Effect of earlier initiation of antiretroviral treatment and increased treatment coverage on HIV-related mortality in China: a national observational cohort study

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Summary

Background **Overall HIV mortality rates in China have not been reported. In this analysis we assess overall mortality in treatment-eligible adults with HIV and attempt to identify risk factors for HIV-related mortality.**

Methods **We used data from the national HIV epidemiology and treatment databases to identify individuals aged 15 years or older with HIV who were eligible for highly active antiretroviral therapy between 1985 and 2009. Mortality rates were calculated in terms of person-years, with risk factors determined by Cox proportional hazard regression. Treatment coverage was calculated as the proportion of time that patients who were eligible for treatment received treatment, with risk factors for not receiving treatment identified by use of logistic regression.**

Findings **Of 323 252 people reported as having HIV in China by the end of 2009, 145 484 (45%) were identified as treatment-eligible and included in this analysis. Median CD4 count was 201 cells per μL (IQR 71–315) at HIV diagnosis and 194 cells per μL (73–293) when first declared eligible for treatment. Overall mortality decreased from 39·3 per 100 person-years in 2002 to 14·2 per 100 person-years in 2009, with treatment coverage concomitantly increasing from almost zero to 63·4%. By 2009, mortality was higher and treatment coverage lower in injecting drug users (15·9 deaths per 100 person-years; 42·7% coverage) and those infected sexually (17·5 deaths per 100 person-years; 61·7% coverage), compared with those infected through plasma donation or blood transfusion (6·7 deaths per 100 person-years; 80·2% coverage). The two strongest risk factors for HIV-related mortality were not receiving highly active antiretroviral therapy (adjusted hazard ratio 4·35, 95% CI 4·10–4·62) and having a CD4 count of less than 50 cells per μL when first declared eligible for treatment (7·92, 7·33–8.57).**

Interpretation **An urgent need exists for earlier HIV diagnosis and better access to treatment for injecting drug users and patients infected with HIV sexually, especially before they become severely immunosuppressed.**

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Introduction

An estimated 740 000 people in China are infected with HIV,[1] most of whom are injecting drug users (IDUs), female sex workers, men who have sex with men, former plasma donors, or blood transfusion recipients. As of Dec 31, 2009, 323 252 people were reported as having HIV in China, 82 540 of whom have been treated through the China National Free Antiretroviral Treatment Programme (NFATP). This programme was piloted in 2002 and was scaled up in 2003, initially to former plasma donors and then to the rest of the country.[2,3] Data from the NFATP show virological suppression, increased CD4 cell counts, and a pronounced decrease in mortality in patients who have received treatment.[4–7] However, overall mortality rates in patients (both treated and untreated) with HIV in China have not been reported.

By December, 2006, highly active antiretroviral therapy (HAART) coverage for former plasma donors with AIDS reached 70·5%, with a concomitant decrease in mortality.[4] Treatment coverage of the entire population, however, has not been reported. Understanding national mortality rates and treatment coverage in patients with HIV is essential for assessment of the national HIV programme, to identify its strengths and weaknesses and the areas in which additional effort and focus is needed. The purpose of this analysis, therefore, is to assess overall mortality trends in adult patients with HIV who are eligible for treatment, to understand the risk factors for mortality and treatment coverage, and to identify ways to improve HIV treatment outcomes in China.

Methods

Data collection

The National Centre for AIDS/STD Control and Prevention (NCAIDS) of the Chinese Centre for Disease Control and Prevention (China CDC) maintains two independent, observational databases of individuals with HIV in China. The first is the national epidemiology database, which tracks everyone who tests positive for HIV in China and records a baseline CD4 cell count for all newly identified individuals. Those who meet national treatment criteria of a CD4 count of less than 350 cells per μL (which increased from <200 cells per μL in 2008) are referred to the NFATP. The others are followed up

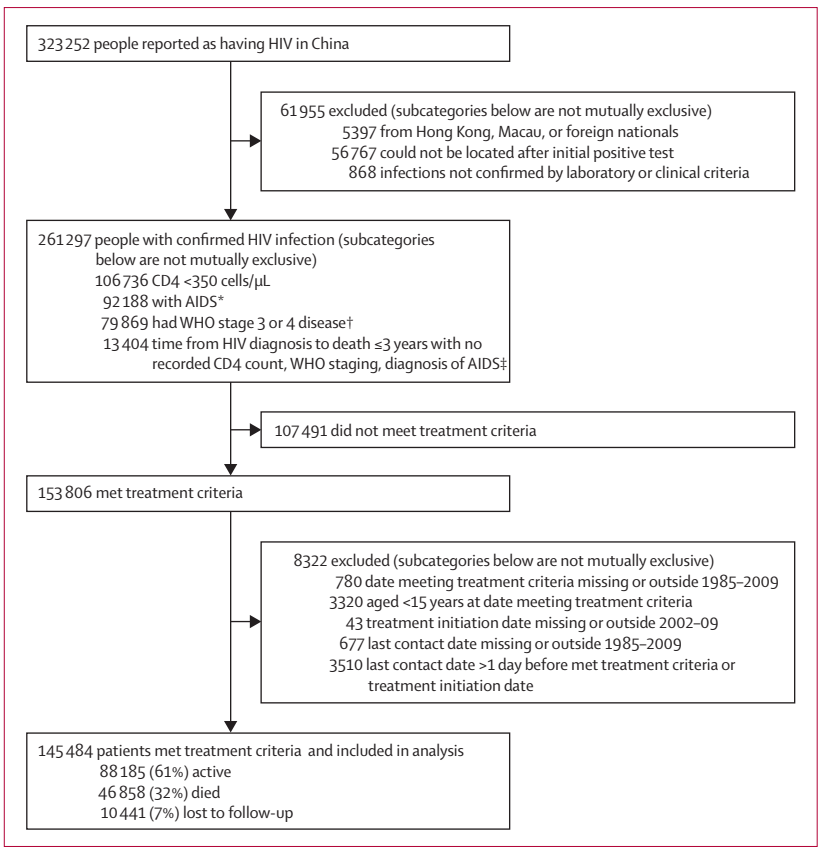

***Figure 1*: Study profile**
*13 405 with CD4 >350/μL excluded. †12 189 with CD4 >350/μL but without tuberculosis excluded. ‡1455 who died from a drug overdose, suicide, or accident excluded.

every 6 months for a repeat CD4 cell count. The second database is the national treatment database, which is described elsewhere.[4,5,8]

We assessed all data from the national epidemiology database from Jan 1, 1985, to Dec 31, 2009 (data downloaded on Dec 31, 2010). Data for individuals not from mainland China or for those who could not be located by local CDC follow-up were excluded from analysis. Of all Chinese nationals with confirmed HIV, those who met the national CD4 cell count treatment criteria, reported as having AIDS, or had WHO stage 3 or 4 HIV/AIDS were included. The date at which an individual was defined as eligible for treatment was when they met the national treatment criteria, reported as having AIDS, or when they were declared as having WHO stage 3 or 4 disease, whichever occurred first. Individuals who died within 3 years of HIV diagnosis without a recorded CD4 cell count, a diagnosis of AIDS, or WHO disease staging were also included—those who died from a drug overdose, suicide, or accident were not included. Finally, patients with inconsistent or missing key data were excluded (figure 1). Adult treatment-eligible patients included in the final analysis were classified as of Dec 31, 2009 as either active (last follow-up within past year), dead, or lost to follow-up (individual could not be located or last follow-up more than a year before). A 1 year cutoff was selected to classify active individuals from individuals lost to follow-up because people whose information was in the epidemiology database were seen every 6 months for a CD4 cell count,[9] meaning that this cutoff allowed for two missed visits. A patient's CD4 cell count at HIV diagnosis was the value from their CD4 cell count closest to the date on which their HIV infection was confirmed by western blot, within 1 year. Patients with CD4 counts of less than 350 cells per μL were deemed eligible for treatment.

Treatment coverage was calculated as the proportion of person-years from treatment-eligible date to last contact that were spent on HAART and expressed as percentage person-years. Individuals in the treatment database (after treatment) were linked to their own record in the epidemiology database (before treatment), because the epidemiology database was used to calculate the denominator (treatment-eligible patients). Some people gave incorrect personal information and their records in the two databases were not linked, causing an underestimation of treatment coverage because these patients were considered untreated in the epidemiology database. To correct for this underestimation, a midpoint treatment coverage was calculated by taking the midpoint between the proportion that included no unlinked individuals in the numerator (actual calculated coverage; assumes all unlinked individuals were untreated) and the proportion that included all unlinked individuals in the numerator (assumes all unlinked individuals were treated).

This analysis was reviewed and approved by the institutional review board of the National Centre for AIDS/STD Control and Prevention, China CDC.

Statistical analysis

Baseline characteristics between cohorts were compared with the Mann-Whitney and Kruskal-Wallis tests for continuous variables because none fulfilled the Kolmogorov-Smirnov test for normality. Mortality was calculated with life tables by dividing the number of people who died in a specified calendar year by the sum of person-years for individuals who met treatment criteria in that year. Individuals for whom data were available for the entire year were counted as 1 person-year; those who became eligible for treatment, who died, or who were lost to follow-up at any time during the year were counted as half a person-year. The number of person-years that each individual received HAART was calculated the same way. For all patients, potential risk factors for death were analysed by Cox proportional hazards regression, with patients still active or lost to follow-up on Dec 31, 2009 censored. Potential risk factors for not receiving HAART were analysed by logistic regression. Univariate factors with $p<0·1$ and factors predetermined to be clinically meaningful were placed

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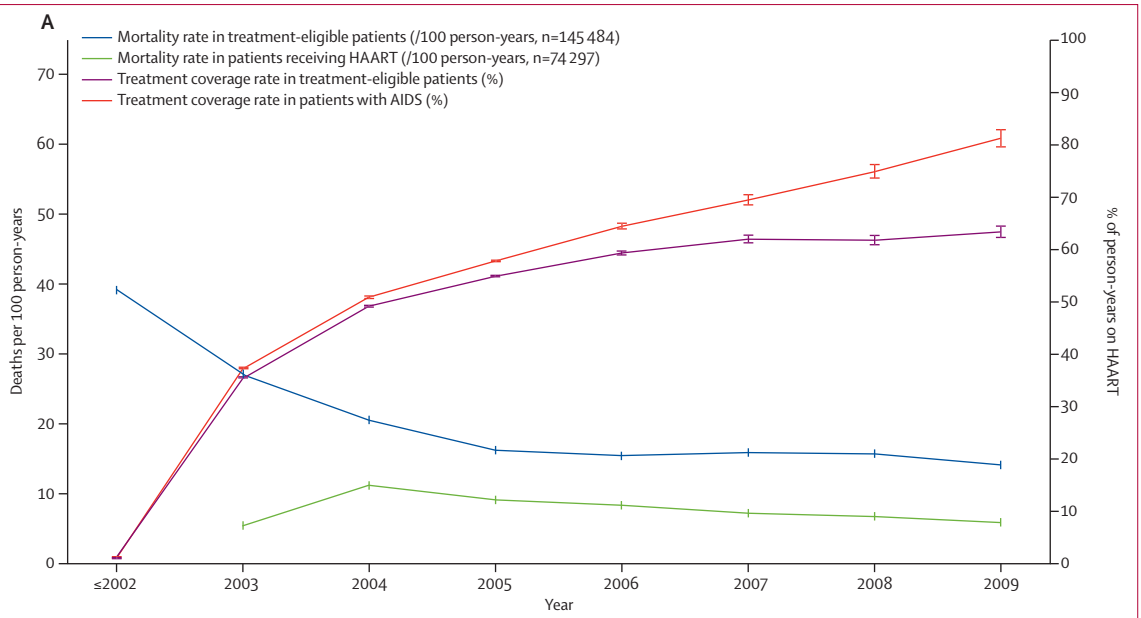
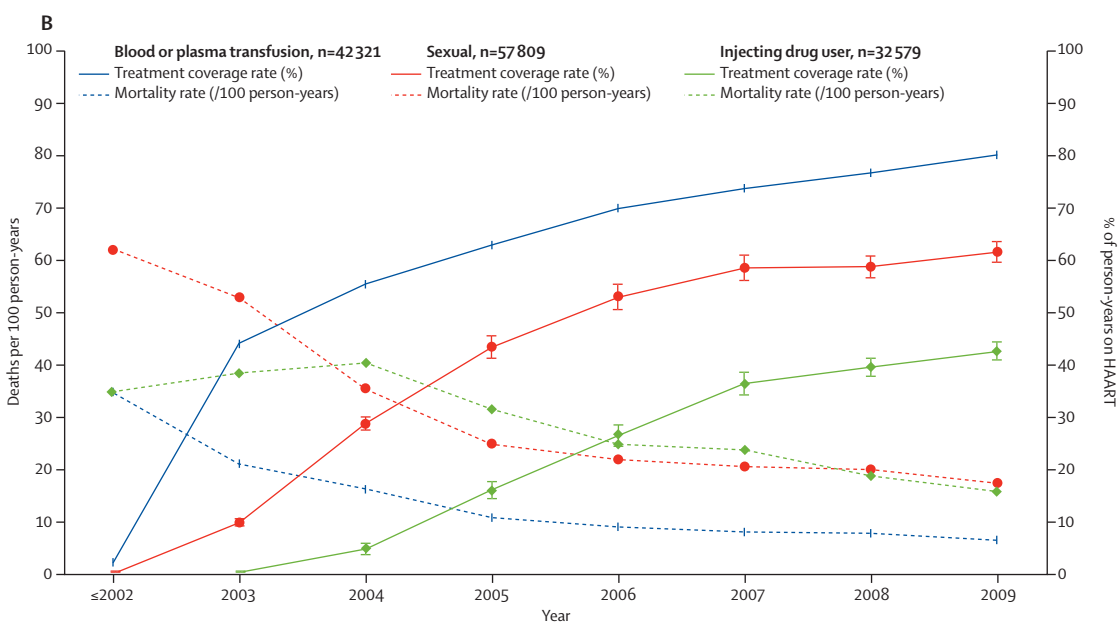


Total number of newly diagnosed patients who are treatment eligible by year (deaths)

4753 (2501)	8038 (1502)	17 857 (3307)	12 878 (4494)	14 469 (5606)	19 854 (7414)	32 884 (10 115)	34 751 (11 919)
χ^2/p value (time trend test for mortality rate through log-linear model):							
1 (reference)	127·8/0·0001	596·7/0·0001	1241·4/0·0001	1494·0/0·0001	1536·7/0·0001	1667·1/0·0001	2142·1/0·0001
			1 (reference)	6·36/0·01	2·12/0·15	3·36/0·07	63·0/0·0001

Total number of newly diagnosed patients initiating HAART by year (deaths)

45 (1)	3944 (108)	9035 (890)	7794 (1395)	8089 (1787)	11 013 (2100)	15 264 (2661)	19 113 (3089)
χ^2/p value (time trend test for mortality rate through Log-linear model):							
..	48·7/0·0001	1 (reference)	21·3/0·0001	50·5/0·0001	113·3/0·0001	165·7/0·0001	286·1/0·0001



Total number of newly diagnosed patients who are treatment eligible, by route of HIV infection

Blood or plasma transfusion	2378	6999	14 614	5195	3953	3228	3563	2391
Sexual	642	428	1542	2988	5096	8953	16 955	21 205
Injecting drug use	1408	375	1125	3062	3499	5461	9382	8267

Figure 2: **Mortality and midpoint treatment coverage**
In all included patients (A) and stratified by route of HIV infection (B). Error bars are midpoint coverage calculations. Haart=highly active antiretroviral therapy.

in full multivariable regression models. For patients who died, time from HIV western-blot confirmation to treatment initiation or death was calculated. Significance was determined at the p≤0·05 level. Data were analysed with SPSS (version 17.0) and SAS (version 9.0.1).

Role of the funding source

The NCAIDS, China CDC, funded this study as part of routine work and was involved in data collection, analysis, and interpretation. The corresponding author had full access to all data and had final responsibility for the decision to submit for publication.

Results

As of Dec 31, 2009, 145 484 individuals were identified as treatment-eligible and included in analysis (figure 1). The median age was 37 years (IQR 31–45), and time from HIV diagnosis to last contact was a median of 21 months (IQR 6–48). Median CD4 count was 201 cells per μL (IQR 71–315) at HIV diagnosis and 194 cells per μL (73–293) when first declared eligible for treatment. 107 645 (74%) were diagnosed as having AIDS. Of all individuals with sexually transmitted infection, 53 224 (92%) self-reported as heterosexual and 4585 (8%) self-reported as homosexual. Of the 82 540 patients in the national treatment database, 79 008 (96%) were linked to their record or confirmed as treated in the epidemiology database. Of these, 74 297 were included in the final analysis.

Between 2002 and 2009, mortality decreased in treatment-eligible patients and treatment coverage increased in eligible patients (figure 2). Mortality in patients receiving HAART increased between 2003 and 2004 (when the national treatment programme was scaled up) and decreased thereafter (figure 2). When stratified by route of infection, treatment coverage was highest in former plasma donors or blood transfusion recipients, and lowest in IDUs; by 2009, mortality rates were lowest in former plasma donors or blood transfusion recipients (figure 2).

	Mortality			Treatment coverage		
	n	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI) n=42 265	n*	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI) n=42 256
Overall	145 484	..	..	140 731	..	..
Sex						
Female	49 016	1·0	1·0	47 574	1·0	1·0
Male	96 468	1·60 (1·57–1·64)	1·21 (1·14–1·29)	93 157	0·55 (0·54–0·57)	0·84 (0·80–0·89)
Age meeting treatment criteria						
15–29 years	30 822	1·0	1·0	29 221	1·0	1·0
30–44 years	78 854	1·01 (0·98–1·03)	1·28 (1·19–1·39)	76 581	1·49 (1·45–1·53)	1·03 (0·98–1·09)
45–59 years	26 957	1·20 (1·16–1·23)	1·54 (1·41–1·69)	26 188	1·79 (1·73–1·85)	0·96 (0·89–1·03)
≥60 years	8 851	2·59 (2·50–2·69)	2·35 (2·11–2·62)	8 741	0·66 (0·63–0·69)	0·66 (0·60–0·73)
Marital status						
Married or lives with partner	92 445	1·0	1·0	89 654	1·0	1·0
Single, divorced, or widowed	47 851	0·96 (0·94–0·98)	0·94 (0·89–1·00)	46 749	0·68 (0·66–0·69)	0·85 (0·81–0·89)
Occupation						
Farmer	84 358	1·0	1·0	81 262	1·0	1·0
Other	54 425	0·99 (0·97–1·01)	0·77 (0·72–0·82)	53 060	0·65 (0·63–0·66)	1·00 (0·95–1·05)
Education						
Primary school or less	61 367	1·0	1·0	58 912	1·0	1·0
Middle school or more	75 115	0·86 (0·84–0·87)	0·84 (0·79–0·89)	73 391	1·05 (1·03–1·08)	1·30 (1·24–1·37)
Race						
Han Chinese	111 009	1·0	1·0	107 332	1·0	1·0
Other	27 835	1·19 (1·16–1·21)	0·99 (0·93–1·06)	26 842	0·51 (0·50–0·53)	0·82 (0·78–0·86)
Route of HIV infection						
Blood or plasma transfusion	42 321	1·0	1·0	39 943	1·0	1·0
Injection drug use	32 579	1·51 (1·47–1·55)	1·01 (0·92–1·12)	31 171	0·18 (0·17–0·19)	0·45 (0·41–0·49)
Sexual	57 809	1·37 (1·34–1·41)	0·90 (0·83–0·97)	57 167	0·34 (0·33–0·35)	0·61 (0·56–0·66)
Other or unknown	12 775	2·62 (2·55–2·70)	1·02 (0·90–1·16)	12 450	0·19 (0·18–0·20)	0·61 (0·54–0·69)
Among IDUs, received methadone maintenance treatment‡						
No	27 973	1·0	..	26 597	1·0	..
Yes	4 606	0·20 (0·18–0·22)	..	4 574	2·39 (2·24–2·54)	..

(Continues on next page)

	Mortality			Treatment coverage		
	n	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI) n=42 265	n*	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI) n=42 256
(Continued from previous page)						
HIV diagnosis location						
Centre for Disease Control system	96 527	1·0	1·0	93 606	1·0	1·0
Hospital system	40 997	2·06 (2·02–2·10)	1·04 (0·98–1·10)	39 758	0·58 (0·57–0·60)	1·03 (0·98–1·08)
Registered home location						
Urban	46 372	1·0	1·0	44 987	1·0	1·0
Rural	89 953	0·94 (0·92–0·96)	1·14 (1·07–1·21)	87 000	1·40 (1·36–1·43)	0·92 (0·88–0·97)
Migrant population						
No	132 718	1·0	1·0	128 179	1·0	1·0
Yes	8 298	0·59 (0·56–0·62)	0·60 (0·52–0·70)	8 218	0·71 (0·68–0·74)	0·87 (0·80–0·94)
Spouse or child also HIV infected†						
No	90 602	1·0	1·0	88 848	1·0	1·0
Yes	40 256	0·49 (0·48–0·50)	0·73 (0·68–0·78)	39 539	2·38 (2·32–2·44)	1·62 (1·54–1·70)
CD4 cell count when eligible for treatment (cells/μL)						
≥200	41 809	1·0	1·0	41 779	1·0	1·0
50–199	27 249	2·19 (2·10–2·28)	3·54 (3·28–3·82)	27 225	2·62 (2·54–2·71)	3·22 (3·06–3·38)
<50	16 884	5·10 (4·90–5·32)	7·92 (7·33–8·57)	16 868	2·71 (2·61–2·82)	3·47 (3·26–3·69)
WHO stage 3 or 4 disease when eligible for treatment						
No	40 754	1·0	1·0	40 628	1·0	1·0
Yes	65 243	2·15 (2·08–2·22)	2·33 (2·18–2·49)	64 581	1·31 (1·28–1·35)	1·34 (1·27–1·40)
Received free opportunistic infection prophylaxis or treatment when eligible†						
No	51 583	1·0	1·0	51 511	1·0	1·0
Yes	18 360	0·70 (0·67–0·73)	0·88 (0·83–0·93)	18 347	4·28 (4·13–4·45)	2·92 (2·77–3·08)
Received highly active antiretroviral therapy						
No	71 187	6·06 (5·93–6·19)	4·35 (4·10–4·62)	..	..	..
Yes	74 297	1·0	1·0	..	..	..

Data were not adjusted for patients for whom data was not linked between treatment and epidemiology databases. IDU=injecting drug user. *Excluding the 4753 individuals with infection in 2002 or before because treatment not yet available. †Variable added to the database in 2008. ‡Not entered into the multivariate model because this cohort represented only a small subset of the total population.

***Table 1*: Mortality and treatment coverage rates and their associated risk factors**

The two risk factors most strongly related to mortality were having not received HAART and having a low CD4 cell count when declared eligible for treatment (table 1). Other risk factors associated with mortality included being a man, living in a rural area, and having WHO stage 3 or 4 disease when declared eligible for treatment; mortality increased with age (table 1). Factors associated with lower mortality included not being a farmer, being a migrant, having a middle school or higher education, having an HIV-infected family member, and receiving free opportunistic infection prophylaxis or treatment (table 1).

Although route of HIV infection was not significantly associated with mortality, a subset of IDUs on methadone maintenance treatment had a very low risk of mortality in the unadjusted analysis (table 1), but were not included in the adjusted analysis because of their small sample size.

Because not receiving HAART was one of the strongest risk factors for death, a logistic regression analysis was done to understand the factors associated with receiving treatment in this population of patients who all met treatment criteria. The strongest factor associated with receiving HAART was having a low CD4 cell count, although having received free opportunistic infection treatment or prophylaxis, having a family member who also had HIV infection, and having a formal education beyond middle school were also significantly associated with receiving HAART (table 1). IDUs and those infected sexually were significantly less likely to receive treatment compared with those infected through plasma donation or blood transfusion. Men, individuals aged 60 years old or older, individuals who were not married or did not live with their partner, people of ethnic origin other than Han, and migrants were also significantly less likely to have received HAART (table 1).

In addition to not receiving HAART, having a low CD4 cell count was the other strong risk factor for mortality (table 1). To understand better why patients were treated so late in their disease course, an analysis of the time from HIV diagnosis to receiving HAART (for those treated) or

	Time from HIV diagnosis to starting HAART or last contact (months)			CD4 cell count (cell/μL) at HIV diagnosis (within 12 months)			Time from treatment eligible to starting HAART or last contact (months)		
	n	IQR	p value	n	IQR	p value	n	IQR	p value
Overall	143 713*	6 (1–24)	..	71 404	201 (71–315)	..	145 484	3 (0–12)	..
Survival status									
Died	46 264	3 (1–14)	<0·0001	12 555	73 (20–212)	<0·0001	46 858	2 (0–10)	<0·0001
Survived	97 449	9 (1–29)	..	58 849	223 (100–324)	..	98 626	3 (0–14)	..
Route of HIV infection									
Plasma or blood transfusion	42 283	5 (1–23)	<0·0001	17 834	189 (70–328)	<0·0001	42 321	3 (0–16)	<0·0001
Injection drug use	31 706	20 (5–44)	..	12 055	237 (118–331)	..	32 579	6 (1–18)	..
Sexual	57 373	3 (1–15)	..	37 567	196 (61–307)	..	57 809	2 (0–8)	..
Other or unknown	12 351	6 (1–21)	..	3 948	177 (55–297)	..	12 775	2 (0–11)	..
Patients who received HAART	73 429	3 (1–16)	..	44 622	164 (55–278)	..	74 297	1 (0–7)	..
Survival status									
Died	11 913	2 (0–9)	<0·0001	6 115	71 (21–193)	<0·0001	12 031	1 (0–5)	<0·0001
Survived	61 516	4 (1–18)	..	38 507	177 (67–287)	..	62 266	1 (0–7)	..
Route of HIV infection									
Plasma or blood transfusion	30 448	3 (1–16)	<0·0001	14 230	174 (65–306)	<0·0001	30 472	2 (0–11)	<0·0001
Injecting drug use	10 412	14 (2–38)	..	5 362	180 (73–286)	..	10 755	1 (0–7)	..
Sexual	28 385	2 (1–10)	..	22 674	155 (47–264)	..	28 646	1 (0–4)	..
Other or unknown	4 184	3 (1–17)	..	2 356	139 (46–252)	..	4 424	1 (0–3)	..

*1771 patients with HIV diagnosis date missing or outside 1985–2009 excluded. HAART=highly active antiretroviral therapy.

***Table 2*: Differences in time to starting treatment (treated patient) or time to last contact (untreated patients) and baseline CD4 cell counts**

to last contact (for those not treated) and from time eligible for HAART to starting HAART or last contact was done, stratified by survival status and route of HIV infection (table 2). On average, the time between HIV diagnosis and starting HAART or last contact was about four to seven times as long in IDUs as it was in patients who contracted HIV sexually or through plasma donation or blood transfusion (table 2). Individuals who died after HIV diagnosis and before starting HAART had significantly lower CD4 cell counts at diagnosis than did those who survived (73 cell per μL *vs* 223 cells per μL, p<0·0001).

Discussion

Our findings show a strong inverse relation between increasing HAART coverage and decreasing HIV-related mortality in China. Treatment coverage was only one of the risk factors strongly correlated to mortality. The other major factor was late treatment initiation, as measured by a low CD4 cell count at HIV diagnosis and when declared treatment eligible. In China, IDUs are identified earlier in their HIV disease course because of routine testing on entry into detoxification centres and methadone maintenance treatment clinics. They consequently had significantly higher CD4 cell counts at HIV diagnosis than did the sexually infected cohort, compensating for the lower treatment coverage and meaning both cohorts had similar mortality.

Increased HAART coverage decreased HIV-related mortality in the mid-to-late 1990s in the USA[10] and Europe.[11] Our study of data from China accords with the results of these studies. Because of the large sample size in the study, we have been able to do subanalyses to better understand the strengths and weaknesses of China's national HIV programme. The highest treatment coverage and lowest mortality were seen in plasma donation or blood transfusion populations, which has been one of the strengths of the national programme since its inception.[4] One reason that treatment has been successful in this cohort is probably because of the attention given to this population by the central government. The State Council formed an AIDS Working Committee, and the Four Frees and One Care policy of benefits was originally targeted at former plasma donors with HIV.[12,13] Such benefits included free antiretroviral treatment to patients with AIDS who live in rural areas and to those in urban areas who do not have insurance, free HIV voluntary counselling and testing, free drugs to HIV-infected pregnant women, HIV testing of newborn babies, free schooling for AIDS orphans, and care and economic assistance to households of people living with HIV/AIDS. The NFATP was also initially piloted and scaled up in former plasma donors.[13] Large-scale HIV screening was done in areas with large populations of former plasma donors, identifying and treating those eligible.[13,14] The response to those infected sexually or through injecting drugs, however, has not been the same because of programmatic, social, and risk-population related factors, with lower treatment coverage and higher

mortality rates than are seen in former plasma donors. However, according to our preliminary analysis, which accords with other studies elsewhere in the world,[15] drug users receiving methadone maintenance treatment have lower mortality and higher treatment coverage than do IDUs not receiving methadone maintenance treatment.

Reported treatment coverage of patients in developing countries varies greatly. The Joint United Nations Programme on HIV/AIDS (UNAIDS) 2008 Report on the Global HIV/AIDS Epidemic[16] calculated treatment coverage with the total estimated number of patients with HIV who are eligible for treatment as the denominator.[17] WHO and UNAIDS estimate global treatment coverage at about 43%.[18] Our analysis uses actual treatment coverage with reported cases as the denominator and thus is not directly comparable. Other analyses have also used actual treatment coverage, with reported proportions from one to multiple clinics ranging from 40% to 95%.[19–22] South Africa reported a treatment coverage of about 40·2% in 2008.[23] China's treatment coverage of 63·4% across 2513 treatment sites within 7 years is remarkable, given the size of the country and the geographical spread of individuals with HIV,[24] but is far from the goal of complete coverage of people who meet treatment criteria. Our analysis of risk factors for treatment coverage showed that coverage was especially low in those who are not former plasma donor populations and in men. Furthermore, populations that can be underserved by the public health system, such as migrants, elderly people, those with low levels of education, and minority groups, also need additional attention.

The other risk factor strongly related to death was late treatment initiation. Many studies have shown increased mortality in patients whose CD4 cell counts are low when they start treatment compared with those who start treatment earlier, when their CD4 cell counts are higher (panel).[4,5,25–34] Although overall time from HIV diagnosis to starting HAART (among those treated) or last contact (among those not treated) was 6 months, which shows room for improvement in initiating treatment earlier, the low CD4 cell count at HIV diagnosis indicates that late treatment initiation was mainly because of late diagnosis. Despite efforts to screen high-risk populations in China for HIV through local CDC outreach programmes and voluntary counselling and testing clinics,[13] individuals with infection are still diagnosed late in their disease course, substantially later than those initially diagnosed with HIV infection in North America.[35] Therefore, urgent expansion of the WHO-recommended provider-initiated testing and counselling strategy[36] to high-risk cohorts or locations with a known higher prevalence of HIV should be considered—this strategy is cost-effective in the USA.[37,38] In China, such high-risk populations in which provider-initiated testing and counselling could be implemented include not only IDUs, female sex workers and their clients, men who have sex with men, and discordant couples, but also individuals attending tuberculosis, sexually transmitted disease, and antenatal care clinics and those in counties with an HIV prevalence above or close to 1%.

Our analysis had a few limitations. First, many of the findings were based on CD4 cell counts. In China, the recording of CD4 cell counts was not scaled up until about 2005. Because very few CD4 cell counts were done before 2005, our results are based largely on data from the past 4 years of the national programme. However, WHO disease staging has been recorded since the NFATP was set up and these results are consistent with the CD4 cell count results. Furthermore, we have no reason to believe that CD4 cell count outcomes would have been different before 2005. Had we had data from before 2005, our results would probably be even more robust. Second, our results were based on observational data and could, therefore, have inherent biases. For example, the former plasma donor cohort has an associated survival bias because large-scale surveys were done in this population roughly 10 years after most infections occurred in the early-mid 1990s, and an

***Panel:* Research in context**

Systematic review

We searched Medline with the terms "mortality", "HIV", "treatment coverage", "developing country", and "resource limited". Several studies have shown a relation between decreased mortality and increased HAART use,[10,11] with other studies showing an association between increased mortality and late initiation of treatment.[4,5,25–34] Reported treatment coverage in patients in developing countries varies greatly, partly because of how treatment coverage is defined. The Joint UN Programme on HIV/AIDS (UNAIDS) 2008 Report on the Global HIV/AIDS Epidemic[16] calculated treatment coverage with the total estimated number of individuals with HIV as the denominator.[17] WHO and UNAIDS estimate global treatment coverage at about 43%.[18] Our analysis uses actual treatment coverage with reported cases as the denominator and thus is not directly comparable to WHO and UNAIDS reported rates. Other analyses have also used actual treatment coverage, with reported proportions from single to multiple clinics ranging from 40% to 95%[19–22] with South Africa reporting treatment coverage of about 40·2% in 2008.[23]

Interpretation

In China, our study confirms the results of previous mortality studies but on a national scale. The recorded HIV treatment coverage (63·4%) is remarkable, considering the size of the country and geographical spread of the individuals with HIV, but is far from the goal of complete coverage of people who meet treatment criteria. Injecting drug users, those infected sexually, men, and those who are underserved by the public health system, such as migrants, the elderly, and minority groups, are at greater risk for not receiving treatment. Increased attention must be given to these populations to diagnose HIV infection earlier and increase treatment coverage.

unknown number of patients had already died before these surveys.[39] Thus, direct mortality comparisons with the IDU and female sex worker cohorts would show this bias and actual differences between the former plasma donors and those who are not former plasma donors might not be as large. Finally, because we were not able to link all of the treated patients with the epidemiology database, we could have underestimated treatment coverage, especially for individuals infected sexually or through injecting drug use. However, this possible underestimation would be small because we were able to link the records of about 96% of all patients, including almost all former plasma donors.

China's national HIV programme has made much progress during the past several years, most notably in the successful diagnosis and treatment of, and resultant decreased mortality in, former plasma donors.[4] This success, however, has not been replicated to the same extent in IDU populations and those infected sexually. To further decrease mortality in these two populations, two steps should be taken. First, large-scale HIV screening of IDUs, sex workers, men who have sex with men, and individuals in regions with a high baseline prevalence of HIV is crucial. Such increased screening should identify substantially more of the people with undiagnosed HIV, and is already done to some extent among IDUs, as those on methadone maintenance treatment[40] and those who are arrested and put in detention centres or labour camps are tested for HIV.[41] Second, patients with HIV found eligible for treatment should be treated as soon as possible, ideally before becoming severely immunosuppressed. Only by substantially earlier identification and much greater treatment coverage in these groups can the mortality be decreased to a level similar to that in former plasma donors. Such broad treatment coverage could even have additional benefits by decreasing HIV transmission.[42–46] Implementation research will be crucial in understanding how best to accomplish these steps.

Contributors

FZ, ZD, RYC designed the study. YM, YZhao, and DZ collected the data. ZD and HZ analysed the data. FZ, ZD, YZhang, SZ, MB, and RYC interpreted the data. YZhang, SZ, and MB suggested additional analyses. ZD made the figures. RYC drafted the report. All authors reviewed, revised, and approved the final report.

Conflicts of interest

All authors declare that they have no conflicts of interest.

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HAART for HIV in China—much achieved, more to be done

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First introduced in the mid-1990s, mainly in developed countries, highly active antiretroviral therapy (HAART) has resulted in unprecedented decreases in the morbidity and mortality caused by HIV/AIDS.[1] To extend the benefits of HAART to resource-limited settings, which bear most of the HIV burden, a public health approach with standardised protocols for antiretroviral regimens, disease monitoring, and follow-up services has been advocated.[2]

In *The Lancet Infectious Diseases*, Fujie Zhang and colleagues[3] report the nationwide coverage and mortality outcomes of the China National Free Antiretroviral Treatment Programme (CNFATP). This programme was one of the first to scale up HIV treatment access in a developing country. The investigators rightly draw attention to the importance of improving treatment coverage with HAART and ensuring treatment initiation before a patient becomes severely immunosuppressed, especially before their CD4 count falls to less than 50 cells per μL. The data are strong and the message is clear on how the mortality outcomes of HAART can be improved. The study also provided evidence for the feasibility of a public health approach to generate continued positive outcomes in a large population of patients. The findings are hence more robust than those from other studies of such an approach, which are smaller and have a shorter follow-up period.[4,5] The continued benefit over time recorded in this study—more than 60% reduction in HIV-related mortality from 2003 to 2009—will provide encouragement to individuals who have participated in and contributed to the CNFATP. Developing countries, including China, have published much information to enrich HIV science worldwide. This is especially true for operational research, which is of crucial importance to combat the HIV/AIDS epidemics in developing countries.

China has come a long way in its HIV/AIDS response, with substantially escalated efforts and scaling up of many crucial services in the past decade.[6] The landmark Four Frees and One Care policy was rolled out in 2003,[7] and increased the number of people with HIV/AIDS who received antiretroviral treatment from some 4600 patients in 2003 to more than 66 000 in 2009.[8] The achievements of the underpinning treatment programme, as shown by Zhang and colleagues' article, is a clear example of the difference that can be made with high-level political commitment.[9] Injecting drug users receiving methadone maintenance treatment were 2·5 times more likely to have received HAART and five times less likely to die than were drug users not receiving such treatment.[3] Of all populations of people with HIV, HAART coverage is lowest in injecting drug users—a clear need exists to expand methadone treatment programmes to such drug users, which will increase the chances of those with HIV receiving and benefiting from HAART.[10]

Several technical challenges exist to make the CNFATP and national treatment programmes in other countries more successful. Zhang and colleagues noted disparities in mortality and treatment coverage in terms of demographic, geographical, and HIV risk factor attributes.[3] Another study from mainland China also reported geographical difference in treatment response.[11] Measures to lessen such disparities would improve overall treatment outcome. However, the long-term outcome of most patients in Zhang and colleagues' study is not clear because the median follow-up was less than 2 years. Also, a mortality rate of 6·7 deaths per 100 person-years in 2009 in former blood donors—the population with the best outcomes—is suboptimum at the clinical level. Viral-load suppression is the most direct and sensitive biological marker to monitor the success of antiviral treatment. Unfortunately, the availability of regular viral-load testing in the CNFATP is not sufficient to promptly detect virological failure in most patients.[12] Furthermore, a high rate of resistance has been reported in patients after a short duration of treatment in the early days of the programme.[13] More resistance could emerge in the future, especially if good treatment adherence cannot be sustained. Lastly, we expect HAART to be an effective, lifelong treatment in most patients, if not all. Taken together, these issues cannot be solved by simply enhancing availability of second-line and third-line drugs or laboratory testing. The CNFATP has to be supplemented by nationwide clinical management systems to cater for patients whose clinical needs are not met by the public health approach.

Through presenting and discussing findings of this study, Zhang and colleagues have shared China's

encouraging experience in the provision of life-saving treatment for its HIV-infected population. The CNFATP has provided a solid base for moving forward, but the challenges ahead will be no less than before.

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