MEETING REPORT ON
ASSESSMENT OF WORLD HEALTH ORGANIZATION
HIV DRUG RESISTANCE EARLY WARNING INDICATORS
Report of the Early Warning Indicator Advisory Panel Meeting

11–12 AUGUST 2011 GENEVA, SWITZERLAND
EXECUTIVE SUMMARY

Early warning indicators (EWIs) of HIV drug resistance (HIVDR) are a key component of the World Health Organization (WHO) public health strategy to minimize and assess HIVDR in countries scaling up antiretroviral therapy (ART). EWIs are quality of care indicators which specifically assess factors at individual antiretroviral therapy clinics associated with emergence of HIVDR. Where widely implemented, EWIs provide the necessary programmatic context to interpret results of surveys of transmitted and acquired HIVDR.

As of mid-2011, 52 countries had implemented 102 rounds of EWI monitoring which assessed over 16,000 patients. The implementation of EWI monitoring has progressively increased over time supported by a simple standardized data abstraction tool. HIVDR EWIs and targets were originally chosen in 2006 based on a review of the available medical literature and expert opinion.

In August 2011, an advisory panel review meeting was held in Geneva to consider revisions of the existing EWIs and associated targets. After a critical review of available medical literature using the GRADE methodology, recommendations were developed to simplify EWI definitions, account for implementation challenges, harmonize with other routinely reported indicators and adjust EWI definitions and targets based on new evidence. The revised recommended set of indicators which is designed to be implemented as a package includes a total of five indicators, one of which (viral load suppression at 12 months), is considered conditional and is designed to be implemented only at clinics where routine viral load monitoring is performed for all patients 12 months after ART initiation.

When possible, indicator definitions were harmonized with UNGASS or PEPFAR indicators and a target appropriate to HIVDR was established. The revised set of indicators is anticipated to require substantially less data abstraction with the abstraction and reporting function performed by the ART clinic rather than by data abstractors sent from the national programme level. Suggested modifications to EWI definitions and abstraction procedures are anticipated to substantially facilitate wider uptake, reporting, and sustainability.
INTRODUCTION

- As of December 2010, 6.6 million people living with HIV in low and middle income countries (LMICs) were receiving ART.

- The emergence and transmission of HIV drug resistance (HIVDR) is an unavoidable consequence of ART, even when appropriate drugs are prescribed and adherence is maximally supported. Nonetheless, efforts must be undertaken to limit HIVDR emergence especially because significant population-level HIVDR may necessitate switch from non-nucleoside reverse transcriptase (NNRTI) based first-line regimens to more expensive and less well tolerated boosted protease inhibitor-based second-line regimens.

- Individual HIVDR testing is not available, nor recommended, in most LMICs. Therefore, routine population-level laboratory based surveillance of HIVDR and assessments of how well ART programmes and clinics function to minimize emergence of HIVDR are required.

- WHO in collaboration with WHO/HIVResNet developed a global strategy for the prevention and assessment of HIVDR. The strategy includes surveillance of transmitted HIVDR in recently infected populations, surveillance of acquired HIVDR in populations failing ART, and the monitoring of site and programme factors associated with emergence of HIVDR.

- HIVDR Early Warning Indicators (EWIs) are quality of care indicators which specifically assess factors at individual clinics associated with HIVDR emergence. EWIs form the foundation of WHO’s HIVDR prevention and assessment strategy, and where widely implemented, provide the necessary programmatic context to interpret results of surveys of transmitted and acquired HIVDR. HIVDR EWIs and targets were originally chosen in 2006 based on a review of the available medical literature and expert opinion. Current WHO-recommended HIVDR EWIs and their corresponding targets are listed in Table 1. 2010 WHO HIVDR EWI guidance is available at: http://www.who.int/hiv/topics/drugresistance/hiv_dr_early_warning_indicators.pdf

1 WHO/HIVResNet is an advisory group of over 50 institutions.
**HIVDR EWI OVERVIEW**

- The purpose of implementing HIVDR EWI monitoring is to assess the extent to which ART programmes function to optimize the prevention of HIVDR. EWIs measure ART site factors known to be associated with good programmatic functioning and the prevention of HIVDR.

- EWIs evaluate factors associated with HIVDR prevention without requiring laboratory testing for drug resistance.

- Strengthening specific aspects of ART programme delivery at the site level will minimize preventable HIVDR and promote the long-term efficacy and durability of available first- and second-line regimens. EWI monitoring provides the evidence base for programmatic change and/or public health action to prevent and address HIVDR.

- Information collected as part of EWI monitoring includes: ART prescribing practices; loss to follow-up 12 months after initiation of ART; retention on appropriate first-line therapy at 12 months; on-time patient appointment keeping and antiretroviral (ARV) drug pick-ups; ARV drug supply continuity, patient adherence to ART through standardized measures (for example pill count), and rates of HIV viral load suppression rates at 12 months.

- The WHO recommends indicator-specific targets that clinics should reach to minimize emergence of HIVDR in ART patients. Currently recommended EWI definitions and targets were established based on a review of the published medical literature and consensus of international experts in 2006.

**TABLE 1 WHO HIVDR EWIs (2010 GUIDANCE)**

<table>
<thead>
<tr>
<th>EWI</th>
<th>EWI target (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Prescribing practices (% of initial ART prescriptions congruent with national/WHO guidelines)</td>
<td>100</td>
</tr>
<tr>
<td>2. Loss to follow-up (% of patients lost to follow-up at 12 months)</td>
<td>&lt;20</td>
</tr>
<tr>
<td>3. Retention on first-line ART (% of patients retained on first-line ART at 12 months)</td>
<td>≥70</td>
</tr>
<tr>
<td>4. On-time pill pickup (% of patients with 100% on-time drug pickups during the first 12 months of ART, or during a specified time period)</td>
<td>≥90</td>
</tr>
<tr>
<td>5. On-time clinic appointment keeping (% of patients who attended all appointments on time during the first 12 months of ART, or during a specified time period)</td>
<td>≥80</td>
</tr>
<tr>
<td>6. Drug supply continuity (% of clinics with antiretroviral drug supply continuity during a 12-month period)</td>
<td>100</td>
</tr>
<tr>
<td>7. Adherence as measured by pill count (% patient adherence to antiretroviral therapy by pill count or other standardized measure)</td>
<td>≥90</td>
</tr>
<tr>
<td>8. Viral load suppression 12 months after ART initiation (% of patients with viral load &lt;1000 copies/mL at 12 months)</td>
<td>≥70</td>
</tr>
</tbody>
</table>

**ART** = antiretroviral therapy; **EWI** = early warning indicator; **HIV** = human immunodeficiency virus; **WHO** = World Health Organization.
Monitoring EWIs alerts national ART programme managers to clinic factors that need increased support to reduce the potential for significant population-level virological failure and emergence of preventable HIVDR. Routine EWI monitoring alerts clinic and district managers to specific areas which require attention and supports overall optimization of patient care.

EWI results form the basis of recommendations for action either at the site level or, if many sites do not achieve targets, at the national ART programme level. Recommendations may include increased training and resources for specific aspects of care, provision of targeted support for adherence, or help with drug supply chain management and reduction of barriers to continuous access to ARVs. Additional assessment, including operational research to clarify the source of problems and the support required to address them, may also be recommended.

2010 EWI guidance recommends that EWIs be monitored at all ART sites within a country or a large number of representative sites. The sites where EWI are monitored are referred to as the primary sample. 2010 guidance does not describe how primary sampling should be performed to achieve results which are likely to be representative of overall ART programme functioning. However, guidance for sampling at an individual site (secondary sampling) for each EWI is provided to achieve a result that can be generalized to the site's entire clinic population. Secondary sampling is based on the total number of patients in care or receiving ART at the time EWI monitoring is performed. A full description of current primary and secondary sampling guidance, including a sample size look-up table is included in the 2010 EWI guidance available at: http://www.who.int/hiv/topics/drugresistance/hiv_dr_early_warning_indicators.pdf

As of mid-2011, 52 countries had implemented 102 rounds of EWI monitoring (largely pilot experiences) which assessed over 16,000 patients receiving ART worldwide. EWIs have been monitored at >2,000 clinics and have formed the basis for public health action in many settings.

**HIVDR EWI MEETING GOALS**

Between 2006 and 2011, important lessons were learnt regarding HIVDR EWIs. Although EWI monitoring provided countries with valuable and actionable programmatic information, and the HIVDR EWI data abstraction tool developed by WHO was simple to use, functional and promoted standardization of results. However, evolving scientific evidence during this time suggested that some EWIs may be more closely associated with HIVDR (or viral load suppression) than others and that the original targets set for each EWI should be reassessed. Additionally, current EWI guidance is a retrospective assessment of cohorts of patients necessitating up to 2 years of data for analysis making results less timely. Finally, operational experiences over the last 5 years have provided evidence that uptake of EWI monitoring would be greatly improved if EWI definitions were simplified and aligned, whenever possible, with other routinely abstracted and reported data.
IN AUGUST 2011, A MEETING OF EXPERTS WAS CONVENED WITH THE FOLLOWING GOALS:

- Review 2010 WHO HIVDR EWI guidance document
- Evaluate medical literature and assess strength of association between currently recommended EWIs and HIVDR
- Evaluate medical literature and assess strength of association between EWI targets and HIVDR
- Advise WHO on updating HIVDR EWIs by eliminating multiple version of existing EWIs and guide their integration into existing national data abstraction/monitoring processes
- Advise WHO on update of HIVDR EWI targets, if indicated
- Maximize relevance of EWI results to current patient populations
- Propose simplified EWI results reporting
METHODS

METHODS OVERVIEW

I. Review of reported global EWI data and country case studies
II. Systematic review of available literature using GRADE methodology for quality of evidence appraisal
III. Assessment of evidence by expert panel following the GRADE methodology
IV. Development of suggested EWIs (definitions, numerators and denominators) based on an up-to-date evidence review
V. Identification of optimal targets using norm, criterion, and "mixed methods" referencing

1. REVIEW OF REPORTED GLOBAL EWI DATA AND COUNTRY CASE STUDIES

- From 2004 – 2009, 50 countries from Africa, Asia, Latin America and the Caribbean monitored EWIs (Appendix 1).

- Broad EWI uptake was noted in a range of LMICs; however, multiple limitations to widespread uptake were noted. The greatest uptake was for EWIs 1 (Prescribing Practices), 2 (Lost to follow up after 12 months of ART) and 3 (Retention on first-line ART after 12 months) with >2,000 sites reporting on these 3 indicators. EWI 5 (On-time appointment keeping) had data from 1,366 clinics, EWI 6 (ARV drug supply continuity) from 723 clinics and EWI 4 (On-time-pill pick-up) from 352 clinics. There was minimal uptake for EWI 8 (Viral load suppression at 12 months) likely due to the lack of routine viral load testing in LMICs; no data were reported for EWI 7 (Pill count). Less than 20% of clinics met the target for EWI 4 while 75% of clinics met the target for EWI 1, 69% met the target for EWI 2, 67% met the target for EWI 3, 58% met the target for EWI 5, and 65% met the target for EWI 6.

- An abridged version of results for all years combined is presented in Table 2.

- In-depth case studies from Vietnam and Namibia were presented: (Appendices 2 and 3).

2. SYSTEMATIC REVIEW OF AVAILABLE MEDICAL LITERATURE USING GRADE METHODOLOGY

- A systematic literature review was performed for each EWI to assess the indicators' association with HIVDR and to support identification of appropriate targets. Separate reviews were performed for adult (≥13 years old) and for paediatric (<13 years old) EWls. Relevant data (demographics, study definition of EWI and proportion meeting that definition) were abstracted.
### TABLE 2 SUMMARY OF GLOBAL EWI DATA COLLECTED FROM 2004 TO 2009 FROM 50 COUNTRIES (NUMBER OF CLINICS MONITORED AND PERCENT MEETING TARGET BY EWI)

<table>
<thead>
<tr>
<th>Region</th>
<th>Prescribing practices</th>
<th>Loss to follow-up</th>
<th>Retention on first-line ART</th>
<th>On-time pill pick-up</th>
<th>On-time clinical appointment keeping</th>
<th>Drug stock-out</th>
<th>Viral load suppression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EWI 1: N=907 73.76</td>
<td>70.77-76.60</td>
<td>55.56-62.51</td>
<td>57.37-63.99</td>
<td>10.96-18.99</td>
<td>37.13-48.44</td>
<td>58.51-66.86</td>
</tr>
<tr>
<td>Africa</td>
<td>73.76</td>
<td></td>
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<tr>
<td></td>
<td>EWI 2: N=794 59.07</td>
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<tr>
<td></td>
<td>EWI 3: N=883 60.72</td>
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<tr>
<td></td>
<td>EWI 4: N=321 14.62</td>
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<td></td>
<td>EWI 5: N=309 42.72</td>
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<tr>
<td></td>
<td>EWI 6: N=537 62.76</td>
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<td></td>
<td>EWI 8: N=24 78.88</td>
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<tr>
<td></td>
<td>n=2040* 67.35</td>
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<tr>
<td>Asia</td>
<td>N=1048* 80.25</td>
<td>37.28-54.34</td>
<td>71.84-77.21</td>
<td>68.62-75.13</td>
<td>00.00-30.85</td>
<td>60.83-66.77</td>
<td>81.17-94.38</td>
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<tr>
<td></td>
<td>EWI 2: N=1043* 74.59</td>
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<td></td>
<td>EWI 3: N=1045* 72.44</td>
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<td></td>
<td>EWI 4: N=10 00.00</td>
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<tr>
<td></td>
<td>EWI 5: N=1037* 63.84</td>
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<td>EWI 6: N=100 89.00</td>
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<td>EWI 8: N=10 00.00</td>
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<tr>
<td></td>
<td>N=1037* 63.84</td>
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<tr>
<td></td>
<td>n=100 89.00</td>
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<tr>
<td>LAC</td>
<td>N=141 45.71</td>
<td>37.28-54.39</td>
<td>76.59-90.54</td>
<td>61.89-78.07</td>
<td>17.64-30.85</td>
<td>60.83-66.77</td>
<td>81.17-94.38</td>
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<tr>
<td></td>
<td>EWI 2: N=116 84.48</td>
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<td></td>
<td>EWI 3: N=132 70.46</td>
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<td>EWI 4: N=21 57.14</td>
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<td>EWI 5: N=20 15.00</td>
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<td></td>
<td>EWI 6: N=86 51.16</td>
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<td></td>
<td>EWI 8: N=22 72.73</td>
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<tr>
<td></td>
<td>n=2040* 67.35</td>
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<tr>
<td>Total All</td>
<td>N=2095* 75.13</td>
<td>73.22-76.97</td>
<td>66.76-70.92</td>
<td>65.27-69.39</td>
<td>13.01-21.08</td>
<td>55.68-60.98</td>
<td>61.41-68.49</td>
</tr>
<tr>
<td>regions</td>
<td>EWI 2: N=1953* 68.87</td>
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<td></td>
<td>EWI 3: N=2040* 67.35</td>
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<td></td>
<td>EWI 4: N=352 16.76</td>
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<tr>
<td></td>
<td>EWI 5: N=723 65.01</td>
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<tr>
<td></td>
<td>EWI 6: N=50 82.00</td>
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<tr>
<td></td>
<td>EWI 8: N=22 72.73</td>
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</table>

*In 2008, Thailand contributed 902 sites to these EWI results in Asia; Cambodia contributed an additional 39–41 sites.

N = number of clinics monitored.

% = percentage of clinics meeting target.

CI = Confidence Interval.

For the purpose of this analysis, data from EWIs having different versions were combined.

Due to limited uptake and reporting of EWI 7 these data are not presented.
Summary measures (medians, range of estimates and weighted means) were determined based on included studies for each EWI. In addition to the systematic review, relevant published and grey literature was reviewed and considered.

- Each EWI was assessed separately. The GRADE methodology was used to assess the strength of evidence assessing the association of the indicators with HIVDR and identifying potential targets.

3. ASSESSMENT OF EVIDENCE BY EXPERT PANEL FOLLOWING THE GRADE METHODOLOGY

The expert panel reviewed the GRADE quality of evidence appraisal being presented (Table 3) and a final ranking of the quality of evidence was achieved by consensus. In addition, the potential value of the indicators to minimize HIVDR was assessed based on a comprehensive risk and benefit evaluation (Table 4) which included the following four domains: benefits and risks, acceptability, feasibility and financial implications. A final evaluation of the strength of the recommendation was achieved by group consensus (Table 5).

### TABLE 3 QUALITY OF EVIDENCE EVALUATION (GRADE)

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Further research is very unlikely to change confidence in the estimate of effect. (Example of type of evidence – randomized trial)</td>
</tr>
<tr>
<td>Moderate</td>
<td>Further research is likely to have an important impact on confidence in the estimate of effect.</td>
</tr>
<tr>
<td>Low</td>
<td>Further research is very likely to have an estimate of effect and is likely to change the estimate. (Example of type of evidence – observational study)</td>
</tr>
<tr>
<td>Very Low</td>
<td>Any estimate of effect is very uncertain.</td>
</tr>
</tbody>
</table>

### TABLE 4 RISK AND BENEFIT ASSESSMENT (GRADE)

<table>
<thead>
<tr>
<th>Domain</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength of the evidence</td>
<td>See table 3.</td>
</tr>
<tr>
<td>Benefits and risks</td>
<td>When developing a new recommendation, desirable effects (benefits) need to be weighed against undesirable effects (risks), considering any previous recommendation or an alternative. The larger the gap or gradient in favour of the benefits compared to the risks; the more likely a strong recommendation will be made.</td>
</tr>
<tr>
<td>Acceptability</td>
<td>If the recommendation is likely to be widely accepted or valued more highly, a strong recommendation will probably be made. If there is a great deal of variability or if there are strong reasons that the recommended course of action is unlikely to be accepted, it is more probable that a conditional recommendation will be made.</td>
</tr>
<tr>
<td>Feasibility</td>
<td>If an intervention is achievable in a setting where the greatest impact is expected to be attained, a strong recommendation is more probable.</td>
</tr>
<tr>
<td>Financial implications</td>
<td>Lower costs (monetary, infrastructure, equipment or human resources), or greater cost-effectiveness will more probably result in a strong recommendation.</td>
</tr>
</tbody>
</table>
TABLE 5 ASSESSMENT OF THE STRENGTH OF THE RECOMMENDATIONS

<table>
<thead>
<tr>
<th>Strength of recommendation</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>The working group is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects.</td>
</tr>
<tr>
<td>Conditional</td>
<td>The working group concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects. However: The recommendation is only applicable to a specific group, population or setting OR new evidence may result in changing the balance of risk to benefit OR the benefits may not warrant the cost or resource requirements in all settings.</td>
</tr>
<tr>
<td>No recommendation possible</td>
<td>Further research is required before any recommendation can be made.</td>
</tr>
</tbody>
</table>

4. DEVELOPMENT OF SUGGESTED EWIs (DEFINITIONS, NUMERATORS AND DENOMINATORS) BASED ON LITERATURE REVIEW

- EWIs were separately evaluated for their association with HIVDR and for the optimal target to be established. EWIs without strong association with HIVDR were eliminated from the revised set of indicators. EWIs which were retained were evaluated to:
  - Ensure that each retained EWI assessed only one area linked to HIVDR emergence
  - Minimize overlap of information obtained by each indicator
  - Maximize efficiency of data abstraction for the entire set of indicators
  - Maximize consistency and harmonize definitions, if possible, with other routinely monitored non-EWI indicators also designed to assess ART programme functioning

5. IDENTIFICATION OF SUGGESTED TARGETS USING NORM, CRITERION, AND “MIXED METHODS” REFERENCING, IF INDICATED

- Three target setting techniques were considered when determining targets: normative referencing, criterion referencing, and mixed method referencing. *Norm-referencing* is the establishment of targets based on normative or mean levels of performance. When using norm-referencing results above a central value are considered “good” performance, and results below a central value are considered “poor” performance. The systematic literature review provided the normative or mean levels of performance for EWIs. An important limitation of norm-referencing is that it may reflect poor existing practices and lack aspiration. *Criterion referencing* is the establishment of targets based on attainment of desirable levels of performance. Criterion referencing is usually evidence-based; however, in some instances evidence may be lacking, necessitating the use of expert opinion to set targets. To balance the strengths and limitations of norm and criterion referencing, a combination method known as a “mixed methods” approach to target setting was used. “Mixed methods” have the advantage of facilitating “score-carding” of targets which facilitates return of results to sites, interpretation and facilitates strategic allocation of resources (3). Score cards produce three classifications: red (poor performance, below desired level), amber (fair performance, not yet at desired level), and green (excellent performance).
Score-carding also allows for a “grey” classification if clinics do not monitor a specific EWI and a “white” classification if an indicator is not reported in a specific year following predetermined national convention. Advantages and disadvantages of the different approaches to target setting are discussed in detail in Appendix 4. An example of a score-card for the revised EWIs is presented in Figure 1. In this theoretical example, the site achieved the target for retention in care and prescribing practices, received a warning for “on time pill pick-up” and fell below standard for having one or more pharmacy stock-outs. Viral load is not monitored at this site, thus a score of grey for “viral load suppression.”

**FIGURE 1 EXAMPLE OF EWI TARGET SCORED CARD**

<table>
<thead>
<tr>
<th>HIV Drug Resistance Early Warning Indicator Score Card</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early Warning Indicator</strong></td>
</tr>
</tbody>
</table>
| 1. On-time Pill Pick-up | Yellow | • Red <80%  
• Amber 80–90%  
• Green >90% |
| 2. Retention in care | Green | • Red <75% retained after 12 months ART  
• Amber 75–85% retained after 12 months ART  
• Green >85% retained after 12 months ART |
| 3. Pharmacy stock-outs | Red | • Red <100% of a 12 month period with no stock-outs  
• Green 100% of a 12 month period with no stock-outs |
| 4. Dispensing practices | Green | • Red >0% dispensing of mono or dual therapy  
• Green 0% dispensing of mono or dual therapy |
| 5. Virological suppression# | Grey | • Red <70% viral load suppression after 12 months of ART  
• Amber 70–85% viral load suppression after 12 months of ART  
• Green >85% viral load suppression after 12 months of ART |

**Notes:**
Red (poor performance, below desired level).  
Amber (fair performance, not yet at desired level but progressing towards desired level).  
Green (excellent performance, achieving desired level).  
Grey (data not available).  
White (not depicted in this example; in non-UNGASS reporting years the retention indicator is “not applicable” and sites receive a “white” score).  
#Targets for virological suppression in children <2 years old.  
• Red <60% viral load suppression after 12 months of ART.  
• Amber 60–70% viral load suppression after 12 months of ART.  
• Green >70% viral load suppression after 12 months of ART.

---

1 The new retention EWI (Table 8) is identical to the UNGASS and PEPFAR retention indicator which is only monitored and reported biannually. Therefore, in non-UNGASS/PEPFAR reporting years, clinics monitoring EWIs report “not applicable” and receive a “white” score for this indicator in that year.
RESULTS

- This section reviews the 2010 HIVDR EWI definitions, strength of association between the existing indicator and HIVDR, risk/benefits and acceptance/feasibility of monitoring of the specified indicator, and presents a summary of discussion and consensus findings related to individual indicators and targets. The complete systematic review relevant to current EWIs is presented in Appendices 5 and 6.

- Table 6 summarizes key findings from the systematic review relevant to retained EWIs. A summary of suggested revisions to EWIs and their relationship to 2010 guidance is presented in Table 7. Revised EWIs were re-numbered to reflect prioritization of the new indicator set, with the first indicator having the highest priority (Table 8).

- As with 2010 EWI guidance, EWIs are monitored separately for adult and paediatric populations except for the revised retention indicator, in which retention of a combined cohort of adults and children is assessed. Recommended targets are identical for adult and paediatric populations in all revised EWIs except for the indicator assessing desirable rates of virological suppression. A detailed summary of findings and recommendations for each EWI appears below.

- The section presenting review results for individual EWIs begins on page 20 and is structured in the following way for each EWI.
  I. Description of current EWI and recommended target
  II. Strength of association between current indicator and HIVDR (high, moderate, low, very low)
  III. Review of appropriateness of current target
  IV. Review of benefits and risks of monitoring current indicator
  V. Review of acceptability and feasibility of monitoring current indicator
  VI. Review of cost considerations of monitoring current indicator
  VII. Suggested wording of new EWI, if indicated
  VIII. Strength of association between new indicator and HIVDR (high, moderate, low, very low); strength of recommendation
  IX. Suggested target for revised EWI, if indicated
### Table 6: Key Findings from Adult EWI Systematic Review of Targets

<table>
<thead>
<tr>
<th>EWI</th>
<th>Identified studies</th>
<th>Studies included in the review</th>
<th>Number of cohorts</th>
<th>Number of subjects</th>
<th>Summary estimates</th>
<th>List of estimates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median (range) (%)</td>
<td>Weighted mean (%)^</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EWI 1 (Prescribing practices)</td>
<td>NA (Narrative Review)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>EWI 3a (% Retention on appropriate 1st line at 12 months)</td>
<td>261 Papers 616 Abstracts</td>
<td>43 Papers 22 Abstracts</td>
<td>83</td>
<td>535438</td>
<td>77.7 (49.7–91.0)</td>
<td>77.1</td>
</tr>
<tr>
<td>EWI 4a (% On-time ARV pick-up [Cross sectional after variable durations of ART])</td>
<td>55 Papers 116 Abstracts</td>
<td>6 Papers 1 Abstract</td>
<td>4</td>
<td>11714</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>EWI 4b (% On-time ARV pick-up for first 12 months ART)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>EWI 6a, 6b, 6c1 and 6c2 (ARV supply continuity, or % affected by ARV stock out)</td>
<td>27 Papers 178 Abstracts</td>
<td>7 Papers 3 Abstracts</td>
<td>9</td>
<td>28307</td>
<td>11 (1–64)</td>
<td>—</td>
</tr>
<tr>
<td>EWI 8 (% Virological suppression at 12 months)*</td>
<td>279 Papers 410 Abstracts</td>
<td>36 Papers 17 Abstracts</td>
<td>29</td>
<td>19527</td>
<td>70 (50–92)</td>
<td>69.8</td>
</tr>
</tbody>
</table>

NA = Not applicable.

^ Weighting by cohort size.

* If small number of available studies (<5) then list of estimates from studies provided.

† Intention to treat studies only include death and lost to follow-up in denominator and exclude transfer out from the denominator if the proportion transferred out reported. If consider on treatment studies with single viral load performed 12 months after ART initiation (VL suppression defined as VL<1000 copies/mL) to define outcome then there were 9 cohorts, n=3192, Median 84%, and Weighted Mean 82%.
# Assessment of World Health Organization HIV Drug Resistance Early Warning Indicators

<table>
<thead>
<tr>
<th>Table 7 Comparison of Original EWIs and Proposed New EWIs</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Current EWIs</strong></td>
<td><strong>Proposed new EWIs</strong></td>
<td><strong>Proposed new EWI targets</strong></td>
<td><strong>Proposed new EWI changes</strong></td>
</tr>
<tr>
<td><strong>Current EWI number and current target</strong></td>
<td><strong>Proposed new EWI number and target</strong></td>
<td><strong>Key Points about current EWI</strong></td>
<td><strong>Key Points about proposed new EWI</strong></td>
</tr>
<tr>
<td>1. Percentage of adult patients initiating ART at the ART clinic who are initially prescribed, or who initially pick-up from the pharmacy, an appropriate first-line ART regimen</td>
<td>1. Percentage of adults or children being dispensed a mono or dual-drug regimen (name change to Dispensing Practices)</td>
<td>1. “Appropriate” is defined as following a national or international standard first-line regimen. Ambiguity has led to classification of “inappropriate prescribing” at sites prescribing protease inhibitors as first-line regimens, yet they are appropriate for prevention of HIVdr.</td>
<td>1. Red: &lt;75%, Amber: 75-95%, Green: &gt;95%</td>
</tr>
<tr>
<td>1. Percentage of adult patients initiating ART at the ART clinic who are lost to follow-up 12 months after ART initiation</td>
<td>2. Percentage of patients initiating ART at the site who are lost to follow-up 12 months after ART initiation</td>
<td>≤20%</td>
<td>Denominator excludes transfers out</td>
</tr>
<tr>
<td>2. Percentage of adult patients initiating ART at the site who are taking an appropriate first-line ART regimen 12 months later</td>
<td>3. Percentage of adult patients initiating ART at the site who are taking an appropriate first-line ART regimen 12 months later</td>
<td>≥70%</td>
<td>Denominator excludes deaths and transfers out</td>
</tr>
</tbody>
</table>

## Key Points about Current EWI:
- **Current EWI 1**: Percentages are calculated based on the number of patients prescribed or dispensed the appropriate regimen, excluding patients who were lost to follow-up or died in the first 12 months.
- **Current EWI 2**: Percentages are calculated based on the number of patients who were lost to follow-up within 12 months, excluding patients who died.
- **Current EWI 3**: Percentages are calculated based on the number of patients taking the appropriate regimen 12 months after initiating ART, excluding patients who died or transferred out.

## Key Points about Proposed New EWI:
- **Proposed New EWI 1**: Percentages are calculated based on the number of patients prescribed or dispensed the appropriate regimen, excluding patients who were lost to follow-up or died in the first 12 months.
- **Proposed New EWI 2**: Percentages are calculated based on the number of patients who were lost to follow-up within 12 months, excluding patients who died.
- **Proposed New EWI 3**: Percentages are calculated based on the number of patients taking the appropriate regimen 12 months after initiating ART, excluding patients who died or transferred out.

## Changes:
- **Proposed New EWI 1**: Definition of “appropriate” regimen is clarified to align with national or international standards.
- **Proposed New EWI 2**: Denominator is expanded to include patients lost to follow-up who died within 12 months.
- **Proposed New EWI 3**: Denominator is expanded to include patients who died or transferred out within 12 months.
<table>
<thead>
<tr>
<th>Current EWI number and definition</th>
<th>Current EWI target</th>
<th>Key points about current EWI</th>
<th>Retain or exclude</th>
<th>Proposed new EWI</th>
<th>Proposed new target</th>
<th>Key Points about EWI changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>3b. Percentage of patients initiating ART at the site whose initial ART regimen was changed during the first 12 months to a regimen that includes a different drug class</td>
<td>0%</td>
<td>• Operationally this is not a measure of pills in hand at 12 months nor of retention at the site</td>
<td>Exclude</td>
<td>NA</td>
<td>NA</td>
<td>• EWI 3b was excluded as only one indicator reflecting the concept of LTFU and retention was retained which was a modified version of EWI 3a.</td>
</tr>
<tr>
<td>4a. Percentage of ART patients picking up all prescribed ARV drugs on-time (baseline + 2 consecutive pick-ups)</td>
<td>≥90%</td>
<td>• Cross sectional, can be after any period of time on ART</td>
<td>Retain with changes</td>
<td>Percentage of patients (adult or paediatric) that pick-up ART no more than two days late at the first pick-up after baseline pick-up</td>
<td>• Red &lt;80% • Amber 80–90% • Green &gt;90% • Paediatric target identical to adult</td>
<td>• Cross-sectional • Modify definition from baseline + 2 pick-up to baseline + 1 pick-up • If no routine remnant pill count performed routinely at the site, use total quantity dispensed. If remnant count recorded, remnant pill data are captured and accounted for in calculation • Data abstraction for on-time pill pick-up integrated into data abstraction for the EWI assessing dispensing practices • If paediatric liquid formulation only the total volume dispensed is assessed. Amount of remnant liquid is not taken into account when calculating this indicator for children • Sampling strategy – calculate minimum sample size based on existing 2010 EWI sample size guidance • EWI assessing pharmacy dispensing practices is a sub-analysis of data obtained for this indicator. Specifically the baseline regimen dispensed is assessed for being a triple drug regimen</td>
</tr>
<tr>
<td>Current EWI number and definition</td>
<td>Current EWI target</td>
<td>Key points about current EWI</td>
<td>Retain or exclude</td>
<td>Proposed new EWI</td>
<td>Proposed new target</td>
<td>Key Points about EWI changes</td>
</tr>
<tr>
<td>----------------------------------</td>
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<td>-----------------------------</td>
<td>-------------------</td>
<td>-----------------</td>
<td>--------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>4b. Percentage of patients initiating ART at the site who picked up all prescribed ARV drugs on-time during their first 12 months of ART</td>
<td>≥90%</td>
<td>NA</td>
<td>Exclude</td>
<td>NA</td>
<td>NA</td>
<td>• EWI 4b was excluded based on working group discussion. Only one indicator reflecting adherence to ART was retained: a modified version of EWI 4a</td>
</tr>
<tr>
<td>5a. Percentage of ART patients who attend clinical consultations within 7 days of scheduled or expected consultation (baseline and 2 consecutive consultation)</td>
<td>≥80%</td>
<td>Cross sectional, can be after any period of time on ART</td>
<td>Exclude</td>
<td>NA</td>
<td>NA</td>
<td>• EWI 5a and 5b were excluded. These EWIs provide information redundant with EWI 4 and there was a lack of strong evidence between attendance at clinical consultations and HIVDR</td>
</tr>
<tr>
<td>5b. Percentage of patients initiating ART who attended all clinical consultations within 7 days of scheduled or expected consultation during the first 12 months of ART</td>
<td>≥80%</td>
<td>NA</td>
<td>Exclude</td>
<td>NA</td>
<td>NA</td>
<td>• EWI 5a and 5b were excluded. These EWIs provide information redundant with EWI 4 and lack of strong evidence between attendance at clinical consultations and HIVDR</td>
</tr>
<tr>
<td>6a and 6b. Percentage of months in a designated year in which there were no ARV drug stock-outs (at the level of the clinic dispensary)</td>
<td>100%</td>
<td>6b same as 6a except additional calculations can be made using collected data (e.g. total stock-out days in a period, longest period of stock-out)</td>
<td>Retain 6a without changes. Exclude 6b</td>
<td>Percentage of months in a designated year in which there were no ARV drug stock-outs</td>
<td>• 100%</td>
<td>• Paediatric target identical to adult</td>
</tr>
<tr>
<td>6c1. Percentage of patients whose regimen was stopped, switched, substituted or incompletely dispensed due to ARV stock-out in a 12-month period</td>
<td>0%</td>
<td>Relies on individual patient data</td>
<td>Exclude</td>
<td>NA</td>
<td>NA</td>
<td>• EWI 6c was excluded as only one indicator reflecting the concept of Pharmacy Stock-outs was retained which was a EWI 6a</td>
</tr>
<tr>
<td>Current EWI number and definition</td>
<td>Current EWI target</td>
<td>Key points about current EWI</td>
<td>Retain or exclude</td>
<td>Proposed new EWI</td>
<td>Proposed new target</td>
<td>Key Points about EWI changes</td>
</tr>
<tr>
<td>----------------------------------</td>
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<td>-----------------------------</td>
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<td>-----------------------------</td>
</tr>
<tr>
<td>6c2. Percentage of patients whose regimen was stopped, switched, substituted or incompletely dispensed due to ARV stock-out during the first 12-months of ART</td>
<td>0%</td>
<td>• Relies on individual patient data</td>
<td>Exclude</td>
<td>NA</td>
<td>NA</td>
<td>• EWI 6c2 was excluded as only one indicator reflecting the concept of Pharmacy Stock-outs was retained which was a EWI 6a</td>
</tr>
<tr>
<td>7a. Percentage of patients initiating ART at the site who demonstrate 100% adherence by pill count</td>
<td>≥90%</td>
<td>• Only monitored by one country</td>
<td>Exclude</td>
<td>NA</td>
<td>NA</td>
<td>• EWI 7 was excluded based on the decision to retain only one indicator monitoring adherence. A modified version of EWI 4a was retained. Additionally there has been minimal uptake of this EWI to this time</td>
</tr>
<tr>
<td>7b. Percentage of patients initiating ART at the site who demonstrate 100% adherence by standardized adherence measure</td>
<td>≥90%</td>
<td>• Only monitored by one country</td>
<td>Exclude</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>8. Percentage of patients initiating ART at the site whose viral load is &lt;1000 copies/ml after 12 months of ART</td>
<td>≥70%</td>
<td>• Excludes transfers out from denominator (therefore includes LTFU, death, stop, switch) • An intention to treat (per protocol) analysis</td>
<td>Retain with changes</td>
<td>Percentage of patients receiving ART at the site after the first 12 months of ART whose viral load is &lt;1000 copies/ml</td>
<td>Adult</td>
<td>• Red &lt;70% • Amber 70–85% • Green &gt;85% Children &lt;2 yrs</td>
</tr>
</tbody>
</table>

NA = Not applicable.
<table>
<thead>
<tr>
<th>EWI</th>
<th>EWI definition</th>
<th>Definition of numerator and denominator</th>
<th>Target</th>
<th>Key points</th>
</tr>
</thead>
</table>
| 1. On-time pill pick-up | Percentage of patients (adult or paediatric) that pick-up ART no more than two days late at the first pick-up after the baseline pick-up | Numerator: Number of patients picking up their ART “on time” at the first drug pick-up after baseline pick-up date  
Denominator: number of patients who picked up ARV drugs on or after the designated EWI sample start date.  
Sampling continues until the full sample size is reached  
“on time” as it relates to pill pick-up is defined as a patient picking up their ART within 2 days of their previous prescription running out if taken according to schedule | Red <80%  
Amber 80–90%  
Green >90%  
Paediatric targets same as adults | Cross-sectional  
Modify definition from baseline + 2 pick-up to baseline + 1 pick-up  
If no routine remnant pill count, use total quantity dispensed.  
If remnant pills recorded then capture remnant pill data and calculate total based on days of remnant pills and days of pills dispensed  
Data abstraction for on-time pill pick-up integrated into data abstraction for prescribing practices  
If paediatric liquid formulation only assess total volume dispensed. Amount of remnant liquid not taken into account  
Sampling strategy – calculate minimum sample size based on existing 2010 EWI sample size guidance |
<table>
<thead>
<tr>
<th>EWI</th>
<th>EWI definition</th>
<th>Definition of numerator and denominator</th>
<th>Target</th>
<th>Key points</th>
</tr>
</thead>
</table>
| 2. Retention in care | Percentage of adults and children known to be alive and on treatment 12 months after initiation of ART | • **Numerator**: Number of adults and children who are still alive and on ART 12 months after initiating treatment  
• **Denominator**: Total number of adults and children who initiated ART who were expected to achieve 12-month outcomes within the reporting period, including those who have died since starting therapy, those who have stopped therapy, and those recorded as lost to follow-up at month 12 | • Red <75%  
• Amber, 75–85%  
• Green >85%  
• Paediatric targets same as adult | • Same as UNGASS #24 / PEPFAR #T1.3.D / Global Fund Impact #HIV-I3 definition of retention  
• Denominator excludes transfers out  
• Now includes children; no suggested separate paediatric EWI  
• Sampling strategy – Census of all patients at site (consistent with UNGASS / PEPFAR)  
• UNGASS/PEPFAR indicator for retention reported biannually. In non-UNGASS reporting years this indicator is “not applicable” and sites receive a “white” score. If the result is available at the site without additional data abstraction (WHO does not provide a data abstraction tool for this indicator) it may be reported and scored as green, amber, or red  
• Target permits statement about HIVDR in relation to this widely reported indicator |
| 3. Pharmacy stock-outs | Percentage of months in a designated year in which there were no ARV drug stock-outs | • **Numerator**: Number of months in the designated year in which there were no stock-out days of any ARV drug routinely used at the site  
• **Denominator**: 12 months | • 100%  
• Paediatric targets same as adult | • Drug stock out assessed at the level of ART clinic dispensary |
<table>
<thead>
<tr>
<th>EWI</th>
<th>EWI definition</th>
<th>Definition of numerator and denominator</th>
<th>Target</th>
<th>Key points</th>
</tr>
</thead>
</table>
| 4. Dispensing practices | Percentage of adults and children prescribed or picking up mono or dual ARV therapy | • **Numerator**: number of patients who pick-up from the pharmacy, a regimen consisting of one or two ARVs  
• **Denominator**: number of patients picking up ART on or after the designated EWI sample start date. Sampling continues until the full sample size is reached. | • 0%  
• Paediatric targets same as adult | • Cross sectional and after any period of time on ART  
• Will incorporate data collection with on-time pill pick-up EWI (newly recommended EWI 1)  
• Sampling strategy – calculate minimum sample size based on 2010 WHO HIVDR EWI guidance  
• Sample the same as for on-time pill pick-up EWI with information abstracted about baseline pick-up assessed to determine dispensing practices |
| 5. Virological suppression | Percentage of patients receiving ART at the site after the first 12 months of ART whose viral load is <1000 copies/ml | • **Numerator**: number of patients receiving ART at the site after the first 12 months of ART whose viral load is <1000 copies/ml  
• **Denominator**: number of patients at the site who by national policy should have had a viral load performed 12 months after ART initiation | Adult and paediatric >2 yrs  
• Red <70%  
• Amber 70–85%  
• Green >85%  
Paediatric ≤2 yrs  
• Red <60%  
• Amber 60–70%  
• Green >70% | • Modify definition to on treatment from intention to treat analysis  
• Intended only for countries performing routine viral load testing  
• Sample size is census of all patients at site 12 months after ART initiation  
• Sites using dried blood spots (DBS) for viral load testing, absence of amplification in an assay with successful positive and negative controls is considered to be undetectable |
EWI 1 – PRESCRIBING PRACTICES

1. DESCRIPTION OF CURRENT EWI AND RECOMMENDED TARGET

<table>
<thead>
<tr>
<th>Percentage of adult patients initiating ART at the site who are initially prescribed, or who initially pick-up from the pharmacy, an appropriate* first-line ART regimen (cross-sectional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suggested target: 100%</td>
</tr>
</tbody>
</table>

**Definition of numerator and denominator:**
- **Numerator:** number of adult patients initiating ART at the site who are prescribed, or who initially pick-up from the pharmacy, an appropriate first-line ART regimen.
- **Denominator:** number of adult patients initiating ART at the site on or after the designated EWI sample start date. Sampling continues until the full sample size is reached.

* An ART regimen that meets one or both of the following definitions is considered appropriate: 1) Standard regimen listed in national ART guidelines and used according to those guidelines or 2) A regimen recommended in the WHO treatment guidelines.

2. REVIEW OF THE STRENGTH OF ASSOCIATION BETWEEN CURRENT INDICATOR AND OCCURRENCE OF HIVDR

- EWI 1 assesses ART provider compliance with prescribing standard first-line regimens according to national or WHO treatment guidelines. Standard recommended first-line regimens contain three drugs (two nucleoside reverse transcriptase inhibitors in combination with one non-nucleoside reverse transcriptase inhibitor). The intention of the indicator is to identify the prescribing of mono- or dual drug regimens (specifically mono- or dual- NRTI regimens or one NRTI in combination with an NNRTI) known to be associated with selection of drug resistant HIV.

- Initial studies of antiretroviral monotherapy reported reductions in levels of circulating HIV in patients participating in clinical trials of the NRTI zidovudine in the late 1980s (4) and subsequently protease inhibitors (PIs) in the mid-1990s (5). Despite these observations, subsequent elevations in HIV viral load and the selection of HIVDR (6) were observed in patients receiving monotherapy; thus stimulating investigation of combination ART. Randomized clinical trials of different ARV combinations reported the virological and clinical superiority of double NRTIs over NRTI monotherapy (7), and subsequently the combination of three drugs, including either a PI or an NNRTI, over double NRTI regimens (8–10). Data from Cote d’Ivoire, where double-NRTI regimens were initiated in some patients due to the higher cost of triple ARV regimens, demonstrate inferior virological efficacy of double-NRTI regimens (11). The evidence that HIVDR is closely associated with the prescription of single-drug and two-drug ART is supported by a large number of prospective randomized studies.

- The current indicator is strongly associated with HIVDR with high quality evidence; however, ambiguity of this indicator definition, as discussed below, has led to misclassification of sites as providing regimens which select for HIVDR when in reality fully active triple drug regimens were being provided.
3. REVIEW OF CURRENT TARGET

- The current target for this indicator is 100%. This target is appropriate as there is no scientific or medical reason for a patient to be prescribed mono or dual therapy.

4. BENEFITS AND RISKS

- The current definition of prescribing practices (Table 7) defines an “appropriate first-line regimen” as a first-line regimen listed in national or international guidelines. Ambiguity in interpretation of the definition has led to classification of “inappropriate prescribing” at sites prescribing PIs in combination with 2 NRTIs as first-line regimens; however, the use of this regimen does not unduly predispose to selection of HIVDR. Additionally, examples have been reported of sites being classified as having prescribed inappropriate regimens in cases where tenofovir was available and substituted for zidovudine or stavudine as part of an NNRTI-based regimen (12). Therefore to avoid the risk of misclassification, it was recommended that this EWI be reformulated to assess the dispensing of mono or dual drug regimens by pharmacies.

5. ACCEPTABILITY AND FEASIBILITY

- Assessment of prescribing or dispensing practices has proven feasible with data abstracted from routine clinical and medical records.

6. COST CONSIDERATIONS

- Cost has proven minimal for this indicator as it is calculated using data which can be abstracted from routine medical and pharmacy records.

7. SUGGESTED WORDING OF NEW INDICATOR

- Given the strength of association between mono or dual drug regimens and HIVDR and the fact that monitoring of this indicator is acceptable and feasible, it was recommended to retain an indicator which assesses prescribing practices. However, changes were introduced to the indicator to avoid ambiguity posed by the definition of “appropriate” and to prevent misclassification of alternative triple drug regimens, including PI containing regimens. The original EWI assessed provider compliance with national guidelines rather than whether patients were receiving regimens likely to select for drug resistant HIV. However, reviewers concluded that what providers were prescribing was less relevant to selection of HIVDR than was actually being dispensed at pharmacies. The indicator was therefore redefined as pharmacy dispensing practices. The change was also made to facilitate abstraction of this indicator from routine pharmacy records, which have proven more robust than individual patient records or clinic logs. Additionally, the change to pharmacy dispensing practices permitted this indicator to be a sub-analysis of the newly reformulated indicator assessing on-time pill pick-up.
• The new pharmacy dispensing practice indicator is defined as percentage of adults (or children) picking up a mono or dual-drug regimen (performed as a sub-analysis of the reformulated on-time pill pick-up indicator; Table 8). The revised indicator is cross sectional in nature and is intended to assess pharmacy dispensing practices for populations on ART after any period of time on ART (including patients receiving second-line ART). While the previous version of EWI 1 assessed prescribing practices only for new ART initiators, the new version will provide needed data for all patients on ART. Because this new indicator is measured in a sub-analysis of data abstracted for "on-time pill pick-up," it does not require a separate data abstraction process, which will facilitate implementation of this EWI. Previous EWI guidance provided for abstraction from patient medical records and not pharmacy records.

• The new indicator assess the percentage of adults and children being dispensed mono or dual ARV therapy
  » Numerator: number of patients who pick up from the pharmacy, a regimen consisting of one or two ARVs
  » Denominator: number of patients picking up ART on or after the designated EWI sample start date.

8. STRENGTH OF RECOMMENDATION (HIGH, MODERATE, LOW, VERY LOW)
• Strong recommendation with high quality evidence and strong association between new indicator and HIVDR.

9. SUGGESTED TARGET FOR REVISED EWI
• The suggested target for the newly formulated pharmacy dispensing practice indicator is binary. Because this indicator is so strongly associated with HIVDR and there is no medical reason to prescribe a mono or dual drug regimen, poor performance (red) is defined as >0% and desirable performance (green) is defined as 0%.
EWI 2 – LOST TO FOLLOW-UP AT 12 MONTHS

1. DESCRIPTION OF CURRENT EWI AND RECOMMENDED TARGET

<table>
<thead>
<tr>
<th>Percentage of patients initiating ART at the site who are lost to follow-up 12 months after ART initiation (cohort)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Suggested target:</strong> ≤20%</td>
</tr>
</tbody>
</table>

**Definition of numerator and denominator:**
- **Numerator:** number of patients initiating ART at the site who, during the first 12 months after ART initiation, did not attend a clinical consultation and did not pick-up ARV drugs within 90 days (≤90 days) after the date of their last missed appointment, or within 90 days (≤90 days) after the last ART run-out date.
- **Denominator:** number of patients initiating ART at the site on or after the designated EWI sample start date. Sampling continues until the full sample size is reached.

2. REVIEW OF THE STRENGTH OF ASSOCIATION BETWEEN CURRENT INDICATOR AND OCCURRENCE OF HIVDR

- Individuals who have become lost to follow-up LTFU have unknown treatment outcomes and may be divided into three general categories: unreported deaths, unknown transfer of care to a different facility without documentation, and disengagement from care. Specific studies reporting the presence of HIVDR in individuals who were LTFU and subsequently traced were not available. However, several studies report the development of virological failure and HIVDR in individuals receiving NNRTI-based regimens experiencing treatment interruptions of >48 hours (13-15). Interruption of NNRTI-based regimens without continuation of NRTIs selects for NNRTI resistance due to differences in drug half-lives (16). A significant proportion of individuals LTFU are therefore likely to have disengaged from care, experienced treatment interruption and thus be at risk for selection of drug-resistant virus.

3. REVIEW OF CURRENT TARGET

- Seventy-five cohorts (n=295,067 patients) were identified that provided an estimate of LTFU as part of the systematic review. A median estimate of 11.0% LTFU and weighted mean 15.3% LTFU were calculated. A separate analysis focusing on 32 cohorts with a definition of LTFU most similar to the EWI definition revealed a median 10.0% LTFU and weighted mean 12.1% LTFU.

- Current normative rates of LTFU are lower than the current EWI target.

4. BENEFITS AND RISKS

- Assessment of LTFU has proven feasible with data abstracted from routine clinical and medical records.
5. ACCEPTABILITY AND FEASIBILITY

- Assessment of LTFU has proven feasible with data exploited from routine medical and pharmacy records.

6. COST CONSIDERATIONS

- Cost has proven minimal for this indicator as it is easily calculated using data which can be abstracted from routine medical and pharmacy records.

7. SUGGESTED WORDING OF NEW INDICATOR

- Given significant overlap of the LTFU indicator and the indicator assessing retention at 12 months (see below), it was recommended that the LTFU indicator be dropped.

8. STRENGTH OF RECOMMENDATION (HIGH, MODERATE, LOW, VERY LOW)

- The indicator assessing LTFU was dropped from the new indicator set for the reasons stated above.

9. SUGGESTED TARGET FOR REVISED EWI

- No suggested wording.
**EWI 3 – RETENTION ON ART AT 12 MONTHS**

### 1. DESCRIPTION OF CURRENT EWI AND RECOMMENDED TARGET

- There are two versions of this indicator: A and B.

#### 3A. Percentage of adult patients initiating ART at the site who are taking an appropriate* first-line ART regimen 12 months later (cohort)

**Suggested target:** ≥70%

**Definition of numerator and denominator:**
- **Numerator:** number of adult patients initiating ART at the site who are on an appropriate first-line ART regimen (including substitutions of one appropriate first-line regimen for another) 12 months after ART initiation.
- **Denominator:** number of adult patients initiating ART at the site on or after the designated EWI sample start date. Sampling continues until the full sample size is reached.

#### 3B. Percentage of patients initiating ART at the site whose initial ART regimen was changed during the first 12 months to a regimen that includes a different drug class (cross-sectional)

**Suggested target:** 0%

**Definition of numerator and denominator:**
- **Numerator:** number of patients initiating ART at the site whose initial ART regimen was changed to a regimen that includes a different drug class during the first 12 months after ART initiation (including switches for regimen failure and substitutions for toxicity).
- **Denominator:** number of patients initiating ART at the site on or after the designated EWI sample start date. Sampling continues until the full sample size is reached.

* An ART regimen that meets one or both of the following definitions is considered appropriate; 1.) Standard regimen listed in national ART guidelines and used according to those guidelines or 2.) A regimen recommended in the WHO treatment guidelines

### 2. REVIEW OF THE STRENGTH OF ASSOCIATION BETWEEN CURRENT INDICATOR AND OCCURRENCE OF HIVDR

- As noted above (EWI 2) there is a close relationship between retention at an ART site and LTFU; thus, monitoring the number of patients retained on ART is important to understand the proportion of individuals potentially dying or experiencing treatment interruptions.

- Unplanned treatment interruptions of >48 hours for patients receiving NNRTI-based regimens in observational studies have been reported to predict virological rebound and the development of HIVDR in both LMICs and HICs (13,14).

- The systematic review identified 83 cohorts, none obtained from clinical trials, where an estimate of patient retention at 12 months could be determined. The minimum requirement for this estimation was the reporting of the proportion that had died and become LTFU. The review (Appendices 5 and 6) details the different methods that were used to estimate patient retention as per the original EWI definition (a) and the commonly used retention definitions
of the Presidents Emergency Plan for AIDS Relief (PEPFAR) and United Nations General Assembly Special Session (UNGASS). Considering different possible definitions of retention from the available data, mean or normative retention ranged from 75-80% after 12 months of ART. An understanding of mean levels of retention formed the basis for target setting by the working group.

3. REVIEW OF CURRENT TARGET

• Different definitions of retention were considered as part of the systematic review. When considering the most inclusive analysis of the 83 identified cohorts (n=535,438) which accepts any reported definition of retention after 12 months of ART the median estimate of retention was 77.7% and weighted mean 77.1%. When limiting the analysis to the 14 cohorts (n=17,908) reporting transfer-out data, the median proportion retained is 71.1% and weighted mean 73.1% when individuals transferred out are considered not retained. If we consider that the EWI and alternative definitions of retention (PEPFAR/UNGASS) exclude individuals who transfer out then this would lead to an upward revision of the retention estimate to approximately 79% individuals retained after 12 months of ART.

• Normative levels of retention in the region of 75-80% after 12 months of ART formed the basis of the lower boundary of the revised target.

4. BENEFITS AND RISKS

The working group determined that while the evidence of a link between HIVDR and retention was less strong than the evidence for other indicators, sufficient evidence related to treatment interruption for NNRTI-based regimens (first-line ART) suggests that patients not retained are at risk for selection of HIVDR due to treatment interruption. Moreover, assessment of retention is easily achieved using routinely collected data and is a commonly reported WHO/UNGASS and PEPFAR indicator.

5. ACCEPTABILITY AND FEASIBILITY

• The working group noted that data on retention are commonly collected in LMICs using the UNGASS/PEPFAR definition. Thus, it was recommended that the UNGASS/PEPFAR definition of retention be adopted as an EWI due to its wide acceptance and feasibility.

• In formulating and including this revised EWI, importance was placed on simplifying indicators on LTFU and retention to a single indicator that was the same as the commonly used retention indicators of UNGASS and PEPFAR. By using the UNGASS/PEPFAR indicator and assigning an appropriate HIVDR target, this indicator can be widely scaled-up with additional site-level data abstraction.

• A separate retention indicator for paediatric patients was deemed unnecessary
6. COST CONSIDERATIONS

- Cost has proven minimal for this indicator as it is calculated using data which can be easily abstracted from routine medical and pharmacy records. Many ART sites can be expected to routinely report retention rates to Ministries of Health and international agencies; therefore, considerably fewer resources are required to abstract these data than in the original EWI, which is anticipated to facilitate uptake.

7. SUGGESTED WORDING OF NEW INDICATOR

- Percentage of adults and children known to be alive and on treatment 12 months after initiation of ART
  - **Numerator:** Number of adults and children who are still alive and on ART 12 months after initiating treatment.
  - **Denominator:** Total number of adults and children who initiated ART who were expected to achieve 12-month outcomes within the reporting period.

- The denominator excludes transfers out.

- The indicator includes children, there is now no separate paediatric EWI.

- Sampling strategy: Census of all patients at site (consistent with UNGASS / PEPFAR). The revised EWI is identical to UNGASS #24 / PEPFAR #T1.3.D / Global Fund Impact #HIV-I3. Sites reporting UNGASS#24 / PEPFAR #T1.3.D / Global Fund Impact #HIV-I3 need not abstract additional data.

- UNGASS reporting cycle is biannual. In non-UNGASS reporting years this indicator is not reportable and clinics receive a score of “white” signalling its non-applicability in that year. However, if this result is known at the clinic without additional data abstraction, it may be reported and scored as green, amber, or red.

8. STRENGTH OF RECOMMENDATION (HIGH, MODERATE, LOW, VERY LOW)

- Strong recommendation (as this indicator is already routinely reported) despite low/moderate quality of evidence.

9. SUGGESTED TARGET FOR REVISED EWI

- The working group suggests a target with three classifications for the new patient retention EWI:
  - Poor Performance (Red) <75%
  - Fair Performance (Amber) 75–85%
  - Desirable Performance (Green) >85%
EWI 4 – ON-TIME PILL PICK-UP

1. DESCRIPTION OF CURRENT EWI AND RECOMMENDED TARGET

• There are two versions of this indicator: A and B.

<table>
<thead>
<tr>
<th>4A. Percentage of patients who picked up prescribed antiretroviral (ARV) drugs on-time (cross-sectional)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Suggested target:</strong> ≥90%</td>
</tr>
<tr>
<td><strong>Definition of numerator and denominator:</strong></td>
</tr>
<tr>
<td>• <strong>Numerator:</strong> number of patients who have picked up all their prescribed ARV drugs on-time for two consecutive drug pick-ups after a baseline pick-up.</td>
</tr>
<tr>
<td>• <strong>Denominator:</strong> number of patients who picked up ARV drugs on or after the designated EWI sample start date. Sampling continues until the full sample size is reached.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4B. Percentage of patients initiating ART at the site who picked up all prescribed ARV drugs on-time during their first 12 months of ART (cohort)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Suggested target:</strong> ≥90%</td>
</tr>
<tr>
<td><strong>Definition of numerator and denominator:</strong></td>
</tr>
<tr>
<td>• <strong>Numerator:</strong> number of patients initiating ART at the site who picked up all their ARV drugs on-time during the first year of ART, or until they were classified as transferred out, dead, or as having stopped ART.</td>
</tr>
<tr>
<td>• <strong>Denominator:</strong> number of patients initiating ART at the site on or after the designated EWI sample start date. Sampling continues until the full sample size is reached</td>
</tr>
</tbody>
</table>

2. REVIEW OF THE STRENGTH OF ASSOCIATION BETWEEN CURRENT INDICATOR AND OCCURRENCE OF HIVDR

• On-time pill pick-up is considered a pharmacy adherence measure (PAM), an objective prescription- or pill-based adherence estimate calculated using dates of prescription refills and/or pill counts performed during routine clinic visits (1). Three studies were found reporting associations between PAMs and HIVDR (17-19). A recent observational study from Cote d’Ivoire of patients initiating NNRTI-based regimens reported that subjects with detectable VL and HIVDR had lower median adherence as measured by PAMs compared to those achieving virological suppression (17). Two North American studies (one observational (18), one randomized control trial (19)) found that pharmacy adherence of 75-90% had the strongest association with development of HIVDR; however, the relevance of these studies was limited by their exclusive (19) or majority (18) focus on non-boosted PI-based regimens where different adherence resistance relationships are observed (20).

• Additional studies using other adherence measures (self report, unannounced pill count) have reported an association with HIVDR (21,22). A prospective study by Bangsberg et al. (21) reported findings by regimen type; for NNRTI-based regimens, decreasing levels of adherence were associated with increasing proportions of individuals with NNRTI resistance. This finding
is consistent with a multivariate analysis in a population receiving NNRTI-based regimens in Cote d’Ivoire which noted increasing odds of HIVDR as the level of adherence decreased (17). In addition to the proportion of time patients are adherent, two previously-cited studies found that the pattern of adherence for those on NNRTI-based regimens is also important (13,14).

3. REVIEW OF CURRENT TARGET

- The current EWIs for on-time ARV pick-up require patients to pick up pills on time (on or before the date on which the previous prescription would run out if taken according to directions). Alternatively this can be stated as 100% adherence when using a PAM such as the medication possession ratio. Therefore, when performing the systematic review, studies were reviewed to determine the proportion of individuals 100% adherent. Despite many studies being identified that reported a pharmacy measure of adherence only 4 studies were identified reporting a proportion 100% adherent in a cross sectional analysis (similar to EWI A) and only 3 studies reporting a proportion 100% adherent over the first 12 months of ART (similar to EWI B). These studies report 40–60% of subjects with 100% adherence in cross section and 12–28% of patients with 100% adherence in the first year. A post-hoc analysis identified 11 studies reporting 50–90% of patients having >95% adherence in cross section and 4 studies reporting 37–87% of patients being >95% adherent over the first 12 months of ART.

4. BENEFITS AND RISKS

- The evidence on the importance of adherence in the development of HIVDR makes this indicator highly beneficial. There are potential risks in managing data issues related to remnant ART at the time of baseline pick-up, which must be addressed.

- Adherence calculations based only on ART that is dispensed would not accurately reflect the days of ART the patient possesses if they have a remnant ART stock. To deal with this potential risk, if data on remnant pills are available and recorded in a standardized fashion at the clinic pharmacy then the total amount of ART is calculated based on days of remnant pills and days of pills dispensed. In the case of paediatric liquid formulae, it is recommended to only assess total volume dispensed and not to take into account remnant liquid. Notably it is difficult to measure remnant volumes of liquid accurately and it is common practice to discard remnant liquid, often due to issues with more rapid expiry of liquid ART compared to pills.

5. ACCEPTABILITY AND FEASIBILITY

- Despite the modest uptake of this indicator compared to other indicators, in most settings monitoring of this indicator is feasible using existing pharmacy and patient medical records.
6. COST CONSIDERATIONS
• The incorporation of an EWI that combines both revised cross-sectional on-time pill pick-up and dispensing practices will mean fewer human and financial resources are required to collect these data.

7. SUGGESTED WORDING OF NEW INDICATOR
• This indicator was retained but in a simplified format that assesses pick-ups of ART in a cross-section over a shorter period of time (Baseline + 1 pick-up). This should allow for an assessment of adherence that can be more easily performed and implemented in a range of settings.

• The drug regimen dispensed by the pharmacy for this indicator will be analyzed to ensure triple drug combination (pharmacy dispensing practices, as detailed above).

• The revised definition of this indicator is the proportion of patients (adult or paediatric) that pick up ART no more than two days late at the first pick-up after the baseline pick-up.
  » **Numerator:** Number of patients picking up their ART “on time” at the first drug pick-up after baseline pick-up date.
  » **Denominator:** number of patients who picked up ARV drugs on or after the designated EWI sample start date.
  » “On time” as it relates to pill pick-up is defined as a patient picking up their ART within 2 days of their previous prescription running out if taken according to schedule.

8. STRENGTH OF RECOMMENDATION (HIGH, MODERATE, LOW, VERY LOW)
• Multiple observational studies have documented the association between increasing levels of adherence and the decreased risk of HIVDR, particularly with NNRTI-based regimens which are commonly used in LMICs. Moderate evidence, strong recommendation.

9. SUGGESTED TARGET FOR REVISED EWI
A three-tiered target for the revised on-time pill pick-up EWI was suggested. The proportion of patients that pick-up ART no more than two days late at the first pick-up after the baseline pick-up:
• Poor Performance (Red) <80%
• Fair Performance (Amber) 80–90%
• Desirable Performance (Green) >90%
EWI 5 – ON-TIME CLINICAL APPOINTMENT KEEPING

1. DESCRIPTION OF CURRENT EWI AND RECOMMENDED TARGET
   - There are two versions of this indicator: A and B.

   **5A. Percentage of ART patients who attend clinical consultations on-time* (cross-sectional)**
   **Suggested target:** ≥80%
   **Definition of numerator and denominator:**
   - **Numerator:** number of patients who attended two consecutive scheduled or expected clinical consultations, after a baseline consultation, on time.
   - **Denominator:** number of patients who attended a clinical consultation on or after the designated EWI sample start date. Sampling continues until the full sample size is reached.

   **5B. Percentage of patients initiating ART at the site who attended all scheduled or expected clinical consultations on-time* during the first 12 months of ART (cohort)**
   **Suggested target:** ≥80%
   **Definition of numerator and denominator:**
   - **Numerator:** number of patients initiating ART at the site who attended all their scheduled or expected clinical consultations on time during their first 12 months of ART, or until they were classified as transferred out, dead, or as having stopped ART.
   - **Denominator:** number of patients initiating ART at the site on or after the designated EWI sample start date. Sampling continues until the full sample size is reached.

   * On-time is defined as within 7 days of the scheduled clinical appointment.

2. REVIEW OF THE STRENGTH OF ASSOCIATION BETWEEN CURRENT INDICATOR AND OCCURRENCE OF HIVDR
   - Despite systematic review of the literature, only two studies and five conference abstracts could be identified that reported on-time clinical appointment keeping of patients receiving ART in LMICs. No studies were found linking appointment keeping with HIVDR, although one study reported an association with late attendance and virological failure (23).

3. REVIEW OF CURRENT TARGET
   - There are limited data to support the current target or to assess its association with HIVDR.

4. BENEFITS AND RISKS
   - Concerns about overlap between on-time pill pick-up and on-time clinical appointment keeping along with the large amount of evidence linking ART-based adherence measures to HIVDR contributed to the working group’s decision to suggest dropping the appointment-keeping EWI.
• Removing EWI 5 simplifies the overall indicator set and is likely to lead to enhanced uptake of EWI monitoring.

5. ACCEPTABILITY AND FEASIBILITY

• The indicator has proven acceptable and feasible to monitor using routine medical records; although, many clinics did not record appointment date so EWI 5 was not possible.

6. COST CONSIDERATIONS

The current indicator is monitored using routine patient medical records but cost/effort considerations led the working group to recommend that it be dropped.

7. SUGGESTED WORDING OF NEW INDICATOR

• Due to very little evidence of association between on-time clinical appointment-keeping and HIVDR, it was recommended that the indicator “on-time clinical appointment-keeping” be dropped.

8. STRENGTH OF RECOMMENDATION (HIGH, MODERATE, LOW, VERY LOW)

• It was recommended that this indicator be dropped due to very poor association between HIVDR and clinical appointment keeping.

9. SUGGESTED TARGET FOR REVISED EWI

• It was recommended that this indicator be dropped.
EWI 6 – PHARMACY STOCK-OUTS

1. DESCRIPTION OF CURRENT EWI AND RECOMMENDED TARGET

- There are four versions of this indicator: A, B, C1, C2

<table>
<thead>
<tr>
<th>EWI 6A. Percentage of months in a designated year in which there were no ARV drug stock-outs (cross-sectional)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Suggested target:</strong> 100%</td>
</tr>
<tr>
<td><strong>Definition of numerator and denominator:</strong></td>
</tr>
<tr>
<td>• Numerator: number of months in the designated year in which</td>
</tr>
<tr>
<td>there were no stock-out days of any ARV drug routinely used</td>
</tr>
<tr>
<td>at the site.</td>
</tr>
<tr>
<td>• Denominator: 12 months.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EWI 6B. Percentage of months in a designated year in which there were no ARV drug stock-outs (cross-sectional)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Suggested target:</strong> 100%</td>
</tr>
<tr>
<td><strong>Definition of numerator and denominator:</strong></td>
</tr>
<tr>
<td>• Numerator: number of months in the designated year in which</td>
</tr>
<tr>
<td>there were no stock-out days of any ARV drug routinely used</td>
</tr>
<tr>
<td>at the site.</td>
</tr>
<tr>
<td>• Denominator: 12 months.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EWI 6C. Percentage of patients on ART whose regimen was stopped, switched, substituted, or incompletely dispensed at the pharmacy due to ARV stock-out in a 12 month period (cross-sectional)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Suggested target:</strong> 0%</td>
</tr>
<tr>
<td><strong>Definition of numerator and denominator:</strong></td>
</tr>
<tr>
<td>• Numerator: number of patients whose regimen was stopped, switched, substituted or</td>
</tr>
<tr>
<td>incompletely dispensed at the pharmacy due to stock-out during a 12-month period, or</td>
</tr>
<tr>
<td>until they were classified as transferred-out, dead, or as having stopped ART.</td>
</tr>
<tr>
<td>• Denominator: number of patients on ART on or after the designated EWI sample start date.</td>
</tr>
<tr>
<td>Sampling continues until the full sample size is reached.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EWI 6C2. Percentage of patients initiating ART at the site whose regimen was stopped, switched, substituted, or incompletely dispensed at the pharmacy due to ARV stock-out during the first 12 months of ART (cohort)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Suggested target:</strong> 0%</td>
</tr>
<tr>
<td><strong>Definition of numerator and denominator:</strong></td>
</tr>
<tr>
<td>• Numerator: number of patients initiating ART at the site whose regimen was stopped,</td>
</tr>
<tr>
<td>switched, substituted, or incompletely dispensed at the pharmacy due to stock-out</td>
</tr>
<tr>
<td>during the first 12 months of ART, or until they were classified as transferred-out,</td>
</tr>
<tr>
<td>dead, or as having stopped ART.</td>
</tr>
<tr>
<td>• Denominator: number of patients initiating ART at the site on or after the designated</td>
</tr>
<tr>
<td>EWI sample start date. Sampling continues until the full sample size is reached.</td>
</tr>
</tbody>
</table>
2. REVIEW OF THE STRENGTH OF ASSOCIATION BETWEEN CURRENT INDICATOR AND OCCURRENCE OF HIVDR

- Monitoring whether sites have a continuous supply of all routinely dispensed ARVs was deemed important particularly considering data linking stock-outs of ART within pharmacies to factors which can predict the development of HIVDR such as treatment interruptions of >48 hrs in LMICs (24).

- Ten studies relevant to this indicator were identified in the systematic review; all but one reported pharmacy stock-outs, with up to 28% of patients being affected by these stock-outs (Appendix 5). While a reporting bias would exist for stock-outs in studies intending to report on this issue, the fact that ARV stock-outs are described in a range of different LMICs raises concern about how this issue may affect the emergence of HIVDR.

3. REVIEW OF CURRENT TARGET

- The current target of 100% of sites having no ARV stock-outs over a 12 month period is considered to reflect desirable performance.

4. BENEFITS AND RISKS

- The working group noted a potential risk that the stock-out indicator lacked the body of evidence linking it to the emergence of HIVDR compared to other indicators such as on-time pill pick-up; however, this concern was outweighed by the potential benefits.

- The working group determined that eliminating alternative stock-out indicators (2010 indicators 6B, 6C1 and 6C2) and focusing on the most feasible indicator capturing the principal of ARV stock-outs would be beneficial. Additionally, the inevitable connection between an ARV stock-out and an unnecessary change in a patient’s ART regimen was considered very important, especially in light of data linking stock-outs to treatment interruptions and poor clinical outcomes.

5. ACCEPTABILITY AND FEASIBILITY

- Assessment of drug supply continuity has proven acceptable and feasible using existing pharmacy stock records.

- Retention of only one of the four stock-out indicators was thought by the working group to enhance acceptance of this indicator. The core principal of pharmacy stock-outs was captured in the original EWI 6A. To harmonize with other retained EWIs the working group propose this be the same 12 month “reporting period” used for the retention and virological suppression indicators (Figure 3). The reporting period is defined as any continuous 12-month period that has ended within a pre-defined number of months from the abstraction of the data. The pre-defined number of months can be determined by national reporting requirements.
6. COST CONSIDERATIONS

- Simplification to a single version of the pharmacy stock-out indicator is a potential cost saving especially compared to the stock-out indicators that required data abstraction from individual patient records.

- Existing pharmacy supply chain management tools support data abstraction of this indicator.

7. SUGGESTED WORDING OF NEW INDICATOR

- Percentage of months in a designated year in which there were no ARV drug stock-outs
  - Numerator: number of months in the designated year in which there were no stock-out days of any ARV drug routinely used at the site.
  - Denominator: 12 months.

8. STRENGTH OF RECOMMENDATION (HIGH, MODERATE, LOW, VERY LOW)

- Strong recommendation, low/moderate level of evidence.

9. SUGGESTED TARGET FOR REVISED EWI

- 100% of sites having no ARV stock-outs over a 12 month period is considered desirable performance. The working group felt that even a single stock-out indicated poor performance for this indicator because it is a reasonable that all ART sites have all routinely dispensed drugs available at all times. For this indicator a binary target with only red and green classifications was recommended. The targets for stock-outs in paediatrics targets were the same as for adults.

- Poor Performance (Red) <100%; Desirable Performance (Green) 100%
1. DESCRIPTION OF CURRENT EWI AND RECOMMENDED TARGET

- There are two versions of this indicator: A and B

<table>
<thead>
<tr>
<th>7A. Percentage of patients initiating ART at the site who demonstrate 100% adherence by pill count (cross-sectional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suggested target: ≥90%</td>
</tr>
<tr>
<td>Definition of numerator and denominator:</td>
</tr>
<tr>
<td>- Numerator: the number of patients who demonstrate that 100% of each of their ARV drugs has been taken as prescribed according to a pill count.</td>
</tr>
<tr>
<td>- Denominator: number of patients initiating ART whose adherence was assessed by pill count performed by a provider or pharmacist, on or before the ‘12-month date’, or until they were classified as transferred-out, dead, or as having stopped ART. Sampling continues of patients initiating ART on or after the EWI sample start date until the full sample size is reached.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7B. Percentage of patients initiating ART at the site who demonstrate 100% adherence by standardized adherence measure (cross-sectional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suggested target: ≥90%</td>
</tr>
<tr>
<td>Definition of numerator and denominator:</td>
</tr>
<tr>
<td>- Numerator: the number of patients who demonstrate that 100% of their ART regimen has been taken as prescribed according to a standardized adherence measure.</td>
</tr>
<tr>
<td>- Denominator: number of patients initiating ART whose adherence was assessed by standardized adherence measure performed by a provider or pharmacist, on or before the ‘12-month date’, or until they were classified as transferred-out, dead, or as having stopped ART. Sampling continues of patients initiating ART on or after the EWI sample start date until the full sample size is reached.</td>
</tr>
</tbody>
</table>

2. REVIEW OF THE STRENGTH OF ASSOCIATION BETWEEN CURRENT INDICATOR AND OCCURRENCE OF HIVDR

- Findings relevant to this indicator were reviewed as part of the review for EWI 4. Pill count measures were not considered separately from other PAMs and any recommendations about using measures of adherence in EWI are encompassed under the new on-time pill pick-up EWI.

- Systematic Reviews were also not performed to encompass all other standardized measures of adherence in addition to PAMs; however, specific studies of interest linking alternate adherence measures to HIVDR were noted in the summary of findings for the on-time pill pick-up EWI.

- Since the introduction of this indicator only one country has monitored this indicator.

- Due to the limited uptake of this EWI, the working group excluded both versions of this EWI.
3. REVIEW OF CURRENT TARGET

• A separate systematic review was not performed for this EWI considering the review already performed for pharmacy adherence measures, of which in-clinic pill counts is one.

• Due to the limited uptake of this EWI and the overlap with the on-time pill pick-up EWI, the working group excluded both versions of EWI 7.

4. BENEFITS AND RISKS

• Given the considerable overlap between this indicator and the on-time ARV pick-up indicator, and the low uptake of this indicator, the benefits of retaining this indicator are negligible. To this point in time meant there was minimal benefit in maintaining this indicator.

5. ACCEPTABILITY AND FEASIBILITY

• Only one country has monitored this indicator. As noted above, pharmacy adherence measures have been shown to be the best population-based measures of adherence and have association with viral load suppression and HIVDR. The working group recommended that this indicator “pill count or standardized adherence measure” be dropped.

6. COST CONSIDERATIONS

• Cost of implementing was considered high. Implementation of this indicator would require change in clinical practice at sites.

7. SUGGESTED WORDING OF NEW INDICATOR

• This indicator was dropped.

8. STRENGTH OF RECOMMENDATION (HIGH, MODERATE, LOW, VERY LOW)

• This indicator was dropped due to lack of feasibility, very low evidence.

9. SUGGESTED TARGET FOR REVISED EWI

• This indicator was dropped.
EWI 8 – VIROLOGICAL SUPPRESSION

1. DESCRIPTION OF CURRENT EWI AND RECOMMENDED TARGET

<table>
<thead>
<tr>
<th>Percentage of patients initiating ART at the site whose viral load is &lt;1000 copies/ml after 12 months of ART (cohort)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Suggested target:</strong> ≥70%</td>
</tr>
</tbody>
</table>

**Definition of numerator and denominator:**
- **Numerator:** number of patients initiating ART at the site who are still taking ART at 12 months and who have a viral load of <1000 copies/ml.
- **Denominator:** number of patients initiating ART at the site on or after the designated EWI sample start date. Sampling continues until the full sample size is reached.

2. REVIEW OF THE STRENGTH OF ASSOCIATION BETWEEN CURRENT INDICATOR AND OCCURRENCE OF HIVDR

- This EWI assesses the proportion of individuals at a site achieving virological suppression 12 months after ART initiation. This EWI has a strong association with HIVDR. Multiple studies were identified reporting HIVDR outcomes after 12 months of ART in LMICs.

- The association between lack of virological suppression and HIVDR is strong. Three randomized control trials report selection of HIVDR in ≥70% patients with virological failure (25–27), with two of the three documenting no HIVDR at ART initiation (26,27). Eight additional studies: three observational studies (28–30) (two with baseline HIVDR status (28,29)) and five cross-sectional studies (31–35) also report HIVDR in significant proportions of patients with virological failure. The quality of evidence linking rates of viral load suppression and rates of virological failure with HIVDR at 12 months was considered high. This is especially true in light of clinical trials where pre-treatment genotyping demonstrated no HIVDR but ≥70% of patients who did not have HIVDR and who had virological failure at 12 months had detected HIVDR.

3. REVIEW OF CURRENT TARGET

- The current target recommends a goal of ≥70% of patients initiating ART at the site should have a viral load <1000 copies/mL after 12 months of ART. This target is for an intention to treat (ITT) analysis that includes individuals who: are LTFU, die, stop ART, and switch ART regimen, and excludes transfers-out from the denominator of the proportion. Summary estimates of ITT analyses from the systematic review at a 1000 copies/mL threshold were median 76% and weighted mean 77% virologically suppressed. The current EWI target of ≥70% of patients achieving virological suppression (ITT at 1000 copies/mL) is below normative levels of virological suppression based on the available literature. Importantly, summary estimates for
virological suppression in on-treatment (OT) analyses using a single viral load test at a 1,000 copies/mL threshold were a median of 84% and weighted mean of 82%.

4. BENEFITS AND RISKS

- Utilizing this EWI for sites or programmes where routine viral load testing is available could offer substantial benefits in understanding the potential for the emergence of HIVDR. Considering the studies in LMICs where HIVDR outcomes were reported, detectable viremia after 12 months of ART represents a significant risk for the presence of HIVDR.

- The simplification of the definition to an “on treatment” classification facilitates data and interpretation of this EWI.

5. ACCEPTABILITY AND FEASIBILITY

- Given that routine viral load testing is not often available in LMICs due to resource or technical constraints the working group agreed that this indicator should only be applied in settings where routine viral load testing is performed on all patients at 12 months. This indicator will be termed a “conditional indicator” and therefore will not appear in the recommended set of HIVDR EWIs as a recommended indicator.

- Importantly, application of this EWI to populations referred for viral load testing or other subgroups would not provide an accurate reflection of virological outcomes and the potential for HIVDR within a site or programme. This indicator should only be performed at sites where all patients routinely receive a viral load 12 months after ART initiation. Operationally, this means that >90% of patients on ART at 12 months must have viral load testing results performed at the clinic for this indicator to be performed. If <90% of patients on ART have viral load testing performed for whatever reason, this indicator should not be performed at the clinic, rather emphasis should be placed on scale-up of viral load testing until such time as ≥90% of patients on ART at the clinic have a viral load test performed as 12 months. When monitoring this indicator, a census of the site population is used. Finally, a 12 month viral load is defined as a viral load test performed 11–15 months after initiation of ART.

- Modifying the definition to include only patients ‘on-treatment’ at 12 months versus the original ‘intention-to-treat’ EWI definition was recommended to simplify the EWI. Furthermore, the additional information about death, LTFU and ART stop reflected by an ‘intention to treat’ indicator will be gathered via the retention EWI.

- A potential barrier to implementing this EWI is the technical and financial burden of performing routine viral load tests on all patients within a site or programme after 12 months of ART. The working group noted that viral load testing was not usual practice in LMICs but due to the importance of viral load testing for understanding the emergence of HIVDR it was included. The issues around cost and feasibility led to the recommendation that this EWI only be performed
in countries and at sites where viral load testing is already routinely performed on all patients 12 months after initiation of ART. As viral load testing is scaled up in LIMCs, it is anticipated that an increasing number of sites will monitor and report this indicator.

6. COST CONSIDERATIONS
Comments regarding the increased cost of viral load testing are noted above; however, if clinics routinely perform viral load testing these data may be abstracted at minimal cost.

7. SUGGESTED WORDING OF NEW INDICATOR
   - Percentage of patients receiving ART at the site after the first 12 months of ART whose viral load is <1000 copies/ml
     - Numerator: number of patients receiving ART at the site after the first 12 months of ART whose viral load is <1000 copies/ml
     - Denominator: number of patients at the site who by national policy should have had a viral load performed 12 months after ART initiation

8. STRENGTH OF RECOMMENDATION (HIGH, MODERATE, LOW, VERY LOW)
   - Conditional recommendation overall. Strong recommendation for sites routinely performing viral load testing on populations 12 months after ART initiation, high quality of evidence

9. SUGGESTED TARGET FOR REVISED EWI
   - Target setting was done by score-carding with the standard of desirable performance for adults being >85% of the on-treatment population virologically suppressed at 12 months. This target was set based on the average proportion of adults in LMICs found to be suppressed at the 1000 copies/mL threshold from the systematic review (Table 6 and Appendix 5). Reported literature on virological outcomes from LMICs likely represents sites with high levels of programme function so setting more stringent targets than current average reported levels of virological suppression was thought to be unrealistic at this time. The stratum for fair performance was 70–84% of adults achieving virological suppression, and sites would be deemed “red” or poor performers if <70% adults were suppressed. While data were more limited in the paediatric population there was sufficient concern about different virological response in children to alter the paediatric targets for children <2 years old. Targets for those ≥2 years old were recommended to be the same as adults. Data concerning children <2 years old suggest that average rates of virological suppression are lower than in adult populations. Several studies documented prolonged periods to virological suppression after ART initiation despite high levels of adherence in children <2 years compared to older children or adults [36–39]. Thus, the level of desirable (green) performance for children <2 years old was >70% virological suppression, the fair (amber) performance stratum was 60–70% virological suppression, and <60% suppression was considered poor (red) performance (Appendix 6).
- Adult target
  - Red <70%
  - Amber 70–85%
  - Green >85%

- Paediatric target stratified: >2 yrs. same as adult and <2 years old as follows:
  - Red <60%
  - Amber 60–70%
  - Green >70%
It has been noted that although 2010 EWI guidance recommended that EWI monitoring be performed at all sites or a large number of representative sites, most countries monitored EWI at sites selected for their convenience. Thus, results are unlikely to be representative of care provided by a national ART programme. The goal that all sites monitor and report EWIs has not changed. However, to support representative sampling as EWI monitoring is being scaled up to all sites, a new primary sampling strategy was recommended. The primary sample (site selection) strategy is discussed fully in Appendix 7. If not all clinics are able to monitor EWIs a sample which is representative of different models of care within the national ART programme is chosen. The sample is spatially representative and is developed based on an organogram delineating fixed effects of the national ART programme.

- **Sampling strategy for selection of sentinel ART clinics**
  - If not all sites in a national ART programme are monitoring and reporting EWIs a sample representative of care provided by the national ART programme should be used. This may be achieved by selection of sentinel sites (Appendix 8). Sentinel sites are selected based on different models of care delivery (primary, secondary, tertiary) and should be further classified by other fixed effects which may include geographic location (rural/urban), available resources, and size of clinic (provider-patient ratio).
  - Different models of care delivery are depicted in an example organogram (Figure 2) and form the basis for selecting these representative or sentinel sites. Sites are selected to include at least one site from each level of care delivery. Additional sites are selected with the probability of inclusion approximately proportional to the number of sites at each level of care delivery. Sampling continues with sites sampled from each node until the maximum number of sites feasible for a given year is reached. It is anticipated that countries will aim to have all sites reporting HIVDR EWIs annually after a period of scale-up. Countries should develop their own ART programme organogram based on fixed effects within their national programme. Countries are actively encouraged to seek WHO technical assistance when preparing organograms defining fixed programme effects to maximize representative of data.
Notes:
ART clinics within the national ART programme are categorized based on fixed and programmatic factors which represent distinguishing features of the clinic. In this organogram, a fixed factor is clinic geographic location (urban versus rural) and programmatic factors are the level of specialization. The models of care delivery are indicated by shaded boxes. This figure is provided for example purposes only.
EWI DATA ABSTRACTION AND TIMELINE OF SAMPLING FOR REVISED HIVDR EWIs

- WHO is developing a revised Excel tool to facilitate EWI data abstraction (Appendix 9). The working group recommends that data abstraction is performed by ART clinic staff with local supervision with results reported annually to the national ART program. This is a significant change from previous practice where EWI data were abstracted by data managers or epidemiologists from the central level. It is anticipated that this change will greatly facilitate widespread monitoring and reporting of HIVDR EWIs in LMICs.

- To achieve EWI results which are related to the clinic population in care at the time of the data "abstraction date" the working group recommended a sampling timeframe Figure 3.

- The timeline for sampling patients for EWIs is based around a 12-month "reporting period" required for the retention, viral load suppression and drug stock-out indicator. The term "reporting period" was chosen as it is the same terminology used by both PEPFAR and UNGASS indicators of retention in care after 12-months ART.

- Assessment of on time pill pick-up and prescribing practices occurs over a period of time that allows a site to cross-sectionally abstract data on a baseline ART pick-up and 1 subsequent pick-up. In this case the EWI sampling starts with the first patient picking up ART at the pharmacy. Data are subsequently abstracted on consecutive patients until the required sample size is achieved.

- As most individuals receiving ART in LMICs pick-up ART every 1–2 months it is anticipated that the EWI sample start date would occur approximately 3 months prior to the end of the 12-month reporting period to allow data to be captured from a baseline ART pick-up and 1 subsequent pick-up on the required sample size.
Notes:
1. Date prior to end of reporting period that allows time for the collection of data for on-time pill pick up and prescribing practices EWIs (e.g., 2–3 months prior to end of reporting period).
2. Individuals initiating ART in this period will constitute outcomes for retention and virological suppression EWIs 12 months after ART initiation.
DISCUSSION

• The proposed revised set of EWIs (Table 8) builds on the strengths of the original EWIs while focusing on site-based factors that have the strongest link to the emergence of preventable HIVDR. Key considerations in this revision include harmonizing EWIs with indicators recommended by other agencies, consolidating EWIs to maximize the efficiency of data collection and selection of EWIs closely associated with HIVDR. Like the original EWI set, revised EWIs provide data for public health action to minimize HIVDR.

• Important distinctions between the original and revised EWIs include the change from eight EWIs (15 possible versions) to five EWIs with no alternative versions. The intention is that programmes interested in monitoring site-based factors that predict the emergence of HIVDR would monitor all four EWIs rather than choosing one or more EWIs as currently occurs. At sites where routine viral load is performed on all patients 12 months after ART initiation, EWI monitoring would be expected to assess viral load suppression and therefore five indicators would be reported. Feedback to site or programme managers would be based on meeting targets for the EWIs, and if a certain EWI could not be monitored, such as virological suppression at 12 months (at a site performing routine viral load testing) this would be noted with a “grey” classification on the score-card.

• Targets and the way in which information about targets is presented for the revised EWIs have also been changed (Figure 1). Score-carding was introduced for the revised version of retention, on-time pill pick-up and virological suppression. Providing three strata of performance allows programme managers to identify areas of greatest need also monitor for degrees of improvement or decline across these indicators. This technique allows for clear presentation of results to Ministries of Health and stakeholders, and is usually easily interpreted. Additionally, the scorecard will reflect if any of the four (or five) indicators cannot be performed at a specific ART clinic by a “grey” classification. A “white” classification is assigned only for the retention indicator and only in non-UNGASS reporting years.

• In addition there is considerable change to the secondary sampling strategy. In the revised EWIs, a “cohort” of consecutive ART starters does need to be established because EWIs relating to those initiating ART (retention and virological suppression) use census of all individuals initiating ART during the reporting period. A representative secondary sampling strategy is employed for the revised EWIs of pharmacy dispensing practices and on-time pill pick-up. There is no change in the secondary sampling strategy for these indicators and the sampling plan is included in Appendix 8.
• Assessment of pharmacy dispensing practices and on-time pill pick use a cross sectional method which allows use of data more temporally related to the data abstraction date. This more timely data will allow for an intervention to alter functioning, if indicated, prior to the next annual assessment.

• With the exception of the viral load suppression indicator, all EWIs are intended to be monitored and reported at sites performing this activity.

• Simplification and consolidation of adult and paediatric EWIs has also taken place for this revision
  » Current EWI guidance has separate EWIs for children in relation to retention on ART. The new EWI set retains the retention indicator and includes modifications to incorporate children into the definition. This practice is consistent with the definition of PEPFAR and UNGASS which incorporates children.
  » Specific consideration was made for target paediatric programmes. Targets set were the same as adults for all EWIs except for targets of virological suppression for children <2 years of age.
  » Sites treating both adult and paediatric populations continue to monitor and report adult and paediatric indicators separately with the exception of the retention indicator.
CONCLUSION

This proposed revised set of EWIs is concise and more directly relates to clinic and programme factors associated with emergence of HIVDR. EWI definitions have been simplified, multiple versions have been eliminated and definitions have been harmonized with indicators from other public health and funding agencies, when possible. Despite these revisions, the goal of EWI monitoring remains the same, to identify factors associated with the emergence of HIVDR at the level of the site and provide results that drive recommendations for ART clinic, ART programme and public health action.
REFERENCES


APPENDICES

Appendix 1
HIV Drug Resistance Early Warning Indicators: Summary from 50 countries, 2004–2009

Appendix 2
Routine data collection and use of HIV DR Early Warning Indicators as an integral strategy to optimize HIV care and treatment in Vietnam

Appendix 3
Namibia HIV Drug Resistance Early Warning Indicators experience

Appendix 4
Indicators, norm-referencing, criterion-referencing, mixed methods, and score-carding

Appendix 5
Review of published findings relevant to World Health Organization HIV Drug Resistance Early Warning Indicator targets

Appendix 6
Early Warning Indicator targets and paediatric populations

Appendix 7
What if you can’t sample all clinics? sample some clinics!

Appendix 8
Secondary sampling of HIVDR Early Warning Indicator monitoring

Appendix 9
HIV drug resistance early warning indicator data abstraction and analysis tool

Appendices 1–8
Available at: http://www.who.int/hiv/pub/ewi_meeting_appendix.pdf

Appendix 9
Available at: http://www.who.int/hiv/pub/ewi_meeting_appendix9.xls