Original Article

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

Introduction

The prevalence of human immunodeficiency virus (HIV) in Chaoyang District, Beijing, China, has been increasing rapidly since the first HIV case was detected in this area in 1990. By the end of 2012, 2450 people were living with HIV/acquired immune deficiency syndrome (AIDS) (PLWHA), with 55 HIV-related deaths.[1] Among all cases, 85.1% were infected via sexual contact, with transmission primarily through homosexual contact. According to statistics from the Chinese Ministry of Health and the Joint United Nations Programme on HIV and AIDS (UNAIDS), sexual transmission comprised 92.2% of all cases in 2014.[2] Notably, Chaoyang is the largest urban district of Beijing with a population size of 4,800,000, roughly one-fourth of the capital's total population. Both the central business district, one of Beijing's major business areas, and the Beijing Capital International Airport are located in Chaoyang District. The densely populated business area together with a large number of international travelers naturally supports increased activities and behaviors that create opportunities for the spread of HIV. Furthermore, the spread of HIV in

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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.[20,23]

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.[27] 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

Table 1: ART-related parameters, and parameters of HIV prevalence among key affected population in Chaoyang District in 2003–2013

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 $CD4^+$ cell count was at 350 cells/μl [Table 2]. However, the number of PLWHA would greatly increase. Our findings suggested that with increased ART coverage, the number of new infections declined by 0.60%, 1.59%, 2.94%, 5.33%, 9.32%, and 14.98%, respectively, in 2014–2020, rebounding slightly after 2020; except for the years with very high coverage (90.0%), new infections decreased [Table 2].

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

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	New infections on different ART coverage							Number of PLWHA on different ART coverage						
	29.7%	40.0%	50.0%	60.0%	70.0%	80.0%	90.0%	29.7%	40.0%	50.0%	60.0%	70.0%	80.0%	90.0%
2014	495	491	483	472	457	437	413	4499	4656	4794	4942	5082	5182	5202
2015	471	467	460	450	436	417	393	4731	4900	5067	5252	5434	5572	5612
2016	479	475	469	461	447	428	401	4936	5119	5317	5542	5771	5957	6024
2017	471	468	463	456	444	424	396	5101	5300	5529	5796	6077	6320	6424
2018	476	473	470	464	453	434	406	5244	5459	5720	6029	6366	6674	6825
2019	474	472	470	466	458	440	411	5362	5592	5885	6237	6633	7012	7222
2020	471	470	470	468	461	446	416	5457	5704	6026	6422	6877	7335	7615
2021	467	466	468	468	463	449	421	5531	5793	6145	6582	7099	7640	8001
2022	467	467	470	472	469	458	430	5592	5868	6248	6727	7304	7931	8385
2023	474	476	480	484	484	475	448	5648	5938	6345	6864	7502	8219	8775
2024	479	481	487	493	496	490	464	5699	6003	6437	6994	7692	8502	9169
2025	484	487	494	502	507	504	480	5747	6064	6523	7119	7876	8779	9565

Year	Number of HIV-related deaths on different ART coverage						
	29.7%	40.0%	50.0%	60.0%	70.0%	80.0%	90.0%
2014	203	189	153	110	61	12	0*
2015	239	223	186	140	84	26	0*
2016	274	257	219	171	111	43	0*
2017	305	287	250	201	137	61	0*
2018	333	314	279	231	164	81	4
2019	356	338	305	258	191	101	13
2020	376	359	328	284	217	123	23
2021	393	377	349	307	242	145	34
2022	406	392	367	327	264	166	46
2023	418	405	383	346	286	187	58
2024	428	416	396	363	305	208	71
2025	436	426	408	378	323	227	84

*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.

Table 3: Projection on the levels of HIV infections and HIV-related deaths under different ART coverage and the initiations of therapy ≤500 cells/μl, in Chaoyang District of Beijing under the AEM, *n*

Year	New infections on different ART coverage							Number of PLWHA on different ART coverage						
	29.7%	40.0%	50.0%	60.0%	70.0%	80.0%	90.0%	29.7%	40.0%	50.0%	60.0%	70.0%	80.0%	90.0%
2014	458	425	395	362	326	290	255	4390	4321	4302	4247	4153	4018	3824
2015	437	406	379	348	314	279	245	4622	4558	4556	4516	4432	4298	4093
2016	446	415	389	358	323	286	250	4830	4775	4794	4774	4706	4578	4365
2017	439	408	383	353	318	280	241	5004	4960	5003	5007	4959	4844	4627
2018	445	415	391	362	327	288	248	5160	5129	5198	5229	5206	5109	4891
2019	444	416	393	365	331	292	250	5293	5277	5374	5434	5441	5367	5153
2020	443	416	396	369	336	297	254	5406	5408	5532	5625	5664	5620	5415
2021	440	414	396	371	340	301	257	5500	5520	5674	5800	5876	5865	5675
2022	442	416	399	376	346	306	260	5582	5620	5803	5964	6078	6105	5934
2023	450	426	410	389	360	321	273	5661	5718	5930	6126	6281	6348	6199
2024	457	433	419	399	371	333	283	5735	5812	6053	6285	6482	6592	6470
2025	463	440	427	409	383	345	294	5807	5903	6175	6442	6683	6838	6745

Year	Number of HIV-related deaths on different ART coverage						
	29.7%	40.0%	50.0%	60.0%	70.0%	80.0%	90.0%
2014	172	141	101	60	22	0*	0*
2015	205	170	125	79	35	0*	0*
2016	237	198	150	100	49	6	0*
2017	265	223	174	120	64	14	0*
2018	289	246	197	140	80	23	0*
2019	311	267	218	160	96	33	0*
2020	330	286	237	178	113	44	0*
2021	346	302	254	196	128	56	0*
2022	360	316	270	212	143	67	2
2023	372	328	283	227	157	78	7
2024	382	339	295	240	170	89	13
2025	391	348	306	252	182	100	19

*The number of deaths was expected to exceed the actual number of deaths under 80%, 90% of the 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 ≤350 cells/μl to CD4 cell count ≤500 cells/μl), 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 ≤500 cells/μl, 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.[5] 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.[46] 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.[42,47] In some studies,[21,22] 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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