Impact of Antiretroviral Therapy on the Spread of Human Immunodeficiency Virus in Chaoyang District, Beijing, China: Using the Asian Epidemic Model

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Abstract

Background: Successful antiretroviral therapy (ART) has been demonstrated to be effective in reducing the infectivity of human immunodeficiency virus (HIV). We conducted a study to predict the potential effect of ART on the spread of HIV in Chaoyang District, Beijing, China, using the Asian Epidemic Model (AEM).

Methods: The AEM baseline workbook was used to determine the current infection status and to project the future spread of HIV under current conditions. We changed the input on the ART coverage from 2014 to 2025 and also modified the treatment eligibility in the AEM intervention workbook, in order to allow for analysis of the projected downstream impact of ART.

Results: By gradually increasing the ART coverage rate from 29.7% (rate of 2013) to 40.0%, 50.0%, 60.0%, 70.0%, 80.0%, and 90.0% (at CD4+ ≤350 cells/µl), and by changing the dates of coverage from 2014 to 2020, the number of new infections showed a cumulative decline of 0.60%, 1.59%, 2.94%, 5.33%, 9.32%, and 14.98%, respectively. After 2020, the projected rates of infection rebounded slightly, so with the exception of the years with very high coverage (90.0%), new infections continued to decrease. When we changed the initial threshold of therapy to CD4+ cell counts ≤500 cells/µl, new infections decreased 6.00%, 11.64%, 15.92%, 21.11%, 26.92%, 33.05%, and 38.75%, respectively, under varying ART coverages.

Conclusion: Our study demonstrates that the early initiation of ART for people living with HIV/acquired immune deficiency syndrome (AIDS) has a positive effect in slowing the spread of HIV.

Key words: Antiretroviral Therapy; Asian Epidemic Model; Human Immunodeficiency Virus; Impact; Transmission
Chaoyang District has implications on the overall spread of HIV in Beijing.

In treatment programs on PLWHA, the development of antiretroviral drugs was viewed as a remarkable scientific achievement. Antiretroviral therapy (ART) led to dramatic decreases in both morbidity and mortality among PLWHA. According to international guidelines, it is highly recommended that ART is initiated prior to the overt display of immune deficiency symptoms.[3,4] The National Free Antiretroviral Treatment Program (NFATP), one of the programs of the “Four Frees and One Care” Policy in China, was piloted in 2002 and scaled up in 2003.[5,6] This program was initially implemented in former plasma donors and then offered to PLWHA throughout all of China.[7,8] In 2003, the Chaoyang District began to implement NFATP. According to the National Treatment Criteria,[9] ART was initiated among those PLWHA who had CD4+ counts ≤200 cells/µl in Chaoyang District, and in 2008, the threshold for treatment was changed to below 350 CD4+ cells/µl. By the end of 2012, 753 people had been treated with ART.[1]

Successful ART contributed to the decrease of viral load both in plasma and in semen.[10] It was determined to be effective in reducing the infectivity of HIV, thus reducing illness and deaths of PLWHA.[11,12] Cohen et al.[13] supported the idea of using ART as a part of a public health strategy to reduce the spread of HIV infection. However, unless complete viral suppression is achieved, ART could cause the pool of potential transmitters of HIV to increase as the result of its effectiveness in increasing the life expectancy of infected individuals.[14] The benefit of ART might also be subsequently offset by increasing high-risk behaviors among PLWHA.[15-17] Data from a study in Canada suggested that by initiating highly active antiretroviral therapy (HAART) at 200 CD4+ cells/µl, an increase in HAART coverage from 50% to 75%, 90%, or 100% would lead to a decrease in the annual number of individuals in the province of British Columbia newly testing positive for HIV by 37%, 54%, and 62%, respectively.[18] Furthermore, it is expected to be an additional decline in the annual number of individuals newly testing positive if the initiation of HAART is reduced from CD4+ cell count ≤200 cells/µl to CD4+ cell count ≤350 cells/µl. Findings from another study revealed that different levels of coverage of ART would not affect benefits such as life-years gained per person per year of treatment because of the limited effect of treatment on transmission.[19]

What then is the overall effect of ART on the epidemiology of HIV? The end result of decreased infectivity, together with an increased duration of infectiousness as a result of ART, remains an area of uncertainty in the battle against HIV.[20]

Therefore, we conducted the present study to predict the potential effect of ART on the epidemiology of HIV in the next 12 years in Chaoyang District, using the Asian Epidemic Model (AEM). AEM, which was developed by the East-West Center in Hawaii, USA, is commonly used to estimate epidemics and to simulate the spread of HIV throughout the world.[21] and to evaluate the effects of preventive measures on HIV. In our study, we used AEM to evaluate the influence of ART on new HIV infections and to measure the morbidity and mortality of treated patients.

**Methods**

**Study design**

The Asian Epidemic Model workbook

The AEM is a full-process model that mathematically replicates the key processes driving HIV transmission in Asia, and it is patterned after the dominant transmission modes in Asia with appropriate behavioral inputs.[21] It was first used to estimate the status of the HIV epidemic, and it reflected the effects related to programs and policies, including input of information on various behaviors and modeling parameters.[22] The AEM model has been fully described previously and has been shown to work well in Asian countries.[20,21]

The calculation by AEM of the impact of AIDS on pediatric patients is based on data from fertility, levels of female infections, and other AIDS/non-AIDS-related (background mortality) deaths.[21] All behavioral inputs could be specified on an annual basis. Both HIV prevalence and incidence were modeled by age and gender. There were two groups (Group 1 and Group 2) in each key population in the model. Group 1 referred to high-risk takers whereas Group 2 referred to low-risk takers. In our study, we assumed that all the key populations were high-risk takers. AEM was used to examine the impact of different prevention efforts on the outcomes of new HIV infections, current HIV infections, and AIDS-related deaths, based on the patterns of HIV transmission observed in Asian countries. The key populations included men who have sex with men (MSM), male sex workers, female sex workers (FSW) and their clients, injecting drug users ([IDUs] both males and females), transgender population, and lower-risk members in the general population. New HIV infections were calculated by multiplying the populations above 15 years of age with a given risk behavior, and corrected for some cofactors, including the prevalence of sexually transmitted infections (STIs), implementation of ART, percentage of condom use, percentage of injections shared, and age distributions for fertility. In addition, the number of current HIV infections and annual HIV-related deaths was calculated from the process model.[21] Researchers could analyze the epidemiological impact of ART by varying ART coverage and eligibility of treatment while assuming that input behaviors and factors such as trends of STI and others remain unchanged.

**Source of data**

The latest AEM software (version 4.0, the East-West Center, Hawaii, USA) requires five parameters.

**Population size**

Demographic data were derived from Statistical Yearbooks (1990 to 2010) of the Chaoyang District of Beijing, China.[24,25]

**Behavioral parameters**

Data related to the trends in behavioral changes including
condom usage (2000–2012), proportions of needle sharing among IDUs (1999–2012), and sexual behavior among IDUs and sex workers (1999–2010) were primarily derived from sentinel surveillance programs, offered by the Beijing Chaoyang District Center for Disease Control and Prevention.[26-32]

**Human immunodeficiency virus prevalence**

Data on HIV prevalence were collected from the relevant population groups including FSW, IDU, and MSM at the sentinel surveillance points (2003–2013) and from other research studies conducted on populations[33-36] in the Chaoyang District of Beijing [Table 1].

**Antiretroviral therapy-related parameters**

ART coverage data (2003–2013) were obtained from the Report of Beijing Chaoyang District Health Bureau,[37] and other ART-related parameters were obtained from the Beijing Chaoyang District AIDS Comprehensive Prevention Information System in China (2003–2013), and other published references [Table 1].[38]

**Epidemiological parameters**

The probabilities of HIV transmission via different routes, including vaginal intercourse transmission from males to females, vaginal intercourse transmission from females to males, anally insertive partners to receptive partners, anally receptive partners to insertive partners, and shared needles for intravenous drug injections, were from published references.[37] Age distributions of fertility statistics were obtained from the Beijing Chaoyang District 2010 census data.[25] The parameters related to the reduction of ART-related infectivity through heterosexual transmission, MSM, and IDU were obtained from other research findings.[39-41]

**Modeling process**

In this study, both the baseline workbook (BW) and the intervention workbook (IW) of AEM were used to assess the impact of ART on the spread of HIV in Chaoyang District, Beijing.

The BW was used to determine the current infection status and to obtain projections of the future spread of HIV under current conditions. Numbers of newly infected, those currently living with HIV/AIDS, and HIV-related deaths were calculated in the BW by filling in a number of key inputs, shown in the “source of data.” To accurately reflecting the situation in Chaoyang District, we adjusted some model parameters after consulting with local experts. Those parameters included STI prevalence and percentage of condom use by clients with FSW, percentage of male IDUs who have ever visited FSW, percentage of IDUs who share needles, and proportions of condom use in MSM. The related behavioral factors only included those which appeared in the baseline survey. These baseline data were then used as the starting point for data analysis, using the IW.

Next, we changed the input on ART coverage and the treatment eligibility from 2014 to 2025 appeared in IW, so as to allow the analysis of the downstream impact of ART to take place. Annual HIV infections and HIV-related deaths were calculated using different levels of coverage and treatment eligibility of antiretroviral use, presuming that behaviors of key populations remained unchanged.

## Results

We used the AEM to model results under different ART coverage and different initial threshold levels. This model allowed us to determine the numbers of new infections and PLWHA as well as HIV-related deaths.

### Impact due to the expansion of antiretroviral therapy coverage on human immunodeficiency virus transmission

In 2003, the ART coverage was 5.1% among individuals in Chaoyang District with symptoms or with CD4+ cell counts ≤200 cells/µl. Since then, coverage has greatly improved, reaching almost 30.0% in 2013. As the first

| Year | ART coverage (%) | Initiation on CD4 cell count (/µl) | HIV prevalence of FSW (%) | HIV prevalence of male IDU (%) | HIV prevalence of female IDU (%) | HIV prevalence of MSM (%) |
|------|------------------|-----------------------------------|---------------------------|-------------------------------|-------------------------------|--------------------------|
| 2003 | 5.06             | 200                               | 0.26                      | 8.01                          | 7.83                          | 1.34                     |
| 2004 | 10.91            | 200                               | 0.34                      | 7.68                          | 6.98                          | 1.55                     |
| 2005 | 13.81            | 200                               | 0.50                      | 6.82                          | 8.00                          | 3.23                     |
| 2006 | 18.27            | 200                               | 0.29                      | 6.48                          | 6.14                          | 4.81                     |
| 2007 | 21.36            | 200                               | 0.71                      | 6.04                          | 5.66                          | 4.50                     |
| 2008 | 20.98            | 350                               | 0.62                      | 5.86                          | 6.45                          | 5.40                     |
| 2009 | 20.11            | 350                               | 0.07                      | 6.22                          | 6.06                          | 6.04                     |
| 2010 | 21.71            | 350                               | 0.15                      | 4.26                          | 6.67                          | 6.09                     |
| 2011 | 24.14            | 350                               | 0.20                      | 3.65                          | 3.00                          | 5.60                     |
| 2012 | 27.40            | 350                               | 0.10                      | 3.95                          | 2.81                          | 6.87                     |
| 2013 | 29.72            | 350                               | 0.10                      | 3.70                          | 2.85                          | 7.12                     |

ART: Antiretroviral therapy; FSW: Female sex workers; HIV: Human immunodeficiency virus; IDU: Injecting drug user; MSM: Men who have sex with men.
step in determining the estimated number of PLWHA from 2003 to 2013, we began analysis of the HIV/AIDS epidemic in Chaoyang District by inputting behavioral and epidemiological data. The estimated number of PLWHA from 2003 to 2013 increased from 903 to 4207. We then explored the potential effect of ART on the spread of HIV in Chaoyang District by comparing the numbers of new infections, PLWHA, and HIV-related deaths, assuming that the future ART coverage rates remain the same as those of 2013. We also simulated the numbers of infections and HIV-related deaths if the ART coverage changed to 40.0%, 50.0%, 60.0%, 70.0%, 80.0%, or 90.0%. Through AEM, we predicted that if the ART coverage increased, HIV-related deaths would have decreased gradually with the initiation of ART when CD4 immune deficiency syndrome.

Table 2: Projection on the levels of HIV infections and HIV-related deaths under different ART coverage and the initiations of therapy ≤350 cells/µl in Chaoyang District of Beijing under the AEM, n

| Year | 2025 | 2024 | 2023 | 2022 | 2021 | 2020 | 2019 | 2018 | 2017 | 2016 | 2015 | 2014 |
|------|------|------|------|------|------|------|------|------|------|------|------|------|
| New infections on different ART coverage | 5747 | 6064 | 6523 | 7119 | 7876 | 8779 | 9565 | 10136 | 10746 | 11355 | 11965 | 12575 |
| Number of PLWHA on different ART coverage | 349 | 470 | 591 | 712 | 833 | 954 | 1075 | 1196 | 1317 | 1438 | 1559 | 1680 |
| Year | 2025 | 2024 | 2023 | 2022 | 2021 | 2020 | 2019 | 2018 | 2017 | 2016 | 2015 | 2014 |
| Number of HIV-related deaths on different ART coverage | 203 | 239 | 274 | 305 | 333 | 356 | 376 | 333 | 356 | 376 | 393 | 406 |

Effect of changes of CD4+ cell counts on human immunodeficiency virus transmission during the initiation of antiretroviral therapy

We further explored the impact of ART on the spread of HIV in the Chaoyang District from 2014 to 2025 by changing the relative ART thresholds, from CD4+ cell count ≤350 to CD4+ cell count ≤500 cells/µl. When comparing the results from Tables 2 and 3, we found a decrease of 6.00%, 11.64%, 15.92%, 21.11%, 26.92%, 33.05%, and 38.75%, respectively, in the numbers of new HIV infections when the CD4+ threshold for treatment eligibility was lowered but the ART coverage was held unchanged. When we held the ART coverage rate at 60.0% and changed the CD4+ cell count threshold from ≤350 to ≤500 cells/µl, new infections from 2014 to 2025 were reduced by 18.53% to 23.31%. We also discovered that there was an obvious decrease in the number of new infections in Chaoyang District if the ART coverage gradually increased to 90.0% [Table 3]. The number of HIV-related deaths would gradually decrease from 2014 to 2025 with the increase of ART coverage and the initiation of ART at CD4+ cell count ≤500 cells/µl [Table 3]. There was a fluctuation

*The number of deaths was expected to exceed the actual number of deaths under the 90% of ART coverage. There had been negative, with a 0 instead.

PLWHA: People living with HIV/AIDS; HIV: Human immunodeficiency virus; ART: Antiretroviral therapy; AEM: Asian Epidemic Model; AIDS: Acquired immune deficiency syndrome.
Regarding the number of PLWHA. If the ART coverage increased, a slight decline occurred from 2014 to 2015. Subsequently, from 2016 to 2019, the number of PLWHA decreased, increased, and then decreased again. After 2019, it increased initially and then decreased [Table 3]. When the threshold for initiation of ART was changed (from CD4 cell count $\leq 350$ cells/$\mu l$ to CD4 cell count $\leq 500$ cells/$\mu l$), the number of PLWHA decreased.

**Discussion**

Mathematical models provide a way to examine the impact of ART on the spread of HIV. Granich et al.\[42\] used a stochastic model to explore the effect of various treatment strategies on the case reproduction number. A linear model was used to evaluate the effects of ART on new HIV infections.\[12\] In this study, we used a process model (AEM) to investigate the potential effect of ART under various levels of ART coverage and thresholds of CD4 cell count for initiation of treatment. Our study shows that ART could have a positive effect in reducing HIV infections in Chaoyang District from 2014 to 2025 if the CD4$^+$ threshold for treatment eligibility is lowered. The impact of ART on HIV transmission is maximized in conjunction with increasing levels of ART coverage.

Data from previous studies presented conflicting results regarding the impact of ART on HIV transmission.\[11,14,15,42-45\] Under different mathematical models, research findings show that ART has the potential to substantially reduce the number of new HIV infections, in conjunction with easier access and high adherence to ART.\[12,42-44\] Among the above studies, Granich’s discovery was quite encouraging. His study indicated that, to some extent, strategies that include universal voluntary HIV testing with immediate ART, combined with other intervention programs, would reduce HIV transmission. There are other studies\[15,16,45\] that show negative results regarding the impact of ART. These studies operate on the assumption that an increase in risky sexual behavior negates the preventive benefits from ART. Data from our study support the theory that the existing ART program in Chaoyang District reduces new HIV infections by changing the CD4$^+$ threshold for initiation of ART from under 350 to $\leq 500$ cells/$\mu l$, assuming that parameters such as sexual and other risky behaviors, as well as incidence of sexually transmitted diseases, remain unchanged. More
potential preventive benefits might have been evident if the CD4+ threshold for treatment eligibility had been reduced along with an increase in ART coverage. In our study, we explored the net effect of ART on the spread of HIV under AEM by keeping the behavior-related factors unchanged. Other factors affecting the HIV epidemic, such as changes in the number of sex partners, rate of condom use, and others, could be set in the design of AEM.

There are two commonly used methods for the calculation of ART coverage. The first one uses the total estimated number of HIV patients who are eligible for the treatment (eligible based on CD4+ count requirements) as the denominator while the second one uses the total reported cases of HIV as the denominator. In our study, we used the first method to calculate ART coverage and the actual number under treatment as the numerator. The World Health Organization (WHO) and UNAIDS estimate that the global treatment coverage was about 43% in 2009, based on quality monitoring systems on patients throughout the world. The ART coverage in our study was lower than the global estimates, possibly because the denominator might have been overestimated.

There are several unique features of our study that are worth mentioning. First, the geographic scope of the study is new. AEM has been used to assess the impact of ART on the spread of HIV in the Chaoyang District of Beijing, China, and the results were compared to the dynamic and linear models which are both commonly used to evaluate the effects of ART. In some studies, AEM has been used to forecast the epidemiology of HIV, as well as to evaluate the impact of intervention measurements such as condom use and standardized STD treatments, other than ART, in Asian countries or regions. Second, the methodology we used in this study can more directly explore the impact of ART on new infections, in contrast with the dynamic model which uses the basic reproductive number as the effect of assessment indicators. Third, we used AEM to prospectively predict the impact of ART on the spread of HIV by adjusting the infectivity-related parameters to match the actual data which were collected from 2003 to 2013 in Chaoyang District. We focused on the pure impact of ART, using the assumption that other high-risk behaviors remain unchanged. Finally, our results indicate that the best initial CD4+ threshold for the prevention of HIV transmission is below 500 cells/µl. For these reasons, we recommend changing the threshold of CD4+ cell count for initiation of ART in Chaoyang District. There are a few limitations in this study since some factors affecting the implementation of ART may have been disregarded due to the related nature of AEM, such as drug resistance or withdrawal from treatment. We observed that when the threshold for initiation of therapy was set below 350 cells/µl, the number of new infections would slightly drop in the beginning stages, but would then increase along with the increase of ART coverage, warranting further study.

In conclusion, the results of our study indicate that adjustments such as the expansion of ART coverage and lowering the CD4+ threshold for initiation of treatment could lead to a substantial reduction of the spread of HIV in Chaoyang District in the future. Our study supports the idea that early initiation of ART for PLWHA would slow the spread of HIV.

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Conflicts of interest
There are no conflicts of interest.

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