HIV DRUG RESISTANCE
EARLY WARNING INDICATORS

World Health Organization
indicators to monitor
HIV drug resistance prevention
at antiretroviral treatment sites

**World Health
Organization**

ACKNOWLEDGEMENTS

CONTENTS

3TC	Lamivudine
ABC	Abacavir
ART	Antiretroviral treatment
ARV	Antiretroviral (drug)
AZT	Zidovudine
D4T	Stavudine
ddI	Didanosine
EWI	Early Warning Indicator
HIVDR	HIV Drug Resistance
LPV/r	Lopinavir/ritonavir
NFV	Nelfinavir
NVP	Nevirapine
TDF	Tenofovir
WG	Working Group
WHO	World Health Organization

iv

HIV DRUG RESISTANCE EARLY WARNING INDICATORS
WORLD HEALTH ORGANIZATION INDICATORS TO MONITOR HIV DRUG RESISTANCE PREVENTION AT ANTIRETROVIRAL TREATMENT SITES

1. INTRODUCTION

In recent years the rapid scale up of antiretroviral treatment (ART) for HIV infection in resource-limited countries has been identified as an international healthcare priority. By December 2006 it was estimated that over two million people living with HIV/AIDS were receiving treatment in low- and middle-income countries, representing coverage of 28% of the estimated 7.1 million people in need of ART. (1) The public health approach to scaling up ART in resource-limited settings involves the use of standardized and simplified treatment regimens that are consistent with international standards, and appropriate to local circumstances. (2) Because of the high mutation rate and high replication rate of HIV, the chronic nature of HIV infection and the need for lifelong treatment, the development of some drug resistance is inevitable in populations taking ART.

In countries scaling up ART, the World Health Organization (WHO) recommends that the Ministry of Health and the National AIDS Council, or equivalent body, work with key partners to establish an HIV Drug Resistance (HIVDR) Working Group (WG). The HIVDR WG should develop a national HIVDR prevention and assessment strategy, and make evidence-based recommendations to support HIVDR prevention. Among the main tasks of the HIVDR WG are the collection of HIVDR indicators, and the implementation of surveys to assess transmission of HIVDR and prevention of HIVDR during antiretroviral treatment. (3)

This document describes one key element in the recommended HIVDR assessment strategy: ART site-based HIVDR Early Warning Indicators (EWIs). These indicators are ART site factors that may be associated with preventable emergence of HIVDR, and can be acted on at the ART site or programme level. Results can inform national decision-making on ART programme planning and other HIVDR prevention measures.

2. PURPOSE OF HIV DRUG RESISTANCE EARLY WARNING INDICATORS

The purpose of implementing an HIVDR EWI monitoring system is to assess the extent to which ART programmes are functioning to optimize prevention of HIVDR.

The national HIVDR WG should select the EWIs to be monitored in the country and should decide whether indicators are to be monitored in all ART sites, or in a selection of representative ART sites.

If national specifications for ART medical records have been implemented, it will usually be possible to abstract appropriate information on one or more EWIs from all ART sites. If indicators are to be monitored at representative sites rather than all sites in the country, a method to select representative sites should be developed. Information may be easy to collect at a particular site, but this does not make the site representative.

EWI results should be used as a basis for action, with targets recommended for each indicator. If the EWI analysis indicates that one or several sites did not meet a target, further assessment may be needed before action can be taken. In this case the WG needs to make a clear plan for investigation and subsequent action.

Drug resistance will not necessarily result immediately if an indicator shows non-optimal performance. However, achieving the best possible performance as measured by these indicators will help to prevent or minimize HIVDR. Sites that do not meet one or more EWI targets may require increased resources, staff training, or additional review to clarify the kind of support needed. If an EWI target is not met at many sites, the HIVDR WG should assess whether action is required at the national level.

2

HIV DRUG RESISTANCE EARLY WARNING INDICATORS
WORLD HEALTH ORGANIZATION INDICATORS TO MONITOR HIV DRUG RESISTANCE PREVENTION AT ANTIRETROVIRAL TREATMENT SITES

3. KEY ELEMENTS

3.1 Selecting HIV Drug Resistance Early Warning Indicators

WHO recommends that countries monitor EWIs for which information is readily available from data currently recorded routinely at sites. Countries should begin by evaluating which of the listed EWIs can be captured from current ART medical and pharmacy record systems.

It is not necessary for countries to monitor all EWIs. Indicators should not be reported if the appropriate data are not available. Countries should select the EWIs to report after evaluating whether appropriate information for each EWI is available in current record systems. On-site evaluation is required to assess whether the relevant information is recorded in standard format.

Six recommended EWIs and two optional indicators are described in Section 4, along with the corresponding WHO-recommended targets. Countries may specify more stringent national targets. However, all sites in a country should have the same targets.

EWIs should be monitored separately for adult and paediatric patients. The actions required to achieve the best possible HIVDR prevention may be different for children and adults. (2,4) The criteria to define "paediatric" will vary according to each country's national guidelines.

3.2 Selecting Early Warning Indicator sites

Once the EWIs to be monitored are selected, data abstraction should be piloted in a subset of ART sites. The pilot sites need not be representative of all ART facilities in the country, but should if possible include different sites using each of the country's important medical record-keeping systems. After piloting has been completed, the national HIVDR strategy should include a plan to move to a representative process. In order to be representative, HIVDR EWIs should be collected from:

1. **all ART sites in the country, or**

2. **representative sentinel sites.**

If EWIs are not to be monitored at all sites, the HIVDR WG should formally develop a selection method for representative sites. Likely important factors include levels of available technology, patient population size, geographic representation, and a representative mix between rural, semi-urban, and urban sites. The site mix should also represent other key factors the national HIVDR WG regards as important (e.g. partner institutions involved at the sites, HIV exposure categories and sex distribution, ethnic and cultural groups, economic status of patients, and barriers to access such as cost or distance to be travelled to obtain care).

If children are treated primarily at paediatric ART sites, the national HIVDR WG should consider selecting representative sites for adult patients, and a separate set of representative sites for paediatric patients.

4. HIV DRUG RESISTANCE EARLY WARNING INDICATORS

Only EWIs that can be abstracted from the current ART record systems should be monitored. If national ART programmes are updating their record system for other purposes, consideration should be given to incorporating relevant items that would support monitoring additional indicators.

Refer to Appendix 1 for data abstraction procedures for HIVDR EWI monitoring. Words or phrases followed by an asterisk (*) are defined in Section 5.

4.1 EWI 1. ART prescribing practices

Countries should monitor either a1, a2, or both.

a1. Percentage of patients initiating ART at the site* during a selected time period who are initially prescribed, or who initially pick up from the pharmacy, an appropriate* first-line ART regimen *(cross-sectional).* (5)

Numerator: number of patients initiating ART at the site who are prescribed, or who initially pick up from the pharmacy, an appropriate first-line ART regimen during the selected time period.

Denominator: number of patients initiating ART at the site during the selected time period.

Suggested target: 100%

a2. Percentage of patients who are prescribed, or who pick up from the pharmacy, an appropriate* ART regimen during a selected time period *(cross-sectional).* (5)

Numerator: number of patients who are prescribed, or pick up from the pharmacy, an appropriate ART regimen (first-line, second-line, or salvage) during the selected time period.

Denominator: number of patients who are prescribed, or pick up from the pharmacy, any ART regimen during the selected time period.

Suggested target: 100%

_____

*Countries should monitor 1b **only** if at least 10% of patients in the country are on second-line ART, and 20% of sites in the country have patients on second-line ART.*

b. Percentage of patients taking second-line ART* during a selected time period who are prescribed, or who pick up from the pharmacy, an appropriate* second-line ART regimen *(cross-sectional).* (5)

Numerator: number of patients on second-line ART at the site who are prescribed, or pick up from the pharmacy, an appropriate second-line ART regimen during the selected time period.

Denominator: number of patients who are prescribed or pick up from the pharmacy, a second-line ART regimen during the selected time period.

Suggested target: 100%

4

HIV DRUG RESISTANCE EARLY WARNING INDICATORS
WORLD HEALTH ORGANIZATION INDICATORS TO MONITOR HIV DRUG RESISTANCE PREVENTION AT ANTIRETROVIRAL TREATMENT SITES

4.2   EWI 2. Patients lost to follow-up during the first 12 months of ART

Percentage of patients initiating ART at the site* in a selected time period who are lost to follow-up* during the 12 months after starting ART *(cohort).* (6-11)

Numerator: number of patients initiating ART at the site in the selected time period who were not seen at the clinic, or pharmacy, $\geq$ 90 days after the date of their last missed appointment or their last missed drug pick-up that occurred within their first 12-months of ART, and who are not known to have transferred out or to have died.

Denominator: number of patients initiating ART at the site during the selected time period.

Suggested target: $\leq$ **20%**

4.3   EWI 3. Patient retention on first-line ART at 12 months

*Countries should monitor either **a** only, or both **a** and **b**.*

a. Percentage of patients initiating ART at the site* during a selected time period who are taking an appropriate* first-line ART regimen 12 months later *(cohort).* (12)

Numerator: number of patients initiating ART at the site during the selected time period who are on an appropriate first-line ART regimen (including substitutions* of one appropriate first-line regimen for another, but not substitutions of dual- or mono-therapy or an inappropriate three-drug regimen) 12 months from ART initiation.

Denominator: number of patients initiating ART at the site during a selected time period, excluding the patients who transferred out (if data are available) during the 12 months after initiating ART. Patients who died, stopped ART, switched to second-line ART*, or were lost to follow-up must be included in the denominator.

Suggested target: $\geq$ **70%**

_____

b. Percentage of patients initiating ART at the site* in a selected time period who are still on ART after 12 months and whose initial ART regimen was changed during the first 12 months of ART to another regimen involving a different drug class *(cross-sectional).* (12)

Numerator: number of patients initiating ART at the site in the selected time period who are still on ART after 12 months and whose initial ART regimen was changed during the first 12 months of ART to another regimen involving a different drug class.

Denominator: number of patients initiating ART at the site during a selected time period who are still on ART at 12 months after initiation.

Suggested target: 0%

4.4   EWI 4. On-time ARV drug pick-up

Countries should monitor either a or b.

a. Percentage of patients picking up all prescribed antiretroviral (ARV) drugs on time*. (13-16)

Numerator: number of patients who have picked up all their prescribed ARV drugs on time for two consecutive drug pick-ups after a selected month.

Denominator: number of patients who picked up ARV drugs during a selected month.

Suggested target: ≥ 90%

Note
Patients who die, who stop ART, or who are transferred out, before the first drug pick-up after the selected month, will be excluded from the numerator and the denominator. Patients who die, who stop ART, or who are transferred out, after the first drug pick-up and never made a second drug pick-up after the selected month, will be classified according to whether their first drug pick-up was on time.

_____

b. Percentage of patients initiating ART at the site* during a selected time period who picked up all prescribed ARV drugs on time* during their first 12 months of ART *(cohort).* (13-16)

Numerator: number of patients initiating ART at the site during the selected time period who picked up all their ARV drugs on-time during the first year of ART, or until they were classified as dead, transferred out, or as having stopped ART.

Denominator: number of patients initiating ART at the site during a selected time period.

Suggested target: ≥ 90%

4.5   EWI 5. ART clinic appointment keeping

*Countries should collect either a or b. These indicators should be monitored **only** in countries where scheduled appointments are recorded in advance, or fixed intervals are used for scheduling patient visits (e.g. every 28 days), so that "expected" appointment dates can be recorded.*

a. Percentage of ART patients attending clinic appointments on-time*. (17)

Numerator: number of patients who attended two consecutive clinic appointments on time after a selected month.

Denominator: number of patients who attended a clinic appointment during a selected month.

Suggested target: ≥ 80%

Note:

Patients who die, who stop ART, or who are transferred out before attending the first clinic appointment after the selected month, will be excluded from the numerator and the denominator. Patients who die, who stop ART, or who are transferred out, after the first clinic appointment and never attended a second appointment after the selected month, will be classified according to whether they attended their first appointment on time.

_____

b. Percentage of patients initiating ART at the site* during a selected time period who attended all clinic appointments on time* during the first 12 months of ART *(cohort).* (17)

Numerator: number of patients initiating ART at the site during the selected time period who kept all their clinic appointments on time during their first 12 months of treatment, or until they were classified as dead, transferred out, or as having stopped ART.

Denominator: number of patients initiating ART at the site during the selected time period.

Suggested target: > 80%

4.6   EWI 6. ARV drug supply continuity

The national HIVDR WG may collect one or more of these four indicators (EWIs 6.a1, 6.a2, 6b and 6c) to assess drug supply continuity. EWI 6.a1 is preferred to a2, but is generally feasible only at sites with electronic records.

a1. Percentage of patients on first-line ART whose regimen was stopped*, modified, or incompletely dispensed at the pharmacy* due to ARV stock-outs or shortages during a designated year *(cross-sectional).* (18-19)

Numerator: number of patients on first-line ART whose regimen was stopped, modified, or incompletely dispensed at the pharmacy due to stock-outs or shortages during the designated year.

Denominator: number of patients on first-line ART during the designated year.

Suggested target: 0%

a2. Percentage of patients initiating ART at the site* during a selected time period, whose regimen was stopped*, modified, or incompletely dispensed at the pharmacy* during the first 12 months of ART due to ARV stock-outs or shortages *(cohort).* (18-19)

Numerator: number of patients initiating ART at the site during the selected time period, whose regimen was stopped, modified, or incompletely dispensed at the pharmacy due to stock-outs or shortages during the first 12 months of ART.

Denominator: Number of patients initiating ART at the site during the selected time period.

Suggested target: 0%

b. Percentage of months in a designated year in which there were <u>no</u> ARV drug stock-outs (*cross-sectional*). (18-19)

<u>Numerator</u>: number of months in the designated year in which there were no stock-out days of any ARV drug routinely used at the site.

<u>Denominator:</u> 12 months.

Suggested target: 100%

_____

c. Maximum duration of incomplete first-line regimen availability during a designated year (*cross-sectional*). (18-19)

<u>Numerator</u>: maximum number of <u>continuous</u> days in the designated year in which there were shortages of one or more first-line ARV drugs used at the site.

<u>Denominator</u>: 365.

Suggested target: $\leq$ 2%

4.7   Optional Early Warning Indicators

Optional EWIs may be relevant in a small number of countries. When ART programme procedures and medical records are being updated, WHO does not recommend adding procedures to support monitoring them, since doing so is generally extremely labour intensive.

Optional EWI 7. Pill Count or Standardized Adherence Measure

Optional EWIs 7a and 7b should <u>only</u> be used if physical pill counts or standardized adherence measurements are systematically performed for all patients who pick up drugs. (19) Provider estimates and patient self-reports, that are not based on pill counts or a standardized measurement tool, <u>should not</u> be used for these indicators. These estimates are important to support individual adherence, but they may not generate useful data for analysis on a population-wide basis as they are not collected in a standardized format.

a. Percentage of patients who, during a selected time period, demonstrate $\geq$ 90% adherence by pill count *(cross-sectional)*. (20)

<u>Numerator</u>: the number of patients who demonstrate that at least 90% of each of their ARVs have been taken as prescribed according to a pill count performed by a provider or pharmacist during the selected time period (Separate pill counts must be performed for each ARV or combination, unless a fixed-dose combination containing all ARVs is used).

Denominator: number of patients whose adherence was assessed by pill count during the selected time period.

Suggested target: ≥ 80%

b. Percentage of patients who, during a selected time period, demonstrate ≥ 90% adherence according to a standardized adherence measurement instrument. (21)

Numerator: number of patients who demonstrate that they took at least 90% of each of their ARVs as prescribed according to a standardized adherence measurement instrument during the selected time period. (Adherence must be measured separately for each ARV drug or combination, unless a fixed-dose combination containing all ARV drugs is used).

Denominator: number of patients whose adherence was assessed by a standardized adherence measurement instrument during the selected time period.

Suggested target: ≥ 80%

_____

Optional EWI 8. Viral load suppression following 12 months of first-line ART

Optional EWI 8 should be collected only in countries where viral loads are performed routinely for all ART patients at 12 months at ≥ 75% of sites.

Percentage of patients initiating ART at the site* during a selected time period whose viral load is <1000 copies/ml after 12 months of first-line ART _(cohort)_. (22)

Numerator: number of patients initiating ART at the site during the selected time period, who are still taking first-line ART at 12 months _and_ who have a viral load of <1000 copies/ml.

Denominator: number of patients initiating ART at the site during the selected time period, excluding those who died or were transferred out before their 12-month evaluation, and including patients recorded as lost to follow-up, stopped, or switched to second-line ART during the 12 months of ART.

Target: ≥ 70%

5. DEFINITIONS

The following definitions are presented in alphabetical order.

- **"Appropriate regimen"** is an ART regimen that meets one or both of the two following definitions:

  1. standard regimen listed in national ART guidelines and used according to those guidelines;

  2. regimen recommended in one or more sets of international ART guidelines. In each country, the international guidelines used to define "appropriate regimens" should be selected by the national HIVDR WG. We recommend that WHO guidelines (2) be used to define "appropriate regimens".

- **"Incompletely dispensed"** is defined as an ARV regimen dispensed at the pharmacy that falls under either of the following conditions:

  1. fewer ARV drugs were dispensed than were prescribed (e.g. only two out of three ARV drugs were dispensed); or

  2. all the prescribed ARV drugs were dispensed, but the quantity of one or more drugs was less than the number of doses prescribed, or insufficient to cover the expected pick-up interval.

- **"Initiating ART at the site"** is defined as first prescription of ART at the site in an individual who has not previously received ART at the site, with the exception of ARV drugs for prevention of mother to child transmission (PMTCT), and who has not transferred in on ART. This definition includes: treatment naïve patients; patients who have received ARV prophylaxis for PMTCT; non-naïve patients who received ART from other sources and are not recorded as transferred in.

- **"Lost to follow-up at 12 months"** is defined as a patient who has not returned to the clinic $\geq$90 days after the last missed appointment or drug-pick up that occurred during the 12 months from the ART start date. Patients known to have transferred out, stopped, or died during the first 12 months of ART are not included in the definition of "lost to follow up". Patients whose status is unknown and who meet the "lost to follow-up" definition are included in that category despite the fact that some may have died or are attending another clinic.

- **"On-time clinic appointment keeping"** is defined as attending the clinic for a scheduled or expected appointment no later than seven days after that appointment was scheduled or expected (or, if HIVDR working groups wish to use a more stringent standard, attendance on or before the day of scheduled or expected appointment may be used). (The word "expected" is used here to cover ART sites where there is no formal appointment system).

- **"On-time pick-up of ARV drugs"** is defined as pick-up of ARV drugs on or before the date the previously dispensed drugs would have run out if they had been taken according to schedule.

- **"Second-line ART"** is defined as a regimen prescribed after clinical, immunological, or virologic failure of a first-line regimen. It does not include substitutions of one drug in the same class for another in a first-line regimen.

- **"Stop"** is a complete halt of the entire ART regimen, without a restart within the "12-month date" (i.e. one calendar year after the date of ART initiation).

- **"Substitution"** is defined as change from one ART regimen to another by substituting one or more ARVs within a drug class that was already used in the original regimen. Certain exceptions apply (2).

- **"Switch"** is defined as a change in an ART regimen after regimen failure. The change involves at least two new drugs; one of which is from a new ARV class. Certain exceptions apply (2).

6. EARLY WARNING INDICATOR MONITORING PLAN

Each national HIVDR WG should develop an EWI monitoring plan that includes:

1. The strategy used for selecting representative sites (or pilot sites for the pilot phase).

2. A list of the sites where EWI monitoring will be initially performed, the areas of the country in which the sites are found, relevant demographic information on the patient populations served, and the percentage of patients receiving ART in the country who are treated at these sites. For each site the plan should specify whether the site is managed by the national ART programme, a partner, or a combination of both. The partner(s) should be listed.

3. A brief description of the electronic or paper medical records, registers and pharmacy record systems that will be used at each site for EWI data abstraction. There is no need to describe forms or modules that will not be used for EWI monitoring.

4. A list of the EWIs that will be monitored and the corresponding national targets.

5. For each EWI, the length of time over which the denominator will be collected (for instance, for EWI 3, "Patient retention on first-line ART at 12 months", the plan should specify if the denominator will be the number of patients initiating ART during three months, six months, or one year).

6. For each EWI, the field(s) or variable(s) in each medical record system that will be used for the denominator, and the method used to abstract the information.

7. For each EWI, the field(s) or variable(s) in each medical record system that will be used for the numerator, and the method used to abstract the information.

For sites with electronic record systems, include a copy of the file structure or data entry screens for electronic medical records, registers and pharmacy systems as an appendix to the plan, and circle the relevant fields for the numerators and denominators of each EWI.

For sites with paper-based systems, include a copy of the relevant paper forms as an appendix to the plan and circle the relevant fields from which the numerator and denominator will be abstracted.

6.1 Selecting denominator time periods for Early Warning Indicator monitoring

WHO recommends that national HIVDR WGs select a denominator time period for each EWI included in the national HIVDR strategy.

For each EWI, the number of patients in the denominator (except EWIs 6b and 6c) ideally should be $\geq$100 patients. Therefore if possible, the denominator time period should be selected to allow sites to achieve this number for each EWI. The minimum number in the denominator should be 30, except at sites where < 30 patients are being treated or being enrolled during one year.

Generally, all ART sites within a country will use the same denominator period. However, in countries with many ART sites with few ART patients a long time period will be required to achieve

an ideal denominator in all ART sites. In these cases, the national HIVDR WG may define a maximum of **two** denominator time periods for each EWI to be used in "small" and "large" ART sites respectively. The criteria adopted to define "small" and "large" ART sites will be set by each national HIVDR WG depending on the available information about the number of patients currently on ART, as well as the number starting ART at each site, the record-keeping systems in place, and the practicality of data abstraction.

For EWIs in which the denominators are based on **cohorts** of patients who start ART during a selected time period (EWIs 1.a1, 2, 3, 4b, 5b, 6.a2 and optional EWI 8), the designated period for collecting the denominator (or respective denominators for small and large sites) should be set to ensure that it will be $\geq$ 30 patients. This means it is likely that over the selected time period, a minimum of 30 patients will initiate ART at each participating EWI site.

For "**cross sectional**" EWIs, which include the ART prescribing practices EWIs 1.a2 and b, and the pill count/adherence measure optional EWIs 7a and 7b, the time period to collect the denominator (or respective denominators for small and large sites) should be selected in a way that ensures it will be $\geq$ 30 patients. For instance, for the pill count/adherence measure optional EWIs 7a or 7b, at least 30 patients need to have their adherence assessed by pill count, or by using a standardized adherence measurement instrument, in each participating EWI site during the selected time period.

For drug supply continuity indicators 6.a1, 6b, and 6c, the denominator period is one calendar year. For the ARV drug pick-up EWI 4a, and the ART clinic appointment-keeping EWI 5a, the denominator period is one calendar month.

After the EWIs have been piloted and the analysis completed, the national HIVDR WG should agree on the denominator time periods for each EWI. The same denominator periods should be used every year so that data will be comparable over time.

6.2   Data abstraction from ART sites

HIVDR EWIs differ from many international indicators in that they are site-based and the abstraction of data to monitor most of them is related to selected time periods, (e.g. periods of months) and not to an entire year. Reporting should not be the responsibility of staff at ART sites.

If paper-based record-keeping systems are in place, abstractors trained under the national HIVDR strategy should abstract the data at each site. Generally data will be abstracted retrospectively once a year. If possible, countries should combine the EWI data abstraction with other indicator and patient monitoring programmes taking place in the country. EWI monitoring may also be used as, or combined with, a quality assurance assessment of record-keeping at ART sites.

If electronic record-keeping systems are in place, a programme to abstract data for EWI monitoring should be guided by experts from the national HIVDR WG. Generally, it is not feasible to obtain EWI information from summary reports already produced by those systems. For

instance, some reporting systems may underestimate the percentage of patients who are lost to follow-up, because they require busy clinical staff to scan records manually to identify and register losses to follow-up on summary sheets. If electronic medical record systems are used to produce EWIs, validation procedures that use abstraction from paper records should be set up.

Appendix I contains a detailed description of the sets of data required for capturing and monitoring each EWI.

As part of an annual national report on the HIV/AIDS epidemic, data on the HIVDR EWIs should be monitored, analysed and published. Results should be used to strengthen the national response to the epidemic. The report for each ART site should be used to optimize its performance. An ART site that does not meet one or more EWI targets may require increased support in the form of additional resources, training, additional staff for follow-up purposes.

The introduction to the annual EWI report should include information on the ART sites in which the indicators have been monitored and about data abstraction for each EWI, including how numerators and denominators were calculated. Table 1 below shows how the report should include the results for each site.

Results should be evaluated both to identify sites that have a problem meeting targets for several indicators (e.g. Site 9 in Table 1), and indicators whose target is not met at many sites (e.g. the on-time drug pick-up indicator in Table 1). More information may be required to determine the type of additional support needed at specific sites, or the programme changes required at many sites.

On the basis of EWI evidence, hypotheses may be generated and subsequently tested. For instance, in Table 1, Site 9's denominator numbers for the last two EWIs are substantially higher than those at other sites. One hypothesis might be that there are not enough resources or personnel, including pharmacy staff, for treating such a large number of patients at this site. The EWIs may be used to support evidence-based recommendations for in-depth surveys, programme changes, or requests for additional support.

Table 1. Example of EWI summary table: results from all 154 sites in the HIVDR EWI monitoring strategy

Site	Percentage of months with no ARV drug stock-outs (2006) Target = 100%	Percentage of appropriate initial ART regimen prescriptions (Jun-Nov 2006) Target = 100%	Percentage of patients starting first-line ART (Jun-Nov 2005) lost to follow-up at 12 months of ART Target = $\leq$ 20%	Percentage of patients on ART keeping all clinical appointments on time (Sep 2006) Target = $\geq$ 80%	Percentage of patients on ART picking up all ARV drugs on time (Sep 2006) Target = $\geq$ 90%
1	12/12 (100%)	94/ 94 (100%)	4/ 96 (4%)	182/ 209 (87%)	184/ 192 (96%)
2	10/12 (83.3%)	81/ 81 (100%)	9/ 74 (12%)	342/402 (85%)	176/ 220 (80%)
3	10/12 (83.3%)	31/ 40 (78%)	12/ 37 (32%)	122/ 244 (50%)	144/ 206 (70%)
4	12/12 (100%)	104/ 104 (100%)	10/ 99 (10%)	891/ 993 (90%)	483/ 508 (95%)
5	12/12 (100%)	112/ 112(100%)	13/ 105 (12%)	262/ 305 (85%)	184/ 202 (91%)
6	10/12 (83.3%)	98/1 01 (97%)	2/ 90 (2%)	416/ 442 (95%)	254/ 359 (71%)
7	12/12 (100%)	98/ 98 (100%)	9/ 88 (10%)	602/ 683 (88%)	369/ 402 (95%)
8	12/12 (100%)	203/ 203 (100%)	43 /195 (22%)	292/356 (82%)	254/ 284 (86%)
9	12/12 (100%)	304/ 305 (99.7%)	117/ 260 (45%)	753/ 1506 (50%)	829/1202 (69%)
10	12/12 (100%)	94/ 94 (100%)	12/ 90 (13%)	271/305 (89%)	269/ 290 (93%)
…	…	…	…	…	…
152	12/12 (100%)	33/ 33(100%)	4/ 31 (13%)	147/ 180 (82%)	143/ 159 (90%)
153	12/12 (100%)	26/ 34 (76%)	7/ 35 (20%)_	148/ 224 (66%)	129/ 182 (71%)
154	12/12 (100%)	73/ 73(100%)	9/ 69 (16%)	178/203 (87%)	146/154 (95%)

It is also recommended that the table contains a list of each indicator target and the percentage of sites that meet it, along with the relevant number of patients covered as shown in Table 2.

Table 2. Example of EWI summary table; targets and outcomes based on data in Table 1

Early Warning Indicator (EWI)	EWI Target for all sites (Time period)	No. of sites that meet EWI target (% of sites that meet target) N=154 ART sites
Percentage of months with no ARV drug stock-outs	100% (2006)	149/154 (96.7 %)
Percentage of appropriate initial ART regimen prescriptions	100% (Jun-Nov 2006)	146/154 (94.8 %)
Percentage of patients starting first-line ART, lost to follow-up at 12 months of ART	$\leq$ 20% (Jun-Nov 2005)	151/154 (98 %)
Percentage of patients on ART keeping all clinical appointments on time	$\geq$ 80% (Sep 2006)	145/154 (94.1 %)
Percentage of patients on ART picking up all ART drugs on time	$\geq$ 90% (Sep 2006)	95/154 (61.7%)

This Appendix contains the detailed sets of data required to capture each EWI. First the national HIVDR WG needs to select the list of indicators to be used in the HIVDR EWI strategy. Then it needs to prepare a plan to collect the corresponding sets of data from available medical and pharmacy record-keeping systems at the sites. Recommended tools to be used for data abstraction at the sites are presented in Appendix II.

_____

EWI 1: ART prescribing practices

a1. Percentage of patients initiating ART at the site during a selected time period who are initially prescribed, or who initially pick up from the pharmacy, an appropriate first-line ART regimen.

Numerator: number of patients initiating ART at the site who are prescribed, or who initially pick up from the pharmacy, an appropriate first-line ART regimen during the selected time period.

Denominator: number of patients initiating ART at the site during the selected time period.

Data abstractors should record the following information for each patient initiating ART at the site during the selected time period:

- a patient identifier;

- the date of ART initiation at the site (either as an ART prescription or an ARV drug pick-up) during the selected time period;

- the ART regimen initially prescribed (or ARV drugs initially picked up);

- HIV type (i.e. HIV-1, HIV-2, mixed HIV-1 and 2) – *to be abstracted only in countries where HIV-2 diagnosis is recorded in the medical record and is considered in regimen selection.*

Notes:

a. If codes are used in medical records to refer to standard first-line ART regimens (e.g. ART regimen "1a" is a code for the standard first-line d4T+3TC+NVP), data abstractors may use these codes while abstracting data at the site. If a code (e.g. "other" or "1e") is used to represent all non-standard ART regimens (i.e. regimens for which there are no specific codes), the data abstractors must record all ARV drugs included in these regimens in addition to the code.

b. Classification of regimens as "appropriate" should not be done at the site by data abstractors, but should be done centrally during analysis.

_____

a2. Percentage of patients who are prescribed an appropriate ART regimen, or who pick one up from the pharmacy during a selected time period.

Numerator: number of patients who are prescribed, or pick up from the pharmacy, an appropriate ART regimen (first-line, second-line, or salvage) during the selected time period.

<u>Denominator</u>: number of patients who are prescribed, or pick up from the pharmacy, any ART regimen during the selected time period.

Data abstractors should record the following information for all patients who are prescribed ART, or who pick up ARV drugs, during the selected time period:

- a patient identifier;
- the first date of ART regimen prescription (or ARV drug pick-up) during the selected time period;
- the ART regimen prescribed (or ARV drugs picked up);
- HIV type (i.e. HIV-1, HIV-2, mixed HIV-1 and 2) – *to be abstracted only in countries where HIV-2 diagnosis is recorded in the medical record and considered in regimen selection.*

Notes:
a. If codes are used in medical records to refer to standard ART regimens (e.g. ART regimen "1a" is a code for the standard first-line d4T+3TC+NVP), data abstractors may use these codes while abstracting data at the site. If a code (e.g. "other" or "1e") is used to define all non-standard ART regimens (i.e. regimens for which there are no specific codes), the data abstractors must record all ARV drugs included in these regimens in addition to the code.

b. Classification of regimens as "appropriate" should not be done at the site by data abstractors, but should be done centrally during analysis.

<div align="center">_____</div>

b. Percentage of patients taking second-line ART during a selected time period who are prescribed, or who pick up from the pharmacy, an appropriate second-line ART regimen.

<u>Numerator</u>: number of patients on second-line ART at the site who are prescribed, or who pick up from the pharmacy, an appropriate second-line ART regimen during the selected time period.

<u>Denominator</u>: number of patients who are prescribed, or who pick up from the pharmacy, a second-line ART regimen during the selected time period.

EWI 1b can be abstracted as a subset of 1.a2. If 1b is to be monitored, patients who have been prescribed, or who picked up from the pharmacy, a second-line ART regimen during the selected time period, should be included in 1.a2 data abstraction, but should be recorded on a separate form.

Data abstractors must be trained in how to identify patients on second-line ART, and should record the following information for all second-line ART prescriptions, or second-line ARV drug pick-ups, during the selected time period:

- a patient identifier;
- the first date of second-line ART regimen prescription (or second-line ARV drug pick-up) during the selected time period;

- the second-line ART regimen prescribed (or second-line ARV drugs picked up);

- HIV type (i.e. HIV-1, HIV-2, mixed HIV-1 and 2) – *to be abstracted only in countries where HIV-2 diagnosis is recorded in the medical record and considered in regimen selection.*

Notes:
a. If codes are used in medical records to refer to standard second line ART regimens (e.g. ART regimen "2a" is a code for the standard second-line ddI+ABC+LPV/r), data abstractors may use these codes while abstracting data at the site. If a code (e.g. "other", or "2e") is used for non-standard ART regimens (i.e. regimens for which there are no specific codes), the data abstractors must record all ARV drugs included in these regimens in addition to the code.

b. Classification of second-line regimens as "appropriate" should not be done at the site by data abstractors, but should be done centrally during analysis.

―――――――――――――――

EWI 2: Patients lost to follow-up during the first 12 months of ART

Percentage of patients initiating ART at the site in a selected time period who are lost to follow-up during the 12 months after starting ART.

Numerator: number of patients initiating ART at the site in the selected time period who were not seen at the clinic, or pharmacy, $\geq$ 90 days after the date of their last missed appointment or their last missed drug pick-up that occurred within their first 12-months of ART, and who are not known to have transferred out or to have died.

Denominator: number of patients initiating ART at the site during the selected time period.

If possible, countries should abstract the data for this indicator from medical and pharmacy records. The use of both types of records will correctly identify patients' "lost to follow-up" status.

Data abstractors should record the following information for each patient initiating ART at the site during the selected time period:

- a patient identifier;

- the date of ART initiation at the site (either as an ART prescription or ARV drug pick-up) during the selected time period;

- the "12-month date" (i.e. one calendar year after the date of ART initiation);

- the "15-month date" (i.e. 15 calendar months after the date of ART initiation);

- the date of the last clinic appointment attended on or before the "12-month date";

- the date of the last scheduled or expected clinic appointment missed on or before the "12-month date" (if applicable);

- the date of the first clinic appointment attended between the "12-month-" and the "15-month date" (if any);

- the date of the last drug pick-up on or before the "12-month date";

- the ARV drugs picked up at the last drug pick-up on or before the "12-month date" including number of days, or strength and pill number dispensed;

- the date of the first drug pick-up between the "12 month-" and the "15-month date" (if any);

- the date of transfer out on or before the "15-month date" (if applicable);

- the date of death on or before the "15-month date" (if applicable).

Notes:
a. Dates of transfer out and death should be collected in order to correctly define the status of patients and to avoid their being misclassified in the "lost to follow-up" category.

b. The list of ARV drugs should include the number of days for which drugs have been dispensed, or the strength and number of pills picked up at the last drug pick-up before the "12-month date". This is crucial for calculating the time interval to the following expected drug pick-up (or "run-out date"). If the patient does not turn up on the "run-out date", the 90-day count that defines "lost to follow-up" starts from then.

c. In order to be able to correctly classify patients as "lost to follow up" during the first 12 months, patient information must be abstracted for up to 15 months after ART initiation.

_____

EWI 3: Patient retention on first-line ART

Countries can abstract data for these indicators from medical (drugs prescribed) or pharmacy records (drugs dispensed). Both types of records should be used if possible.

a. Percentage of patients initiating ART at the site during a selected time period who are taking an appropriate first-line ART regimen 12 months later.

Numerator: number of patients initiating ART at the site during the selected time period who are on an appropriate first-line ART regimen (including substitutions of one appropriate first-line regimen for another, but not substitutions of dual- or mono-therapy or an inappropriate three-drug regimen) 12 months from ART initiation.

Denominator: number of patients initiating ART at the site during a selected time period, excluding the patients who transferred out (if data are available) during the 12 months after initiating ART. Patients who died, stopped ART, switched to second-line ART, or were lost to follow-up must be included in the denominator.

Data abstractors should record the following information for each patient initiating ART at the site during the selected time period:

- a patient identifier;

- the date of ART initiation at the site (either as an ART prescription or an ARV drug pick-up) during the selected time period;

- "12-month date" (i.e. one calendar year after the date of ART initiation);

20

HIV DRUG RESISTANCE EARLY WARNING INDICATORS
WORLD HEALTH ORGANIZATION INDICATORS TO MONITOR HIV DRUG RESISTANCE PREVENTION AT ANTIRETROVIRAL TREATMENT SITES

- the date of the last clinic appointment attended on or before the "12-month date";

- the ART regimen prescribed at the last clinic appointment on or before the "12-month date", including number of days, or strength and pill number dispensed;

- the date of the last ARV drug pick-up attended on or before the "12-month date";

- the ARV drugs picked up at the last pick-up on or before the "12-month date", including number of days, or strength and number dispensed;

- the date of transfer out on or before the "12-month date" (if applicable);

- the date of death on or before the "12-month date" (if applicable);

- the date ART was stopped, without a restart, on or before the "12-month date" (if applicable);

- HIV type (i.e. HIV-1, HIV-2, mixed HIV-1 and -2) – *to be abstracted only in countries where HIV-2 diagnosis is recorded in the medical record and is considered in regimen selection.*

Notes:

a. If codes are used in medical records to refer to standard first-line ART regimens (e.g. ART regimen "1a" is a code for the standard first-line d4T+3TC+NVP), data abstractors can use these codes while abstracting data at the site. If a code (e.g. "other" or "1e") is used to define all non-standard ART regimens (i.e. regimens for which there are no specific codes), the data abstractors must record all ARV drugs included in these regimens in addition to the code.

b. Classification of regimens as "appropriate" should not be done at the site by data abstractors, but should be done centrally during analysis.

———————————————

b. Percentage of patients initiating ART at the site in a selected time period who are still on ART after 12 months, and whose initial ART regimen was changed during the first 12 months of ART to another regimen involving a different drug class.

Numerator: number of patients initiating ART at the site in the selected time period who are still on ART after 12 months and whose initial ART regimen was changed during the first 12 months of ART to another regimen involving a different drug class.

Denominator: number of patients initiating ART at the site during a selected time period who are still on ART 12 months after initiation.

Data abstractors should record the following information for each patient initiating ART at the site during the selected time period:

- a patient identifier;

- the date of ART initiation at the site (either as an ART prescription or an ARV drug pick-up) during the selected time period;

- the ART regimen initially prescribed (or ARV drugs initially picked up);

- "12-month date" (i.e. one calendar year after the date of ART initiation);

- the date of the last clinic appointment attended on or before the "12-month date";

- the ART regimen prescribed at the last clinic appointment on or before the "12-month date", including number of days, or strength and pill number dispensed;

- the date of the last ARV drug pick-up attended on or before the "12-month date"

- the ARV drugs picked up at the last pick-up on or before the "12-month date", including number of days, or strength and pill number dispensed.

Notes:

a. If codes are used in medical records to refer to standard first-line ART regimens (e.g. ART regimen "1a" is a code for the standard first-line d4T+3TC+NVP), data abstractors can use these codes while abstracting data at the site. If a code (e.g. "other" or "1e") is used to define all non-standard ART regimens (i.e. regimens for which there are no specific codes), the data abstractors must record all ARV drugs included in these regimens in addition to the code.

———————————————

EWI 4: On-time ARV drug pick-up

a. Percentage of patients picking up all prescribed ARV drugs on time.

Numerator: number of patients who have picked up all their prescribed ARV drugs on time for two consecutive drug pick-ups, after a selected month.

Denominator: number of patients who picked up ARV drugs during a selected month.

At ART sites with electronic or manual ARV drug pick-up pharmacy registers or dispensing records that include patient identifiers arranged sequentially by date, it is easy to identify the patients who picked up ARV drugs during the selected month. Data abstractors should record the following information for each patient who picked up ARV drugs in the selected month:

- a patient identifier;

- the last ARV drug pick-up date during the selected month ("baseline pick-up");

- the two consecutive ARV drug pick-up dates after the selected month ("pick-up 1" and "pick-up 2");

- the list of ARV drugs, including number of days, *or* strength and pill number dispensed at "baseline pick-up" and "pick-up 1";

- the date of transfer out after "baseline pick-up" if two ARV drug pick-ups were not recorded after the "baseline pick-up";

- the date of death after "baseline pick-up" if two ARV drug pick-ups were not recorded after the "baseline pick-up".

- the date of ART stop after "baseline pick-up" (that is, a recorded decision by the patient or physician that ARV should be stopped) if two ARV drug pick-ups were not recorded after the "baseline pick-up"

Notes:

a. If the site allows ARV drug pick-ups by a designated treatment "buddy", partner, or relative, the dates ARV drugs are picked up on behalf of the patient are counted as ARV drug pick-ups for this EWI.

b. No patient should be counted more than once in the denominator of EWI 4a. (i.e. if a patient picked up ARV drugs more than once during the selected month, only the last pick-up should be recorded).

c. If the exact number of days of ARV drugs dispensed at "baseline pick-up" and "pick-up 1" is not available, strength and pill number dispensed should be recorded so that the "run-out" date can be calculated, i.e. the date when the ARV drugs are expected to finish if taken according to prescription (see Appendix IV). The "run-out date" sets the limit by which drug pick-up should occur in order to be defined as "on time".

d. If the "number of days dispensed" is not available, the monitoring of this EWI for paediatric patients will require staff to abstract additional information.

e. If pill counts are performed, or other standard objective measurements are used to calculate the number of pills "in hand" (that is, number of pills remaining with the patient from previous pick-ups, plus number of pills dispensed at this pick-up), the EWI should be calculated using the number of pills "in hand" on the pick-up date, rather than the number of pills dispensed.

———————————————

b. Percentage of patients initiating ART at the site during a selected time period who picked up all prescribed ARV drugs on time during their first 12 months of ART.

<u>Numerator</u>: number of patients initiating ART at the site during the selected time period who picked up all their ARV drugs on time during the first year of ART, or until they were classified as dead, transferred out, or as having stopped ART.

<u>Denominator</u>: number of patients initiating ART at the site during a selected time period.

The data for monitoring EWI 4b may be abstracted along with EWI 3a, but some additional information is needed.

Data abstractors should record the following information for each patient initiating ART at the site during the selected time period:

- a patient identifier;
- the date of ART initiation at the site (preferably initial ARV drug pick-up) during the selected time period;
- the "12-month date" (i.e. one calendar year after the date of ART initiation);
- the dates of each ARV drug pick-up attended on or before the "12-month date";
- the list of ARV drugs, including number of days dispensed, *or* strength and pill number dispensed at each drug pick-up on or before the "12-month date";
- the date(s) of ART stop, without a restart, on or before the "12-month date" (if applicable);

- the date of transfer out on or before the "12-month date" (if applicable);

- the date of death on or before the "12-month date" (if applicable).

Notes:
a. If the site allows ARV drug pick-ups by a designated treatment "buddy", partner, or relative, the dates ARV drugs are picked up on behalf of the patient are counted as ARV drug pick-ups for this EWI.

b. If the exact number of days of ARV drugs dispensed at each drug pick-up is not available, strength and pill number dispensed should be recorded so that the "run-out" date can be calculated, i.e. the date when ARV drugs are expected to finish if taken according to prescription (see Appendix IV). The "run-out date" sets the limit when drug pick-up should occur in order to be defined as "on time".

c. If the "number of days dispensed" is not available, the monitoring of this EWI for paediatric patients will require abstraction of additional information.

d. If pill counts are performed, or other standard objective measurements are used to calculate the number of pills "in hand" (that is, number of pills remaining with the patient from previous pick-ups, plus number of pills dispensed at this pick-up), the EWI should be calculated using the number of pills "in hand" on the pick-up date, rather than the number of pills dispensed.

_____

EWI 5: ART clinic appointment-keeping

a. Percentage of ART patients who attend clinic appointments on time.

Numerator: number of patients who attended two consecutive clinic appointments on time after a selected month.

Denominator: number of patients who attended a clinic appointment during a selected month.

At ART sites with electronic or manual clinic appointment booking systems, it is easy to identify the patients who attended a clinic appointment during the selected month. If such record systems are not available, this indicator may be monitored only at ART sites where fixed time intervals are used for scheduling patient visits (e.g. every 28 days), and expected clinic appointments may be calculated.

Data abstractors should record the following information for each patient who attended a clinic appointment during the selected month:

- a patient identifier;

- the date of last clinic appointment attended during the selected month ("baseline clinic appointment");

- the dates of the two consecutive clinic appointments scheduled or expected after the selected month;

- the dates of the two consecutive clinic appointments attended after the selected month (i.e. "clinic appointment 1" and "clinic appointment 2");

- the date of transfer out after "baseline clinic appointment" (if two clinic appointments were not attended after "baseline clinic appointment");

- the date of death after "baseline clinic appointment" (if two clinic appointments were not attended after "baseline clinic appointment").

Notes:
a. Clinic appointments attended by a treatment "buddy", partner, relative, etc. do not count as an appointment "attended" by the patient for the purpose of this EWI. At sites where no distinction can be made between attendance by the patient or a surrogate, this EWI should not be collected.

b. A patient should not be counted more than once in the denominator of EWI 5a. (i.e. if a patient attended more than one clinic appointment during the selected month, only the last one should be recorded).

———————————————

b. Percentage of patients initiating ART at the site during a selected time period who attended all clinic appointments on time during the first 12 months of ART.

Numerator: number of patients initiating ART at the site during the selected time period who kept all their clinic appointments on time during their first 12 months of treatment, or until they were classified as dead, transferred out, or as having stopped ART.

Denominator: number of patients initiating ART at the site during the selected time period.

At ART sites with electronic or manual clinic appointment booking systems, data on scheduled clinic appointments can be easily abstracted for this group of patients. If such record systems are not available, this indicator may be monitored only at ART sites where fixed time intervals are used for scheduling patient visits (e.g. every 28 days), and expected clinic appointments can be calculated.

Data abstractors should record the following information for each patient initiating ART at the site during the selected time period:

- a patient identifier;

- the date of ART initiation at the site (preferably the ART prescription date) during the selected time period ;

- the "12-month date" (i.e. one calendar year after the date of ART initiation);

- the dates of all clinic appointments scheduled or expected after ART initiation, and on or before the "12-month date";

- the dates of all clinic appointments attended after ART initiation and on or before the "12-month date";

- the date(s) of ART stop, without a restart, on or before the "12-month date" (if applicable);

- the date of transfer out on or before the "12-month date" (if applicable);

- the date of death on or before the "12-month date" (if applicable).

Note:
Clinic appointments attended by a treatment "buddy", partner, relative, etc. do not count as an appointment "attended" by the patient for the purpose of this EWI. At sites where no distinction can be made between attendance by the patient or a surrogate, this EWI should not be collected.

_____

EWI 6. Drug supply continuity

The national HIVDR WG may decide to measure one or more of four EWI 6 indicators to assess drug supply continuity.

EWI 6.a1 and 6.a2 may be used only in cases where reasons for ART substitution, switch, stop or incompletely dispensed ART regimens are recorded in a standard format, and if "ARV drug supply shortage" or equivalent, is one of the standard reasons. EWI 6.a1 is preferred to 6.a2, but is generally feasible only at sites with electronic records.

a1. Percentage of patients on first-line ART whose regimen was stopped, modified or incompletely dispensed at the pharmacy due to stock-outs or shortages during a designated year.

Numerator: number of patients on first-line ART whose regimen was stopped, modified or incompletely dispensed at the pharmacy due to stock-outs or shortages during the designated year.

Denominator: number of patients on first-line ART during the designated year.

Data abstractors should record the following information for each patient who was prescribed, or picked up, a first-line ART regimen during a designated calendar year:

- a patient identifier;

- the date(s) of ART stop during the designated year due to stock-out or shortage and the name(s) of the ARV drug(s) stopped (if applicable);

- the date of ART modification during the designated year due to stock-out or shortage and the name(s) of the ARV drug(s) modified (if applicable);

- the date when the ART regimen was incompletely dispensed during the designated year due to stock-out or shortage and the name(s) of the ARV drug(s) of the regimen that were incompletely dispensed (if applicable).

_____

The data for monitoring EWI 6.a2 may be abstracted along with EWIs 4b and 5b, but some additional information is needed.

a2. Percentage of patients initiating ART at the site during a selected time period whose regimen was stopped, modified, or incompletely dispensed at the pharmacy during the first 12 months of ART due to ARV stock-outs or shortages.

Numerator: number of patients initiating ART at the site during the selected time period whose regimen was stopped, modified or incompletely dispensed at the pharmacy due to stock-outs or shortages during the first 12 months of ART.

Denominator: number of patients initiating ART at the site during the selected time period.

Data abstractors should record the following information for each patient initiating ART at the site during the selected time period, and for the first 12 months of treatment:

- a patient identifier;

- the date of ART initiation at the site (either as an ART prescription or an ARV drug pick-up) during the selected time period ;

- the "12-month date" (i.e. one calendar year after the date of ART initiation);

- the date(s) of ART stop on or before the "12-month date" due to stock-out or shortage and the name(s) of ARV drug(s) stopped (if applicable);

- the date of ART modification on or before the "12-month date" due to stock-out or shortage and the name(s) of ARV drug(s) modified (if applicable);

- the date when the ART regimen was incompletely dispensed on or before the "12-month date" due to stock-out or shortage and the name(s) of the ARV drug(s) of the regimen that were incompletely dispensed (if applicable).

_____

Methods of abstracting data for EWIs 6b and 6c should be developed in conjunction with staff implementing the ARV drug supply monitoring system at the site. A separate evaluation may be performed for each ARV drug routinely used at the site.

b. 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 days of stock-out of any ARV drug routinely used at the site.

Denominator: 12 months.

Data abstractors should record the following information for each month of the designated year:

- dates of stock-out of any ARV drug routinely used at the site.

Note:
a. If a separate evaluation is planned for each ARV drug routinely used at the site, data abstractors should record the name of the drugs and the corresponding stock-out dates.

b. In countries where ARV drug stock-outs are routinely reported quarterly, EWI 6b may be calculated as a percentage of quarters in a designated year in which there were no ARV drug stock-outs (in this case the denominator will be 4 quarters).

c. Maximum duration of incomplete first-line regimen availability during a designated year.

Numerator: maximum number of continuous days in the designated year in which there were shortages of one or more first-line ARV drugs used at the site.

Denominator: 365.

Data abstractors should record the following information for the designated year:

• the dates of shortages of one or more first-line ARV drugs used at the site.

Note:
If a separate evaluation is planned for each first-line ARV drug routinely used at the site, data abstractors should record the name of the drugs and the corresponding shortage dates.

_____

Optional EWI 7. Pill count or standardized adherence measure

*Clinician or nurse estimates, even if expressed as percentage (e.g. "90 %" of pills taken or "90%" of patient adherence) **cannot** be used for this indicator. Only percentages based on recorded pill numbers or scores from standardized adherence measurement instruments (e.g. visual analog scale) should be used for these indicators.*

a. Percentage of patients who, during a selected time period, demonstrate $\geq$ 90% adherence by pill count.

Numerator: the number of patients who demonstrate that at least 90% of each of their ARVs have been taken as prescribed according to a pill count performed by a provider or pharmacist during the selected time period (Separate pill counts must be performed for each ARV or combination, unless a fixed-dose combination containing all ARVs is used).

Denominator: number of patients whose adherence was assessed by pill count during the selected time period.

Data abstractors should record the following information for all ART patients who pick up ARV drugs during the selected time period:

• a patient identifier;

• the last ARV pick-up or clinic appointment date during the selected period when pill count was assessed;

• the list of ARV drugs or combinations and the percentage of pills taken for each.

b. Percentage of patients who, during a selected time period, demonstrate $\geq$ 90% adherence according to a standardized adherence measurement instrument.

Numerator: number of patients who demonstrate that they took at least 90% of each of their ARVs as prescribed according to a standardized adherence measurement instrument during the selected time period. (Adherence must be measured separately for each ARV drug or combination, unless a fixed-dose combination containing all ARV drugs is used).

Denominator: number of patients whose adherence was assessed by a standardized adherence measurement instrument during the selected time period.

Data abstractors should record the following information for all ART patients who pick up drugs during the selected time period:

- a patient identifier;

- the last ARV pick-up or clinic appointment date during the selected time period when adherence was assessed;

- the score of the standardized adherence measurement instrument used at the site to assess adherence.

_____

Optional EWI 8. Viral load suppression following 12 months of first-line ART

Percentage of patients initiating ART at the site in a selected time period whose viral load is <1000 copies/ml after 12 months of first-line ART.

Numerator: number of patients initiating ART at the site during the selected time period, who are still taking first-line ART at 12 months *and* who have a viral load of <1000 copies/ml.

Denominator: number of patients initiating ART at the site during the selected time period, excluding those who died or were transferred out before their 12-month evaluation, and including patients recorded as lost to follow-up, stopped, or switched during the 12 months of ART.

Data abstractors should record the following information for each patient initiating ART during the designated time period:

- a patient identifier;

- the date of ART initiation at the site (either as ART prescription or ARV drug pick-up);

- the ART regimen initially prescribed (or ARV drugs initially picked up);

- the "12-month date" (i.e. one calendar year after the ART initiation date);

- the date of the last clinic appointment attended on or before the "12-month date";

- the ART regimen prescribed at the last clinic appointment on or before the "12-month date", including number of days, or strength and pill number dispensed;

- the date of the last ARV drug pick-up attended on or before the "12-month date";

- the ARV drugs picked up at the last pick-up on or before the "12-month date", including number of days, or strength and pill number dispensed;

- the date of blood collection for HIV viral load test closest to the "12-month date";

- HIV viral load test result (copies/ml);

- the date of death on or before the "12-month date" (if applicable);

- the date of transfer out on or before the "12-month date" (if applicable).

Notes:
a. If codes are used in medical records to refer to standard first-line ART regimens (e.g. ART regimen "1a" is a code for the standard first-line d4T+3TC+NVP), data abstractors may use these codes while abstracting data at the site. If a code (e.g. "other" or "1e") is used to define all non-standard ART regimens (i.e. regimens for which there are no specific codes), the data abstractors must record all ARV drugs included in these regimens in addition to the code.

b. The denominator must include individuals recorded as lost to follow-up, stopped, or switched during the 12 months. This means the denominator includes all patients for whom no viral load is available at 12 months, with the exception of those who have transferred out or have died.

In this appendix a set of data abstraction tools for EWI monitoring is presented. As anticipated in Appendix I, each EWI can be captured and monitored by abstracting a specific set of data from medical and/or pharmacy records available at the site. The following tools are meant to be used during the data abstraction phase at the site, as well as during the subsequent analysis performed centrally by national HIVDR WG staff.

On request, EWI data abstraction tools will be provided to each country that implements the WHO HIVDR EWI monitoring strategy.

Data abstraction tools for EWI monitoring are user friendly instruments that can be used as spreadsheet files (electronic tools) if computers are available for EWI monitoring, and data abstractors are staff who are computer literate and trained to transfer information from medical and pharmacy records directly into a database. The tools can also be printed out as forms for manual recording (manual tools).

Every WHO's electronic tool has a built-in system of functions that automatically calculate the specific EWIs once complete data are entered. In a few cases (e.g. defining appropriate ART regimens for EWI 1), the electronic tool requires some additional information (e.g. the list of "appropriate regimens") to be entered centrally by HIVDR WG staff. Extra columns and an "EWI result box" are "hidden" in the electronic spreadsheet, and should be "unhidden" during central data analysis. If data are abstracted onto paper forms at the sites, they should be centrally entered in the electronic tool if the tool is to be used to perform analyses.

Every data abstraction tool has an initial table (see Figure 1) with a series of fields that cover fundamental information about the data. The list of fields and data entry instructions below refer to this initial table:

Country: the country in which the data collection takes place and the overall HIVDR EWI strategy is being implemented.
Facility: the name of the ART site at which data are collected (may also include the region or district in which the facility is located).
Data entry date: the date when data entry starts (a new date may be entered on subsequent sheets if manual tools are used as forms for data recording).
Total number of sheets (to be recorded only if paper abstraction tools are used): to be entered to clarify the total number of sheets subsequently to be put into the electronic system.
Time period: the selected denominator time period expressed as months, quarters or a designated calendar year according to the different EWIs.
Total number of patients: the total number of patients whose data have been recorded for the relevant EWIs. The total number is automatically generated in the electronic tool.
Adult or paediatric patients: a required field that is used to define whether the data collected on the tool belong to the adult (enter "A") or paediatric (enter "P") EWI monitoring strategy.
Data abstractor (name/last name/contact information): the name of the person(s) involved in the process of data abstraction at the site and their contact information, in case specific data is queried or needs clarifying.

The second part of the tool is a self-explanatory data entry table, in which the sets of data (presented for each EWI in Appendix I) are manually or electronically recorded according to recommended instructions.

Fig. 1 Example of a data abstraction tool (Data Abstraction Tool for EWI 1.a1)

HIV DRUG RESISTANCE EARLY WARNING INDICATORS - DATA ABSTRACTION TOOL HIVResnet

COUNTRY :	FACILITY :

Data entry date (dd/mm/yyyy) :

Indicator: ART Prescribing practices (EWI 1.a1) - Percentage of patients initiating ART at the site during a selected time period who are initially prescribed, or who initially pick up from the pharmacy, an appropriate first-line ART regimen

Time Period (These data refer to patients who initiated ART at this facility during the selected time period) :

Total number of patients : **0** Adult or paediatric patients (A / P) :

Data abstractor at the facility (name / last name / contact phone) :

No.	Patient ID (exclude if transferred in on ART)	ART initiation date Initial ART prescription or ARV drug pick-up (dd/mm/yyyy)	ART regimen initially prescribed (or picked up) List of ARV drugs as recorded on medical or pharmacy record - Codes for standard ART regimens, if used, may be entered; if a code is used for non-standard ART regimens (e.g. "other", "1e", etc) the complete list of ARV drugs must be entered	HIV type (HIV-1; HIV-2; HIV-1 and 2) to be abstracted only in countries where HIV-2 is considered in regimen

Fig. 2 Example of a data abstraction tool with visible columns and EWI result box

HIV DRUG RESISTANCE EARLY WARNING INDICATORS - DATA ABSTRACTION TOOL HIVResNet

COUNTRY :	FACILITY :

Data entry date (dd/mm/yyyy) :

Indicator: ART Prescribing practices (EWI 1.a1) - Percentage of patients initiating ART at the site during a selected time period who are initially prescribed, or who initially pick up from the pharmacy, an appropriate first-line ART regimen

Time Period (These data refer to patients who initiated ART at this facility during the selected time period) :	EWI 1.a1 target	100%
Total number of patients : 0 Adult or paediatric patients (A / P) :	EWI 1.a1 at the site	

Data abstractor at the facility (name / last name / contact phone) :

No.	Patient ID (exclude if transferred in on ART)	ART initiation date Initial ART prescription or ARV drug pick-up (dd/mm/yyyy)	ART regimen initially prescribed (or picked up) List of ARV drugs as recorded on medical or pharmacy records. Codes for standard ART regimens, if used, may be entered; if a code is used for non-standard ART regimens (e.g. "other", "1e", etc) the complete list of ARV drugs must be entered	HIV type (HIV-1; HIV-2; HIV-1 and 2) to be abstracted only in countries where HIV-2 is considered in regimen	Appropriate ART regimen (Code "1" if ART regimen is appropriate; code "0" if ART regimen is not appropriate)

In this Appendix we present two examples of data abstraction and analysis for EWI monitoring. These examples show how data should be abstracted, explained and analysed using the WHO HIVDR EWI tools in Appendix II.

Example 1: EWI 1. ART prescribing practices

Among other EWIs, EWI 1.a1 has been selected by the National HIVDR WG of **Country X** for the EWI monitoring strategy.

EWI 1.a1 definition (from section 4.1):

Percentage of patients initiating ART at the site during a selected time period who are initially prescribed, or who initially pick up from the pharmacy, an appropriate first-line ART regimen.

Numerator: number of patients initiating ART at the site who are prescribed, or who initially pick up from the pharmacy, an appropriate first-line ART regimen during the selected time period.

Denominator: number of patients initiating ART at the site during the selected time period.

Definition of appropriate regimen (from section 5):

- standard regimen listed and used according to national ART guidelines;

- regimen recommended in one or more sets of international ART guidelines. In each country, the international guidelines used to define "appropriate regimens" should be selected by the national HIVDR WG. We recommend that WHO guidelines be used to define "appropriate regimens".

Data abstraction for EWI 1.a1 monitoring

As recommended in Appendix I, in order to capture EWI 1.a1, the following data are required for each patient initiating ART at the site during a selected time period:

- a patient identifier;

- the date of ART initiation at the site (either as an ART prescription or an ARV drug pick-up) during the selected time period;

- the ART regimen initially prescribed (or ARV drugs initially picked up).

In our example of Country X, all sites are quite homogeneous as far as volume of patients is concerned. The denominator time period for all sites selected by the HIVDR WG for EWI 1.1a is the quarter from 1 July to 30 September of a designated year X (e.g. 2007). The recommended set of data presented above will be abstracted in all ART facilities for the patients who initiate ART at each site during the selected time period. All EWI will be captured and analysed separately for each site.

Data abstraction teams should be trained to abstract the required set of data from available record-keeping systems at the sites. Examples of records actually filled in at sites should be used in training. In Country X, an ART cohort register and "HIV Care/ART Cards" are used at all sites. Preliminary evaluations have also confirmed that the relevant information is being filled in for EWI 1.a.1 in the relevant fields at all selected sites. Therefore, the HIVDR WG has planned to use the registers and cards and has trained abstractors accordingly (see Figure 3).

Fig. 3   Example of source document for data abstraction: "HIV Care/ART Cards" used to abstract information for EWI monitoring in Country X.

Note: The data required to capture EWI 1.a1 are indicated by arrows.

ART cohort registers (not shown) are used to identify the ART numbers and medical record identification numbers of patients who initiate treatment in the selected time period. Data abstractors will locate the "HIV Care/ART Cards" of patients who began ART in the selected time period, as shown in Figure 3, and abstract the relevant information. If the data abstraction team has been supplied with laptop computers and trained to use them, the data abstractor can transfer these data into the specific EWI 1.a1 electronic tool (see Figure 1 in Appendix II). If laptops are not available, or abstractors are not computer-trained, the data abstraction tools may be printed out as forms for manual paper recording.

In the case of EWI 1.a1, a patient identifier, the ART start date, and the initial regimen prescribed are abstracted. If codes are used in medical records to refer to standard first-line ART regimens (e.g. ART regimen "1a" is a code for the standard first-line d4T+3TC+NVP), data abstractors may use these codes while collecting data at the site. If a separate code (e.g. "other", "1e", etc.) is used to define all non-standard ART regimens (i.e. regimens for which there are no specific codes), the data abstractors must record all ARV drugs included in these regimens, in addition to the code.

The purpose of this EWI is to evaluate whether prescribing practices of initial ART regimens are appropriate at each ART site in Country X. The decision whether a regimen is appropriate should not be made by data abstractors at the site. HIVDR WG staff will decide if regimens are appropriate during analysis.

Once data abstraction has been completed (see Figure 4), the electronic forms can be sent by e-mail. Otherwise, laptops or flash drives can be delivered and the data downloaded to staff at the institution that the national HIVDR WG designates to perform the analysis. If paper forms are used, they should be hand-delivered if possible to ensure confidentiality. If the forms are to be faxed or sent by regular post mail, a system must be devised to ensure confidentiality and guarantee delivery.

Fig. 4 Example of electronic or manual data abstraction tool filled in with the required information, ready to be e-mailed, faxed or posted to the national HIVDR WG for analysis

HIV DRUG RESISTANCE EARLY WARNING INDICATORS - DATA ABSTRACTION TOOL   **HIV**Resnet

COUNTRY : COUNTRY X	FACILITY : Hospital X

Data entry date (dd/mm/yyyy) : 01/02/2008

Indicator: ART Prescribing practices (EWI 1.a1) - Percentage of patients initiating ART at the site during a selected time period who are initially prescribed, or who initially pick up from the pharmacy, an appropriate first-line ART regimen

Time Period (These data refer to patients who initiated ART at this facility during the selected time period) : Jul 07-Sep 07

Total number of patients :   **186** Adult or paediatric patients (A / P) : A

Data abstractor at the facility (name / last name / contact phone) :

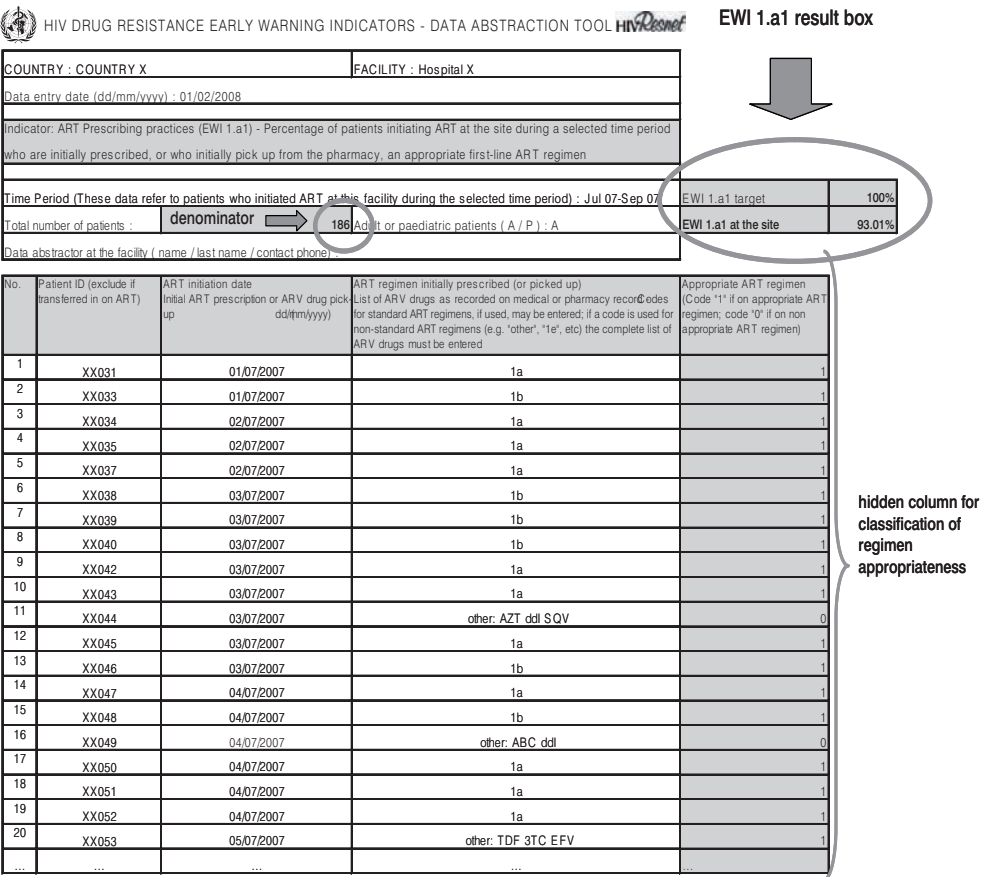| No.	Patient ID (exclude if transferred in on ART)	ART initiation date Initial ART prescription or ARV drug pick-up (dd/mm/yyyy)	ART regimen initially prescribed (or picked up) List of ARV drugs as recorded on medical or pharmacy record - Codes for standard ART regimens, if used, may be entered; if a code is used for r standard ART regimens (e.g. "other", "1e", etc) the complete list of ARV drugs must be entered
1	XX031	01/07/2007	1a
2	XX033	01/07/2007	1b
3	XX034	02/07/2007	1a
4	XX035	02/07/2007	1a
5	XX037	02/07/2007	1a
6	XX038	03/07/2007	1b
7	XX039	03/07/2007	1b
8	XX040	03/07/2007	1b
9	XX042	03/07/2007	1a
10	XX043	03/07/2007	1a
11	XX044	03/07/2007	other: AZT ddl SQV
12	XX045	03/07/2007	1a
13	XX046	03/07/2007	1b
14	XX047	04/07/2007	1a
15	XX048	04/07/2007	1b
16	XX049	04/07/2007	other: ABC ddl
17	XX050	04/07/2007	1a
18	XX051	04/07/2007	1a
19	XX052	04/07/2007	1a
20	XX053	05/07/2007	other: TDF 3TC EFV
…	…	…	…

Data analysis for EWI 1.a1 monitoring

Data entered directly into the electronic tool at the site can be used for EWI data analysis. However, transfer of data from paper abstraction forms will need to be carried out at the central level.

Electronic tools have a built-in system requiring additional information to be entered in hidden columns at the central level before the EWI calculation and data analysis can be completed. In case of EWI 1.a1, the "unhide" function will show an additional column for categorization of the appropriateness of the prescribed regimen (see Figure 5). Staff at the central level will categorize the abstracted regimens as "appropriate" or "inappropriate" according to national and/or international treatment guidelines.

Fig. 5   Example of additional information entered and analysis performed at central level by HIVDR WG staff using the hidden functions of the EWI electronic data abstraction tool

Note: For EWI 1.a, the sum of the "appropriate ART regimens" will be the numerator. The "total number of patients" who initiate ART at the site in the selected time period will be the denominator.

HIV DRUG RESISTANCE EARLY WARNING INDICATORS - DATA ABSTRACTION TOOL HIVResnet   **EWI 1.a1 result box**

COUNTRY : COUNTRY X	FACILITY : Hospital X

Data entry date (dd/mm/yyyy) : 01/02/2008

Indicator: ART Prescribing practices (EWI 1.a1) - Percentage of patients initiating ART at the site during a selected time period who are initially prescribed, or who initially pick up from the pharmacy, an appropriate first-line ART regimen

Time Period (These data refer to patients who initiated ART at this facility during the selected time period) : Jul 07-Sep 07

Total number of patients :   **denominator** →   186 Adult or paediatric patients (A / P) : A

Data abstractor at the facility (name / last name / contact phone)

EWI 1.a1 target	100%
EWI 1.a1 at the site	93.01%

No.	Patient ID (exclude if transferred in on ART)	ART initiation date Initial ART prescription or ARV drug pick-up dd/mm/yyyy	ART regimen initially prescribed (or picked up) List of ARV drugs as recorded on medical or pharmacy records for standard ART regimens, if used, may be entered; if a code is used for non-standard ART regimens (e.g. "other", "1e", etc) the complete list of ARV drugs must be entered	Appropriate ART regimen (Code "1" if on appropriate ART regimen; code "0" if on non appropriate ART regimen)
1	XX031	01/07/2007	1a	1
2	XX033	01/07/2007	1b	1
3	XX034	02/07/2007	1a	1
4	XX035	02/07/2007	1a	1
5	XX037	02/07/2007	1a	1
6	XX038	03/07/2007	1b	1
7	XX039	03/07/2007	1b	1
8	XX040	03/07/2007	1b	1
9	XX042	03/07/2007	1a	1
10	XX043	03/07/2007	1a	1
11	XX044	03/07/2007	other: AZT ddl SQV	0
12	XX045	03/07/2007	1a	1
13	XX046	03/07/2007	1b	1
14	XX047	04/07/2007	1a	1
15	XX048	04/07/2007	1b	1
16	XX049	04/07/2007	other: ABC ddl	0
17	XX050	04/07/2007	1a	1
18	XX051	04/07/2007	1a	1
19	XX052	04/07/2007	1a	1
20	XX053	05/07/2007	other: TDF 3TC EFV	1
...	...	...	...	...

hidden column for classification of regimen appropriateness

The calculation of EWI 1.a1 will require additional information to be entered at central level (i.e. classification of regimen appropriateness). As shown in Figure 5, HIVDR WG staff will have to unhide the function of the electronic tool and fill in the required additional information.

The HIVDR WG of Country X has defined appropriate regimens as standard regimens that meet national guidelines, as well as additional regimens that meet WHO guidelines. Individuals who classify regimens for EWI 1.a1 should refer to the list of appropriate first-line regimens based on the definition developed by the WG.

In the column in which "appropriateness" is assessed, appropriate ART regimens will be coded "1"; non-appropriate ART regimens will be coded "0". In the example shown in Figure 5, most ART regimens were recorded in medical records as either "1a" or "1b" (codes adopted in Country X for standard ART regimens according to national guidelines). These are on the list of regimens considered as appropriate first-line and are coded "1" in the tool. The observation No. 20 was recorded in the medical record as "other"; the actual regimen prescribed was TDF+3TC+EFV. This is on the list of appropriate regimens because it meets WHO guidelines and is coded "1" in the tool. Observations No. 11 and No. 16 were recorded in the medical record as "other"; the actual regimens prescribed were AZT+ddI+SQV and ABC+ddI. These do not meet the definition of appropriate first-line ART regimens in Country X, and are therefore coded "0" in the tool.

Once the "appropriate ART regimen" variable has been entered for all observations, the electronic tool automatically calculates the EWI score. This can be compared with the EWI target, and both can be seen in the tool's EWI result box.

The same operation will be carried out for all sites that participate in the EWI monitoring strategy.

Validation of EWI 1.a for each site

Validation exercises should be performed for each indicator. Information abstracted for EWI monitoring should be re-acquired from a different set of records for a proportion of patients for whom data was originally abstracted. If alternative records are not available, validation abstractors should re-acquire the information from the original source document (if possible, from a different area of the record).

If fewer than 300 patients are in the denominator for this EWI, use a random number process to select 30 patient identifiers from the list of patients for whom data was abstracted for HIVDR EWI 1.1a at the site. If more than 300 are in the denominator, use a random number process to select a number of patient identifiers equal to 10% of the denominator. The selected identifiers and the date of the initial ART prescription for each of the patients should then be given to the validation abstractors, who are not given the ART regimen information previously abstracted.

The validation abstractors in Country X will then go to the pharmacy at the ART site with the list of patent identifiers and the list of initial ART prescription dates. Abstractors will examine individual pharmacy records to see whether each patient picked up ARV drugs on the prescription date. If no drug pick-up is recorded on the provided dates, the validation abstractors will look at pick-ups over the following days until an ARV drug pick-up is registered. Patient identification, initial ART pick-up date, and the regimen picked up should be recorded on the electronic or

paper HIVDR EWI tool used for abstraction. Transporting the data to the central level should be performed as described previously in the EWI abstraction section.

At the central level, the regimen information from the validation exercise is compared with the information originally abstracted. If there is a discrepancy between the information recorded in the validation exercise and the routine EWI data abstraction for even one patient, information from the alternative set of records used for validation (in Country X, the individual pharmacy records) should be abstracted for all patients included in the EWI monitoring.

Note: If countries use pharmacy records for the initial abstraction, then clinical records should be used for the validation exercise.

Example 2: EWI 4a. On-time ARV drug pick-up

Country X's national HIVDR WG has also selected EWI 4a about on-time ARV drug pick-up for its EWI monitoring strategy.

EWI 4a definition (from section 4.4):

Percentage of patients picking up all prescribed ARV drugs on-time.

Numerator: the number of patients who picked up all their prescribed ARV drugs on time for two consecutive drug pick-ups after a selected month.

Denominator: the number of patients who picked up ARV drugs during a selected month.

Definition of "on-time pick-up of ARV drugs" (from section 5):

"On-time pick-up of ARV drugs" is defined as pick-up of ARV drugs on or before the day the previously dispensed drugs would have run out if taken according to schedule. Abstractors do not make the decision about whether a pick-up is "on time"; they only record the pick-up dates.

Data collection for EWI 4a monitoring

In order to capture EWI 4a as recommended in Appendix I, the following data are required for each patient who picked up ARV drugs during the selected month:

- a patient identifier;

- the last ARV drug pick-up date during the selected month ("baseline pick-up");

- the two consecutive ARV drug pick-up dates after the selected month ("pick-up 1" and "pick-up 2");

- the list of ARV drugs, including number of days dispensed, *or* strength and pill number dispensed at "baseline pick-up" and "pick-up 1";

- the date of transfer out after "baseline pick-up" (if two ARV drug pick-ups were not recorded after the "baseline pick-up");

- the date of death after "baseline pick-up" (if two ARV drug pick-ups were not recorded after the "baseline pick-up").

- the date of ART stop after "baseline pick-up" (that is, a recorded decision by the patient or physician that ARV should be stopped) if two ARV drug pick-ups were not recorded after the "baseline pick-up"

As explained in the previous example, before data abstraction is planned, the national HIVDR WG will have defined a denominator time period. In the Country X example, the denominator time period was set as the month of September of a designated year X (e.g. 2007). The recommended set of data shown above will be abstracted in all ART facilities, but only for patients who picked up ARV drugs during the selected month.

If available and reliable, pharmacy records (pharmacy registers and individual files) are the best source for this EWI. If pharmacy records cannot be used, prescription dates and prescription information from medical records may be used rather than actual pick-up dates and the names of ARV drugs picked up. Data abstraction teams should be trained to abstract the required set of data from available record-keeping systems at the sites. Examples of records actually filled in at sites should be used in the training. In Country X, ARV pick-up dates, regimens picked up, and number of days for which drugs have been dispensed are recorded sequentially by pick-up date on the pharmacy cards of individual patients (see Figure 6). Dates of death and transfer out are recorded on "HIV Care/ART Cards" (see Figure 7).

ART pharmacy registers (not shown) can be used to identify the ART numbers and medical record identification numbers of the patients who pick up ARV drugs during the selected denominator month. Data abstractors will locate the individual pharmacy cards of these patients and abstract the "baseline pick-up" date, the next two pick-up dates, and drug information for "baseline pick-up" and "pick-up 1". If there are not two pick-up dates after "baseline pick-up" recorded on the individual pharmacy card, data abstractors should go to the individual "HIV Care/ART Cards" and record the date of death, or transfer out (if applicable).

If a patient picked up ARV drugs more than once during the selected denominator month, data abstractors will record only the last drug pick-up in that month as the "baseline pick-up".

If the data abstraction team has been supplied with laptop computers and trained to use them, the data abstractor can transfer these data into the specific EWI 4a electronic tool (see Figure 8). If laptops are not available, or abstractors are not computer-trained, the data abstraction tools may be printed out as forms for manual recording.

Fig. 6   Example of source document for data abstraction: pharmacy records used to abstract information for EWI monitoring

Note: The data required to capture EWI 4a are indicated by arrows.

ARV drug pick-up dates

**Fig. 7   Example of source document for data abstraction: "HIV Care/ART
Cards" used to abstract information for EWI monitoring in Country X**

Note: The data required to capture EWI 4a are indicated by arrows.

Fig. 8 Data abstraction tool for EWI 4a

Once the data abstraction is completed (see Figure 9), the electronic forms can be sent by e-mail. Otherwise, laptops or flash drives can be delivered and the data downloaded to staff at the institution the national HIVDR WG designates to perform the analysis. If paper forms are used, they should be hand-delivered if possible to ensure confidentiality. If the forms are to be faxed, or sent by regular mail, a system must be devised to ensure confidentiality and guarantee delivery.

Data analysis for EWI 4a monitoring

As explained in our previous example, data entered directly into the electronic tool at the site can be used for EWI data analysis. However, data transfer from paper abstraction forms will have to be done at the central level.

Electronic tools have a built-in system that requires additional information to be entered in hidden columns at the central level before the EWI calculation and data analysis can be done.

In the case of EWI 4a, the "unhide" function will show three additional columns: "run-out date 1", "run-out date 2", and "death or transfer out before pick-up 1" (see Figure 10).

44

HIV DRUG RESISTANCE EARLY WARNING INDICATORS
WORLD HEALTH ORGANIZATION INDICATORS TO MONITOR HIV DRUG RESISTANCE PREVENTION AT ANTIRETROVIRAL TREATMENT SITES

Fig. 9 Example of electronic or manual data abstraction tool filled in with the required information, ready to be e-mailed, faxed or posted to the national HIVDR WG for analysis

HIV DRUG RESISTANCE EARLY WARNING INDICATORS - DATA ABSTRACTION TOOL   HIVResNet

COUNTRY: Country X	FACILITY: Hospital X
Data entry date:	01 February 2008

Indicator: On-Time ARV Drug Pick-Up (EWI 4a) - Percentage of patients picking up all prescribed ARV drugs on time

Time Period (These data refer to patients who have picked up ARV drugs during the selected month): Sep 2007

Total number of patients:	186	Adult or paediatric patients (A/P): A

Data abstractor (name/last name/contact phone):

No.	Patient ID	"baseline pick-up" – the date of the last drug pick-up during the selected month	ARV drugs picked up at "baseline pick-up" (List of ARV drugs dispensed; if number of days of ART dispensed is available, should be recorded in the appropriate column, otherwise strength and pill number should be specified)	Number of days of ART picked up at "baseline pick-up" - if available	"pick-up 1" – date of first drug pick-up after "baseline pick-up"	ARV drugs picked up at "pick-up 1" (List of ARV drugs dispensed; if number of days of ART dispensed is available, should be recorded in the appropriate column, otherwise strength and pill number should be specified)	Number of days of ART picked up at "pick-up 1" if available	"pick-up 2" – date of second drug pick-up after "baseline pick-up"	date of transfer out after "baseline pick-up" - if applicable	date of death after "baseline pick-up" - if applicable
1	xx31	01 September 2007	AZT 300/3TC 150 (60 tabs) + NVP 200 (60 tabs)	30	01 October 2007	AZT 300/3TC 150 (60 tabs) + NVP 200 (60 tabs)	30	30 October 2007		
2	xx32	01 September 2007	AZT 300/3TC 150 (60 tabs) + NVP 200 (60 tabs)	30	01 October 2007	AZT 300/3TC 150 (60 tabs) + NVP 200 (60 tabs)	30	30 October 2007		
3	xx35	01 September 2007	AZT 300/3TC 150 (60 tabs) + NVP 200 (60 tabs)	30	01 October 2007	AZT 300/3TC 150 (60 tabs) + NVP 200 (60 tabs)	30	30 October 2007		
4	xx37	01 September 2007	AZT 300/3TC 150 (60 tabs) + EFV 600 (30 tabs)	30					15 September 2007	
5	xx41	01 September 2007	AZT 300/3TC 150 (60 tabs) + EFV 600 (30 tabs)	30	01 October 2007	AZT 300/3TC 150 (60 tabs) + EFV 600 (30 tabs)	30	30 October 2007		
6	xx42	01 September 2007	AZT 300/3TC 150 (60 tabs) + EFV 600 (30 tabs)	30	01 October 2007	AZT 300/3TC 150 (60 tabs) + EFV 600 (30 tabs)	30	30 October 2007		
7	xx43	01 September 2007	AZT 300/3TC 150 (60 tabs) + EFV 600 (30 tabs)	30	01 October 2007	AZT 300/3TC 150 (60 tabs) + EFV 600 (30 tabs)	30	30 October 2007		
8	xx45	01 September 2007	AZT 300/3TC 150 (60 tabs) + EFV 600 (30 tabs)	30	01 October 2007	AZT 300/3TC 150 (60 tabs) + EFV 600 (30 tabs)	30	30 October 2007		
9	xx46	02 September 2007	AZT 300/3TC 150 (60 tabs) + NVP 200 (60 tabs)	30	02 October 2007	AZT 300/3TC 150 (60 tabs) + NVP 200 (60 tabs)	30	30 October 2007		
10	xx48	02 September 2007	AZT 300/3TC 150 (60 tabs) + NVP 200 (60 tabs)	30	02 October 2007	AZT 300/3TC 150 (60 tabs) + NVP 200 (60 tabs)	30	31 October 2007		
11	xx49	02 September 2007	AZT 300/3TC 150 (60 tabs) + NVP 200 (60 tabs)	30	02 October 2007	AZT 300/3TC 150 (60 tabs) + NVP 200 (60 tabs)	30			
12	xx50	02 September 2007	AZT 300/3TC 150 (60 tabs) + EFV 600 (30 tabs)	30	02 October 2007	AZT 300/3TC 150 (60 tabs) + EFV 600 (30 tabs)	30	31 October 2007		
13	xx52	02 September 2007	AZT 300/3TC 150 (60 tabs) + EFV 600 (30 tabs)	30	02 October 2007	AZT 300/3TC 150 (60 tabs) + EFV 600 (30 tabs)	30	31 October 2007		
14	xx54	02 September 2007	AZT 300/3TC 150 (60 tabs) + EFV 600 (30 tabs)	30	02 October 2007	AZT 300/3TC 150 (60 tabs) + EFV 600 (30 tabs)	30	31 October 2007		
15	xx55	03 September 2007	AZT 300/3TC 150 (60 tabs) + EFV 600 (30 tabs)	30	02 October 2007	AZT 300/3TC 150 (60 tabs) + EFV 600 (30 tabs)	30	31 October 2007		
16	xx56	03 September 2007	AZT 300/3TC 150 (60 tabs) + NVP 200 (60 tabs)	30	02 October 2007	AZT 300/3TC 150 (60 tabs) + NVP 200 (60 tabs)	30	31 October 2007		
17	xx60	03 September 2007	AZT 300/3TC 150 (60 tabs) + NVP 200 (60 tabs)	30	03 October 2007	AZT 300/3TC 150 (60 tabs) + NVP 200 (60 tabs)	30	31 October 2007		
18	xx61	03 September 2007	AZT 300/3TC 150 (60 tabs) + NVP 200 (60 tabs)	30	03 October 2007	AZT 300/3TC 150 (60 tabs) + NVP 200 (60 tabs)	30	31 October 2007		
19	xx62	03 September 2007	AZT 300/3TC 150 (60 tabs) + EFV 600 (30 tabs)	30	03 October 2007	AZT 300/3TC 150 (60 tabs) + EFV 600 (30 tabs)	30			
20	xx63	03 September 2007	AZT 300/3TC 150 (60 tabs) + EFV 600 (30 tabs)	30	03 October 2007	AZT 300/3TC 150 (60 tabs) + EFV 600 (30 tabs)	30	31 October 2007		25 October 2007

Fig. 10 Example of data additional information entered and analysis performed at central level by the HIVDR WG staff using the hidden functions of the EWI electronic data collection tool

Calculating EWI 4a will require some additional information to be entered at central level. As shown in figure 10, HIVDR WG staff will have to "unhide" columns and functions of the electronic tool, and fill in the required additional information. In Country X, data abstractors were able to record the number of days of ART dispensed at "baseline pick-up" and "pick-up 1", and the electronic tool automatically calculated the corresponding "run-out date 1" and " run-out date 2" (i.e. the dates when the drugs dispensed at "baseline pick-up" and "pick-up 1" respectively are expected to finish if taken according to correct schedule. The "run-out date" is also the date that sets the time interval by which the following drug pick-up is expected to occur). "Run-out date 1" and "run out date 2" are shown in the first two "unhidden" columns of the electronic tool (see Figure 10).

Depending on the source document used at the site, the exact number of days of ARV drugs dispensed to the patient may not be available for data abstraction. In these cases, the HIVDR WG staff will have to calculate "the number of days of ARV drugs dispensed" from available strength and pill number dispensed (see Appendix IV).

The third unhidden column in the electronic tool is "death or transfer out ". If a date of death or transfer out was recorded by the data abstractor, the central staff should classify that date in this column. If the patient died or was transferred out after "baseline pick-up" and no "pick-up 1" was made afterwards, code "1" should be entered in the tool. If the patient died or was transferred out after the date of "pick-up 1", code "0" should be entered in the tool. If a date of death or transfer out was not recorded, no code should be entered.

Once "death or transfer out before pick up 1" has been classified for all observations, the electronic tool automatically calculates the EWI score which can be compared with the EWI target; both are visible in the tool's EWI result box.

The same operation will be carried out at all sites participating in the EWI monitoring strategy.

Validation for each site

Validation exercises should be performed for each indicator. Information abstracted for EWI monitoring should be re-acquired from a different set of records for a proportion of patients for whom data was originally abstracted. If alternative records are not available, validation abstractors should re-acquire the information from the original source document (if possible, from a different area of it).

If fewer than 300 patients are in the denominator for this EWI, use a random number process to select 30 patient identifiers from the list of patients for whom data was abstracted for HIVDR EWI 4a at the site, and for whom a "pick-up 1" date was recorded. If more than 300 are in the denominator, use a random number process to select a number of patient identifiers equal to 10% of the denominator. The selected identification numbers and the date of the "pick-up 1" for each of the patients should then be given to the validation abstractors, who are not given the complete information previously abstracted.

For this indicator, the validation abstractors in Country X will use prescription forms that are filed by date of drug pick-up rather than by patient file number at ART site pharmacies. The validation

abstractors go to the pharmacy at the site with the list of patient identifiers and the list of "pick-up 1" dates. They examine individual prescriptions recorded on the "pick-up 1" dates to see whether each patient was dispensed ARV drugs on that date. If no prescription is recorded for the individual on the date listed, the validation abstractors will look at pick-ups over the next several days to see if an ARV drug pick-up is registered. Patient ID, ART pick-up date, and the regimen picked up should be recorded from the prescription form onto the electronic or paper HIVDR EWI tool used for abstraction. Transporting data to the central level should take place in the manner previously described for EWI abstraction.

At the central level, the regimen information from the validation exercise is compared with the information originally abstracted. If there is a discrepancy between the information recorded in the validation exercise and the routine EWI data abstraction for even one patient, information from alternative set of records used for validation (in Country X, the pharmacy prescription forms) should be abstracted for all patients included in the EWI monitoring.

Note: If countries use pharmacy records for the initial abstraction, if possible an alternative set should be used for validation. For instance, pharmacy registers or prescription forms filed by date of pick-up at the pharmacy should be used for validation, if the initial abstraction was performed using individual pharmacy records. In some countries, medical records can also be used for validation of this EWI, but only if, without exception, patients always pick up drugs on the day they are prescribed at all sites. Otherwise, comparing date of prescription with date of pick-up will not reliably validate the date of pick-up.

EWI electronic tools for EWIs 2, 3, 4a, and 4b have a built-in system that is able to automatically calculate the date an ART regimen that has been picked up will "run out" ("ART run-out date"). This is the date that all dispensed drugs will be finished if they were taken on schedule. The expected ART "run-out date" is automatically calculated when the "number of days of ARV drugs" dispensed is entered in the relevant column. If this information cannot be abstracted at the site, it must be calculated at the central level.

As shown in Example 2 of Appendix III, data abstractors will usually be able to abstract from patient cards, pharmacy registers, or individual pharmacy files, the name, strength and the pill number of each ARV drug dispensed at a certain drug pick up. If the exact number of days of doses dispensed is also recorded at the pharmacy, it can be abstracted and no additional calculations are required.

If the number of days of treatment dispensed is not recorded for all patients at all EWI sites, HIVDR WG staff at the central level should develop a look-up table for calculating the "number of days of ARV drugs" dispensed based on regimens, strengths, and dosing schedules used in the country. A knowledgeable member of the HIVDR WG, either a clinician or a pharmacist, should oversee the creation of the table. Staff involved in the creation of the table should initially refer to available national guidelines and dosing tables for standard prescribing practices for adult patients. They should also refer to the national drug registry for the exact list of ARV drugs registered for use in each country, including formulations, fixed-dose combinations, and strength and volumes of liquid formulations of ARV drugs. Different formulations for drugs described in national guidelines should be included in the table. The national drug registry may also assist staff in identifying additional drugs/formulations that should be included in the table. See Figure 11 for an example of a table for calculating the "number of days of ARV drugs" dispensed.

Fig. 11 Partial example of look-up table for calculating "number of days of ARV drugs" in adult patients on standard daily dosing schedules.

TABLE FOR CALCULATING "NUMBER OF DAYS OF ARV DRUGS" DISPENSED IN ADULT PATIENTS

ARV drug	strength (mg)	standard daily dose (mg)	No. dispensed	No. days
AZT	300	600	60	30
	300	600	120	60
	100	600	180	30
	100	600	360	60
d4T	40	80	60	30
	40	80	120	60
	30	60	60	30
	30	60	120	60
3TC	150	300	60	30
	150	300	120	60
	300	300	30	30
	300	300	60	60
TDF	300	300	30	30
	300	300	60	60
ABC	300	600	60	30
	300	600	120	60
NVP	200	400	60	30
	200	400	120	60
	200	200*	30	15

* During the first two weeks of tretment, and before dose escalation to the adult standard daily dose, NVP is prescribed as 200 mg once a day.

EFV	600	600	30	30
	600	600	60	60
	200	600	90	30
	200	600	180	60

For EWI sites where non-standard regimens are used, responsible staff members should review the table with a site-based pharmacist and add additional regimens that are used at that site, translating ARV drug strength and pill numbers dispensed into "number of days".

If information for a regimen does not appear in the table when calculations are being performed, the staff member should consult the designated knowledgeable member of the HIVDR WG for assistance in calculating the "number of days". Calculations for non-standard drugs or regimens can be done as follows:

Calculating the number of days of ARV drugs dispensed for discrete formulations (pills, tablets, capsule) for adult patients taking standard drug doses:

Item = pill, tablet, or capsule

Number of items per dose = dose (mg) / strength (mg/item)

Number of items per day = frequency of doses in one day multiplied by the number of items per dose

Number of days dispensed (i.e. duration in days of the number of items dispensed) = number of items dispensed/number of items per day.

Example:

Among other ARV drugs, patient X collected 60 tablets of AZT 300 mg. The standard AZT dose for adult patients is 300 mg. The dose frequency (the number of times a dose is taken) is two times per day. Calculating the number of days of ART for discrete formulations would then take place as follows:

Item dispensed: AZT tablet, 300 mg

Number of items dispensed: 60

The person making the calculation should refer to a tool on standard regimens and dosing frequencies in the country, which would state:

Dose and frequency of adult AZT prescription: 300 mg, two times daily

Number of items per dose = 300 mg/ (300 mg/item) = one item per dose

Number of doses per day = two doses per day multiplied by one item per dose = two items per day

Duration of items dispensed (i.e. number of days dispensed) = 60 items/two items per day = 30 days of AZT.

However, if patient X collected 80 tablets of AZT 150 mg, among other ARV drugs, the calculation would be different. The standard AZT dose in adult patients is still 300 mg, and the frequency is still two times per day. But because the strength of the tablet dispensed is different, the calculation changes.

Item dispensed: AZT tablet, 150 mg

Number of items dispensed: 80

Dose and frequency of adult AZT prescription: 300 mg, two times daily

Item = AZT tablet, 150 mg

Number of items per dose = 300 mg/ (150 mg/item) = two items per dose

Number of items per day = two doses per day multiplied by two items per dose = four items per day

Duration of items dispensed (i.e. number of days dispensed) = 80 items/four items per day = 20 days of AZT.

Calculating the number of days of ARV drugs dispensed for liquid formulations in paediatric patients who are taking individualized drug doses.

The number of days dispensed of ARV liquid formulations (syrup, solution, etc.) usually used in paediatric patients may be more difficult to capture. This is because the prescriptions are not standard and daily doses are individually calculated for each patient (according to weight, and body surface area), and are constantly adjusted over time.

However, if the prescribed daily dose is recorded, the following calculation can be performed.

Item: bottle of liquid formulation of a certain volume (in ml) with a certain drug concentration (mg/ml)

Number of mg in one item = drug concentration (mg/ml) multiplied by volume of the item (ml)

Prescribed Daily dose (mg) = number of doses per day multiplied by dose (mg)

Duration of items dispensed = (total dose in one item (mg) multiplied by number of items dispensed)/daily dose (mg/day)

Example

Among other ARV drugs, the caregiver of patient X collected three bottles of AZT syrup, for which the prescribed dose was 80 mg twice a day. Calculating the number of days of ART for liquid formulations in paediatric patients would then be as follows:

Item: 240 ml bottle of AZT liquid formulation with an AZT concentration of 10 mg/ml

Number of items: three

Number of mg in one item (mg) = 10 mg/ml multiplied by 240 ml = 2400 mg

Daily dose (mg) = two per day multiplied by 80 mg = 160 mg per day

Duration of items dispensed = (2400 mg multiplied by 3)/160 mg per day = 7200/160 = 45 days of AZT syrup.

52

HIV DRUG RESISTANCE EARLY WARNING INDICATORS
WORLD HEALTH ORGANIZATION INDICATORS TO MONITOR HIV DRUG RESISTANCE PREVENTION AT ANTIRETROVIRAL TREATMENT SITES

APPENDIX V
ANTIRETROVIRAL TREATMENT SITE PROFILES

To support interpretation of EWI results for an ART site and planning of public health actions, it is helpful to refer to relevant information recorded in a standardized format. WHO recommends that an ART site profile be filled in for each EWI site at least annually, preferably at the beginning of each calendar year. For the first year in which EWIs are monitored, a profile should be filled in for both the current year and the previous year. If a particular bulleted item in the profile has changed since the previous profile, the month in which the change took place should be noted. The following information is likely to be relevant (HIVDR WG may specify additional information to be recorded):

- name of ART site;
- date of profile;
- types of patients treated at site;
- number of patients with HIV who are not on ART;
- number of patients with HIV receiving ART;
- role of staff who dispense ARV drugs: physician, nurse, pharmacist, other (specify);
- location of ARV drug pick-ups: pharmacy in clinic, pharmacy off-site, treatment room in clinic, other (specify);
- role of staff who dispense ARV drugs (physician, nurse, pharmacist, other (specify);
- procedures for monitoring, reporting, and acting on drug shortages;
- procedures for following up patients who do not return to clinic for ART appointments (write "None" if no procedures);
- type of adherence support provided (describe type of support, staffing);
- "prevention for positives" program (describe program and staffing);
- costs of care to patient (record 0 if no cost):
  — cost of initial registration at clinic;
  — cost of each appointment;
  — cost of first-line ARV drugs and/or pharmacy pick-up charge;
  — cost of each routine laboratory test used in ART;
  — cost of special laboratory tests used in ART;
- maximum, minimum, and mean distance traveled by patients to clinic (brief description of most common means of transport);
- longest, shortest, and mean waiting times for routine ART appointment at clinic;
- longest, shortest, and mean waiting times for ART drug pick-ups;
- days of the week, and clinic opening and closing times for ART clinical appointments;
- days of the week and pharmacy opening and closing times for ARV drug pick-ups;
- needs identified by site personnel for better care delivery.

REFERENCES

1. World Health Organization, Joint United Nations Program on HIV/AIDS, UNICEF. TOWARDS UNIVERSAL ACCESS: Scaling up priority HIV/AIDS interventions in the health sector. Progress Report, April 2007. Available from: http://www.who.int/hiv/mediacentre/universal_access_progress_report_en.pdf

2. World Health Organization. Antiretroviral Therapy for HIV Infection in Adults and Adolescents in Resource-Limited Settings: Towards Universal Access: Recommendations for a public health approach. 2006. Available from: http://www.who.int/hiv/pub/guidelines/adult/en/index.html

3. Bennett DE, Bertagnolio S, Sutherland D, Gilks CF. The World Health Organization's Global Strategy for Prevention and Assessment of HIV Drug Resistance. *Antiviral Therapy* 2008; **13 Suppl 2**:1-13.

4. World Health Organization. Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: towards universal access. Recommendations for a public health approach. 2006. Available from: http://www.who.int/hiv/pub/guidelines/art/en/index.html

5. Bautista-Arredondo S, Mane A, Bertozzi SM. Economic impact of antiretroviral therapy prescription decisions in the context of rapid scaling-up of access to treatment: Lessons from Mexico. *AIDS* 2006; **20**:101-109.

6. Spacek LA, Shihab HM, Kamya MR et al. Response to antiretroviral therapy in HIV-infected patients attending a public, urban clinic in Kampala, Uganda. *Clin Infect Dis* 2006; **42**:252-259.

7. Oyugi JH, Byakika-Tusiime J, Ragland K et al. Treatment interruptions predict resistance in HIV-positive individuals purchasing fixed-dose combination antiretroviral therapy in Kampala, Uganda. *AIDS* 2007; **21**:965-971.

8. World Health Organization. Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants in Resource-Limited Settings: Towards Universal Access: Recommendations for a Public Health Approach. 2006. Available from: http://www.who.int/hiv/pub/guidelines/pmtct/en/index.html

9. Bangsberg DR. Adherence, viral suppression, and resistance to antiretroviral therapy. *AIDS Reader* 2007; **17 Suppl S**:S11-S15.

10. Parienti JJ, Massari V, Descamps D et al. Predictors of virologic failure and resistance in HIV-infected patients treated with nevirapine- or efavirenz-based antiretroviral therapy. *Clin Infect Dis* 2004; **38**:1311-1316.

11. Parienti,JJ, Das-Douglas,M, Massari,V, Guzman,D, Deeks,SG, Verdon,R, and Bangsberg,DR. Not all missed doses are the same: sustained NNRTI treatment interruptions predict HIV rebound at low-to-moderate adherence levels. *PLoS ONE.*, 2008;**3**:e2783-

12. Orrell C, Harling G, Lawn SD et al. Conservation of first-line antiretroviral treatment regimen where therapeutic options are limited. *Antivir Ther* 2007; **12**:83-88.

54

HIV DRUG RESISTANCE EARLY WARNING INDICATORS
WORLD HEALTH ORGANIZATION INDICATORS TO MONITOR HIV DRUG RESISTANCE PREVENTION AT ANTIRETROVIRAL TREATMENT SITES

13. Gross R, Yip B, Lo Re V et al. A Simple, Dynamic Measure of Antiretroviral Therapy Adherence Predicts Failure to Maintain HIV-1 Suppression. *JID* 2006; **194**:1108-1114.

14. Grossberg R, Zhang Y, Gross R. A time-to-prescription-refill measure of antiretroviral adherence predicted changes in viral load in HIV. *J Clin Epidemiol* 2004; **57**:1107-1110.

15. Bisson GP, Gross R, Bellamy S., Chittams J, Hislop M, Regensberg L, Frank I, Maartens G, and Nachega JB. Pharmacy Refill Adherence Compared with CD4 Count Changes for Monitoring HIV-Infected Adults on Antiretroviral Therapy. *PLoS Med*, 2008;**5**:e109-

16. Gardner,EM, Burman,WJ, Maravi,ME, and Davidson,AJ. Selective drug taking during combination antiretroviral therapy in an unselected clinic population. *J.Acquir.Immune. Defic.Syndr.*, 1-11-2005;**40**:294-300

17. Mukherjee JS, Ivers L, Leandre F. Antiretorivral Therapy in Resource-Poor Settings: Decreasing Barriers to Access and Promoting Adherence. *J Acquir Immune Defic Syndr* 2006; **43**:S123-S126

18. Okeke IN, Klugman KP, Bhutta ZA et al. Antimicrobial resistance in developing countries. Part II: Strategies for containment. *Lancet Infectious Diseases* 2005; **5**:568-580.

19. Laurent C, Meilo H, Guiard-Schmid JB, Mapoure Y, Noël JM, M'Bangué M. Antiretroviral therapy in public and private routine health care clinics in Cameroon: lessons from the Douala antiretroviral (DARVIR) initiative. Clin Infect Dis . *Clin Infect Dis* 2005; **41**:108-111.

20. Bangsberg DR, Hecht FM, Charlebois ED, Chesney,M, and Moss,A. Comparing Objective Measures of Adherence to HIV Antiretroviral Therapy: Electronic Medication Monitors and Unannounced Pill Counts. *AIDS and Behavior*, 2001;**5**:275-281.

21. Giordano TP, Guzman D, Clark R, Charlebois ED, Bangsberg DR. Measuring adherence to antiretroviral therapy in a diverse population using a visual analogue scale. *HIV Clin Trials* 2004; **5**:74-79.

22. Havlir DV, Richman DD. Viral dynamics of HIV: implications for drug development and therapeutic strategies. *JAMA* 2006; **296**:847-843..