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SHORT COMMUNICATION

Antiretroviral drug switches to zidovudine-based regimens and loss to follow-up during the first COVID-19 lockdown in Bali, Indonesia

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Abstract

Objectives: International lockdowns during the COVID-19 pandemic impacted antiretroviral drug supplies in Indonesia. We assessed the impact of antiretroviral treatment (ART) provision and being lost to follow-up (LTFU) on people living with HIV, attending a key population-focused HIV clinic in Denpasar, Bali.

Methods: This was a retrospective note review of anonymized data from adult Indonesian patients living with HIV. We collected demographic data and information on being LTFU, and assessed the numbers of patients impacted by ART switches from fixed-dose combination (FDC) tenofovir/lamivudine/efavirenz to multi-pill zidovudine-based regimens, during the first international lockdown from March 2020.

Results: Records of 260 Indonesian adult patients registered for HIV care and prescribed ART were reviewed; 240 (92.3%) were men, and 90% were men who have sex with men. Between 13 March and 28 May 2020, 214 (87%) out of 247 patients (previously diagnosed with HIV) had to switch to individual, multi-pill zidovudine-based regimens from their FDC. The switch lasted a mean of 35 days (range 10–85). Twenty-five patients (10%) were LTFU; patients who switched were more likely to remain in care. Data on viral load status and toxicity are lacking as laboratory testing requires self-payment.

Conclusions: The majority of patients living with HIV had no choice but to switch to multi-pill, zidovudine-based regimens.

Despite significant efforts to minimize the impact of lockdown on care, 10% of patients were LTFU. Patients switching ART required greater clinic attention and support, improving retention.

Complete national data are needed to understand the impact of ART stockouts on virological suppression and drug resistance throughout Indonesia.

KEYWORDS

antiretroviral treatment, COVID-19, HIV, Indonesia, lockdown

INTRODUCTION

Indonesia is experiencing a fast-growing HIV epidemic. The most updated UNAIDS 90–90–90 goals from 2018 demonstrate that 51% of people living with HIV know their status, 17% are receiving antiretroviral treatment (ART), and there are no reliable data on the proportion who are virologically suppressed (but this is estimated at 1%) [1].

High prevalence rates exist among key affected populations. However, men who have sex with men (MSM) have seen the greatest increases in HIV infections [1,2]. National HIV prevalence estimates were 25.8% among MSM in 2018, compared with only 8.5% in 2011 [1,2]. In major districts of Denpasar in Bali and Jakarta, one in three MSM are infected with HIV [2].

There are concerns that the COVID-19 pandemic will exacerbate this situation due to changes in healthcare access and provision amid COVID-19 control strategies, the negative socio-economic impact that further marginalizes at-risk migrant populations, and ART shortages [3–6].

Indonesia is geographically diverse with high internal migration rates among key populations, particularly following HIV diagnosis [2,7,8]. Our study is based in the province of Bali, a popular tourist destination. Bali relies on tourism and attracts workers from other Indonesian islands. Due to the COVID-19 pandemic, Bali closed its borders to tourists in March 2020, aligned with a national lockdown, decimating the tourist industry. There are concerns that people living with HIV and other at-risk communities moved back to home provinces in remote areas due to lack of work, further fracturing access to and retention in care [3,4,9].

Importantly, international lockdowns during the COVID-19 pandemic severely impacted supplies of antiretroviral drugs (ARVs) for HIV treatment into Indonesia [3,5,9]. There were significant shortages in stocks of first-line fixed-dose combinations (FDCs) of tenofovir/lamivudine/efavirenz (TDF/3TC/EFZ), particularly in deprioritized areas in Indonesia [3], which started in March 2020. TDF/3TC/EFZ FDCs provide the mainstay of ART to people living with HIV following diagnosis, with minimal switch options available. ART was halted following lockdown in India, where the Ministry of Health centrally procures all TDF/3TC/EFZ FDCs.

There have been longstanding issues of ARV stockouts in Indonesia. Until February 2020, there has only been one pharmaceutical company with a licence in Indonesia to produce and supply branded or generic versions of older ART regimens for the treatment of HIV. These are restricted to single and combination formulations of 3TC, nevirapine and zidovudine [10]. Indonesia also procures generic EFZ and a lopinavir/ritonavir combination, which is limited to third-line use and restricted via government service assessment [2,11]. Rilpivirine has limited procurement via the government, and up until the introduction of dolutegravir in late 2020, there was no access to integrase inhibitor class drugs.

Disruptions, lack of consistent ARV supply and unscheduled changes can confuse patients living with HIV and interfere with HIV treatment adherence, leading to virological failure (and onward HIV transmission), drug resistance and disease progression.

HIV/sexual health clinics in the capital city, Denpasar in Bali, were first made aware of significant stock issues to first-line ART in March 2020 following announcements of international lockdowns.

We assessed the impact on ART provision and being lost to follow-up (LTFU) on people living with HIV, attending a key population-focused HIV/sexual health clinic in Denpasar, Bali, during the first COVID-19 international lockdown.

METHODS

All adult Indonesian patients (aged > 16 years) living with HIV, prescribed ART and registered for care at the Bali Peduli HIV/sexual health clinic at the time of the study period were included in this retrospective record review.

Clinical notes were reviewed to evaluate the proportion of patients living with HIV on ART who were affected by ART drug switches and/or stockouts from March 2020. Data were also collected on demographics and risk category, educational level, birth/home province, nadir CD4 count, whether a viral load test had been done within 1 year following ART initiation (viral load monitoring is not routine in Indonesia and requires full payment by the patient) and being LTFU. Patients defined as LTFU were those who did not return for scheduled review in person or by phone and/or did not collect their ART or were uncontactable for repeated delivery attempts of their ART medication during the study period. Patients who received their ART late and may have had multiple missed doses but did return or eventually receive their drugs within the study period, and continued to remain in care, were not included as LTFU.

The review of notes took place between 1 August 2020 and 31 December 2020.

Bali Peduli is a non-governmental organization (NGO) that provides key population-focused HIV and sexual health services, predominantly to MSM; other key populations and female partners of MSM are welcome.

Non-governmental organization, key population-focused HIV services are provided parallel to district government general community services. Most exist in major

cities and provinces like Jakarta, Surabaya, Medan and Bali. However, in Indonesia, the provision of HIV care depends on state healthcare institutions, which has been associated with the marginalization of key populations given high rates of institutional and healthcare-related stigma [2,7,8,12].

Bali Peduli opened in January 2015 and has two sites in Bali, one in Denpasar and the other in Ubud, integrated within a government community service. It aims to provide a friendly, stigma-free, accessible service and makes significant efforts to streamline HIV care despite constraints [2,7,12]. HIV testing, assessment for and provision of ART, and clinical care are provided free of charge. However, administration fees of 30 000 IDR per visit (equivalent to £2.00) may apply to patients. There are also costs for laboratory tests, including HIV viral load testing (approximately £35 for an HIV viral load). The clinic is run as a charity and has an inclusive staff culture that includes people living with HIV, MSM and transgender female staff. More details on HIV care provision in Indonesia can be found in the literature references [2,7,12].

This was a retrospective review of fully anonymized data. This research has ethical committee approval within a wider research project from Atma Jaya Catholic University, Jakarta, Indonesia (ethics ref: 0846/III/LPPM-PM.10.05/07/2019) and the Liverpool School of Tropical Medicine, Liverpool, UK (19-080).

RESULTS

During the study period, there were 260 Indonesian adults (aged > 16 years) living with HIV, registered for HIV care and prescribed ART at the clinic; 240 (92.3%) were men and 20 (7.7%) were women. The median average age was 30 years (range 17–72). All patients were born in Indonesia; 184 (70.8%) were born on an island outside of Bali (non-Balinese); 142 (55%) had completed secondary school education or above. Of the total, 235 (90%) were MSM, 60 (25%) of whom also reported sex with women (these data were missing for 101 MSM; Table 1).

The median nadir CD4 count was 257 cells/μL (35% had a nadir CD4 < 200 cells/μL). In all, 252 patients (97%) had been prescribed TDF/3TC/EFZ as an FDC at treatment initiation before pandemic stockouts; 116 (44.6%) of all registered patients on ART had a viral load test (requires self-payment) within 1 year of starting ART.

Antiretroviral treatment switching due to stockouts began on 13 March 2020. Between 13 March 2020 and 28 May 2020, 214 (87%) of 247 patients previously diagnosed with HIV had to switch to individual pill regimens

TABLE 1 Data on demographics, risk group, early monitoring, antiretroviral treatment (ART) switch and being lost to follow-up (LTFU; frequency/proportional) for patients living with HIV attending for care at the Bali Peduli clinic, Denpasar

	Number	Proportion (%)
Sex		
Male	240	92.3%
Female	20	7.7%
Total	260	
Age (years)		
17–30	130	50%
31–50	121	46.5%
51–75	9	3.5%
Total	260	
Risk group		
MSM	235	90.4%
(MSM who also report sex with women/bisexual – missing data in 101 MSM)	60	25.5% of MSM
Heterosexual	21	8.1%
Transgender female	1	0.4%
Female sex worker	1	0.4%
People who inject drugs	1	0.4%
Male client of sex worker	1	0.4%
Total	260	
Province of birth in Indonesia		
Bali	76	29.2%
Province of birth outside of Bali	184	70.8%
Total	260	
Educational level (last completed education)		
0 – No school	0	0
1– Primary/elementary school	4	1.5%
2 – Junior high school	79	30.4%
3 – General secondary school	47	18.1%
4 – Post-secondary education/university	95	36.5%
Not recorded	35	13.5%
Total	260	
Nadir CD4 count (cells/μL)		
< 100	46	17.7%
100–200	46	17.7%
201–350	88	33.8%
351–500	47	18.1%

(Continues)

TABLE 1 (Continued)

	Number	Proportion (%)
> 500	27	10.4%
Not done at baseline (e.g. no reagent to carry out test at diagnosis)	2	0.8%
Not recorded	4	1.5%
Total	260	
Median nadir CD4 count	257 cells/μL	
Viral load (VL) testing		
VL test done within 1 year of HIV diagnosis	116	44.6%
VL test within > 1 to 5 years of HIV diagnosis	52	20%
No VL test done	69	26.5%
Not done and diagnosis within year of data collection	23	8.8%
Total	260	
ART switch during COVID-19 lockdown from TDF-based regimens ($n = 260$) 252 (97%) on FDC (TDF/3TC/EFZ)		
ZDV/3TC/EFZ (including ZDV/3TC/EFZ with period of ZDV/3TC/NVP)	210 (70)	80.8%
ZDV/3TC/NVP only	3	1.2%
ZDV/3TC/RPV	1	0.4%
No ART switch/remained in care (including 13 newly diagnosed patients)	33	12.7%
No ART switch/LTFU and LTFU pre-ART switch	13	5%
Total	260	
Time on switch regimen (days) [mean (range)]	35 (10–85)	
Total LTFU during first COVID-19 international lockdown of 247 patients diagnosed prior to March 2020		
	25	10.1%

Abbreviations: 3TC, lamivudine; EFZ, efavirenz; FDC, fixed-dose combination; MSM, men who have sex with men; NVP, nevirapine; RPV, rilpivirine; TDF, tenofovir; ZDV, zidovudine.

consisting of zidovudine, 3TC plus EFZ or nevirapine (one with rilpivirine) from their FDC. The switch lasted a mean of 35 days (range 10–85).

Nevirapine was used when the stock of single-tablet EFZ was low. Seventy of the 214 (33%) patients were switched to nevirapine (directly from EFZ, no prior history of reaction to nevirapine) for an average of 7 days duration. There were two reports of rash associated following nevirapine switch.

Viral load assessment is only available by self-payment throughout Indonesia, and no patients were willing to pay this either before or after ART switch.

Due to uncertainty of drug stock levels, switch and non-switch patients were provided with 5–20 days of ART at a time compared with the usual 30-day supply before lockdown. This was primarily due to the uncertainty of drug stock levels, the provision of alternative drug regimens (with higher toxicity profiles) and the requirement for clinical assessment following drug switches.

Patients were required to attend more frequently or opt for phone consultations and ART delivery service via self-paid motorbike taxi service.

Twenty-five patients (10% of 247 diagnosed with HIV before 28 May 2020) were LTFU. Twelve of those were LTFU after switch to a zidovudine-based regimen [mean of 23 days post-switch before becoming LTFU; 12/214 (6%) of switch patients].

During the 6 months between 1 September 2019 and 28 February 2020, before lockdown, no-one was LTFU.

On univariable analysis, of 247 patients previously diagnosed, those who experienced ART switch were significantly less likely to be LTFU [$p < 0.001$, odds ratio (OR) = 0.09, 95% confidence interval (CI): 0.04–0.23]. Additionally, there was a trend to non-Balinese patients having greater odds of being LTFU (OR = 1.7, $p = 0.36$, 95% CI: 0.6–4.8).

DISCUSSION

Most patients living with HIV attending Bali Peduli, subjectively known to be stable on ART, had no choice but to switch to multi-pill, zidovudine-based ART from FDC TDF-based regimens, from 13 March through to September 2020.

The clinic initiated several innovations to facilitate people to remain in care, on consistent ART and to minimize the number becoming LTFU. These included staff training and clinic restructures to align with provincial COVID-19 control strategies (e.g. an appointment triage service to limit numbers in the clinic and enforce social distancing, mask and hand hygiene stations and protective equipment for staff), ART drug delivery schemes, WhatsApp messaging groups for clinic information, and drug switch protocols.

To reduce the impact of prolonged stockouts, staff and research team members from the study clinic and other local NGOs made efforts to communicate the challenges rapidly to the district and national ministry of health, the Global Fund, and the wider international community [3,4]. We believe this reduced the impact of stockouts on our service to an average of 35 days, which is unlikely to have been translated as effectively across the country. Additionally, there were reports from other districts that patients were advised to take single and dual ARVs to lengthen their supply and manage the fear of running out of medication [3].

Over two-thirds of registered Indonesian patients living with HIV were non-Balinese, and despite efforts to reduce disruption to care, 10% of patients were LTFU. Being non-Balinese (suggesting possible internal migration to Bali for work) appeared to increase the odds of being LTFU, but this was not significant. Those who experienced ART switch were less likely to be LTFU. Patients switching ART required greater clinic attention and encountered additional support, which improved retention.

Due to limited resources and national policies, clinics cannot carry out routine viral load monitoring for patients unless they self-pay. Routine blood counts and liver and renal testing are also done case by case and may require additional fees and patient visits at alternative clinics or government hospitals.

Therefore, we have few data on toxicity and virological status, reflecting long-standing barriers within clinical practice nationally [2,7,12].

Limitations include the retrospective nature of data collection from clinical paper notes and missing data. However, clinical record-keeping follows standardized methods, which limits missing data.

Indonesia has limited ARV choices to manage drug-resistant HIV and challenges concerning poor tolerability and toxicity. Dolutegravir has recently been approved for distribution in Indonesia in late 2020 and is currently prioritized for those who are newly diagnosed. No other integrase inhibitors are available, and protease inhibitors are limited to lopinavir/ritonavir.

The country's 90–90–90 targets highlight existing challenges in getting people tested, getting those living with HIV on to ART and poor rates of virological suppression; the COVID-19 pandemic may worsen this situation [5,6].

These data highlight the high proportion of patients who faced drug switches to regimens with higher side-effect profiles and pill burdens. We anticipate that people living with HIV were particularly vulnerable during the pandemic and may be at risk of taking ineffective mono/dual therapy given the lack of drugs and be at risk of poorer health. To what extent government facilities have been affected by stock issues and the impact on their patient populations is unclear.

More comprehensive sources and complete national data are urgently needed to understand the impact of ARV stockouts on virological status and drug resistance in Indonesia [13].

It is also urgent that Indonesia streamline its ARV supply chain management to prevent repeated stockouts; provide continuous supplies of better tolerated, robust ART regimens at the point of care [10]; and access to free viral load monitoring if 90–90–90 targets are to be achieved and maintained.

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CONFLICT OF INTEREST

No conflicts of interest are declared.

AUTHOR CONTRIBUTIONS

KG and FSW are lead author and senior author, respectively. The lead author led on research conception, data collection, analysis and article writing. NR was involved in data collection, data cleaning and administrative support. HL was involved in data collection, data cleaning and article review. II and ES were involved in article writing and review.

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