Combining Cohort Analysis and Monitoring of HIV Early-Warning Indicators of Drug Resistance to Assess Antiretroviral Therapy Services in Vietnam

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Antiretroviral therapy (ART) retention and 5 early-warning indicators (EWIs) of HIV drug resistance (HIVDR) were abstracted at 27 adult and 4 pediatric clinics in Vietnam in 2009. Of 4531 adults and 313 children, 81.2% and 84.4% respectively were still on ART at 12 months. More than 90% of the clinics monitored achieved the World Health Organization (WHO) targets for lost-to-follow-up (LTFU), ART prescribing practices, and ARV supply continuity. Only 83.9% of the clinics met the target for first-line ART retention and 79.3% met the target for clinic appointment-keeping. Clinic factors (i.e. number of patients, administrative level, and geographical region) were associated with ART retention and LTFU. Data were useful in guiding public health action to optimize ART services.

The Vietnamese Ministry of Health estimated that there were 243,000 people living with HIV and 67,047 adults needing antiretroviral therapy (ART) in Vietnam in 2009 [1]. Vietnam has a concentrated HIV epidemic. In 2009, the overall adult HIV prevalence (ages 15–49) was estimated at 0.43%; the estimated HIV prevalence among people who inject drugs (PWID) was 18.4% and among female sex workers the prevalence was 3.2% [2].

Vietnam has addressed the need for HIV care and treatment through rapid scale-up of ART. The number of people receiving ART increased from 2700 in 2005 to 37,995 in 2009 [2]. This rapid scale-up was realized by establishing 288 public-sector ART clinics throughout the country [2]. These clinics have diverse characteristics.

In 2009, 14 clinics were at the national/central level, 125 clinics were at the provincial level, and 149 were at the district levels [2]. Some clinics treat more than 2000 patients while others treat <10. Resources supporting HIV-related services also differ greatly depending on the availability of donor support.

In the context of rapid and decentralized ART scale-up, the importance of monitoring and optimizing ART service delivery in order to improve treatment outcomes and maximize programmatic efficiency is increasingly acknowledged. In response, in 2006 the Vietnam Authority of HIV/AIDS Control (VAAC) introduced a national standardized patient monitoring and recording system that follows World Health Organization (WHO) guidelines [3, 4]. In 2008, VAAC also approved a 5-year country plan to assess and prevent HIV drug resistance (HIVDR) by following WHO-recommended guidance [5]. The WHO HIVDR prevention and assessment strategy supports optimization of treatment programs in order to minimize the emergence of HIVDR, thus maximizing the long-term effectiveness of...
METHODS

Study Clinics and Data Collection

ART cohort indicators and HIVDR EWIs were monitored at 27 adult and 4 pediatric ART clinics. Clinics were chosen to epitomize the ART program in Vietnam and included diverse categories with regard to donor support, administrative levels, geographical areas, and number of patients on ART. Data were abstracted between March 2009 and April 2009 using standardized data abstraction forms. Data were abstracted from national standard ART registers and HIV care record forms [12] and pharmacy records by a team of public health staff from regional institutes, provincial AIDS centers, and projects supported by the President Emergency Plan for AIDS Relief and Global Fund to fight AIDS, tuberculosis, and malaria. All data abstractors received training on abstraction procedures and patient confidentiality. Abstractors were supervised by members of VAAC, faculty from the Hanoi School of Public Health, and the WHO Vietnam Country Office.

Indicators

Definitions of the indicators monitored in Vietnam were, for the most part, in line with WHO guidance [3, 6] and are summarized below.

Retention on ART at 6 and 12 months

The numerator was the number of patients starting ART in 2007 who were still alive and on ART at 6 or 12 months after treatment initiation. The denominator was the “net cohort,” or the individuals who started ART in 2007 including those who died, were lost to follow-up (LTFU), or stopped ART. Individuals who had initiated ART at another facility and were transferred to the clinic being monitored (transfers-in) were included; those who had been transferred to a different facility (transfers-out) were excluded.

Lost to follow-up at 12 months

Patients were classified as LTFU if they had not been seen for 3 months since their last ART clinic visit. The numerator was the number of patients starting ART in 2007 who were classified as LTFU before 12 months after ART initiation. The denominator was the net cohort and was the same as that used in calculating ART retention.

Retention on first-line ART at 12 months

The numerator was the number of patients who started ART with the appropriate first-line regimen in 2007 and were still on a first-line regimen at 12 months. The denominator was the number of patients who started first-line ART in 2007 including those who died, were LTFU, or stopped therapy. Transfers-in and transfers-out cases and those who initiated ART with a second-line regimen or regimens that were not deemed appropriate based on available clinical documentation were excluded.

ART prescribing practices

The numerator was the number of patients initiating ART who were prescribed an appropriate initial ART regimen in 2008. The denominator was the number of patients initiating ART in 2008. Where nonstandard regimens were prescribed, their appropriateness was judged by the national team in consultation with international experts using the documented justification found in the patients’ medical records.

ART clinical appointment-keeping

The denominator was the number of patients who had been receiving ART at the end June 2008 or who started ART during July 2008–September 2008 and who were sampled according to the following procedures: all patients at the clinics with <100 ART patients; every second ART start-up group at clinics with 100–300 ART patients; every third ART start-up group at clinics with 301–500 patients; every fifth ART start-up group at clinics with >500 patients. The numerator was the number of sampled patients who kept all their clinic appointments on time or presented before the appointment date during July 2008–September 2008 or until they were classified as LTFU, dead, or transferred out within the same 3-month period.

Antiretroviral drug supply continuity

The numerator was the number of patients in quarters in which there were no stock-outs of any antiretroviral (ARV) drug routinely used at the clinic. The denominator was 4 (quarters).

Data Analysis

ART retention and LTFU were analyzed for each clinic using the simplified cohort analysis tool suggested by WHO [3]. HIVDR EWIs were calculated for each clinic and compared against the national targets (which were identical to WHO targets [6]). In addition, to examine possible association between clinic factors and their performance, bivariate logistic regression for grouped data (blogit function in STATA; patients in the same clinics were grouped) was conducted for data from 27 adult clinics using STATA version 11.0 (StataCorp, College Station, Texas). Clinic factors analyzed included administrative levels, geographical regions and number of patients on ART.
Association was not tested for appropriate initial prescription and drug supply continuity because most clinics achieved 100% for these indicators.

**RESULTS**

Data on cohort outcomes and HIVDR EWIs of 27 adult and 4 pediatric ART clinics are summarized in Table 1. The total number of active patients receiving ART at these clinics in June 2008 was 9686 adults and 678 children, representing 47% of adults and 56% of children receiving ART nationwide at that time.

At the 27 adult ART clinics, the aggregated retention rate on ART was 86.0% (range, 65.8%–96.6%) at 6 months and 81.2% (range, 56.1%–96.6%) at 12 months. The size of the net cohort was 4580 and 4531 at 6 and 12 months, respectively. In the first 6 months, the major cause of attrition was death, which accounted for nearly 70% of attrition (431 cases), followed by LTFU at 22% (141 cases) and stop at 10% (65 cases). In contrast, during the second 6-month period, there were a similar number of deaths (101) as LTFUs (114) and 63 stops.

At the 4 pediatric ART clinics, the aggregated ART retention rate was 86.7% (range, 85.2%–90.5%) at 6 months and 84.4% (range, 83.2%–90.5%) at 12 months. The net cohort size was 324 and 313 at 6 and 12 months, respectively. There were 43 cases of attrition (24 deaths, 17 LTFUs, 2 stops) during the first 6 months, while there were only 6 additional attrition cases by the end of the second 6-month period (27 deaths, 20 LTFUs, 2 stops).

All adult and pediatric clinics met the WHO target of <20% LTFU at 12 months, except for 1 adult ART clinic that had 23.7% LTFU. Notably, at 4 adult clinics and 1 pediatric clinic, LTFU ranged from 10% to 20%.

Eighty-five percent of adult clinics and 100% of pediatric clinics achieved the target of 70% retention on first-line ART at 12 months. Only 81 patients (0.74%) were switched to second-line ART; thus first-line retention was driven by attrition (death, LTFU, stop). As a result, the proportion retained on ART and the proportion retained on first-line ART at 12 months were highly correlated ($r^2 = 0.989$).

All clinics except 3 achieved the target of 100% appropriate initial ART regimen prescribing. At these 3 clinics, values were high (>98%). Twenty percent of adult clinics (5 clinics) and 25% of pediatric clinics (1 clinic) failed to meet the target of >80% of patients attending scheduled appointments on time. Results were unavailable at 2 adult clinics due to incomplete recording of data.

ARV supply continuity data were unavailable at 7 clinics. At the remaining 24 clinics, 1 experienced ARV stock-outs in 3 of

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Targeta, %</th>
<th>Time Period</th>
<th>Adult Clinics</th>
<th>Pediatric Clinics</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Retained on ART at 12 months</td>
<td>Not applicablec</td>
<td>Jan–Dec 2008d</td>
<td>81.2</td>
<td>84.3</td>
</tr>
<tr>
<td>% Lost to follow-up during the first 12 months</td>
<td>&lt;20</td>
<td>Jan–Dec 2008d</td>
<td>5.6</td>
<td>6.4</td>
</tr>
<tr>
<td>% Retained on first-line ART at 12 months</td>
<td>&gt;70</td>
<td>Jan–Dec 2008d</td>
<td>79.3</td>
<td>81.8</td>
</tr>
<tr>
<td>% Appropriate initial ART regimen prescriptions</td>
<td>100</td>
<td>Jan–Dec 2008</td>
<td>99.9</td>
<td>99.7</td>
</tr>
<tr>
<td>% ART patients keeping all appointments on time</td>
<td>&gt;80</td>
<td>July–Sept 2008</td>
<td>89.7</td>
<td>87.6</td>
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</tbody>
</table>

Data were collected from 27 adult clinics and 4 pediatric clinics that epitomize the antiretroviral therapy program in Vietnam. Abbreviations: ART, antiretroviral therapy; ARV, antiretroviral; EWI, early-warning indicator, HIVDR, HIV drug resistance.

* These are the targets proposed by WHO for the HIVDR EWIs.

b Average was calculated for the clinics where data were available by weighting the sample size at each clinic.

c No target was set for ART retention at 12 months.

d People who initiated ART from January 2007 to December 2007 were included and their 12-month outcomes were assessed in 2008.

e Appointment-keeping data were not available for 2 adult clinics.

f ARV supply continuity (stock out) data were not available at 6 adult clinics and 1 pediatric clinic.
Table 2. Associations of Clinic Characteristics and Performance Measured by Retention on Antiretroviral Therapy (ART) and World Health Organization Early-Warning Indicators in Adult ART Clinics

<table>
<thead>
<tr>
<th>Administration level</th>
<th>ART Retention at 12 months</th>
<th>Lost to Follow-Up at 12 months</th>
<th>First-Line Retention at 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clinic Location</td>
<td>Clinic (N)</td>
<td>Patient (N)</td>
</tr>
<tr>
<td>District</td>
<td>12</td>
<td>2698</td>
<td>80.7</td>
</tr>
<tr>
<td>Provincial</td>
<td>13</td>
<td>1186</td>
<td>78.2</td>
</tr>
<tr>
<td>Tertiary</td>
<td>2</td>
<td>647</td>
<td>89.2</td>
</tr>
</tbody>
</table>

Region

Hanoi 4 | 406 | 90.1 | 1 | 3.0 | 1 | 402 | 89.8 | 1
North 8 | 932 | 79.1 | 0.41 (0.21–0.81)* | 5.4 | 1.86 (0.73–4.73) | 895 | 78.1 | 0.41 (0.20–0.81)*
Ho Chi Minh 7 | 2665 | 82.4 | 0.51 (0.25–1.03) | 6.0 | 2.11 (0.95–4.71) | 2495 | 79.7 | 0.45 (0.22–0.90)*
South 8 | 528 | 72.2 | 0.28 (0.13–0.60)** | 6.1 | 2.12 (0.64–7.04) | 511 | 71.0 | 0.28 (0.13–0.59)**

Number of patients

>500 7 | 2829 | 82.3 | 1 | 5.9 | 1 | 2665 | 79.6 | 1
201–500 7 | 909 | 82.2 | 0.99 (0.62–1.60) | 5.5 | 0.93 (0.47–1.85) | 857 | 81.2 | 1.11 (0.71–1.74)
101–200 6 | 564 | 79.6 | 0.84 (0.52–1.34) | 1.6 | 0.26 (0.15–0.44)** | 556 | 79.0 | 0.96 (0.63–1.47)
<100 7 | 229 | 68.6 | 0.47 (0.28–0.79)** | 12.7 | 2.31 (1.26–4.24)** | 225 | 68.9 | 0.57 (0.35–0.93)*

* < 0.05, ** < 0.01, *** < 0.001. Association was examined through bivariate logistic regression for grouped data (patients at each clinic were grouped) for the data from 27 adult clinics. The denominator was the “net cohort” (as defined by WHO) for % ART retention and % LTFU (lost-to-follow-up), which included transfers-in and excluded transfers-out cases. The denominator for % first-line retention was limited to those who started ART with appropriate first-line regimen and excluded transfers-in and transfers-out cases. Appointment-keeping was not associated with any clinic factors examined. Association was not tested for appropriate initial prescription (all except 2 clinics achieved 100%) and supply continuity (all except 1 clinic achieved 100%).

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; OR, odds ratio.

“North” includes clinics in Northern provinces except Hanoi. “South” includes clinics in Southern provinces except Ho Chi Minh City.

4 quarters, while all 23 remaining clinics had no ARV stock-outs in 2008.

The results of bivariate analysis between clinic characteristics and clinic performance are shown in Table 2. ART retention at 12 months was positively associated with tertiary-level facilities (odds ratio [OR] = 1.93, district level as reference), while negatively associated with clinics having <100 patients (OR = 0.47, >500 as reference). Provinces outside of large urban cities (Hanoi and Ho Chi Minh City) had lower 12-month retention rates (OR = 0.41 for the northern provinces, OR = 0.28 for the southern provinces; Hanoi as reference). Retention on first-line ART at 12 months had similar patterns as retention on ART at 12 months.

LTFU at 12 months was significantly less at tertiary-level clinics (OR = 0.65) and at those with moderate patient numbers (101–200) (OR = 0.26). In contrast, having <100 patients was associated with higher rates of LTFU at 12 months (OR = 2.31). Appointment-keeping was not associated with any clinic factors assessed.

DISCUSSION

Our data suggest that the 12-month ART retention rate in Vietnam is equivalent to or slightly higher than average rates reported from the other low- and middle-income countries (LMICs). Our data show a 12-month ART retention rate of 81.2% among adults and 84.4% among children. According to data reported from 70 LMICs in 2008 [13, 14], the average 12-month retention rate was 79.9% globally and 80.3% in East, South, and Southeast Asia. A systematic review of 33 cohorts comprising 74,192 patients from 13 sub-Saharan countries estimated a 12-month retention rate of 75.0% [10]. Another more recent review of 226,307 patients in sub-Saharan Africa calculated a 12-month retention rate of 80.2% [9].

Achieving >80% retention at 12 months is important when considering the fact that a substantial portion of patients on ART in Vietnam are PWID. In a study in Ho Chi Minh City, 66% reported current or past opiate injection, 73% reported current or past smoking or injecting of any opiate or non-opiate drug [15]. This finding is consistent with anecdotal estimates that 60%–70% of ART patients in Vietnam are PWID. Some studies reported that retention and mortality of PWID were not significantly different from those of non-PWID [16–18], although other studies reported PWID had higher mortality and LTFU compared with non-PWID [19–22]. Our data suggest that the PWID-dominant patient population in Vietnam is retained on ART to a degree that is equivalent to that observed in countries where injection drug use is not the predominant mode of HIV transmission. Our findings are also consistent with other studies that suggest that PWID are responding well to ART in Vietnam. For example, the increase in median CD4 T cells count over 24 month after initiating ART was...
equivalent between PWID and non-PWID at 2 clinics in Ho Chi Minh City [15]. A study conducted in Hanoi reported activity to detect high LTFU rates is minor.

The number of patients being treated at a clinic was associated with LTFU. Clinics with moderate numbers of patients (101–200) had significantly less LTFU compared with clinics with small numbers of patients (<100). This observation is consistent with data reported from the United States where clinics with >100 patients had significantly less LTFU than clinics with <33 patients [20]. Possible reasons for our findings may be that smaller clinics in Vietnam tend to have less experience following up patients and receive disproportionately fewer resources and technical support.

Moreover, clinics with large numbers of patients (>500) had higher LTFU rates compared with those with moderate patient numbers (101–200). This finding is in line with a study suggesting that clinics with large numbers of patients were less likely to actively trace patients who did not return and therefore had higher LTFU rates [11]. In Vietnam, it is plausible that follow-up and active patient tracing becomes harder as the patient population increases at a given clinic. Therefore, it may be necessary for program managers to review existing patient tracing systems and the amount of human and financial resources dedicated to patient tracing at clinics that serve large patient populations. Additionally, further decentralization should be considered to reduce the burden at large clinics.

Community support has been shown to be associated with improved ART outcomes in Malawi [24]. Additionally, an analysis in 15 countries also found that LTFU was negatively associated with the presence of active patient tracing activities [25]. Based on the ART retention and LTFU results presented here, local care teams in Vietnam should consider defining and implementing community support systems to improve patient retention.

There were differences between Vietnam’s national definition of LTFU, which follows WHO 2006 patient monitoring guidelines [3], and that of WHO HIVDR EWI guidelines [6]. The former classifies an individual as LTFU if he/she does not return to a clinic for 3 months or more after the last visit, while the latter defines as LTFU if he/she does not attend a clinic appointment or a drug pick-up within 90 days after the date of his/her last scheduled appointment. The former definition allows the clinic to classify LTFU at 12 months after ART initiation, whereas the latter definition requires the clinic to wait 15 months. Our preliminary analysis shows that the values derived by these 2 definitions are highly correlated; thus, the impact of such differences on the sensitivity to detect high LTFU rates is minor.

In this analysis, retention on a first-line ART regimen at 12 months was highly correlated with ART retention at 12 months (r = .989). This was the case because major causes affecting both indicators were death, LTFU, and stop; overall, very few patients switched to second-line regimens. An aim of monitoring retention on first-line ART at 12 months, as described by the WHO HIVDR EWI, is to monitor for an excessive and unnecessary switch to second-line ART during the first 12 months. Consequently, it might be appropriate for Vietnam to introduce an additional indicator, such as proportion of patients taking second-line ART, among those retained on ART at 12 months.

Of 29 clinics, 21% failed to meet the target of >80% on-time appointment-keeping. Efforts are needed to improve appointment-keeping across clinics where this value was low. Appointment-keeping is important for the following reasons. In Vietnam, patients receive ART at clinics; hence, patients may experience ART interruption if they do not attend clinical appointments on time. Moreover, appointment-keeping has been reported to be associated with adherence [26, 27]. Although it may not be as sensitive as more rigorous methods such as pharmacy-based adherence measures or unannounced pill count, use of appointment-keeping as a surrogate of ART adherence enables rough population level estimates of adherence at clinics.

There was a challenge in capturing ARV stock status at some clinics because ARV stock was stored at multiple places, eg, a pharmacy dedicated to an HIV care clinic, a general pharmacy of the same facility, and provincial AIDS centers near the facility. This system was developed to minimize the ARV stock at the HIV care clinic due to security concerns. However, based on these data, it is recommended that national guidance be adjusted to allow all ARV drugs to be maintained at primary pharmacies that dispense ART drugs in order to minimize the likelihood that any interruption in stock would lead to patient treatment interruptions.

The strengths of this data monitoring exercise include broad coverage (the sampled clinics treated 48% of all ART patients in the country) and inclusion of diverse types of ART clinics. Despite these strengths, we recognize specific limitations. First, some clinics had incomplete records, which prevented us from monitoring specific EWIs. However, this finding also served as an opportunity to retrain local health teams to improve and align record-keeping with national standards. Second, we lacked local evidence on how each HIVDR EWI actually predicts HIVDR emergence. Currently, Vietnam is implementing a WHO survey of acquired HIVDR and associated factors [28], which may provide local evidence linking EWIs and HIVDR and further inform optimization of HIVDR EWIs.

Third, clinics included in this analysis were not representative of the entire ART program in Vietnam; thus, findings cannot be broadly generalized. However, the clinics included in this analysis treated nearly half (48%) of patients receiving ART in
the country, and we believe our findings are a robust reflection of the current situation in Vietnam. Fourth, our data monitoring was planned as a public health survey and did not collect potential confounders, which may affect treatment outcomes and HIVDR EWIs. Nonetheless, we anticipate that clinic-specific findings will be used by local health teams to investigate causes of EWIs results if values fall short of international targets and will facilitate development of targeted public health interventions to optimize patient care.

In conclusion, this data monitoring exercise, which integrated cohort indicators and WHO HIVDR EWIs, was deemed feasible for large-scale monitoring of ART services in Vietnam. The results suggest that Vietnam’s ART program is, overall, effective. Additionally, LTFU could be further reduced at small (<100 patients) and large (>500 patients) clinics and efforts are generally needed to improve patient appointment-keeping. These data were extremely useful for planning and developing service quality improvement initiatives. Empowerment and active involvement of local teams in abstraction, analysis, and use of these data are considered important next steps.

**Notes**

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**References**


