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Response to first-line antiretroviral treatment among human immunodeficiency virus-infected patients with and without a history of injecting drug use in Indonesia

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ABSTRACT

Background There is a common belief that injecting drug use (IDU) is associated with lower uptake, retention and success of antiretroviral treatment (ART) in human immunodeficiency virus (HIV)-infected patients. We examined this in an Indonesian setting, where IDU is the main risk factor for HIV infection. **Methods** Patient characteristics and response to ART were recorded for all patients diagnosed with HIV infection in the referral hospital for West Java (40 million people). Kaplan–Meier estimates and Cox's regression were used to compare mortality, loss to follow-up and virological failure between patients with and without a history of IDU. **Result** A total of 773 adult HIV patients (81.9% IDUs) presented between January 1996 and April 2008. IDUs had a median CD4 cell count of 33 [interquartile ratio (IQR), 12–111] cells/mm^3 compared to 84 (IQR, 28–224) cells/mm^3 in non-IDUs. Among patients with a history of IDU, 87.7% were coinfected with hepatitis C (HCV). Mortality was associated strongly with CD4 count; after 6 months of ART, 18.3, 20.3, 7.1 and 0.7% of patients with CD4 cell counts <25, 25–99, 100–199, respectively, ≥200/mm^3 had died ($P < 0.0001$). Mortality [adjusted for CD4; hazard ratio (HR) = 0.65; 95% confidence interval (CI) 0.35–1.23], loss to follow-up (HR = 0.85, 95% CI 0.51–1.41) and virological failure (HR = 0.47, 95% CI 0.19–1.13) were not significantly different in IDUs and non-IDUs. **Conclusion** Intravenous drug users (IDUs) in Indonesia with HIV/acquired immune deficiency syndrome tend to have more advanced disease but respond similarly to non-IDUs to antiretroviral therapy.

Keywords Antiretroviral therapy, highly active, HIV infections, Indonesia, intravenous, substance abuse, treatment outcome.

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INTRODUCTION

Indonesia is facing one of the most rapidly growing human immunodeficiency virus (HIV) epidemics in Asia which, except for Papua, is driven mainly by injecting drug use (IDU) [1]. Currently, HIV prevalence is still low (0.2%) in the general population, but among intravenous drug users (IDUs) HIV prevalence rates higher than 50% have been found [2]. Unprotected sex, also with commercial sex workers, is common among IDUs and it seems a matter of time before Indonesia, which has the fourth biggest population in the world, has a more generalized HIV epidemic [1]. Until now, however, the majority of HIV-infected Indonesians who are in need of antiretroviral treatment (outside Papua) are IDUs.

A number of factors may hamper treatment of HIV-infected IDUs in Indonesia. First, access to care is limited because drug use is illegal and therefore patients may be

reluctant to look for medical care [3]. Stigmatization from the site of the health-care worker may also contribute to this [4,5]. Secondly, HIV treatment itself may be more difficult in IDUs because of non-compliance [6–8], psychiatric conditions [3], concurrent infections such as hepatitis C and late presentation [9–11]. Harm reduction, especially opioid substitution, not only reduces HIV transmission but may also increase access and retention to highly active antiretroviral therapy (HAART) [3,6,8]. In Indonesia, however, harm reduction has become available only recently and only on a limited scale.

Physicians may be reluctant to start antiretroviral treatment (ART) in HIV-infected IDUs, although a number of studies have shown that IDU is not associated with increased mortality during HIV treatment [12–14] or with development of drug resistance [15]. However, these studies were conducted mainly in western countries. To the best of our knowledge, no studies from Asia have described the response to ART among HIV-infected IDUs. We have examined clinical presentation and response to first-line antiretroviral treatment in a cohort of Indonesian HIV-infected patients with and without a history of IDU.

METHODS

Setting and patients

All HIV-positive patients more than 14 years of age presenting between 1996 and April 2008 at Hasan Sadikin hospital as the referral hospital for HIV in West Java (population 40 million) were included in this cohort study. As one of the first 25 hospitals selected by the government to provide HIV care, Hasan Sadikin hospital has delivered free antiretroviral treatment and pneumocystis pneumonia (PCP) prophylaxis since December 2004. Following World Health Organization (WHO) guidelines, ART is indicated for patients presenting with WHO clinical stage IV and/or a CD4 count less than 200/mm^3. For patients who cannot afford CD4 cell measurement, total lymphocyte count (TLC) is used as a surrogate. After 2006, HIV patients with WHO clinical stage III and CD4 cell counts between 200 and 350/mm^3 are also offered ART. The national programme provides a choice of nevirapine (NVP), efavirenz (EFV), zidovudine (ZDV), stavudine (d4T) and lamivudine (3TC) for first-line ART. Laboratory testing is not supported by the programme and CD4 testing was not available in this hospital until September 2007. Measurement of HIV-RNA has only become available in this hospital since January 2008.

Data collection and analysis

Patient data were retrieved retrospectively from medical records. In addition, all patients presenting between September 2007 and April 2008 were characterized prospectively using a standard questionnaire, physical examination and laboratory examination. For all patients, data collected included age, sex, history of injecting drug use, body mass index (BMI, kg/m^2), CD4 count at first presentation, hepatitis B and C virus (HBV, HBC) status and history of tuberculosis (TB) treatment. For patients starting ART, drug regimens and CD4 counts before and after ART were recorded. After September 2007, HIV-RNA was measured for patients with more than 6 months ART, and adherence (correct intake of medication) was evaluated by 3-day, 1-week and 1-month self-report [16]. CD4 cell measurements were carried out using Facscount flow cytometry technology (BD Biosciences, Jakarta, Indonesia). HIV-RNA was quantified by real-time polymerase chain reaction (PCR) (Abbott, IL, USA) with a detection limit of 150 copies HIV-RNA/mm^3. External quality assurance for HIV, HBV and HCV serology was performed (National Serology Reference Laboratory, Fitzroy, Australia) showing 100% accuracy.

The primary end-points during follow-up were survival, retention to treatment and virological response. Death was recorded from medical records. In addition, patients were classified as dead if reported by family or community organizations or confirmed by telephone calls from the clinic. Patients not returning for more than 3 months without confirmation of death or transfer were considered lost to follow-up. Virological failure was defined as a plasma HIV-RNA concentration higher than 400 copies/mm^3, at two different time-points, after at least 6 months of ART.

Data are presented as mean [standard deviation (SD)] if distributed normally, median [interquartile range (IQR)] if not distributed normally, or as a proportion. Comparisons between groups were performed using χ^2 and parametric and non-parametric tests as appropriate. Progression to death, loss to follow-up and virological failure was measured by Kaplan–Meier estimates. Differences between groups in retention, mortality and virological failure were calculated by Cox's regression and expressed as hazard ratios (HR) with 95% confidence intervals (CI). All statistical analyses were conducted using SPSS version 13.00.

RESULTS

Patient's characteristics

Between January 1996 and April 2008, a total of 888 patients were referred or newly diagnosed with HIV infection at Hasan Sadikin Hospital. One hundred and six patients were excluded because of unknown age, age less than 14 years old or absence of information on IDU. Nine

Table 1 Patient characteristics ($n = 773$).

	IDU ($n = 633$)	*No IDU ($n = 140$)*	*P-value*
Male gender, %	91.2	27.1	<0.001
Mean age, years (SD)	28.1 (5.0)	28.9 (7.2)	0.15
Marital status			
Single, %	52.3	20.3	<0.001
Married, %	32.4	55.8	<0.001
Divorced, %	5.3	20.3	<0.001
Education			
Less than senior high school, %	18.0	33.3	<0.001
Senior high school, %	44.3	36.2	0.003
Academy or university, %	27.9	26.8	0.05
BMI at presentation			
<18.5 kg/m^2, %	52.9	39.3	0.08
Median, kg/m^2 (IQR)	18.4 (16.6–21.1)	19.9 (16.5–22.4)	0.02
HBsAg-positive, %	8.0	3.3	0.12
Anti HCV-positive, %	87.7	0[a]	
History of TB treatment, %	46.5	21.6	<0.001
CD4 at time of first presentation			
<200/mm^3, %	89.1	76.4	0.001
Median, cells/mm^3 (IQR)	33 (12–111)	84 (28–224)	0.001

IDU: injecting drug use; BMI: body mass index; TB: tuberculosis; IQR: interquartile range. Marital status available in 649 patients, education level in 652 patients, BMI in 262 patients, hepatitis B surface antigen (HbsAg) in 530 patients, anti-hepatitis C virus (HCV) in 518 patients, history of TB treatment in 604 patients and CD4 in 514 patients. [a]By definition. SD: standard deviation.

patients who denied having a history of IDU but who were positive for anti-HCV antibodies were also excluded. A total of 773 patients were included for further analysis.

Most patients were young, 59.7% were or had been married and 77.3% had completed higher education. Most patients (81.9%) had a history of IDU. IDUs reported to have started IDU at a median age of 19 years ($n = 295$; IQR, 17–22), and to have engaged in IDU for a median duration of 5 years ($n = 393$; IQR, 3–7). Patients with a history of IDU were more often male, single and younger than patients without a history of IDU (Table 1). The median CD4 cell count (available for 514 patients) at presentation was 39 cells/mm^3 (IQR 13–126), and significantly lower among IDUs (median 33 cells/mm^3, IQR 12–111) compared to non-IDUs (median 84 cells/mm^3, IQR 28–224). IDUs also had a lower BMI. Of those patients with a history of IDU, 87.7% were coinfected with hepatitis C. A history of TB treatment at any time was found in 42% of patients, and significantly more often among patients with a history of IDU (Table 1).

Treatment response

From 773 patients, 626 (81.0%) were started on ART. A history of IDU did not appear to have a negative effect on access to ART; 83.6% of patients with a history of IDU compared to 69.3% of patients without a history of IDU were started on ART ($P < 0.001$). One-quarter of patients (24.4%) were started on ART on the same day that they entered the clinic and 22.2% without measurement of CD4 cell count. The median CD4 cell count before the start of ART was 99 (IQR 24–227) cells/mm^3 (Table 2). From 616 patients (98.4%) whose ART regimen could be established, the most common combination used was NVP/ZDV/3TC (59.6%), followed by EFV/ZDV/3TC (15.0%), NVP/d4T/3TC (12.6%) and EFV/d4T/3TC (10.9%). Only two patients (0.3%) were started on a protease inhibitor-based regimen. Patients with a history of IDU were less often prescribed NVP-containing regimens compared to patients without a history of IDU, probably due to (anticipated) liver dysfunction or combined TB treatment at the time of initiating ART.

The median duration of follow-up under ART was 348 days (IQR 65–867) for patients with a history of IDU, and 251 days (IQR 46–477) for non-IDUs. Treatment substitutions were recorded in 162 patients (25.9%), mainly because of ZDV-related anaemia or NVP-related allergy or liver dysfunction. Patients with a history of IDU experienced significantly more NVP-related toxicity compared to patients without a history of IDU, but not more ZDV-related anaemia (Table 2). The median time to treatment substitutions was 48 days (IQR 23–163). Patients with a history of IDU had significantly more substitutions than patients without a history of IDU (Table 2). Missed clinic visits and adherence (self-reported medication intake) were not significantly different between groups.

Table 2 Antiretroviral treatment (ART) in patients with and without a history of IDU ($n = 626$).

	IDU ($n = 530$)	*No IDU* ($n = 96$)	*P-value*
Starting ART			
Median CD4, cell/mm^3 (IQR)	98 (23–233)	115 (28–220)	0.90
No baseline measurement of CD4, %	21.9	24.0	0.76
First ART regimen			
Containing ZDV, %	76.2	74.0	0.64
Containing NVP, %	71.3	84.4	0.008
ART substitution			
Ever received substitution, %	27.5	16.7	0.03
Median time to substitution (IQR), days	50 (23–163)	38 (14–208)	0.48
ZDV to d4T, %	15.7	9.9	0.20
NVP to EFV, %	19.4	8.6	0.02
Adherence			
Ever missed clinic visit >1 month, %	17.2	12.3	0.36
Missed ART dose in last 3 days, %	11.2	7.8	0.47
Missed ART dose in last week, %	12.8	9.8	0.76
Missed ART dose in last month, %	19.3	13.5	0.55

IDU: injecting drug use; d4T: stavudine; ZDV: zidovudine; NVP: nevirapine; EFV: efavirenz; IQR: interquartile range. ART regimen available from 616 patients; CD4 from 487 patients and adherence data from 412 patients.

Both mortality and loss of follow-up were high, with 82.8% of mortality and 71.9% of loss to follow-up occurring in the first 6 months. Using Kaplan–Meier estimates from all 626 ART patients' complete data, mortality at 6 months was 18.3% (95% CI 11.5–25.0%) for patients with CD4 cell counts below 25 cells/mm^3 before the start of ART, 20.3% (13.1–27.6%) for patients with CD4 cell counts of 25–99 cells/mm^3, 7.1% (0.2–12.2%) for patients with CD4 cell counts of 100–199 cells/mm^3 and 0.7% (0.0–2.0%) for patients with CD4 cell counts the same as or more than 200 cells/mm^3 ($P < 0.0001$).

A history of IDU appeared not to have a negative effect on patients' survival and retention to treatment. Mortality following start of ART among patients with and without a history of IDU was not significantly different (HR = 0.90; 95% CI 0.55–1.47) (Fig. 1a, Table 3), even if adjusted for CD4 (HR = 0.65; 95% CI 0.35–1.23). Since 2007, mortality following ART has decreased significantly in this cohort. For patients who started ART after September 2007, the 6-month mortality was 5.1% for IDUs and 8.1% for non-IDUs (HR = 0.56; 95% CI 0.09–3.61). Similar to mortality, loss to follow-up was not different between patients with and without a history of IDU (HR = 0.85; 95% CI 0.51–1.41) (Fig. 1b, Table 3).

IDU did not show a negative effect on immunological or virological response to treatment. CD4 cell counts were available for 377 patients on ART (median duration 615 days, IQR 294–964). Among patients with a history of IDU, 66.2% had a CD4 cell count >200 cells/mm^3 compared with 67.3% of patients without a history of IDU ($P = 0.870$). HIV-RNA measurements were available for 310 patients. After a median duration of ART of 606 days (IQR 291–965), HIV-RNA was below 400 copies/ml in 87.9% of patients with a history of IDU compared to 84.2% of patients without a history of IDU (Fig. 2). Using Cox regression, the risk of virological failure appeared to

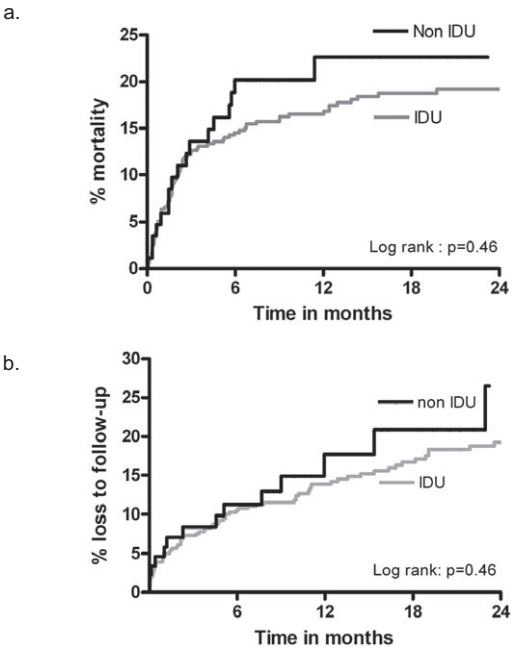
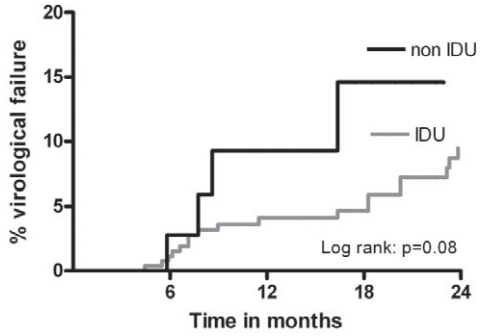


Figure 1 Kaplan–Meier curve for (a) mortality; and (b) loss to follow-up according to history of injecting drug use (IDU)

Table 3 Six-month response to antiretroviral treatment (ART) ($n = 626$).

	IDU (n = 530)	*No IDU (n = 96)*	*RR (95% CI)*
Alive, on original regimen	53.0	55.2	0.96 (0.79–1.20)
Alive, altered regimen	14.7	7.3	2.02 (0.95–4.70)
Died	15.7	18.8	0.84 (0.52–1.59)
Lost to follow-up	13.0	13.5	0.96 (0.55–1.78)
Transferred	3.6	5.2	0.69 (0.25–2.08)

All data presented as %; IDU: injecting drug user; RR: relative risk; CI: confidence interval.



Number at risk

IDU	272	257	192	159	120
Non IDU	38	35	19	14	8

Figure 2 Kaplan–Meier curve for virological failure according to injecting drug use (IDU)

be lower among patients with a history of IDU, but this was not statistically significant (HR = 0.47, 95% CI 0.19–1.13).

DISCUSSION

We have compared clinical presentation and outcome between HIV patients with and without a history of injecting drug use (IDU) in Indonesia. HIV patients with a history of IDU in this setting were mainly young males, presenting with HCV coinfection and more severe immunosuppression than HIV patients without a history of IDU. IDU did not have a negative effect on mortality, retention to treatment and virological or immunological response to ART.

Our cohort reflects the specific nature of the HIV epidemic in Indonesia which, except for Papua, is driven mainly by IDU. No fewer than 80% of patients in our cohort had a history of IDU. This is different from many neighbouring countries, where unprotected sex is the main route of HIV transmission [1,17,18]. Our data show that young people, often highly educated, engage in IDU at a young age. Needle sharing is common [1], leading to a high prevalence of hepatitis C coinfection, even higher than reported previously among IDUs in other countries [19]. Also typical for the HIV epidemic in Indonesia is the fact that patients present mainly with advanced HIV disease or acquired immune deficiency syndrome (AIDS), as reflected by their median CD4 count of 39 cells/mm^3, lower than in many other resource-limited settings [17,18,20–22]. As shown by our data, IDUs presented with more advanced and more symptomatic disease than patients without a history of IDU. Similar to many other settings, several factors may be involved [3]. National policy leads to marginalization of IDUs in Indonesia and stigmatization in the medical system [4]. In addition, drug use and associated socio-financial and psychiatric problems may create barriers to entering HIV care. Finally, health providers may be reluctant to treat patients with a history of IDU. Our data do not support this last possibility, however; the proportion of patients who were started on ART was not lower among those with a history of IDU.

A systemic review has shown that IDU is associated with increased mortality and a poor response to treatment, due largely to differences in treatment adherence [23], but individual cohort studies from western countries [14] have found no negative effect of IDU. Mortality among HIV patients starting ART in our cohort was high, in line with national data [24] and comparable to data from Africa [25]. The early high mortality is related probably to late presentation, extensive comorbidity and lack of diagnostic facilities and adequate treatment of opportunistic infections. Immune reconstitution to *Mycobacterium tuberculosis* or other pathogens may also have contributed, but further study is needed to confirm this. Our study, as far as we know, is the first to compare HIV patients with and without a history of IDU from a low-income or transitional setting. Similar to the recent cohort in Canada [14], we found no difference in mortality, despite the fact that patients with IDU had more advanced disease. In addition, in contrast with common belief and results from most studies in western countries [3], patients with a history of IDU had a similar (good) immunological and virological response to treatment.

Retention to treatment was lower than reported in other studies from Asia [21,22], but higher compared to data from Africa [26]. There was no clear association between IDU and retention to treatment. We should be cautious in interpreting this finding, as the true outcome of patients lost to follow-up is unknown; many might have died or transferred to other clinics for treatment [27]. Most probably, costs for transportation and medical services contribute to loss to follow-up in both groups. This and other factors, such as disclosure of HIV status to family, patient's trust and relationship with the doctor, need further investigation.

Our study was observational and partly retrospective, which limits the conclusions that can be made. Furthermore, no urine testing or other investigations were performed to identify patients with active drug use, and patients may have falsely denied drug use from fear of the negative influences of illicit drug policies [3]. However, although HCV prevalence was close to 90% in those who admitted IDU, only 6% of patients who denied IDU were HCV positive, compared with estimates of 2–3% in the general population [28]. Loss to follow-up may have affected the estimated mortality, and mortality has decreased dramatically in recent years, although this did not affect our results. There may also have been selection at the time of enrolment in HIV care. Approximately 15% of those who need ART in Indonesia actually receive this treatment [24] and IDUs in this cohort, although they came late, might be a selected group with fewer drug-related problems, better health status or better treatment adherence. Treatment adherence also affected by severity of HIV infection, presence or absence of HIV symptoms can be either an incentive or a restraint to treatment adherence.

Despite these limitations, our study demonstrates clearly that HIV patients with a history of IDU in Indonesia have a similar response to ART compared to those without a history of IDU, despite the fact that they present with more coinfections and more advanced immunosuppression. Our data also confirm the urgent need for effective control of HIV in Indonesia among IDUs whereby sharing of needles and unsafe sex need to be addressed.

Declarations of interest

None.

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