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Decreasing Excess Mortality of HIV-infected Patients Initiating Antiretroviral Therapy: Comparison with Mortality in General Population in China, 2003 – 2009

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Abstract

Objective—To evaluate excess mortality across calendar time comparing HIV-infected patients receiving cART with the general Chinese population.

Methods—Patients receiving free cART through the National Free Antiretroviral Therapy Program (NFATP) between 1 January 2003 and 31 December 2009 were included. Observed mortality rates, excess mortality rates and standardized mortality ratios were calculated by calendar periods. Factors associated with excess mortality across calendar time were evaluated in multivariable Poisson regression models.

Results—Among 64,836 HIV-infected patients the observed and excess mortality rates in 2003/2004 were 9.5 deaths/100 person-years (95% confidence interval [95% CI]: 8.8, 10.2) and 9.1 (8.5, 9.8); in 2008/2009 these decreased to 5.6 (5.4, 5.8) and 5.2 (5.0, 5.4) respectively. The adjusted excess hazard ratio (eHR) for 2003/2004 in comparison to 2008/2009 was 1.27 (95% CI: 1.11, 1.45). Patients initiating cART at CD4 cell counts <50 cells/μL in comparison to ≥350 cells/μL had an adjusted eHR of 9.92 (95% CI: 8.59, 11.44). Patients starting cART at older ages also had greater excess mortality with an eHR of 1.63 (95% CI: 1.47, 1.82) comparing ages ≥ 45 to 18–29. Standardized mortality ratio results were consistent with those for excess mortality.

Conclusion—Substantial decreases in excess mortality were observed from 2003 to 2009 in China among HIV-infected patients receiving free cART. However, mortality among HIV-infected patients remained higher than the general Chinese population. As more efficacious first and second line cART regimens become increasingly available to Chinese HIV-infected patients, further reductions in overall and excess mortality are likely.

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Conflicts of Interest:
For the remaining authors none were declared.

Keywords

HIV; Mortality; China; Antiretroviral Therapy

Introduction

Combination antiretroviral therapy (cART) provision enables human immunodeficiency virus (HIV)-infected patients to suppress HIV replication [1–3], leading to substantially lower morbidity and mortality in both resource rich and poor areas of the world [4, 5]. A number of prior studies have observed notable reductions in mortality across calendar time with increasing uptake of more efficacious cART [6–8]. However, mortality among HIV-infected patients remains higher in resource poor areas even where cART is available [9].

Reductions in mortality from HIV-infection have also been narrowing the gap in life expectancy comparing HIV-infected patients to the general population [10–13]. Among some HIV-infected patients life expectancy may approach that observed in the general population [14, 15]. For example, among West and South African patients participating in the International epidemiological Databases to Evaluate AIDS project who initiated cART at higher CD4 counts life expectancy estimates approach those of HIV-uninfected individuals [16]. Mortality and life expectancy contrasts comparing HIV-infected patients receiving cART to the general population assess the effectiveness of provided HIV therapy at a population level. These types of analyses also provide data for policy makers for assessing future needs of HIV-infected patients and in planning allocation of health care and other resources.

The Joint United Nations Programme on HIV/AIDS estimated that as of 2009, 740,000 (range 540,000–1,000,000) adults and children were living with HIV in China [17]. Since 2002, HIV-infected patients in China have had access to free cART through the National Free Antiretroviral Treatment Program (NFATP) [18], and as of 2009 over 80,000 patients received cART through this program [19]. As elsewhere around the world, HIV-infected patients receiving cART experience notable reductions in morbidity and mortality in China [19–21]. Although NFATP only launched the national free cART program in the last decade, notable decreases in mortality across calendar time have already been reported [22]. However, this prior work has concentrated on internal comparisons of mortality among HIV-infected patients over time, and therefore cannot distinguish mortality time trends among HIV infected patients from temporal trends in the Chinese population. In the present study we compare mortality estimates between HIV-infected patients receiving cART through NFATP with the general Chinese population from 2003 and 2009. We estimated both excess mortality and standardized mortality ratios over calendar time and evaluated risk factors for excess mortality.

Methods

Study population

Patients receiving free cART through NFATP between 1 January 2003 and 31 December 2009 were included [18, 23, 24]. Patients were cART eligible if they had a CD4 count below 200 cells/μL (increased to 350 cells/μL in 2008), a total lymphocyte counts <1200 cells/μL or a World Health Organization stage III or IV clinical condition [25]. Standardized paper-based case report forms were completed by local health workers. Information included demographic data, HIV exposure route, clinical symptoms and signs, cART administered and laboratory test results. Subsequent follow up visits occurred at 2, 4, 8 and 12 weeks following cART initiation, and then every 3 months thereafter. We excluded patients who

did not have information on area of residence (n=10,669) and who did not have any follow-up visit information before 15 December 2009 (n=714). This study was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill and the National Center for AIDS/STD Control and Prevention at China Center for Disease Control and Prevention.

Measurements

Factors measured at the first visit included age, sex, likely HIV exposure route, initial cART regimen, CD4 cell count, type of health care setting and area of residence (rural versus urban). Antiretroviral therapy regimens were categorized as: neviripine (NVP) with lamivudine (3TC) and either zidovudine (AZT) or stavudine (d4T); efavirenz (EFV) with 3TC and either AZT or D4T; NVP and didanosine (DDI) and either AZT or D4T; and all other regimens. HIV exposure route included infection through blood transfusion/former plasma donation, sexual transmission and injection drug use (IDU). Information on death, including reason and date of death, was available through the NFATP treatment withdrawal forms. These forms were also completed by local health workers and sent to central NFATP offices by DataFax (Clinical DataFax Systems, Hamilton, Ontario, Canada). Forms were completed on all patients known to have died at the local level through passive surveillance. Mortality data for the general Chinese population was obtained from *China Health Statistic Year Book 2004* to *2010* [26]. These national death statistics are based on a passive surveillance system, i.e. the Ministry of Health-vital registration system, to report death cases to a central national repository [27].

Statistical analysis

Person-time was calculated from the date when patients initiated cART to the date of death or date of censoring. Patients were censored either at the date of withdrawal from NFATP or 31 December 2009, whichever occurred first. The reason for withdrawal included loss to follow up, treatment interruption or transferring to another health care facility. Loss to follow-up was defined as missing more than 3 visits and we used the latest date seen in clinic as the date of withdrawal.

Observed mortality rates were calculated as number of deaths divided by person-years at risk and corresponding 95% confidence intervals (95% CIs) were calculated as:[28]

$$95\%\ \mathrm{CI\ for}\ R=\mathrm{Exp}\left[\ln(R)\pm 1.96*\left(\frac{1}{\sqrt{n}}\right)\right]$$

Where R is observed mortality rates and n is the number of deaths. Expected number of deaths was estimated by applying the probability of death in the general Chinese population to the study population in each calendar year. Patients were matched to the general population on age (by 5 year age group), sex, area of residence (urban versus rural) and calendar year.

Excess mortality rates were calculated as the difference between observed deaths in the study population and that expected based on estimates from the general population. Standardized mortality ratios (SMR) were calculated as the ratio of the observed number of deaths in the study population to that expected from estimates based on the general population. As measures of precision we calculated 95% CIs for both excess mortality rates and standardized mortality ratios[28]. Excess mortality rates and standardized mortality ratios were estimated within strata defined by calendar year interval (2003–2004, 2005–2007 and

2008–2009). This categorization was chosen to: minimize heterogeneity within groups; correspond with major therapeutic changes across calendar time; and preserve adequate sample sizes within strata. Further stratification of estimates was done according to patients' age, sex, HIV exposure route, CD4 count at cART initiation, area of residence, type of health care settings and type of first cART regimen received.

We further evaluated changes in excess mortality across calendar time in multivariable Poisson regression models [29]. In this relative survival model, the observed number of deaths in each patient stratum was modeled with a Poisson process and we used the expected number of deaths in each stratum as an offset. Time was categorized into one year increments from cART initiation, assuming a piecewise constant hazard within each year after starting cART. Excess hazard ratios (eHRs) and associated 95% CIs were obtained as the antilog of the coefficient from this relative survival model. We examined changes in relative survival across calendar time adjusting for age, sex, HIV-exposure category, CD4 count, initial cART regimen, type of health care setting and area of residence. In this case the interpretation of eHR comparing calendar years is similar to other survival models, such that the index group of patients experiences an instantaneous risk of death "eHR" times the risk among patients in the reference group, accounting for expected background mortality and the other patient characteristics included in the model. In all analyses hypothesis testing was 2-sided and an alpha of 0.05 was used to indicate a statistically significant difference. All analyses were done using SAS version 9.2 (SAS Institute, Cary NC, USA).

Results

Overall 64,836 HIV-infected patients with known area of residence initiated cART in the Chinese NFATP between 2003 and 2009 and were included in this analysis. The proportion of patients receiving treatment increased up over time and almost half of patients initiated cART during 2008 and 2009 (47%) (Table 1). The median age at cART initiation was 38 years [interquartile range (IQR): 33 – 46], 40% of patients were women, and 70% lived in rural areas. In more recent years patients appeared younger at cART initiation, were more likely to be men, and more likely to live in urban areas. In 2003 and 2004 95% of patients were infected through blood transfusion/former plasma donation, and this decreased to 18% by 2008 and 2009.

The median CD4 count at cART initiation decreased across time from 223 cells/mL in 2003/2004 to 141 cells/mL in 2008/2009. Although NVP remained the most common anchor agent provided, the use of 3TC replaced DDI in 2005/2006. Specifically in 2003/2004 patients predominantly received NVP and DDI with either AZT or D4T (89%), in comparison in 2008/2009 the most common first cART regimen was NVP and 3TC with either AZT or D4T (73%).

Patients were followed on average for a median of 1.5 years (IQR: 0.5 – 3.4), contributing a total of 135,509 person-years of follow-up (Table 2). Overall 13% of patients were known to have died (n=8,577), with an observed mortality rate of 6.3 deaths/100 person-years (95% CI: 6.2 – 6.4). The crude observed mortality rate decreased across calendar time from 9.5 to 5.6 deaths/100 person-years from 2003/2004 to 2008/2009.

The overall excess mortality rate was 6.0 deaths/100 person-years (95% CI: 5.9, 6.1). Excess mortality fell from 9.1 deaths/100 person-years (95% CI: 8.5, 9.8) in 2003/2004 to 5.2 deaths/100 person-years (95% CI: 5.0, 5.4) in 2008/2009 (Table 2). The reductions in excess mortality rates across calendar time were evident within all strata of patient characteristics, including age, sex, CD4 count at cART initiation and type of initial cART (Table 3). In unadjusted analyses excess mortality rates were higher among older patients in each stratum

of calendar years, although younger patients in 2003/2004 also had high excess mortality. After adjustment for other patient characteristics, including age, sex, HIV exposure route, CD4 count, number of baseline symptoms, initial cART regimen, area of residence, and health care setting, the adjusted excess mortality rates were higher in older patients across all calendar periods (data not shown here). The most dramatic reductions in unadjusted excess mortality rates across calendar time occurred among patients with low CD4 counts at cART initiation and comparable results were obtained in all strata of CD4 in the adjusted analyses (data not shown here).

The overall SMR was 20.1 (95% CI: 19.7, 20.5). The SMR decreased from 30.8 (95% CI: 28.6, 33.1) to 17.0 (95% CI: 16.5, 17.6) from 2003/2004 to 2008/2009 (Table 2). In general SMR results stratified by patient characteristic were comparable to results observed for excess mortality rates (Table 4). As observed with excess mortality rates, the reduction in SMR across calendar time was most dramatic among patients initiating cART at low CD4 counts. Among patients with CD4 counts below 50 cells/μL the SMR declined from 103.6 (95% CI: 86.2, 124.5) to 32.2 (95% CI: 30.5, 34.0) from 2003/2004 to 2008/2009.

The adjusted excess mortality rate decreased from 2003/2004 to 2008/2009, with an eHR of 1.27 (95% CI: 1.11, 1.45), indicating the risk of death was nearly 30% higher in 2003/2004 than 2007/2008, adjusting for background mortality and other patient characteristics including age, sex, HIV exposure route, area of residence, health care setting, CD4 count, number of baseline symptoms, and initial cART regimen (Table 5). Patients who were older at cART initiation were at a greater risk of dying with an eHR of 1.63 (95% CI: 1.47, 1.82) comparing patients more than 45 years of age to those 18–29. Men, patients living in rural areas, and those exposed to HIV through IDU were also at higher risk of death. Patients who received care at larger and centralized medical care facilities appeared to be at lower risk than those who received care at smaller local centers. Excess mortality decreased with increasing CD4 counts at cART initiation, with patients who started cART with CD4 counts less than 50 cells/μL at almost 10 times the risk of death compared to patients with CD4 counts greater than 350 cells/μL (eHR=9.92; 95% CI, 8.59 – 11.44).

Discussion

In this study including over 64,000 HIV-infected patients initiating cART in China, we found both observed and excess mortality rates decreased more than 30% from 2003 to 2009. Mortality ratios standardized to the general Chinese population also decreased by over 30% from 2003 to 2009. The decreases in excess mortality rates and SMRs across calendar time were relatively consistently observed within all patient demographic and clinical characteristics, and after adjusting for a number of factors including age, CD4 count and cART regimen at therapy initiation, excess mortality decreased by over 20% from 2003/2004 to 2008/2009. These findings are consistent with prior studies which have reported reductions in observed and expected mortality rates and SMRs across calendar time among patients initiating cART in both resource rich and poor areas of the world [15, 16, 30–32].

The observed mortality rate in this study population (6 deaths/100 person-years) was higher in comparison to results from resource wealthy areas of the world (1 death/100 person-years) [31], but lower than that observed in Sub-Saharan Africa (8 deaths/100 person-years) [16]. The overall excess mortality we observed was similar to estimates from Sub-Saharan Africa (6 vs. 7 deaths/100 person-years, respectively), as were the SMRs (20 and 19, respectively) [16], but higher than reported in Europe and North America (excess mortality rate = 2 deaths/100 person-years [30] and SMR= 3 [31])

Notwithstanding the substantial decreases in mortality rates across calendar time, HIV-infected patients in this study population consistently had greater excess mortality in comparison to the general Chinese population. However there were notable differences in excess mortality rates among groups of patients defined by demographic and clinical characteristics. Among some groups of patient's mortality was less than 10 times the general population whereas among other groups this rose to over 100 times. The greatest differences in mortality were observed within CD4 count and age strata. The lowest excess mortality rates were among patients initiating cART at CD4 counts greater than 350 cells/μL. This group of patients had less than 10 times the mortality of the general population in all calendar years. In comparison the highest excess mortality rates were observed among patients initiating cART with CD4 counts less than 50 cells/μL. This group of patients had over 30 times the mortality of the general population even in the most recent calendar years. In adjusted analyses patients starting cART with CD4 counts less than 50 cells/μL had nearly a 10-fold higher excess mortality compared to patients initiating cART at CD4 counts greater than 350 cells/μL. These findings have been consistently reported from all areas of the world [12, 16] and underscore recent recommendations that cART be initiated at higher CD4 counts to optimize overall survival [33–35] and that additional efforts are needed for earlier HIV diagnosis and treatment initiation among many HIV-infected patients [36].

Overall excess mortality rates increased with increasing age. In multivariable analyses adjusting for CD4 count and other patient characteristics patients at least 45 years of age had over 1.6 times excess mortality in comparison to patients 18–29 years of age. Other independent factors associated with excess mortality in multivariable analyses included being a male, patients infected through IDU in comparison to sexual transmission, patients residing in rural versus urban areas, and patients receiving HIV care at local health care centers in comparison to larger centralized hospital settings. Prior studies have also reported older age, male sex, and IDU as risk factors for excess mortality [9, 30, 32].

It is possible that the HIV-infected patients in this study population were different from the general population in other characteristics that we were not able to account for (i.e., age, sex, area of residence and calendar year) [13]. In other words, HIV-infected patients in China may be at greater risk of death than the general population for reasons other than HIV, such as a higher prevalence of other comorbidities (e.g., Hepatitis B or C infection). Death ascertainment relied on reports to HIV care providers, rather than links with centralized death registries, therefore we may be underestimating the true mortality rates. Mortality rates of the general Chinese population were based on a passive surveillance system, the Ministry of Health-vital registration system, which may not capture all deaths in each province, with some variation by province. We were also unable to account for duration of HIV-infection, or virologic or immunologic response to cART due to insufficient data. Observed mortality rates, excess rates and standardized mortality ratios would likely be lower among patients with better response to cART.

In summary, among HIV-infected patients receiving cART through the Chinese NFATP we have observed substantial decreases in excess mortality in comparison to the general Chinese population from 2003 to 2009. Further reductions will likely be achieved as NFATP is able to provide more efficacious first and second line cART regimens. Our results indicate that further reductions in mortality will follow if patients are identified earlier after HIV-infection and are successfully linked with HIV care.

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References

1. May MT, Sterne JA, Costagliola D, et al. HIV treatment response and prognosis in Europe and North America in the first decade of highly active antiretroviral therapy: a collaborative analysis. Lancet. Aug 5; 2006 368(9534):451–458. [PubMed: 16890831]
2. Srikantiah P, Ghidinelli M, Bachani D, et al. Scale-up of national antiretroviral therapy programs: progress and challenges in the Asia Pacific region. Aids. Sep; 2010 24(Suppl 3):S62–71. [PubMed: 20926930]
3. Keiser O, Anastos K, Schechter M, et al. Antiretroviral therapy in resource-limited settings 1996 to 2006: patient characteristics, treatment regimens and monitoring in sub-Saharan Africa, Asia and Latin America. Trop Med Int Health. Jul; 2008 13(7):870–879. [PubMed: 18373510]
4. Cornell M, Grimsrud A, Fairall L, et al. Temporal changes in programme outcomes among adult patients initiating antiretroviral therapy across South Africa, 2002–2007. Aids. Sep 10; 2010 24(14): 2263–2270. [PubMed: 20683318]
5. ART-CC. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. Lancet. Jul 26; 2008 372(9635):293–299. [PubMed: 18657708]
6. Ewings FM, Bhaskaran K, McLean K, et al. Survival following HIV infection of a cohort followed up from seroconversion in the UK. Aids. Jan 2; 2008 22(1):89–95. [PubMed: 18090396]
7. Porter K, Babiker A, Bhaskaran K, et al. Determinants of survival following HIV-1 seroconversion after the introduction of HAART. Lancet. Oct 18; 2003 362(9392):1267–1274. [PubMed: 14575971]
8. Etard JF, Ndiaye I, Thierry-Mieg M, et al. Mortality and causes of death in adults receiving highly active antiretroviral therapy in Senegal: a 7-year cohort study. Aids. May 12; 2006 20(8):1181–1189. [PubMed: 16691070]
9. Braitstein P, Brinkhof MW, Dabis F, et al. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. Lancet. Mar 11; 2006 367(9513):817–824. [PubMed: 16530575]
10. Keiser O, Taffe P, Zwahlen M, et al. All cause mortality in the Swiss HIV Cohort Study from 1990 to 2001 in comparison with the Swiss population. Aids. Sep 3; 2004 18(13):1835–1843. [PubMed: 15316345]
11. Lohse N, Hansen AB, Pedersen G, et al. Survival of persons with and without HIV infection in Denmark, 1995–2005. Ann Intern Med. Jan 16; 2007 146(2):87–95. [PubMed: 17227932]
12. Jensen-Fangel S, Pedersen L, Pedersen C, et al. Low mortality in HIV-infected patients starting highly active antiretroviral therapy: a comparison with the general population. Aids. Jan 2; 2004 18(1):89–97. [PubMed: 15090834]
13. Losina E, Schackman BR, Sadownik SN, et al. Racial and sex disparities in life expectancy losses among HIV-infected persons in the united states: impact of risk behavior, late initiation, and early discontinuation of antiretroviral therapy. Clin Infect Dis. Nov 15; 2009 49(10):1570–1578. [PubMed: 19845472]
14. Jaggy C, von Overbeck J, Ledergerber B, et al. Mortality in the Swiss HIV Cohort Study (SHCS) and the Swiss general population. Lancet. Sep 13; 2003 362(9387):877–878. [PubMed: 13678976]

15. van Sighem AI, Gras LA, Reiss P, Brinkman K, de Wolf F. Life expectancy of recently diagnosed asymptomatic HIV-infected patients approaches that of uninfected individuals. Aids. Jun 19; 2010 24(10):1527–1535. [PubMed: 20467289]
16. Brinkhof MW, Boulle A, Weigel R, et al. Mortality of HIV-infected patients starting antiretroviral therapy in sub-Saharan Africa: comparison with HIV-unrelated mortality. PLoS Med. Apr 28.2009 6(4):e1000066. [PubMed: 19399157]
17. UNAIDS. Report on the Global AIDS Epidemic. Joint United Nations Programme on HIV/AIDS; Geneva: 2010.
18. Zhang F, Haberer JE, Wang Y, et al. The Chinese free antiretroviral treatment program: challenges and responses. Aids. Dec; 2007 21(Suppl 8):S143–148. [PubMed: 18172383]
19. Zhang F, Dou Z, Ma Y, et al. Five-year outcomes of the China National Free Antiretroviral Treatment Program. Ann Intern Med. Aug 18; 2009 151(4):241–251. W-252. [PubMed: 19687491]
20. Dou Z, Chen RY, Wang Z, et al. HIV-infected former plasma donors in rural Central China: from infection to survival outcomes, 1985–2008. PLoS One. 2010; 5(10):e13737. [PubMed: 21060835]
21. Ma Y, Zhao D, Yu L, et al. Predictors of virologic failure in HIV-1-infected adults receiving first-line antiretroviral therapy in 8 provinces in China. Clin Infect Dis. Jan 15; 50(2):264–271. [PubMed: 20017637]
22. Zhang F, Dou Z, Ma Y, et al. Effect of earlier initiation of antiretroviral treatment and increased treatment coverage on HIV-related mortality in China: a national observational cohort study. Lancet Infect Dis. Jul; 2010 11(7):516–524. [PubMed: 21600849]
23. Zhang FJ, Pan J, Yu L, et al. Current progress of China's free ART program. Cell Res. Nov-Dec; 2005 15(11–12):877–882. [PubMed: 16354563]
24. Ma Y, Zhang F, Zhao Y, et al. Cohort profile: the Chinese national free antiretroviral treatment cohort. Int J Epidemiol. Aug; 2009 39(4):973–979. [PubMed: 19556327]
25. Zhang, F. China Free Antiretroviral Therapy Manual. 2008. 2008.
26. Ministry of Health, China. China Health Statistic Year Book, 2004–2010. Available at: http://www.moh.gov.cn/zwgkzt/ptjnj/list.shtml
27. Hu Y, Zhou M, Wang L, et al. Analysis on characteristics of death patients in hospital in China, 2006. Disease Surveillance. 2008; 23(12):788–791.
28. Rothman, K.; Greenland, S. Modern Epidemiology. 2. 1998.
29. Dickman PW, Sloggett A, Hills M, Hakulinen T. Regression models for relative survival. Stat Med. Jan 15; 2004 23(1):51–64. [PubMed: 14695639]
30. Bhaskaran K, Hamouda O, Sannes M, et al. Changes in the risk of death after HIV seroconversion compared with mortality in the general population. Jama. Jul 2; 2008 300(1):51–59. [PubMed: 18594040]
31. Zwahlen M, Harris R, May M, et al. Mortality of HIV-infected patients starting potent antiretroviral therapy: comparison with the general population in nine industrialized countries. Int J Epidemiol. Dec; 2009 38(6):1624–1633. [PubMed: 19820106]
32. May M, Boulle A, Phiri S, et al. Prognosis of patients with HIV-1 infection starting antiretroviral therapy in sub-Saharan Africa: a collaborative analysis of scale-up programmes. Lancet. Aug 7; 2010 376(9739):449–457. [PubMed: 20638120]
33. Kitahata MM, Gange SJ, Abraham AG, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. N Engl J Med. Apr 30; 2009 360(18):1815–1826. [PubMed: 19339714]
34. Sterne JA, May M, Costagliola D, et al. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. Lancet. Apr 18; 2009 373(9672):1352–1363. [PubMed: 19361855]
35. Cain LE, Robins JM, Lanoy E, Logan R, et al. When to start treatment? A systematic approach to the comparison of dynamic regimes using observational data. Int J Biostat. 2010; 6(2):Article 18. [PubMed: 21972433]
36. Althoff KN, Gange SJ, Klein MB, et al. Late presentation for human immunodeficiency virus care in the United States and Canada. Clin Infect Dis. Jun 1; 2010 50(11):1512–1520. [PubMed: 20415573]

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Table 1

Characteristics of 64,836 HIV-infected patients at combination antiretroviral therapy initiation, the China National Free Antiretroviral Treatment Program 2003 – 2009

Characteristic[†]	2003–2004	2005–2007	2008–2009	Total
Total	11,366 (18%)	22,755 (35%)	30,715 (47%)	64,836 (100%)
Age (years) *				
Median	41 (36 – 48)	38 (32 – 45)	38 (32 – 45)	38 (33 – 46)
18–29	507 (5%)	3,191 (14%)	5,307 (17%)	9,005 (14%)
30–44	6,722 (59%)	13,548 (60%)	16,979 (55%)	37,249 (57%)
≥45	4,137 (36%)	6,016 (26%)	8,429 (28%)	18,582 (29%)
Sex				
Men	5,620 (49%)	13,497 (59%)	19,578 (64%)	38,695 (60%)
Women	5,746 (51%)	9,255 (41%)	11,136 (36%)	26,137 (40%)
HIV exposure *				
Blood transfusion/former plasma donation	10,787 (95%)	10,133 (47%)	5,114 (18%)	26,034 (42%)
Intravenous drug use	51 (1%)	3,667 (17%)	6,130 (21%)	9,848 (16%)
Sexual transmission	470 (4%)	7,652 (36%)	17,578 (61%)	25,700 (42%)
Area of residence				
Urban	469 (4%)	6,746 (30%)	12,531 (41%)	19,746 (30%)
Rural	10,897 (96%)	16,009 (70%)	18,184 (59%)	45,090 (70%)
Health care setting *				
General hospital	189 (2%)	6,344 (28%)	13,360 (44%)	19,893 (31%)
Infectious diseases hospital	234 (2%)	2,915 (13%)	5,304 (18%)	8,453 (13%)
Centers for diseases control clinic	873 (8%)	4,211 (19%)	6,551 (21%)	11,635 (18%)
Health care township level/prison hospital	10,042 (88%)	9,169 (40%)	5,270 (17%)	24,481 (38%)
CD4 count (cells/μL) *				
Median	223 (120 – 361)	132 (45 – 217)	141 (46 – 230)	147 (51 – 240)
0–49	869 (11%)	5,552 (27%)	7,753 (26%)	14,174 (24%)
50–199	2,466 (32%)	9,082 (44%)	12,107 (41%)	23,655 (41%)
200–349	2,320 (30%)	4,724 (23%)	8,993 (30%)	16,037 (28%)
≥350	2,086 (27%)	1,411 (7%)	816 (3%)	4,313 (7%)

Characteristic†	2003–2004	2005–2007	2008–2009	Total
Number of baseline symptom				
0	1,313 (12%)	5,211 (23%)	11,855 (39%)	18,379 (28%)
1	1,097 (10%)	2,772 (12%)	4,271 (14%)	8,140 (13%)
2–3	3,116 (27%)	5,859 (26%)	6,763 (22%)	15,738 (24%)
≥4	5,840 (51%)	8,913 (39%)	7,826 (25%)	22,579 (35%)
Initiation regimen‡				
NVP+3TC+AZT	292 (2%)	2,958 (13%)	12,699 (41%)	15,949 (25%)
NVP+3TC+D4T	389 (3%)	11,897 (52%)	9,723 (32%)	22,009 (34%)
NVP+DDI+AZT	8,326 (73%)	4,027 (18%)	807 (3%)	13,160 (20%)
NVP+DDI+D4T	1,799 (16%)	916 (4%)	234 (1%)	2,949 (5%)
EFV+3TC+AZT	75 (1%)	897 (4%)	3,665 (12%)	4,637 (7%)
EFV+3TC+D4T	72 (1%)	1,534 (7%)	2,952 (9%)	4,558 (7%)
Other regimens	413 (4%)	526 (2%)	635 (2%)	1,574 (2%)

†Data are median (IQR) or number (%) unless otherwise stated;

*Missing values: Sex (n=4), HIV exposure (n=3,254), Health care setting (n=374), CD4 cell count (n=6,657)

‡NVP= nevirapine; 3TC=lamivudine; AZT= zidovudine; d4T=stavudine; DDI=didanosine; EFV=efavirenz.

Table 2

Observed and excess mortality rates, and standardized mortality ratios, among 64,836 HIV-infected patients initiating combination antiretroviral therapy in the China National Free Antiretroviral Treatment Program from 2003 – 2009

Mortality	2003–2004	2005–2007	2008–2009	Total
Observed death	733	3,815	4,029	8,577
Expected death	23.8	166.4	236.6	426.8
Person year at follow up	7,754	55,336	72,419	135,509
Observed mortality rate (95% CI)[†] (per 100 person-years)	9.5 (8.8 – 10.2)	6.9 (6.7 – 7.1)	5.6 (5.4 – 5.8)	6.3 (6.2 – 6.4)
Excess mortality rate (95% CI)[‡] (per 100 person-years)	9.1 (8.5 – 9.8)	6.6 (6.4 – 6.8)	5.2 (5.0 – 5.4)	6.0 (5.9 – 6.1)
Standardized mortality ratio (95% CI) [*]	30.8 (28.6 – 33.1)	22.9 (22.2 – 23.7)	17.0 (16.5 – 17.6)	20.1 (19.7 – 20.5)

[†]Calculated as 100× (observed death/person years at follow up)

[‡]Calculated as 100× [(observed death-expected death)/person years at follow up)]

[*]Calculated as 100× (observed death/expected death)

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Table 3

Excess mortality rates among 64,836 HIV-infected patients initiating combination antiretroviral therapy stratified by patient characteristics, the China National Free Antiretroviral Treatment Program 2003 – 2009[†]

Characteristic	2003–2004	2005–2007	2008–2009
Age			
18–29	11.0 (8.0 – 15.1)	5.9 (5.2 – 6.7)	3.3 (3.0 – 3.7)
30–44	9.2 (8.4 – 10.1)	6.1 (5.8 – 6.4)	5.1 (4.9 – 5.3)
≥45	8.8 (7.8 – 10.0)	7.7 (7.3 – 8.1)	6.5 (6.2 – 6.9)
Gender			
Men	11.3 (10.3 – 12.4)	7.9 (7.6 – 8.2)	6.1 (5.9 – 6.3)
Women	7.2 (6.4 – 8.1)	5.2 (4.9 – 5.5)	4.1 (3.9 – 4.3)
HIV exposure			
Blood transfusion/former plasma donation	9.1 (8.4 – 9.8)	6.7 (6.5 – 7.0)	5.5 (5.3 – 5.8)
Intravenous drug use	N/A[≠]	6.0 (5.2 – 6.9)	7.3 (6.8 – 7.9)
Sexual transmission	8.6 (5.3 – 13.8)	6.4 (5.9 – 7.0)	4.0 (3.8 – 4.3)
Area of residence			
Rural	9.1 (8.4 – 9.8)	6.6 (6.4 – 6.8)	5.6 (5.4 – 5.8)
Urban	10.9 (7.1 – 16.7)	6.4 (5.9 – 7.0)	4.3 (4.0 – 4.6)
Health care setting			
General hospital	19.1 (11.5 – 31.7)	6.5 (5.9 – 7.2)	5.2 (4.9 – 5.5)
Infectious diseases hospital	5.0 (2.4 – 10.5)	4.6 (4.0 – 5.4)	2.4 (2.1 – 2.7)
Centers for diseases control clinic	13.5 (10.7 – 17.1)	7.4 (6.8 – 8.1)	6.1 (5.7 – 6.5)
Health care under township level/prison hospital	8.8 (8.1 – 9.5)	6.6 (6.3 – 6.9)	5.7 (5.4 – 6.0)
CD4 count (cells/μL)			
0–49	27.8 (23.1 – 33.4)	15.5 (14.6 – 16.4)	9.1 (8.6 – 9.6)
50–199	7.8 (6.4 – 9.4)	5.9 (5.5 – 6.3)	4.9 (4.6 – 5.2)
200–349	1.2 (0.7 – 1.9)	2.5 (2.2 – 2.8)	2.7 (2.5 – 3.0)
≥350	1.9 (1.3 – 2.8)	1.4 (1.2 – 1.7)	2.1 (1.8 – 2.5)
Number of baseline symptom			
0	8.0 (6.3 – 10.1)	2.9 (2.6 – 3.3)	2.6 (2.4 – 2.8)
1	5.6 (4.2 – 7.5)	4.8 (4.3 – 5.4)	4.5 (4.1 – 5.0)

Characteristic	2003–2004	2005–2007	2008–2009
2–3	6.3 (5.4 – 7.4)	6.4 (6.0 – 6.8)	5.6 (5.3 – 6.0)
≥4	12.1 (11.0 – 13.3)	8.5 (8.1 – 8.9)	7.1 (6.8 – 7.4)
Initiation regimen *			
NVP+3TC+AZT	5.2 (2.3 – 11.6)	5.7 (5.0 – 6.5)	4.7 (4.4 – 5.1)
NVP+3TC+D4T	0.8 (0.2 – 3.2)	7.6 (7.2 – 8.1)	4.9 (4.6 – 5.2)
NVP+DDI+AZT	10.8 (10.0 – 11.7)	6.8 (6.5 – 7.1)	6.0 (5.6 – 6.4)
NVP+DDI+D4T	6.5 (5.4 – 7.9)	4.8 (4.3 – 5.4)	4.0 (3.4 – 4.7)
EFV+3TC+AZT	N/A‡	2.9 (2.1 – 4.1)	4.8 (4.2 – 5.5)
EFV+3TC+D4T	N/A‡	7.5 (6.2 – 9.0)	6.7 (6.0 – 7.5)
Other regimens	4.8 (3.0 – 7.6)	4.8 (3.9 – 5.9)	7.1 (6.0 – 8.5)

† All of excess mortality rates were per 100 person-years

‡ N/A: excess mortality rates were not estimated within strata with fewer than 100 patients.

* NVP= nevirapine; 3TC=lamivudine; AZT= zidovudine; d4T=stavudine; DDI=didanosine; EFV=efavirenz.

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Table 4

Standardized mortality ratios among 64,836 HIV-infected patients initiating combination antiretroviral therapy stratified by patient characteristics, the China National Free Antiretroviral Treatment Program 2003 – 2009

Characteristic	2003–2004	2005–2007	2008–2009
Age			
18–29	N/A *	114.9 (102.0 – 129.5)	70.8 (63.5 – 79.0)
30–44	54.1 (49.2 – 59.4)	37.8 (36.2 – 39.4)	31.6 (30.4 – 33.0)
≥45	16.8 (14.9 – 18.9)	13.4 (12.7 – 14.1)	9.1 (8.6 – 9.6)
Gender			
Men	30.9 (28.1 – 33.9)	21.9 (21.0 – 22.8)	15.6 (15.0 – 16.2)
Women	30.7 (27.4 – 34.3)	24.9 (23.7 – 26.2)	20.7 (19.6 – 21.8)
HIV exposure			
Blood transfusion/former plasma donation	30.7 (28.6 – 33.1)	22.5 (21.7 – 23.3)	16.2 (15.5 – 16.9)
Intravenous drug use	N/A *	47.6 (41.5 – 54.5)	53.9 (50.1 – 57.9)
Sexual transmission	28.2 (17.8 – 44.7)	22.6 (20.8 – 24.5)	13.3 (12.5 – 14.1)
Area of residence			
Rural	30.6 (28.5 – 33.0)	22.5 (21.7 – 23.3)	16.9 (16.3 – 17.5)
Urban	37.1 (24.4 – 56.3)	26.4 (24.2 – 28.7)	17.4 (16.4 – 18.6)
Health care setting			
General hospital	N/A *	29.0 (26.3 – 31.9)	19.8 (18.5 – 20.9)
Infectious diseases hospital	N/A *	16.4 (14.1 – 19.1)	9.0 (7.9 – 10.2)
Centers for diseases control clinic	56.7 (44.9 – 71.7)	28.8 (26.4 – 31.4)	20.9 (19.5 – 22.4)
Health care under township level/prison hospital	29.3 (27.1 – 31.7)	21.9 (21.1 – 22.7)	16.3 (15.6 – 17.1)
CD4 cell count (cells/μL)			
0–49	103.6 (86.2 – 124.5)	61.3 (57.8 – 64.9)	32.2 (30.5 – 34.0)
50–199	25.0 (20.8 – 30.2)	20.0 (18.8 – 21.2)	15.4 (14.6 – 16.3)
200–349	4.8 (3.1 – 7.2)	9.4 (8.5 – 10.4)	9.7 (8.8 – 10.5)
≥350	7.1 (5.0 – 10.2)	5.6 (4.8 – 6.6)	6.7 (5.7 – 7.9)
Number of baseline symptom			
0	32.0 (25.5 – 40.2)	11.9 (10.6 – 13.4)	10.2 (9.4 – 11.1)
1	20.6 (15.5 – 27.3)	17.8 (15.9 – 19.9)	15.1 (13.8 – 16.6)

Characteristic	2003–2004	2005–2007	2008–2009
2–3	21.0 (18.0 – 24.6)	21.8 (20.5 – 23.2)	17.1 (16.1 – 18.2)
≥4	38.8 (35.4 – 42.6)	28.0 (26.8 – 29.2)	21.5 (20.6 – 22.5)
Initiation regimen †			
NVP+3TC+AZT	N/A*	24.8 (21.7 – 28.3)	17.4 (16.2 – 18.8)
NVP+3TC+D4T	3.4 (1.1 – 10.5)	28.3 (26.7 – 30.0)	16.5 (15.7 – 17.4)
NVP+DDI+AZT	35.7 (32.9 – 38.7)	22.1 (21.2 – 23.2)	16.4 (15.5 – 17.4)
NVP+DDI+D4T	22.7 (18.7 – 27.4)	16.6 (14.9 – 18.6)	12.1 (10.5 – 14.0)
EFV+3TC+AZT	N/A*	12.2 (8.8 – 16.9)	20.5 (17.9 – 23.5)
EFV+3TC+D4T	N/A*	25.6 (21.4 – 30.6)	21.5 (19.3 – 23.9)
Other regimens	18.9 (12.1 – 29.6)	19.0 (15.4 – 23.3)	23.8 (20.1 – 28.3)

*N/A: Standardized mortality ratios were not estimated within strata with expected deaths fewer than 0.5 patients.

†NVP= nevirapine; 3TC=lamivudine; AZT= zidovudine; d4T=stavudine; DDI=didanosine; EFV=efavirenz.

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Table 5

Adjusted excess hazard ratios among 64,836 HIV-infected patients initiating combination antiretroviral therapy, the China National Free Antiretroviral Treatment Program 2003 – 2009[†]

	eHR (95% CI)
Calendar period of follow up	
2003–2004	1.27 (1.11 – 1.45)
2005–2007	1.16 (1.09 – 1.23)
2008–2009	1.00
Age (years)	
≥45	1.63 (1.47 – 1.82)
30–44	1.27 (1.15 – 1.40)
18–29	1.00
Gender	
Men	1.37 (1.29 – 1.45)
Women	1.00
HIV exposure	
Blood transfusion/former plasma donation	0.98 (0.89 – 1.08)
Intravenous drug use	1.72 (1.57 – 1.88)
Sexual transmission	1.00
Area of residence	
Rural	1.17 (1.08 – 1.26)
Urban	1.00
Health care setting	
General hospital	0.85 (0.76 – 0.95)
Infectious diseases hospital	0.34 (0.30 – 0.40)
Centers for diseases control clinic	0.89 (0.81 – 0.97)
Health care under township level/prison hospital	1.00
CD4 count (cells/μL)	
0–49	9.92 (8.59 – 11.44)
50–199	4.08 (3.55 – 4.70)
200–349	1.82 (1.56 – 2.11)
≥350	1.00
Number of baseline symptom	
≥4	2.10 (1.91 – 2.31)
2–3	1.65 (1.49 – 1.82)
1	1.35 (1.19 – 1.52)
0	1.00
Initiation regimen[‡]	
NVP+3TC+AZT	1.11 (0.94 – 1.31)
NVP+3TC+D4T	1.09 (0.93 – 1.27)
NVP+DDI+AZT	1.37 (1.17 – 1.62)
NVP+DDI+D4T	0.97 (0.80 – 1.17)

	eHR (95% CI)
Other regimens	1.24 (1.00 – 1.54)
EFV+3TC+D4T	1.20 (1.00 – 1.43)
EFV+3TC+AZT	1.00

† Estimates from one model including all characteristics listed in table

‡ NVP= nevirapine; 3TC=lamivudine; AZT= zidovudine; d4T=stavudine; DDI=didanosine; EFV=efavirenz.