Tropical Medicine and International Health doi:10.1111/j.1365-3156.2012.03056.x

VOLUME 17 NO 10 PP 1255–1263 OCTOBER 2012

Incidence, risk factors and causes of death in an HIV care programme with a large proportion of injecting drug users

Heidi Spillane[1], Sarala Nicholas[2], Zhirong Tang[3], Elisabeth Szumilin[4], Suna Balkan[4] and Mar Pujades-Rodriguez[2]

1 *Médecins Sans Frontières, Nanning, China*
2 *Epicentre, Paris, France*
3 *Guangxi Centre for Disease Control, Nanning, China*
4 *Médecins Sans Frontières, Paris, France*

Abstract

OBJECTIVES To identify factors influencing mortality in an HIV programme providing care to large numbers of injecting drug users (IDUs) and patients co-infected with hepatitis C (HCV).

METHODS A longitudinal analysis of monitoring data from HIV-infected adults who started antiretroviral therapy (ART) between 2003 and 2009 was performed. Mortality and programme attrition rates within 2 years of ART initiation were estimated. Associations with individual-level factors were assessed with multivariable Cox and piece-wise Cox regression.

RESULTS A total of 1671 person-years of follow-up from 1014 individuals was analysed. Thirty-four percent of patients were women and 33% were current or ex-IDUs. 36.2% of patients (90.8% of IDUs) were co-infected with HCV. Two-year all-cause mortality rate was 5.4 per 100 person-years (95% CI, 4.4–6.7). Most HIV-related deaths occurred within 6 months of ART start (36, 67.9%), but only 5 (25.0%) non-HIV-related deaths were recorded during this period. Mortality was higher in older patients (HR = 2.50; 95% CI, 1.42–4.40 for ≥40 compared to 15–29 years), and in those with initial BMI < 18.5 kg/m^2 (HR = 3.38; 95% CI, 1.82–5.32), poor adherence to treatment (HR = 5.13; 95% CI, 2.47–10.65 during the second year of therapy), or low initial CD4 cell count (HR = 4.55; 95% CI, 1.54–13.41 for <100 compared to ≥100 cells/μl). Risk of death was not associated with IDU status (P = 0.38).

CONCLUSION Increased mortality was associated with late presentation of patients. In this programme, death rates were similar regardless of injection drug exposure, supporting the notion that satisfactory treatment outcomes can be achieved when comprehensive care is provided to these patients.

keywords antiretroviral therapy, cohort study, HIV, injecting drug use, mortality, risk factor

Introduction

By the end of 2009 approximately, 740 000 people were living with HIV and AIDS in China (Ministry of Health of the People's Republic of China 2010). Although the national HIV prevalence is estimated at 0.06% (Ministry of Health of the People's Republic of China 2010), large disparities are observed both regionally and within different population groups: more than 50% of HIV-infected individuals live in only five of China's 22 Chinese provinces, and HIV prevalence rates of more than 50% are observed among injecting drug users (IDUs) in some prefectures and cities (Ministry of Health, People's Republic of China, Joint United Nations Programme on HIV/AIDS, and World Health Organization 2010). In 2003, China launched its National Antiretroviral Therapy (ART) Program and started implementing the 'Four Frees and One Care' policy, which included the provision of free blood testing, screening and therapy for pregnant women and education for orphans born of HIV-infected parents. At the end of that year, the Chinese Center for Disease Control and Prevention, in collaboration with Médecins Sans Frontières (MSF), started a comprehensive HIV programme in Guangxi province, where HIV prevalence is estimated at 0.08% in the general population (National Center for AIDS/STD Control and Prevention 2011), and at 25% among IDUs (Liu *et al.* 2006).

Injection of illicit drugs is an important mode of HIV transmission in the region and ensuring access to and provision of optimal care to this high-risk group is a major challenge (Celentano *et al.* 2001; Gebo *et al.* 2005). An additional complication is that co-infection of HIV and hepatitis C virus (HCV) is very common in Guangxi, especially among heroin users. In one longitudinal cohort of 547 IDUs, the prevalence of HCV was 17.6% overall and 95.1% in HIV-infected individuals (Garten *et al.*

2005). Approximately 80% of individuals exposed to HCV develop chronic infection (Te & Jensen 2010), which is associated with increased risk of liver failure and hepatocellular carcinoma (Nelson *et al.* 2011). 3–11% of individuals with chronic infection will develop liver cirrhosis within 20 years (Dore *et al.* 2002). Furthermore, evidence suggests that HIV infection can accelerate HCV-related disease progression and mortality (Benhamou *et al.* 1999; Mohsen *et al.* 2003; Smit *et al.* 2008).

In this paper, we describe trends in patient characteristics, all-cause mortality and causes of death in an HIV programme providing care for a large number of IDUs and patients co-infected with HCV. We also report on risk factors influencing mortality, including history of injecting drug use, and on whether causes of death differed according to length of time receiving ART.

Methods

The Guangxi CDC/MSF HIV programme

The Guangxi CDC/MSF HIV programme offered a combination of HIV counselling and testing, comprehensive HIV care for HIV positive patients and training for health professionals. Specific interventions to improve access to care for high-risk groups included targeted prevention outreach activities and referral for HIV testing, training of staff in prisons and detoxification centres, work with peer groups, and referral of IDUs to methadone and needle and syringe programmes.

Free HIV care, including combined ART, hospitalisation costs and psychosocial and nutritional support, was provided. Financial support for patient transport was also offered under specific circumstances. A strong emphasis was placed on the counselling component of the programme before ART initiation and also in the early stages of treatment. The provision of psychosocial support was enhanced in 2007 when counsellors from the Red Ribbon Center joined the team.

Patients were eligible for ART when either the CD4 cell count was <200 cells/μl or their disease had reached WHO clinical stage 3 or 4. In 2009, The CD4 threshold for ART initiation was increased to <350 cells/μl. The most widely prescribed first-line ART regimen contained two nucleoside reverse transcriptase drugs (NRTI) and one non-NRTI (NNRTI). Protease-inhibitor second-line regimens were available for patients diagnosed with treatment failure. CD4 cell counts were measured every 6 months and viral load testing was performed when treatment failure was suspected (WHO 2006 criteria). Cotrimoxazole prophylaxis was provided to patients with CD4 cell count below 200 cells/μl.

Patients who missed a clinical appointment were contacted by phone. During the handover phase of the programme (from January to September 2010), concerted efforts were made to ascertain outcomes of patients lost to care.

Study population and data collection

All patients aged 15 years or older who initiated ART in the programme between 1 December 2003 and 31 December 2009 were included in the analysis. Programme data collected until 31 October 2010 were analysed.

Clinicians collected socio-demographic, clinical and treatment information at each patient visit using standardised questionnaires, and data were entered daily into the FUCHIA software (Epicentre, Paris). An active search of patients lost to follow-up was performed before closure of the programme. For patients who died during follow-up, two physicians retrospectively determined the cause of death after reviewing all available medical records. The primary cause of death was classified into one of the following categories: infectious, hepatic, non-hepatic malignancy, other or unknown. Deaths were further grouped into HIV-related (i.e. the primary cause of death was a WHO AIDS-defining condition), non-HIV-related or unknown.

Lost to follow-up was defined as missing an appointment by more than 3 months on the date of analysis. Initial haemoglobin, CD4 cell count and body mass index (BMI) were defined as the measurement recorded closest to ART start (between 3 months before and 1 month after this date).

Statistical methods

Standard basic statistics were used to describe patient characteristics at ART start per year of ART inclusion. Because the risk of AIDS-defining conditions potentially leading to death is higher during the first 6 months after ART start (Martinez *et al.* 2007), causes of death within and after 6 months were described separately. Kaplan–Meier naïve methods were used to estimate the probability of death and programme attrition (deaths and lost-to-follow-up) at 6 months, 1 and 2 years after ART initiation. The incidences of all-cause, AIDS-related and non-AIDS-related mortality were estimated by time-to-event analysis.

Risk factors associated with 2-year mortality were studied using multivariable Cox's regression models. Factors studied included sex, age (5–29, 30–39, ≥40 years), IDU status (current or history of IDU, never IDU), history of ART use, tuberculosis (TB) diagnosis,

WHO clinical stage (1 or 2, 3, 4), BMI (≥18.5, <18.5, missing, kg/m^2), CD4 cell count (≥100, <100, missing, cells/μl) and haemoglobin (≥11, <11, missing, g/dl) at ART start; year of therapy initiation (2003–2005, 2006–2007, 2008–2009); and a recently validated marker for treatment adherence based on the proportion of clinical appointments attended with no delay over the 2 years of study follow-up (>95%, ≤95%) (Pujades-Rodriguez *et al.* 2010).

The proportional hazards assumption was tested by plotting scaled Schoenfeld residuals against time (Grambsch & Therneau 1994). Factors for which this assumption did not hold (IDU status, initial CD4 cell count and adherence) were analysed by fitting piece-wise Cox's models (Collett 1994) to obtain stratum-specific estimates of hazard ratio for the periods 0–6 months, 6–12 and 12–24 months of follow-up.

Multivariable analyses were performed in two steps. First, factors associated with the outcome in univariate analyses ($P < 0.1$) were included in a transition model. The final model was then obtained after reintroducing each non-significant factor to assess whether it induced at least a 10% change in the estimated adjusted hazard ratios (aHR). Associations were assessed using likelihood ratio tests. Two-sided *P*-values <0.05 were considered statistically significant. Two sensitivity analyses were performed. First, multivariable analyses were repeated using attrition as the main outcome. Second, we performed complete case analyses excluding individuals with missing BMI and CD4 cell count data. All analyses were done in Stata 11.0 (StataCorps, TX, USA).

Results

Patient characteristics at ART initiation

A total of 1014 adults started ART during the study period and contributed 1671 person-years of follow-up. Thirty-four percent were women, and median age at therapy initiation was 34 years (Table 1). Thirty-three percent were currently IDUs or had a history of injecting drug use. Results of HCV antibody testing in 898 patients showed that 325 (36.2%) were positive (90.8% of IDUs), while hepatitis B surface antigen test results from 952 patients showed 15% to be positive (92.8% of the IDU patients tested).

At ART start, median time since programme entry was 1 month [IQR 0.5–3.0]. The proportion of patients with initial clinical stage 3 or 4 decreased over time from 82.8% in 2003–2004 to 49.6% in 2009, and median CD4 cell count gradually increased from 53 to 167 cells/μl. The most commonly prescribed ART regimen, except during 2006–2007, was AZT-based, and 80% of patients achieved good adherence during the first 2 years of ART use (index category ≥95%).

Mortality and causes of death

A total of 91 (9.0%) patients died during the first 2 years of ART use. This figure includes 53 (58.2%) deaths from AIDS-related causes, 20 (22.0%) from non-AIDS-related conditions and unknown causes of death for the remaining 18 patients (Table 2). The Kaplan–Meier probability of death at 2 years was 10.0% (95% CI, 8.2–12.2%; Figure 1), which corresponds to an all-cause mortality rate of 5.4 per 100 person years (95% CI, 4.4–6.7). Mortality was highest during the 6 months after ART start, with 9.68 deaths per 100 person years (95% CI, 7.27–12.88), and fell thereafter (to 2.63 per 100 person-years, 95% CI, 1.50–4.64 in the 6- to 12-month period; and 4.39 per person years; 95% CI, 3.10–6.20 in 12–24 months).

The majority of AIDS-related deaths also occurred within the first 6 months of ART (36, 67.9%), while only 5 (25.0%) non-AIDS-related deaths during the same time period. Sixty-eight percent of deaths from known causes were attributed to infections, 8 (12.9%) to malignancies, 6 (9.7%) to hepatic disease and 6 (9.7%) to other causes. For 30%, the cause of death could not be determined (Figure 2).

Programme attrition

The vital status of 27 (2.7%) patients lost to follow-up could not be determined and 52% were lost within the first 3 months of therapy. The Kaplan–Meier probability of attrition was 6.3% (95% CI, 5.0–8.0) at 6 months, 8.1% (95% CI, 6.5–9.9%) at 1 year and 12.7% (95% CI, 10.7–15.0%) at 2 years of ART start (Figure 1). The overall attrition rate was 7.06 per 100 person years (95% CI, 5.90–8.46). It was highest in the 0- to 6-month period (13.18 per 100 person years; 95% CI, 10.31–16.84) and dropped thereafter (3.73 per 100 person-years, 95% CI, 2.32–6.00 in the 6-to 12-month period; and 5.07 per 100 person-years; 95% CI, 3.67–7.00 in the 12- to 24-month period; Table 2).

Risk factors for death and programme attrition

Multivariable analyses showed increased mortality in patients aged ≥40 years (aHR = 2.50; 95% CI, 1.42–4.40) and in those with BMI < 18.5 kg/m^2 (aHR = 3.11; 95% CI, 1.82–5.32; Table 3). Poor adherence and CD4 cell count <100 cells/μl or unknown were also associated with higher mortality. The effect of adherence increased with

Table 1 Evolution of patient characteristics at ART initiation and of treatment adherence stratified by year of ART start

	Year of ART start						
	2003–2004	2005	2006	2007	2008	2009	Total
	N = 142	*N* = 111	*N* = 146	*N* = 190	*N* = 282	*N* = 143	*N* = 1014
Median age, years [IQR]	31.1 [27.1–40.2]	32.4 [27.5–40.6]	33.7 [30.0–42.4]	35.2 [29.3–40.6]	36.5 [29.9–43.5]	32.7 [28.3–41.7]	34.1 [29.0–42.1]
Women (%)	42 (29.6)	40 (36.0)	43 (29.5)	68 (35.8)	87 (30.9)	64 (44.8)	344 (33.9)
History of ART use (%)	50 (35.2)	2 (1.8)	7 (4.8)	12 (6.3)	23 (8.2)	3 (2.1)	97 (9.6)
Ex- or current IDU (%)	43 (30.3)	42 (37.8)	62 (42.5)	58 (30.5)	90 (31.9)	40 (28.0)	335 (33.0)
WHO clinical stage (%)							
1 or 2	27 (19.0)	29 (26.1)	50 (34.2)	71 (37.4)	103 (36.5)	73 (51.0)	353 (34.8)
3	45 (31.7)	34 (30.6)	49 (33.6)	53 (27.9)	82 (29.1)	44 (30.8)	307 (30.3)
4	70 (49.3)	48 (43.2)	47 (32.2)	66 (34.7)	97 (34.4)	26 (18.2)	354 (34.9)
Tuberculosis diagnosis (%)	42 (29.6)	23 (20.7)	41 (28.1)	38 (20.0)	63 (22.3)	22 (15.4)	229 (22.6)
BMI, kg/m^2	*n* = 99	*n* = 106	*n* = 139	*n* = 183	*n* = 264	*n* = 132	*n* = 923
≥18.5	62 (62.6)	61 (57.5)	87 (62.6)	109 (59.6)	145 (54.9)	95 (72.0)	559 (60.6)
CD4 cell count, cells/μl	*n* = 124	*n* = 85	*n* = 119	*n* = 164	*n* = 214	*n* = 87	*n* = 793
Median [IQR]	52.5 [21.0–120.5]	64.0 [15.0–128.0]	59.0 [17.0–146.0]	104.0 [32.0–179.5]	119.5 [32.0–214.0]	167.0 [58.0–239.0]	91.0 [27.0–182.0]
Haemoglobin, g/dl (%)	*n* = 128	*n* = 107	*n* = 144	*n* = 179	*n* = 265	*n* = 129	*n* = 952
<11 g/dl	76 (59.4)	60 (56.1)	94 (65.3)	114 (63.7)	150 (56.6)	79 (61.2)	573 (60.2)
Prescribed ART regimen (%)							
NRTI component							
AZT	105 (73.9)	94 (84.7)	28 (19.2)	46 (24.2)	205 (72.7)	111 (77.6)	589 (58.1)
d4T	37 (26.1)	17 (15.3)	118 (80.8)	144 (75.8)	76 (27.0)	31 (21.7)	423 (41.7)
NNRTI component							
NVP	69 (48.6)	78 (70.3)	98 (67.1)	139 (73.2)	167 (59.2)	101 (70.6)	652 (64.3)
Treatment adherence							
≥95%	134 (94.4)	76 (68.5)	118 (80.8)	152 (80.0)	218 (77.6)	114 (79.7)	812 (80.2)
<95%	8 (5.6)	35 (31.5)	28 (19.1)	38 (20.0)	63 (22.4)	29 (20.3)	201 (19.9)

AZT, zidovudine; ART, antiretroviral therapy; BMI, body mass index; d4T, stavudine; IDU, intravenous drug user; NRTI, nucleoside reverse transcriptase inhibitor drug; NNRTI, non-nucleoside reverse transcriptase inhibitor drug.

Table 2 Mortality and attrition rates stratified by period of follow-up on ART

	No. of deaths	Person-years of follow-up	Mortality per 100 person-years (95% CI)
All-cause mortality			
At 6 months	47	485.65	9.68 (7.27–12.88)
At 1 year	12	455.92	2.63 (1.50–4.64)
At 2 years	32	729.51	4.39 (3.10–6.20)
Total	91	1671.08	5.44 (4.43–6.69)
AIDS-related mortality			
At 6 months	36	485.65	7.41 (5.34–10.28)
At 1 year	4	455.92	0.88 (0.33–2.34)
At 2 years	13	729.51	1.78 (1.03–3.07)
Total	53	1671.08	3.17 (2.42–4.15)
Non-AIDS-related mortality			
At 6 months	5	485.65	1.03 (0.43–2.47)
At 1 year	5	455.92	1.10 (0.46–2.63)
At 2 years	10	729.51	1.37 (0.74–2.55)
Total	20	1671.08	1.20 (0.77–1.86)
Attrition			
At 6 months	64	485.65	13.18 (10.31–16.84)
At 1 year	17	455.92	3.73 (2.32–6.00)
At 2 years	37	729.51	5.07 (3.67–7.00)
Total	118	1671.08	7.06 (5.90–8.46)

CI, confidence interval.

longer treatment duration, so that no difference in mortality between compliant and non-compliant patients was observed during the first 6 months of ART (aHR = 1.02; 95% CI, 0.48–2.15), but mortality ratios for poor *vs.* good adherence subsequently increased (aHR = 14.38; 95% CI, 3.80–54.44 for the 6- to 12-month period; and aHR = 5.13; 95% CI, 2.47–10.65 during the second year of therapy). In contrast, the effect of initial CD4 cell counts was seen only during the first 6 months of ART (aHR = 4.55; 95% CI, 1.54–13.41 for patients with CD4 cell count <100 cells/μl compared to ≥100 cells/μl).

The effect of previous or current intravenous drug use was also time dependent in univariate analyses, with higher mortality observed among IDUs compared with non-IDUs during the second year of ART (HR = 2.33; 95% CI, 1.17–4.67). Nevertheless, this effect disappeared after adjusting for other risk factors, namely sex and age. Adjusting for differences in adherence levels between these two groups did not change the estimates (data not shown).

Risk factors associated with attrition were similar to those described for mortality, but generally of lower magnitude (Table S1). Analyses restricted to patients with complete clinico-immunological data identified identical risk factors (Table 3).

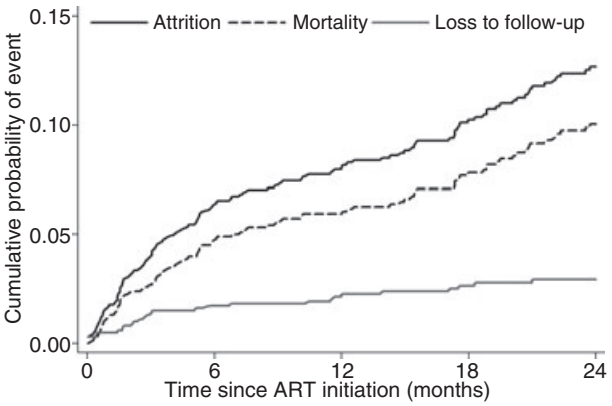

Figure 1 Kaplan–Meier cumulative probabilities of death, loss to follow-up and programme attrition.

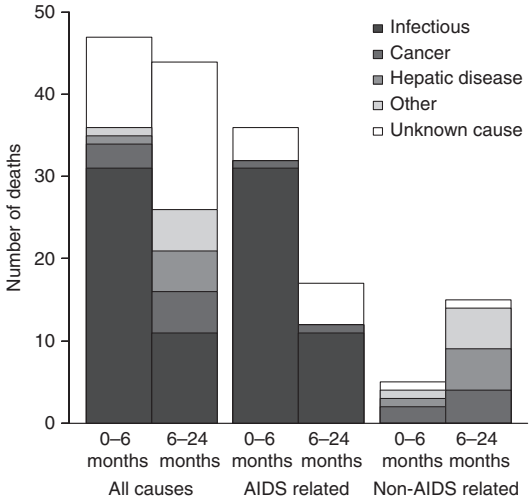

Figure 2 Distribution of causes of death stratified by duration of ART. Cause of death for 18 patients were unknown (six occurred within 6 months and 12 in the 6- to 24-month period after ART start).

Discussion

In this HIV programme with a large proportion of current or ex-IDUs in the Nanning province, 88% of patients were alive and receiving HIV care 2 years after starting ART; only 9% had died. Mortality was highest during the initial 6 months of treatment, with 68% of deaths being AIDS-related, and most commonly from an infection-related cause. With longer follow-up on ART, the proportion of deaths related to AIDS decreased but non-AIDS-related deaths (i.e. cancer or hepatic disease) became more common.

Table 3 Two-year mortality and associations with individual factors measured at ART start

	No. of deaths	Person-years	Rate per 100 person-years (95% CI)	Crude HRR (95% CI)	Adjusted HR from model 1 (95% CI)	Adjusted HR from model 2 (95% CI)
Age group, years				$P = 0.002$	$P = 0.004$	$P = 0.173$
15–29	22	512.4	4.3 (2.8–6.5)	1.00	1.00	1.00
30–39	27	682.3	4.0 (2.7–5.8)	0.92 (0.53–1.62)	0.94 (0.52–1.68)	1.04 (0.51–2.13)
≥40	42	476.4	8.8 (6.5–11.9)	2.03 (1.21–3.41)	2.50 (1.42–4.40)	1.79 (0.88–3.63)
Sex				$P < 0.001$	$P = 0.065$	$P = 0.222$
Women	16	570.8	2.8 (1.7–4.6)	1.00	1.00	1.00
Men	75	1100.3	6.8 (5.4–8.5)	2.43 (1.42–4.16)	1.71 (0.95–3.10)	1.79 (0.90–3.56)
History of ART exposure				$P = 0.095$	$P = 0.132$	
No	86	1494	5.8 (4.7–7.1)	1.00	1.00	
Yes	5	177.1	2.8 (1.2–6.8)	0.50 (0.20–1.23)	0.51 (0.20–1.32)	
Year of ART start				$P = 0.954$		
2003–2005	26	464.3	5.6 (3.8–8.2)	1.00		
2006–2007	33	614.9	5.4 (3.8–7.5)	0.96 (0.57–1.61)		
2008–2009	32	591.9	5.4 (3.8–7.6)	0.92 (0.55–1.55)		
Clinical stage				$P < 0.001$	$P = 0.078$	
1 or 2	14	570.2	2.5 (1.5–4.1)	1.00	1.00	
3	24	510.8	4.7 (3.1–7.0)	1.93 (1.00–3.73)	0.76 (0.36–1.61)	
4	53	590.1	9.0 (6.9–11.8)	3.70 (2.05–6.67)	1.34 (0.65–2.78)	
Tuberculosis diagnosis				$P = 0.001$	$P = 0.079$	$P = 0.158$
No	57	1293.2	4.4 (3.4–5.7)	1.00	1.00	1.00
Yes	34	377.9	9.0 (6.4–12.6)	2.05 (1.34–3.14)	1.53 (0.96–2.45)	1.57 (0.85–2.91)
BMI, kg/m^2				$P < 0.001$	$P < 0.001$	$P < 0.001$
≥18.5	21	935	2.2 (1.5–3.4)	1.00	1.00	1.00
<18.5	47	604.4	7.8 (5.8–10.3)	3.50 (2.09–5.85)	3.11 (1.82–5.32)	3.38 (1.85–6.18)
Unknown	23	131.7	17.5 (11.6–26.3)	7.63 (4.22–13.79)	7.04 (3.80–13.03)	NA
Haemoglobin, g/dl				$P = 0.172$	$P = 0.589$	
≥11	43	949.3	4.5 (3.4–6.1)	1.00	1.00	
<11	41	630.1	6.5 (4.8–8.8)	1.45 (0.94–2.22)	0.83 (0.51–1.33)	
Unknown	7	91.6	7.6 (3.6–16.0)	1.68 (0.75–3.73)	1.29 (0.50–3.00)	

	No. of deaths	Person-years	Rate per 100 person-years (95% CI)	Unadjusted HRR (95% CI)	Adjusted HR from model 1 (95% CI)	Adjusted HR from model 2 (95% CI)
IDU Status				$P = 0.116$	$P = 0.380$	
0–6 months						
Never	33	324.7	10.2 (7.2–14.3)	1.00	1.00	
Ever	14	161	8.7 (5.2–14.7)	0.86 (0.46–1.60)	0.78 (0.40–1.52)	
6–12 months						
Never	8	304.9	2.6 (1.3–5.2)	1.00	1.00	
Ever	4	151	2.6 (1.0–7.1)	1.01 (0.30–3.36)	0.59 (0.17–2.03)	
12–24 months						
Never	15	490.6	3.1 (1.8–5.1)	1.00	1.00	
Ever	17	238.9	7.1 (4.4–11.4)	2.33 (1.17–4.67)	1.60 (0.75–3.41)	
CD4 cell count, cells/μl				$P < 0.001$	$P = 0.040$	$P = 0.060$
0–6 months						
≥100	4	186.2	2.1 (0.8–5.7)	1.00	1.00	1.00
<100	31	196.4	15.8 (11.1–22.4)	7.32 (2.59–20.75)	4.55 (1.54–13.41)	3.62 (1.22–10.75)
Unknown	12	103.1	11.6 (6.6–20.5)	5.42 (1.75–16.79)	3.34 (1.04–10.76)	–
6–12 months						
≥100	3	174.9	1.7 (0.6–5.3)	1.00	1.00	1.00
<100	7	185.2	3.8 (1.8–7.9)	2.21 (0.57–8.56)	1.55 (0.39–6.19)	1.34 (0.31–5.73)
Unknown	2	95.9	2.1 (0.5–8.3)	1.21 (0.20–7.25)	0.64 (0.10–3.99)	–

Table 3 *(Continued)*

	No. of deaths	Person-years	Rate per 100 person-years (95% CI)	Unadjusted HRR (95% CI)	Adjusted HR from model 1 (95% CI)	Adjusted HR from model 2 (95% CI)
12–24 months						
≥100	10	276.5	3.6 (1.9–6.7)	1.00	1.00	1.00
<100	12	318	3.8 (2.1–6.6)	1.04 (0.45–2.40)	0.72 (0.29–1.75)	0.78 (0.30–2.03)
Unknown	10	135.1	7.4 (4.0–13.8)	2.07 (0.86–4.96)	1.10 (0.42–2.89)	–
Treatment adherence				$P < 0.001$	$P < 0.001$	$P < 0.001$
0–6 months						
≥95%	38	388.8	9.8 (7.1–13.4)	1.00	1.00	1.00
<95%	9	96.9	9.3 (4.8–17.9)	0.95 (0.46–1.96)	1.02 (0.48–2.15)	0.95 (0.36–2.52)
6–12 months						
≥95%	3	367.5	0.8 (0.3–2.5)	1.00	1.00	
<95%	9	88.5	10.2 (5.3–19.6)	12.33 (3.34–45.54)	14.38 (3.80–54.44)	
12–24 months						
≥95%	14	601.4	2.3 (1.4–3.9)	1.00	1.00	1.00
<95%	18	128.1	14.0 (8.8–22.3)	6.14 (3.05–12.35)	5.13 (2.47–10.65)	4.49 (1.77–11.35)

ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; HR, hazard rate ratio; IDU, injecting drug user; model 1 includes all eligible patients; model 2 includes only eligible patients with initial BMI and CD4 cell count data.

The IDU and non-IDU populations showed similar levels of mortality and programme attrition.

Success of the comprehensive, patient cost-free model of care implemented in Nanning was reflected in the high programme retention rate achieved, 91.9% one year after ART start and 87.3% after 2 years. These figures are higher than overall retention estimates from 13 Asian HIV programmes, 80.2% and 68.7% at 12 and 24 months, respectively (Tassie *et al.* 2010). Furthermore, although the percentage of HIV patients who enter care with a CD4 count <50 cells/μl in China has remained relatively constant at 25% since 2006 (Dou *et al.* 2010), in our programme, this proportion decreased over time, most likely as a result of intensive efforts to improve access to HIV testing and care in the area. Still, one in two patients treated in Nanning presented with advanced HIV disease, indicating that further efforts are still needed to diagnose and treat HIV patients at earlier stages of infection.

Intensive efforts to trace patients lost to follow-up and to ascertain mortality in the months before handover of the programme, and low rates of loss to follow-up, contributed to the low mortality observed during the first 2 years of ART (9% of patients). This estimate is lower than mortality reported in an HIV programme in Phnom Penh, Cambodia [12.7% (Ferradini *et al.* 2007)] and similar to published aggregated national figures from China (Zhang *et al.* 2009). As previously reported (Coetzee *et al.* 2004; Braitstein *et al.* 2006; Zachariah *et al.* 2006), higher mortality was observed during the first 6 months of ART (9.68 deaths per 100 person years in the first 6 months on ART). Not surprisingly, the majority of deaths recorded during this time period were AIDS-related (68%) and, with longer ART use and improved immune function, the proportion of these deaths decreased. Although the primary cause of death was classified retrospectively in this study and could not be determined for approximately 20% of patients, and because the proportion of deaths from unknown causes increased with time on ART, misclassifications of causes are unlikely to be related to treatment duration. Furthermore, reports of changes in the distribution of causes of death over time have also being described in other cohorts in resource-rich countries (2010; Bonnet *et al.* 2002).

Factors associated with mortality in this HIV programme were male sex, age older than 40 years, low initial BMI and a diagnosis of TB at therapy start, all known from previous studies to be important risk factors for HIV progression and death. Unsurprisingly, patients with poor adherence rates (especially in the longer-term) and those who initiated ART at low CD4 counts were also at a higher risk of death.

A large proportion of the patients treated in the programme were known ex- or current IDUs, and many were co-infected with hepatitis C and B (38% and 15% of patients, respectively). Provision of HIV care to IDUs is challenging. Barriers to accessing care, including national drug policies and strategies that lead to marginalisation of IDUs (Rhodes *et al.* 2003; Wood *et al.* 2007), along with social instability and homelessness (Bassetti *et al.* 1999; Chander *et al.* 2006; Knowlton *et al.* 2006) and with patient (Bassetti *et al.* 1999; Kerr *et al.* 2005) or physician (Bassetti *et al.* 1999; Gross *et al.* 2002) reluctance to start ART

because of perceptions that IDUs are less likely to be adherent and/or might develop and transmit ART-resistant virus (Wainberg & Friedland 1998; Ding *et al.* 2005; Mills *et al.* 2006) have been well described (Wood *et al.* 2008b).

Yet, despite these challenges, IDUs treated in the Nanning comprehensive care programme did not experience higher mortality or attrition rates than other patients during their first 2 years of ART. Even if the patients treated in the Nanning programme may not represent the general IDU population, IDUs might be more likely to experience accidental death from non-HIV-related causes such as drug overdose (Wood *et al.* 2008a). Furthermore, the lack of a difference in mortality regardless of IDU status is consistent with evidence from a Canadian study reporting similar all-cause mortality and non-accidental mortality in HIV-infected IDUs and non-IDUs treated with ART for 84 months (Wood *et al.* 2008a) and with results of a meta-analysis of 12 observational studies that reported a similar risk of ARV resistance in IDUs and non-IDUs (Werb *et al.* 2010). In the ART era, co-infection with hepatitis B and C has been associated with increased mortality (Chen *et al.* 2009; Chun *et al.* 2012). The large proportion of co-infection among IDUs treated in the programme did not allow us to examine the independent effect of hepatitis on patient mortality. Nevertheless, hepatic and non-AIDS-related cancer, including hepatic cancer, were responsible for the majority of non-AIDS-related deaths, suggesting that the burden of disease related to hepatitis infection is important in this setting. Future models of HIV care that consider hepatitis B and C co-infection-related issues such as ART-related hepatotoxicities, choice of ART regimen and access to hepatitis C treatments [despite significant challenges regarding hepatitis C treatments, including expense, complexity, variable success rates and significant side effects (Dou *et al.* 2010)], may further decrease non-AIDS-related mortality in HIV programmes.

Conclusions

Mortality associated with HIV disease was higher during the first 6 months of treatment and among late presenters, highlighting the need to improve both early access to HIV testing and earlier start of therapy. Patients with history of IDU experienced mortality and attrition rates similar to other patients in this programme, findings that support the feasibility of achieving satisfactory treatment outcomes in this high-risk group.

Acknowledgements

We thank the clinic staff of Nanning for their commitment and hard work, all the MSF personnel who have contributed to the work of this project over the years and Patricia Kahn for her editorial work.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1 Two-year attrition and associations with individual factors measured at ART start.

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Corresponding Author **Mar Pujades-Rodríguez**, 8 rue Saint Sabin, 75012 Paris, France. Tel.: +33 1 4021 5513; Fax: +33 1 4021 5500; E-mail: mar.pujades@epicentre.msf.org