HIV drug-resistance early-warning indicators and quality care in India: preliminary findings from a pilot study in Pune city

Manisha Ghate¹, Dileep Kadam², Nitin Gaikwad³, Subramanian Shankar⁴, Shraddha Gurav⁵, Girish Rahane¹, Sukarma Tanwar⁶, Bharat Rewari⁷, Raman Gangakhedkar¹

ABSTRACT

Background: India has rapidly scaled up its programme for antiretroviral therapy (ART). There is high potential for the emergence of HIV drug resistance (HIVDR), with an increasing number of patients on ART. It is not feasible to perform testing for HIVDR using laboratory genotyping, owing to economic constraints. This study piloted World Health Organization (WHO) early-warning indicators (EWIs) for HIVDR, and quality-of-care indicators (QCIs), in four ART clinics in Pune city.

Methods: A retrospective study was conducted in 2015, among four ART clinics in Pune city, India. The data on four standardized EWIs (EWI 1: On-time pill pick-up, EWI 2: Retention of patients in ART care at 12 months after initiation, EWI 3: Pharmacy stock-out, EWI 4: Pharmacy dispensing practices) and three QCIs (QCI 1: Regularity in CD4 testing in patients taking ART, QCI 2: Percentage of patients initiating ART within 30 days of medical eligibility, QCI 3: Percentage of patients initiating ART within 30 days of initiation of anti-tuberculosis therapy) were abstracted into WHO Excel HIV data abstractor tools, from the patient records from April 2013 to March 2014.

Results: All four ART clinics met the EWI 4 target (100%) for ART dispensing practices. The target for EWIs on-time pill-pick (EWI 1 >90%) and pharmacy stock-outs (EWI 3: no stock-outs, 100%) were achieved in one clinic. None of the clinics met the EWI 2 target for retention in care at 12 months (>90%) and the overall retention was 76% (95% confidence interval: 73% to 79%). The targets for QCI 1 and QCI 2 (>90% each) were achieved in one and two clinics respectively. None of the clinics achieved the target for QCI 3 (>90%).

Conclusion: ART dispensing practices (EWI 4) were excellent in all clinics. Efforts are required to strengthen retention in care and timely pill pick-up and ensure continuity of clinic-level drug supply among the programme clinics in Pune city. The clinics should focus on regularity in testing CD4 count and timely initiation of ART.

Key words: AIDS, antiretroviral therapy (ART), early-warning indicators, HIV, HIV drug resistance (HIVDR), India

BACKGROUND

India has an estimated population of 2.09 million individuals infected with HIV, with an adult prevalence of 0.27%.¹ The antiretroviral therapy (ART) programme in India was started in 2004 and has been scaled up rapidly to over 1200 sites across the country, with phased decentralized service delivery to district and subdistrict health facilities. Up to March 2014, 0.768 million people living with HIV (PLHIV) were on first-line ART at 425 ART centres.² Monitoring of ART care at service sites is based on both paper (for monthly ART-centre reporting) and case-based patient monitoring electronic systems (PLHA software), where every patient visit is recorded. As the ART programme approaches universal access for all those in
need, it is critical to establish monitoring systems for treatment outcomes and other programme indicators that can provide data on the quality of ART services.

The national programme has completed a decade and it is expected that the number of patients with treatment failure will be on rise. Since the development of HIV drug resistance (HIVDR) is a paramount concern in mature ART programmes, close monitoring to limit emerging HIV drug resistance and ensure the success of first-line ART is important. HIVDR may necessitate a switch from non-nucleoside reverse transcriptase (NNRTI)-based first-line regimens to more expensive and less tolerated boosted protease inhibitor-based regimens, leading to limited drug options available in the programme and an increase in the overall cost. Owing to non-availability of routine viral load and HIVDR testing in resource-limited settings, the World Health Organization (WHO), as part of its global strategy for prevention and assessment of HIVDR, developed a set of early-warning indicators (EWIs) that assess ART clinic-, patient- and programme-related factors associated with the emergence of HIVDR. These indicators are based on the data that are routinely collected in patients’ medical and pharmacy records, are comparatively inexpensive to collect and may alert national ART programme planners to issues that can be adjusted to minimize the emergence of HIVDR.

In order to strengthen the quality of ART services, the National AIDS Control Organization (NACO) has recommended regular monitoring of quality-of-care indicators (QCIs) in HIV care, in addition to EWIs. These include regularity in testing CD4 count in patients taking ART, the percentage of patients initiating ART within 30 days of medical eligibility, and the percentage of patients initiating ART within 30 days of initiation of anti-tuberculosis therapy (ATT).

These QCIs are deemed more important in providing data for the ART programme to improve patient care at ART sites and minimize the emergence of HIVDR. They also allow comparison across time about whether the quality of ART services improves and evolves.

This pilot study assessed four standardized HIVDR EWIs and three QCIs, at four ART programme clinics in Pune city, in order to identify potential strengths and weaknesses of the programme and improve the quality of clinical care

**METHODS**

**Study design**

This retrospective study was conducted at four government ART clinics in Pune city, in 2015, to evaluate HIVDR EWIs and QCIs, from 1 April 2013 to 31 March 2014.

All four ART clinics followed the same national and operational guidelines for management of individuals with HIV infection. As per the guidelines, ART was initiated at a CD4 count of \( \leq 350 \text{ cells/mm}^3 \), or WHO clinical stage III and IV irrespective of CD4 count. The preferred regimen was zidovudine/lamivudine/nevirapine. The patients were provided drugs for one month and were requested to come back after a month for a follow-up visit and to collect drugs for the next one month. The patients who were on regimens containing zidovudine, tenofovir or nevirapine were requested to come after every 15 days initially for one month, to be tested for haemoglobin, renal function tests or alanine aminotransferase, respectively. A patient-centred approach was used to promote adherence, which was assessed by pill counts. Co-trimoxazole chemoprophylaxis was given as per the national guidelines.

**Early-warning indicators**

Four EWIs based on the WHO 2012 guidelines were considered for this study, and are summarized in Table 1.

**Quality-of-care indicators**

The three QCIs, namely regularity in testing CD4 count in patients taking ART, the percentage of patients initiating ART within 30 days of medical eligibility, and the percentage of patients initiating ART within 30 days of initiation of ATT, were considered for analysis and are summarized in Table 2.

**Sampling and data abstraction:**

The sample size for EWI 1, EWI 2 and EWI 4 at each ART site was calculated as per the WHO sampling method. The sample size for EWI 1 and EWI 4 was calculated based on the total number of patients alive and on ART in March 2014 and the data were abstracted for consecutive patients that came for drug pick-up. The sample size for EWI 2 and QCI 1, QCI 2 and QCI 3 was based on the number of patients newly initiated on ART during April 2012 and March 2013, and the data were abstracted from medical registers. The data for EWI 3 were abstracted for the targeted year from the pharmacy records.

**Ethics statement**

Approval was obtained from NACO for use of routine programmatic data for EWIs. The analysis of the routinely collected programme data was approved by the ethics committee of the National AIDS Research Institute.

**RESULTS**

**Profiles of the study sites**

Profiles of the study sites were described, to support the interpretation of the EWI and QCI results. The staff-to-patient ratio was different in the four different clinics (see Table 3). Clinic B was the first government programme ART clinic established in Pune City and also functions as a reference centre where all patients from Pune district that are failing on first-line treatment are referred for second-line ART and subsequently followed up. Clinic C was established in 2010 and the staff-to-patient ratio was better as compared to other clinics.
### Table 1: WHO updated HIV drug-resistance early-warning indicators and targets (2012)

<table>
<thead>
<tr>
<th>Early-warning indicator (EWI)</th>
<th>Target</th>
<th>Definition</th>
<th>Numerator</th>
<th>Denominator</th>
</tr>
</thead>
<tbody>
<tr>
<td>EWI 1: On-time pill pick-up</td>
<td>Red &lt;80%</td>
<td>Percentage of on-time ART drug pick-up by the patients</td>
<td>Number of patients who have picked up all their prescribed ART drugs at first pick-up after baseline pick-up</td>
<td>Number of patients who picked up ART drugs on or after the designated EWI sample start date until the sample size is reached</td>
</tr>
<tr>
<td></td>
<td>Amber 80–90%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Green &gt;90%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EWI 2: Retention in ART care at 12 months</td>
<td>Red &lt;75%</td>
<td>Percentage of patients initiating ART at the site who are retained in the care at 12 months after ART initiation</td>
<td>Number of patients who are alive and on ART at 12 months after initiating ART</td>
<td>Number of patients initiating ART who were expected to achieve 12-month outcomes within the reporting period</td>
</tr>
<tr>
<td></td>
<td>Amber 75–85%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Green &gt;85%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EWI 3: Pharmacy stock-out</td>
<td>Red &lt;100%</td>
<td>Percentage of months in a designated year in which there were no ARV drug stock-outs</td>
<td>Number of months in the designated year in which there were no stock-out days of any ART drug routinely used at the site</td>
<td>12 months</td>
</tr>
<tr>
<td></td>
<td>Green 100%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EWI 4: Pharmacy dispensing practices</td>
<td>Red &gt;0%</td>
<td>Percentage of patients prescribed or picking up mono or dual ART</td>
<td>Number of individuals who have picked up a mono or dual prescribed ART drug</td>
<td>Number of patients who picked up ART drugs on or after the designated EWI sample start date until the sample size is reached</td>
</tr>
<tr>
<td></td>
<td>Green 0%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ART: antiretroviral therapy.

### Table 2: Quality-of-care indicators in ART clinics in Pune, India

<table>
<thead>
<tr>
<th>Quality-of-care indicator (QCI)</th>
<th>Target</th>
<th>Definition</th>
<th>Numerator</th>
<th>Denominator</th>
</tr>
</thead>
<tbody>
<tr>
<td>QCI 1 Target:</td>
<td>Good: &gt;90%</td>
<td>Percentage of patients on ART care undergoing 6-monthly CD4 tests</td>
<td>Number of patients who underwent CD4 count at 6-monthly interval in ART care</td>
<td>Total number of patients who are enrolled in ART care and currently on treatment</td>
</tr>
<tr>
<td></td>
<td>Poor: &lt;90%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QCI 2 Target:</td>
<td>Good: &gt;90%</td>
<td>Percentage of patients initiating ART within 30 days of medical eligibility in the designated year</td>
<td>Number of patients who received ART within 30 days of their medical eligibility in the designated year</td>
<td>Total number of patients eligible for ART initiation</td>
</tr>
<tr>
<td></td>
<td>Medium: 80–90%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poor: &lt;80%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QCI 3 Target:</td>
<td>Good: &gt;90%</td>
<td>Percentage of patients initiating ART within 30 days of initiation of ATT</td>
<td>Number of patients starting ART within 30 days of initiation of ATT</td>
<td>Total number of patients starting ART who have initiated ATT</td>
</tr>
<tr>
<td></td>
<td>Medium: 80–90%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poor: &lt;80%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ART: antiretroviral therapy; ATT: anti-tuberculosis therapy.

### Table 3: Profile of four ART clinics in Pune, India

<table>
<thead>
<tr>
<th>Clinic</th>
<th>Year of clinic establishment</th>
<th>Total number of patient in active care up to March 2014</th>
<th>Total number of patients alive and on ART up to March 2014</th>
<th>Total number of patients registered for ART in April 2013 to March 2014</th>
<th>Average number of ART clinic staff (doctor, nurse, counsellor, laboratory technician and pharmacist in April 2013 to March 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic A</td>
<td>2009</td>
<td>3362</td>
<td>2737</td>
<td>1319</td>
<td>6</td>
</tr>
<tr>
<td>Clinic B</td>
<td>2005</td>
<td>15 462</td>
<td>6518</td>
<td>2795</td>
<td>9</td>
</tr>
<tr>
<td>Clinic C</td>
<td>2010</td>
<td>2979</td>
<td>2706</td>
<td>672</td>
<td>9</td>
</tr>
<tr>
<td>Clinic D</td>
<td>2008</td>
<td>6098</td>
<td>5286</td>
<td>1490</td>
<td>10</td>
</tr>
</tbody>
</table>

ART: antiretroviral therapy.
Early-warning indicators in adults

The data on four adult EWIs from four ART clinics in Pune are summarized in Table 4.

**EWI 1: On-time pill pick-up**

Clinic C met the target for on-time pill pick-up (>90%) and clinics A and D reached near target (80–90%) with 84% (95% confidence interval [CI]: 79% to 89%) and 81% (95% CI: 76% to 86%) respectively.

**EWI 2: Retention in ART care at 12 months after initiation**

No clinic met the target (>85%) for retention in care at 12 months. Clinics A and C reached near target (75–85%). The overall retention in all four clinics was 76% (95% CI: 73% to 79%). Some of the significant causes of attrition among those who could not be retained at one year were loss to follow-up 39% (95% CI: 32% to 45%), deaths 38% (95% CI: 31% to 45%), and self-stopping 16% (95% CI: 11% to 21%). The overall percentage of patients who were initiated on second-line treatment was 1.6% (95% CI: 0.73% to 2.46%).

**EWI 3: Pharmacy stock-out**

Clinic C had sufficient pharmacy stock for the designated year, while Clinics A, B and D had pharmacy stock-outs.

**EWI 4: Pharmacy dispensing practices**

All four sites met the target of 100%, and appropriate initial ART regimens were prescribed according to national ART guidelines. No patient at any site received mono or dual therapy.

Quality-of-care indicators in adults

**QCI 1: Regularity in CD4 testing in patients taking ART**

Clinic C reached the target (>90%). Clinic A had good performance at month 6 but did not reach the target at months 12 and 24. Clinics B and D did not reach the target for regularity of testing CD4 count at months 6, 12 and 24 (see Fig. 1).  

**QCI 2: Percentage of patients initiating ART within 30 days of medical eligibility**

The target was achieved by Clinics B and D but was not achieved in Clinic A (78.6% [95% CI: 72.8% to 84.3%]) and Clinic C (70.3% [95% CI: 63.3% to 77.3%]) (see Fig. 2).

**QCI 3: Percentage of patients initiating ART within 30 days of initiation of ATT**

The target was not achieved by any of the clinics (see Fig. 2). Considering the operational guidelines for ART initiation between 2 weeks and 2 months after initiation of ATT, Clinic B (90.6% [95% CI: 82.7% to 98.4%]) and Clinic D (94.8% [95% CI: 89.1% to 100.5%]) achieved this target.

**DISCUSSION**

As per the recommendations of operational guidelines for ART services, ART-preparedness counselling was carried out in 2–3 sessions in the ART clinics while the patients had their clinical and laboratory screening. The clinic counsellors informed the patients that the treatment was lifelong. This was further stressed on the adherence counselling, which was subsequently reiterated at each monthly clinic visit. The study results showed that the target for EWI 1 (on-time pill pick-up, >90%) was not achieved in three of the four ART clinics, in spite of these counselling sessions, which indicates the additional effort required to increase adherence and minimize visits missed by patients. The pill counts and pharmacy records also need to be appropriate so that patients can come in time before their supply.

### Table 4. Early-warning Indicators for adults in four ART clinics in Pune, India

<table>
<thead>
<tr>
<th>ART clinic</th>
<th>EWI 1: On-time pill pick-up, % (number of patients)</th>
<th>EWI 2: Retention in ART care at 12 months, % (number of patients)</th>
<th>EWI 3: Pharmacy stock-out, % of months with no pharmacy stock-outs (12 months)</th>
<th>EWI 4: Pharmacy dispensing practices, % of patients with mono or dual therapy (number of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic A</td>
<td>Red: &lt;80% Amber: 80–90% Green: &gt;90%</td>
<td>Red: &lt;75% Amber: 75–85% Green: &gt;85%</td>
<td>Red: &lt;100% Green: 100%</td>
<td>Red: &gt;0% Green: 0%</td>
</tr>
<tr>
<td>Clinic B</td>
<td>84 (201)</td>
<td>82 (187)</td>
<td>83</td>
<td>0 (203)</td>
</tr>
<tr>
<td>Clinic C</td>
<td>77 (216)</td>
<td>67 (232)</td>
<td>42</td>
<td>0 (224)</td>
</tr>
<tr>
<td>Clinic D</td>
<td>94 (200)</td>
<td>83 (160)</td>
<td>100</td>
<td>0 (201)</td>
</tr>
<tr>
<td>Clinic C</td>
<td>81 (216)</td>
<td>74 (190)</td>
<td>92</td>
<td>0 (217)</td>
</tr>
</tbody>
</table>

ART: antiretroviral therapy; EWI: early-warning indicator.
of pills runs out. A study has reported that picking up ART in time has been shown to be associated with viral suppression. A report from the Caribbean recommended that health-care services that deliver ART should have supportive mechanisms in place to promote adequate adherence and should proactively trace clients who fail to return for scheduled visits. A separate study should be conducted in India to find out the various causes of delay for on-time pill pick-up, so that counselling can be strengthened to avoid treatment interruptions. This will help in increasing viral suppression at population level and, in turn, avoid development of drug resistance. Approaches like the use of mobile phones for pill pick-up reminders can be implemented to increase the adherence.
None of the ART clinics in the study achieved the target (>90%) for retention in care. The main reasons for attrition at the end of one year were loss to follow-up and death. The average retention rate at 12 months was lower as compared to a report from 70 low- and middle-income countries in 2008, where it was 79.9% globally and 80.3% in east, south, and south-east Asia.\textsuperscript{10,11} It was slightly lower than reported from urban ART sites in Cameroon (77.8%)\textsuperscript{12} and similar to those in a report from 33 cohorts comprising 74,192 patients from 13 sub-Saharan countries(75.0%).\textsuperscript{13} If the national programme moves towards adopting WHO guidelines of increasing the CD4 count for treatment initiation to 500 cells/mm\textsuperscript{3}, it becomes even more crucial to retain patients in the treatment, considering the limited availability of second-line drugs in the programme.\textsuperscript{14} The high rate of discontinuity in drug supply in three of the four clinics was an important concern. The drug stock-outs may increase treatment interruption, loss to follow-up and delay in drug pick-up. A risk of developing HIVDR remains, even though alternative therapeutic options are provided during stock-outs. It is important for the programme managers to sort out the issues related to supply management and provide continuous ART drug stock in all the ART clinics. The option of decentralization of drug procurement may be considered, and additional staff could be provided for monitoring the continuity of drug supply. The systems for calculating drug requirements and the time required for procurement and distribution must be prioritized to prevent ART drug stock-outs. Stock-outs in ART supply have also been reported in other countries.\textsuperscript{15,16}

The present study showed that good dispensing practices (EWI 4) are performed in all the ART clinics in the city, which is similar to the results from 35 clinics in the United Republic of Tanzania;\textsuperscript{17} this was probably due to the training of clinicians by the national programme and the ongoing supervision by the nodal officers of the clinics.

In Clinic B, suboptimal performance was observed in three EWIs, though this was the first of the four clinics to be established. This clinic functions as an ART reference centre and the number of staff should be increased, considering the patient burden, which will be important in achieving the targets.

The QCIs are being introduced in the programme to monitor the clinical care provided to patients. The target for overall regularity in CD4 testing was achieved in one clinic over the period of 2 years and irregularities were observed in the remaining three clinics at either 6, 12 or 24 months. This could be due to high patient burden, missed visits or an inadequate number or increased turnover of phlebotomy staff. In a country like India, where assay of viral load is not a part of routine monitoring, and targeted assay of viral load is performed to detect treatment failure, this QCI plays an important role for detecting immunological failure, for performing assays of viral load and for switching patients on second-line treatment, even though the CD4 marker is associated with delayed detection of ART failure and development of HIVDR.\textsuperscript{18} The clinics should strengthen the mechanism for regular listing of patients who are due for CD4 testing, and tracking of patients who are missed for CD4 testing, by adhering to the operational guidelines. This will increase the regularity in CD4 testing and monitoring of ART over the long term. The laboratory managers in the programme should ensure timely supply of reagents for CD4 assays, so that no clinic faces a shortage, and regularity in CD4 testing can be maintained.

Timely initiation of ART benefits patients infected with HIV, by reducing their morbidity and mortality. In the present study, the target for the percentage of patients initiating ART within 30 days of medical eligibility (QCI 2) was achieved by two of the four clinics. The common reasons for delay in treatment initiation beyond 30 days include delay in laboratory investigations, lack of patient preparedness for ART initiation, co-existing tuberculosis (TB) infection and patients not approaching the clinics in time, because of their own problems.\textsuperscript{3} In a report from two public clinics in Malawi, the duration of the pre-ART period was found to be the most significant predictor of starting ART among eligible patients. In the Malawi study, patients who were immediately eligible for ART at initial registration had lower odds of initiating treatment than patients who spent 1–3 months in pre-ART care. The authors concluded that better understanding of the motivation for retention in pre-ART care may reduce attrition along the treatment cascade.\textsuperscript{19} A study from southern India on predictors of delayed ART initiation observed that diagnosis of TB, being homeless, lower CD4 count, longer duration of pre-ART care, being widowed and belonging to a disadvantaged community were associated with delayed initiation of ART.\textsuperscript{20} The report recommended implementing targeted interventions for patients at high risk of programme attrition.

The target for the percentage of patients initiating ART within 30 days of initiation of ATT (QCI 3) was not achieved by any of the four clinics in this study. However, two clinics could achieve the target for starting ART within 60 days after initiation of ATT.

TB remains an important cause of death among patients infected with HIV. The operational guidelines recommend that ART should be started between 2 weeks and 2 months after initiation of ATT, as soon as the TB treatment is tolerated. A study from northern India on early versus delayed initiation of ART for Indian individuals infected with HIV and on ATT stated that early initiation of highly-active antiretroviral therapy (HAART) for patients with HIV and TB significantly decreases the incidence of HIV disease progression and has good tolerability.\textsuperscript{21} The ART clinics should strengthen their mechanism for tracking TB patients infected with HIV who are referred to TB centres, and proactively retain them under care for early initiation of ART. This will improve the quality of care provided to the patients in the national programme who are co-infected with HIV and TB.

The study has limitations. It was not possible to include EWI 5, on viral suppression at 12 months, as this was a retrospective study and routine testing of viral load is not recommended in the programme. The data on HIVDR could not be used to predict the association of each EWI with viral load. The study sites were limited and hence the findings are not representative of ART clinics nationally. Data on EWIs for paediatric groups were not included. The data were abstracted by a trained team but were not validated. The date of starting ATT was not
obtained for all patients and so the date of diagnosis of TB was used as a proxy, which may overestimate the results.

CONCLUSIONS

The study has shown good ART dispensing practices in all the four clinics studied but retention in care, on-time pill pick-up, drug supply, and the number of days required for ART initiation after eligibility did not meet the desired target. This survey can be used by programme managers to identify areas of weakness and take measures accordingly. The quality of patient care will improve by integrating EWI and QCI into routine monitoring of ART clinics in the national programme.

REFERENCES


