load.
* Including blood transfusion, mother-to-child transfusion and unknown.
[†] HBsAg, hepatitis B surface antigen, data of HBsAg were not available for 3,880 patients.
[§] HCV, hepatitis C virus, data of anti-HCV were not available for 4,214 patients.