HIV DRUG RESISTANCE (HIVDR) EARLY WARNING INDICATORS (EWIs) SURVEY IN ETHIOPIA

October , 2012

THE ETHIOPIAN HEALTH AND NUTRITION RESEARCH INSTITUTE (EHNRI)

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List of Tables 6
Lists of figures 6
Preface 7
Acronyms 8
Summary 9
1. INTRODUCTION 11
2. BACKGROUND AND JUSTIFICATION 11
2.1. Background 11
2.2. Justification 13
3.0 OBJECTIVE 14
3.1. General Objective: 14
3.2. Specific Objectives; 14
4. MATERIALS AND METHODS 15
4.1. Study design 15
4.2. Selection of sites 15
4.3. Source population and sample size calculations 15
5. SURVEY PROCEDURE 17
5.1. Data collection 17
5.2. Training 17
5.3. Inclusion criterion for the sites 17
5.4. Exclusion criteria 17
5.5. Data collection and management 17
5.6. Data collection procedure 18
5.7. Data quality management 18
5.8. Study variables 20
6. FINDINGS 20
6.1. Settings 20
6.2. Number of patients on ART: 22
6.3. Findings on the Early Warning indicators (EWIs) 23
6.3.1. Early Warning Indicator-1. ART prescribing practices 23
6.3.2. Early Warning Indicator-2. Patients lost to follow-up during the first 12 months of ART 24
6.3.3. Early Warning Indicator-3a. Patient retention on first-line ART at 12 months 25

6.3.4. Early Warning Indicator-5b. ART clinic appointment keeping..... 26
6.3.5. Early Warning Indicator-6b. ARV drug supply continuity 27
6.3.6. Transfer outs and deaths 31
7. CONCLUSIONS..... 31
8. GENERAL RECOMMENDATIONS 32
9. ACKNOWLEDGMENTS..... 33
10. REFERENCES..... 34
Annex-1. Early Warning Indicators (EWIs)..... 36

List of Tables

Table-1. Sample size calculation for the determination of each EWIs in selected Health institutions.....16

Table-2. Number of health institutions included in each rounds of surveys in 2008, 2009 and 2010 20

Table-3. Name, regions, affiliation, ART start date and current status of the assessed health facilities 21

Table-4. Summarized determined EWIs for each health facility in 2008, 2009 and 2010. 28

Lists of figures

Figure-1. Schematic diagram for data flow in the EWIs surveys 19

Figure-2. Number of new patients, currently on ART, calculated, WHO sample size and collected data in the survey periods 22

Figure-3. Average percentages of three EWIs in 2008, 2009 and 2010 29

Figure-4. Percentage of health facilities which did not meet WHO criteria for the three EWIs In the survey years 30

Preface

As the HIV epidemic matures, the number of HIV infected individuals may be influenced by the presence of drug resistance strains. Because of this, the World Health Organization recommends the countries to survey and monitor the presence/emergence and level of HIVDR in their respective countries. Therefore, the presence of data on three aspects of HIVDR is recommended by each national program such as Early Warning Indicators for HIVDR, surveying threshold levels of HIVDR and prevention and monitoring of HIVDR in selected and representative sites of the country.

In Ethiopia, ART started freely in 2005. However, complete and continuous data was not available related to HIVDR. Due to this and the increasing people on ART, it is wise to see the levels of each parameter for HIVDR. Therefore, EWIs were surveyed for three years in more than 40 representative sites of the country. This will help to know the level of factors related to HIVDR and the documentation system of the sites such as prescription patterns, lost to follow-ups, retention of patients on the first line drugs, appointment keeping of the patients and continuity of drug supply.

I hope this will give an insight for the programmers to see the status of health facilities for the indicated indicators for their successes and challenges and will help in providing some additional tools to solve the problems. As one of the major activities of the institute in supporting the HIV/AIDS control program is producing evidences, EHNRI will continue to produce data for decision making to improve programs.

Amha Kebede (PhD)

Director General, EHNRI

Acronyms

AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretroviral Therapy
AZT	Zidovudine (also known as ZDV)
EWI	Early Warning Indicator
HAART	Highly active anti-retroviral therapy
HIV	Human immunodeficiency virus
HIVDR	HIV drug resistance
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
PI	Protease Inhibitor
PR	Protease
RNA	Ribonucleic Acid
RT	Reverse Transcriptase
TWG	Technical Working Group
UNAIDS	Joint United Nations Programme on HIV/AIDS
VL	Viral Load
WHO	World Health organization

Summary

Background: *Drug resistance for HIV therapy is monitored using three methods: Determination of Early Warning Indicators (EWIs), survey of newly transmitted HIV drug resistance (threshold), and monitoring and prevention survey. Until now, one threshold survey in 2005 was conducted in Addis Ababa that showed the absence of major HIV drug resistance mutations. However, more evidence is required on the performance of the health facilities, which indicates their ART program to monitor early emergence of HIVDR.*

Objective: *To determine the level of Early Warning Indictors (EWIs) for HIV Drug Resistance (HIVDR) in Ethiopia*

Methodology: *The World Health Organization (WHO) developed a new MS-EXCEL tool for the determination of EWIs for HIVDR from health facilities by reviewing patient's follow-up chart. The tool is currently being used in all WHO supported countries. In 2008, 2009 and 2010 in Ethiopia, a facility based survey was conducted in 45 (2008) and 49 (2009 and 2010) health facilities for a period of 15 months data abstraction. The value of each EWI indicator was directly calculated by the tool. In this survey data was collected on 5 out of 8 EWIs. They were: Percentage of adult patients initiating ART at the site who are initially prescribed, or who initially pick up from the pharmacy, an appropriate first-line ART regimen (**EWI-1**), Percentage of patients initiating ART at the site who are lost to follow-up 12 months after ART initiation (**EWI-2**), Percentage of adult patients initiating ART at the site who are taking an appropriate first-line ART regimen 12 months later **(EWI-3a)**, Percentage of patients initiating ART at the site who attended all scheduled or expected clinical consultations on-time during the first 12 months of ART (**EWI-5b)** and Percentage of months in a designated year in which there were no ARV drug stock-outs **(EWI-6a).***

Result: *Nationally, during the survey period 18,539 (2008), 20,222 (2009) and 17,074(2010) new patients were enrolled for ART in the selected health institutions. In this survey, in the selected health institutions, 77:23 ratio new patients were served in Hospitals and health centers. Of the new patients enrolled in the selected health facilities, based on the WHO guideline, the sample size calculated was 5564 (36.4%) in 2008, 5894(35.5%) in 2009 and 5637(42.0%) in 2010. However, data was collected for 6,302 (41.2% in 2008), 6,357(38.3%, in 2009) and 6,236 (46.5% in 2010 of the new patients. EWI-1 and EWI-6a were 100% in all health institutions surveyed in all the*

surveying years. There were some complaints about the short life stocks of ARV drugs reported from some health institutions. However, EWI-2 varied 0-35% in 2008, 0-30% in 2009 and 0-29% in 2010 (expected level ≤20%). Of the health institutions surveyed in 2008, 2009 and 2010, 40%, 4.1% and 4.1% of the health institutions had above 20% lost-to-follow-up cases, respectively. In the same manner, EWI-3a was in the range 54% to 94% (2008), 38.3-95% (2009) and 42.9%-93.9% (2010). However, 44.4 % (2008), 22.4% (2009) and 20.4% (2010) were less than 70% (expected level ≥70%). Ranges for EWI-5b varied 69%-100% (2008), 78%-100% (2009) and 71%-100% (2010) [expected level ≥80%]. However, 13.3% (2008), 2.0% (2009) and 4.1% (2010) were below 80%. In the process of collecting data problems related to the archiving and retrieving records in the health facilities for use was the major challenge in most of the health facilities assessed. The use of computerized data base system is available in all hospitals but only some health centers.

***Conclusion**: Prescription for the first line and the drug supply for ARVs remain higher and need to be further strengthened. However, most of the health facilities are found to be out of the expected ranges of WHO recommendation such as lost-follow-up and patient retention on appropriate first line drugs at 12 months of ART. Thus, strong programmatic intervention is highly recommended to prevent the early emergence of HIVDR, which could be a threat for the future success of ART program.*

1. INTRODUCTION

Initiation of ART is the hall mark for the reduction of plasma viral load and increase in CD4+ T cell number as indicator for the better performance of patients and the drug itself. However, in some patients, despite all the procedures required for ART are followed, some both virological and immunological failures could exist. This may lead to the occurrence of HIV drug resistance to the currently used first line drugs and will lead to the introduction of the second line drugs. To prevent and monitor HIVDR, the World Health Organization (WHO) recommends three types of surveys, namely Early Warning Indicators (EWI) survey threshold survey to assess transmitted HIVDR strains in a population and prevention monitoring survey to assess drug resistance emerging during treatment [1]. The last two survey are somewhat expensive, require laboratory procedures and are recommended to be done periodically and in selected settings. On the other hand, EWI survey is less expensive, relatively easy to implement and gives valuable information on how the ART program is functioning to prevent emergence of HIVDR WHO recommends six major and two optional early warning indicators to be assessed in the health facilities that provide ART services. It is with this objective that the present survey were conducted to determine the EWI in selected geographically representative Hospitals and health centers nationally, which initiates ART since 2005. This will help to predict HIV drug resistance in the treated population and recommend mechanisms for monitoring, better treatment outcomes and patient management.

2. BACKGROUND AND JUSTIFICATION

2.1. Background

Since its identification in the early 1980's [2,3], the Human Immunodeficiency Virus pandemic has been mounting its attack globally at an alarming rate. According to reports from UNAIDS/WHO [4], the global burden of HIV at the

end of 2010 was estimated to be 33.2 million, of whom nearly 67% of them were from Sub-Saharan Africa.

The availability and widespread use of Highly Active Antiretroviral Therapy (HAART) in developed countries has shown that HIV/AIDS-related mortality and morbidity can be reduced significantly [5,6]. Unfortunately, access and monitoring of these drugs to the developing world remained a challenge due to its unaffordable cost and methods of monitoring.

In Ethiopia, with nearly 80 million people, about 759,000 people are estimated to be living with HIV/AIDS [4]. The projection of HIV from the Demographic Health survey (DHS) for the year 2012 revealed that the national HIV prevalence was 1.3% (urban 3.8 % and rural 0.5%)[7].

The expansion of the services, however, may raised serious concerns regarding potential barriers that could hamper the long-term success of the program [9, 10]. The most prominent of these fears is the potential of emergence of an epidemic of drug-resistant HIV strains. Experience from the use of HAART in the developed world has indicated that antiretroviral-associated resistance is common among HIV 1-infected individuals who are naïve to the drugs [11, 12]. Such transmitted drug resistance can reach 15% or more in populations in which ARV has been in use for longer periods of time [9]. Therefore, monitoring the prevalence of transmitted drug resistance in areas where ART is introduced extensively is, therefore, important if the treatment program is to be a success.

Although it is universally recognized that combined ART has dramatically reduced HIV-related mortality, one major concern over the rapid scaling up of ART is the emergence and transmission of HIV drug resistant strains at the population level. This could lead to the failure of basic ART programs as well as strategies to prevent HIV transmission through pre-exposure prophylaxis or the use of topical microbicides.

Antiretroviral treatment (ART) was started in Ethiopia in 2003 formally with cost sharing [8]. The launching of the ART program in 2003 helped make five ARV drugs (three NRTIs: Zidovudine, Lamivudine, and Stavudine; and two NNRTIs: Nevirapine and Efavirenz) available to the public. The drugs were distributed to a few selected pharmacies, and were available for patients by prescription from ART-certified physicians [8].

However, the country initiated free ART in 2005 with a support of Global Fund for Tuberculosis, AIDS and Malaria (GFTAM), and the U.S. President's Emergency Plan for AIDS Relief (PEPFAR). Of those enrolled for HIV care (>500,000) more than 300,000 of them had ever started ART. For these patients , currently there are 838 sites delivering the service and 274,708 HIV infected patients are currently on ART as of August 2012 [9,13,14]

Despite some challenges such as monitoring methods for ART, the presence of national guidelines in the country helped the ART program to expand and more people to get the treatment [8]. Currently, two first line NNRTI-based regimens are in use for adults and adolescents: TDF/Zidovudine (AZT), Lamivudine (3TC), and Nevirapine (NVP)/ Efavirenz (EFV). Second line regimens include Abacavir (ABC) or Tenofovir Disoproxil Fumarate (TDF) or Zidovudine (if not used), plus Didanosine (ddI), plus either of the following low-dose Ritonavir-boosted protease inhibitors: Lopinavir (LPV), or Saquinavir (SQV), or Indinavir (IDV). There are also separate regimens recommended for pregnant women and children.

2.2. Justification

The World Health Organization recommends three major methods of monitoring drug resistance of HIV [15]. The first method which is expected to be simple and gives the closest proxy indicator of HIVDR is the monitoring of Early Warning Indicators (EWI). These are indicators which can be monitored at the health institution level to see how far the patients are relatively liable to

HIVDR. The second method is the identification of recently transmitted drug resistance strains using DNA sequencing. This method requires a more sophisticated laboratory method such as using DNA sequencing which cannot be feasible or of limited application in developing countries both technically and economically. The third method, which used the method of DNA sequencing like the second one, however, is based on the follow-up of cohorts of patients in clinical settings before and after the initiation of ART after 12 months of treatment. Although few studies conducted, in Ethiopia, the prevalence of recently transmitted HIVDR is reported to be below 5% [16]. However, since all the methods used in these studies are very unlikely to be used for routine monitoring of HIVDR, the use of EWI, which includes, lost follow-up, pill count, adherences, continuity of drugs, missed appointments among others are the simplest ones to indicate the occurrence of HIVDR. These indicators can be retrieved from the documentation of the health institution which delivers ART. One major challenge in these types of indicators could be the presence of weak documentation system.

3.0 OBJECTIVE

3.1. General Objective:

To assess how ART program is functioning in representative ART sites to prevent emergence of HIVDR based on the WHO-recommended early warning indicators (EWIs) for HIV drug resistance.

3.2. Specific Objectives;

1. To collect and analyze HIVDR early warning indicators in selected Hospitals and Health Centers
2. To identify ART program factors that may predispose to emergence of HIV drug resistance in the survey health facilities

3. To provide recommendations for the survey health facilities and ART Program to improve on factors that may facilitate emergence of HIV drug resistance

4. MATERIALS AND METHODS

4.1. ***Study design***

This survey was a cross sectional one time point health facility based survey for consecutively three years (2008, 2009 and 2010). Data available in the selected health institutions were abstracted in 45 (2008) and 49 (2009 and 2010) selected geographically representative hospitals and health centers nationally in the indicated years

4.2. Selection of sites

The selected sites were based on the following criteria

1. The hospitals with a minimum of 500 patients on ART
2. Health centers with a minimum of 200 patients on ART
3. The Hospital to Health center patient load was assumed to be 70:30
4. Of the hospitals in the regions random selection was made out of those which fulfilled the above criteria to have

4.3. Source population and sample size calculations

The source population for the study was those HIV infected individuals who were enrolled for ART since 2005 and had at least one year complete data on the recommended early warning indicators (EWIs) in the year 2008, 2009 and 2010 for 15 months visit. The sample size of each site was calculated based on the formula and Table given below from WHO (Table-1)..

Table-1. Sample size calculation for the determination of each EWIs in selected Health institutions.

Annual number of eligible patients at the site	Number to be samples at the site (Sample size)
1-75	All
76-110	75
111-199	100
200-250	110
251-299	120
300-350	130
351-400	135
401-450	140
451-550	145
551-700	155
701-850	160
851-1600	175
1601-2150	180
2151-4340	200
4341-5670	210
5671-10000	215
>10000	WHO

WHO- if the number of new patients per year is >10,000 for the sample size determination consulting WHO is recommended

5. SURVEY PROCEDURE

5.1. Data collection

Both electronic MS-EXCELL tool developed by WHO and paper formats (printed from MS-EXCELL tool) were used for the data collection to abstract the data from patient follow-up charts [17].

5.2. Training

In these surveys, two levels of training were given. The first level was done by the support of WHO AFRO and WHO country office for supervisors (n=5). Later on, the training was given on the basics of the HIVDR, the methodologies which are currently used to determine the level of HIVDR worldwide, on the definitions of each EWIs and the new tool developed by WHO to collect data from each facilities using MS-EXCELL sheet for 21 individuals from WHO (n=1), CDC-Ethiopia (n=3), FHAPCO (n=1), EHNRI (n=6) and other data collectors (n=10).

5.3. Inclusion criterion for the sites

ART sites which gave service for at least 15 months. Hospitals were selected if they had at least 500 patients currently on ART and health centers were selected if they had at least 200 patients on ART for the year 2008, 2009 and 2010.

5.4. Exclusion criteria

ART sites with data less than 15 months for 2008/2009, 2009/2010 and 2010/2011, and Hospitals with less than 500 patients on ART.

5.5. Data collection and management

Data collected from the sites was entered using MS-EXEL program tool developed by WHO. The data was analyzed based on the values calculated directly from the tool and are reported to the FMOH for action

5.6. Data collection procedure

According to the recommendation by WHO for such type of surveys, all ART sites in the country, *or* representative sentinel sites are recommended. We used the second option (representative sentinel sites from all regions in the country) due to logistic problems to cover all the ART sites in the country. In detail, all the sites that initiated ART in 2005 were enumerated. Of these enumerated sites, 70 sites were selected according to their geographical distributions in the regions. At least one Hospital from one region (from a total of 9 regions and 2 city administrations) was selected. However, larger regions and those with high patient loads had better representation. The data collection procedure was the following: A group of people form EHNRI, WHO, FHAPCO and CDC-Ethiopia including data collectors were visited the sites. A pilot study was conducted in two health institutions in Addis Ababa. A lesson learnt from the pilot phase was used for the field work and was coordinated for each group. A group of at least three people (one supervisor and two data abstractors) were included in the teams. At the health facility level, at least three people were involved in the process. They were: data base section heads, patient follow-up chart collectors from the archives and nurses/pharmacists for data collection from either the Pre-ART register or from the pharmacy.

5.7. Data quality management

Pre-data collection training was given for the data abstractors. Moreover, during data collection supervisors were in the team to see the quality of data collection tools and others. The planned data flow was as indicated in the following figure.

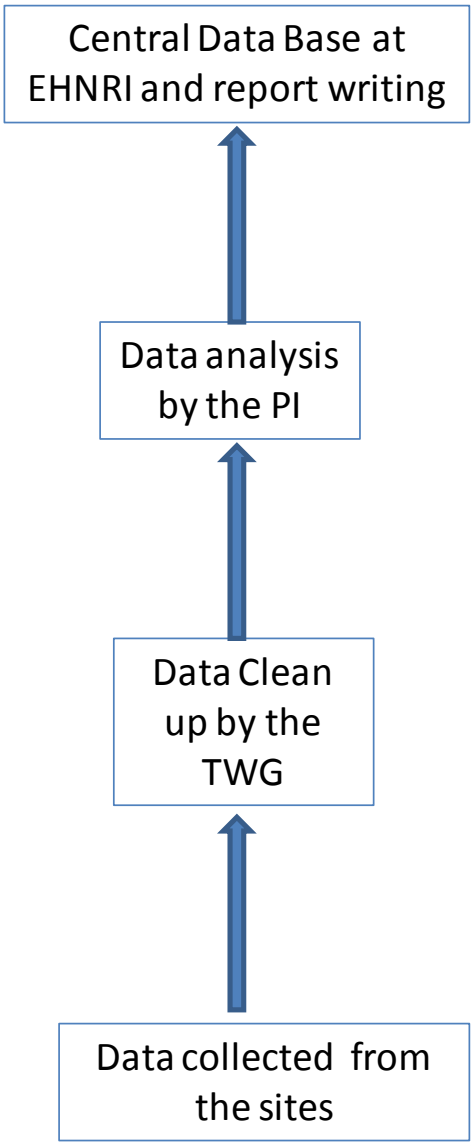


Figure-1. Schematic diagram for data flow in the EWIs surveys

5.8. Study variables

According to WHO, there are eight survey indicators, out of which two of them are optional. These variables are annexed as Annex-1.

6. FINDINGS

6.1. Settings

As indicated in Table –2, complete data was available for a total of 45 (in 2008) and 49 (in 2009 and 2010) sites. The detailed health institution classification is given below.

Table-2. Number of health institutions included in each rounds of surveys in 2008, 2009 and 2010

Year of data abstraction (GC)	Type of health facility		
	Hospital	Health center	Total
2008	28	17	45
2009	33	16	49
2010	33	16	49
2009/2010	33	16	49
2008/2009/2010	26	11	37

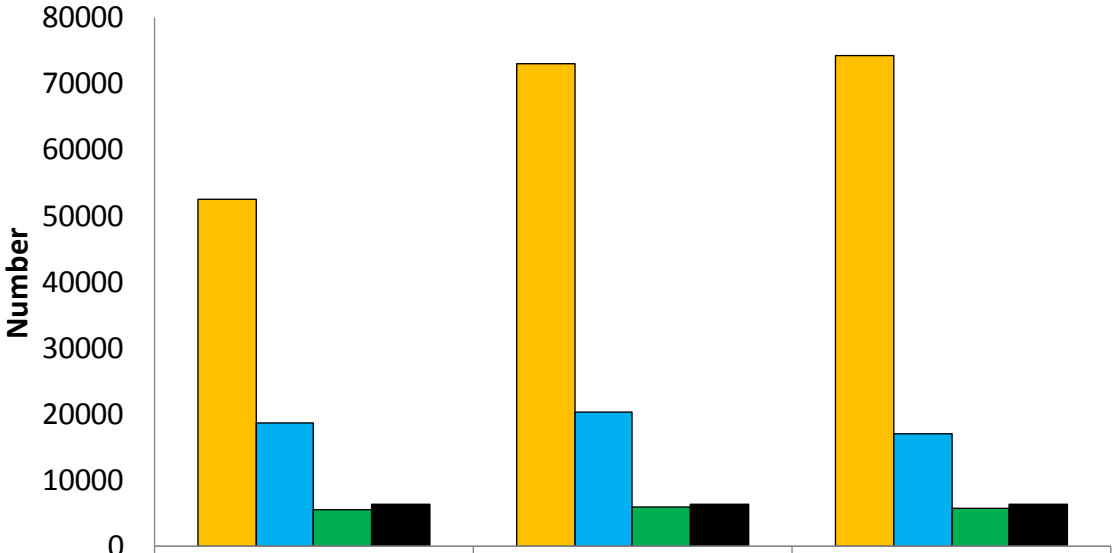
The ratio of selection of hospitals and health centers was assumed to be 70:30 patient load at the time of the survey. All the hospitals had patients ≥ 500 patients on ART, while the health centers had ≥ 200 patients on ARV on the time of the survey. Table-1 indicates the name, affiliation, ART start date and current status of the assessed health facilities in the selected regions of the country. As can be seen from Table-3, majority of them were public health institutions with one exception (private hospital).

Table-3. Name, regions, affiliation, ART start date and current status of the assessed health facilities

	Site	Health facility	Region	Affilaton	start date	Started ART as
1	Adama	Hosp	ORO	Public	2005	free
2	Addis Zemen	HC	AMH	Public	Sep-06	free
3	Adigrat	Hosp	TIG	Public	2005	free
4	Akaki	HC	AA	Public	2007	free
5	Alamata	Hosp	TIG	Public	Aug-06	free
6	Alert	Hosp	AA	Public	2005	free
7	Ambo	Hosp	ORO	Public	2005	free
8	Arbaminch	Hosp	SNNP	Public	2005	free
9	Assosa	Hosp	BENSH	Public	2005	free
10	Awash	HC	AFAR	Public	2007	free
11	Axum	Hosp	TIG	Public	2005	free
12	Bambasi	HC	BENSH	Public	Oct-06	free
13	Bedele	HC	ORO	Public	Mar-07	free
14	Betezata	Hosp	AA	Private	2003	Paying
15	Bole HC 17	HC	AA	Public	2006	free
16	Dangila	HC	AMH	Public	Sep-06	free
17	Debrebirhan	Hosp	AMH	Public	2005	free
18	Debretabor	Hosp	AMH	Public	2005	free
19	Debre Markos	Hosp	AMH	Public	2005	free
20	Dessie	Hosp	AMH	Public	2005	free
21	Dila	Hosp	SNNP	Public	2005	free
22	Dilchora	Hosp	DD	Public	2005	free
23	Dupti	Hosp	AFAR	Public	2006	free
24	Este	HC	AMH	Public	Nov-06	free
25	Felegehiwot	Hosp	AMH	Public	2005	free
26	Finoteselam	Hosp	AMH	Public	2005	free
27	Gebreguracha	HC	ORO	Public	Mar-07	free
28	Ghandi	Hosp	AA	Public	2005	free
29	Gondar	Hosp	AMH	Public	2005	free
30	Hiwo Fana	Hosp	HAR	Public	2005	free
31	Jima	Hosp	ORO	Public	2005	free
32	Karamara	Hosp	SOM	Public	2005	free
33	Kazanchis	HC	AA	Public	Sep-06	free
34	Kemmisie	HC	AMH	Public	Aug-06	free
35	Kombolcha	Hosp	AMH	Public	Sep-06	free
36	Kotebe	HC	AA	Public	2007	free
37	Lalibela	Hosp	AMH	Public	2005	free
38	Legehare	HC	DD	Public	Sep-06	free
39	Maychew	Hosp	TIG	Public	2005	free
40	Mekele	HC	TIG	Public	Nov-06	free
41	Mekelle	Hosp	TIG	Public	2005	free
42	Metema	Hosp	AMH	Public	2005	free
43	Metu	Hosp	ORO	Public	2005	free
44	Minilik II	Hosp	AA	Public	2005	free
45	Modjo	HC	ORO	Public	Dec-06	free
46	Nefas silk Lafto	HC	AA	Public	2007	free
47	Nekemte	Hosp	ORO	Public	2005	free
48	Police	Hosp	AA	Public	2003	free
49	Ras Desta	Hosp	AA	Public	2003	Paying
50	Sawula	HC	ORO	Public	Aug-06	free
51	Shewarobit	HC	AMH	Public	Sep-06	free
52	Shiromeda	HC	AA	Public	Aug-06	free
53	St Paul	Hosp	AA	Public	2003	Paying
54	Tepi	Hosp	SNNP	Public	Nov-06	free
55	Woldiya	Hosp	AMH	Public	2005	free
56	Yekatit	Hosp	AA	Public	2005	free
57	Zewditu	Hosp	AA	Public	2003	Paying

6.2. Number of patients on ART:

As indicated in figure-2, during the survey period and the surveyed sites (year 2008, 2009 and 2010), more than 50,000 patients were on ART in each year. In these surveys there were also 18,539 in 2008, 20,222 in 2009 and 17,074 in 2010 new patients. Based on the WHO guideline, the sample size calculated was a minimum was nearly 30.0%, 29% and 33% of the newly enrolled patients in the health facilities in the years 2008, 2009 and 2010, respectively. However, data collected were 34%, 31% and 37% of the new patients for the indicated years, respectively. This indicates additional 12%, 7% and 10% data were abstracted beyond the WHO sample size calculated in the survey years.



	2008	2009	2010
ON ART	52,457	72,936	74,135
NEW Pts	18,539	20,222	17,074
WHO SS	5,564	5,894	5,637
Collected	6,302	6,357	6,236

Figure-2. Number of new patients, currently on ART, calculated, WHO sample size and collected data in the survey periods

6.3. Findings on the Early Warning indicators (EWIs)

In the surveyed ART sites, it was possible to collect five EWIs (EWI-1, EWI-2, EWI-3a, EWI-5b and EWI-6b) out of the eight. Detailed information of the survey sites is summarized in Tables -2 and 3.

6.3.1. Early Warning Indicator-1. ART prescribing practices

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.

Suggested target: 100%

Findings:

In all health institutions for the years 2008 (n=45), 2009 and 2010 (n=49), 100% of the patients were prescribed the appropriate first line ARV based on the national ART guidelines. This is irrespective of the level of health institutions at both hospitals and health centers

Conclusion

The prescription pattern for the appropriate first line ARVs in the selected health institutions was very good and according to the level of WHO recommendation and the National ART guideline of the country. This achievement need to be maintained, which will support to minimize drug resistance and shift to second line drugs which are expensive.

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6.3.2. Early Warning Indicator-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, ≥ 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: ≤ 20%

Findings:

The level of EW2 is heterogeneous among the assessed facilities and ranged from 0-35%, 0-30% and 0-29% for the years 2008, 2009 and 2010, respectively. However, 40%, 4.1% and 4.1% of the health facilities had above the 20% recommendation of WHO. This indicates the numbers of lost follow-up cases are high in these health institutions especially in 2008 and decreased in the subsequent years, which intern influence the use of ARVs in the lost patients that might contribute for HIVDR.

Conclusion

Much has to be done to reduce the lost follow-up cases in the selected and assessed sites since lost follow-up for different reasons (except death) are totally related to the development of HIVDR for ARVs. Therefore, adherence counseling and follow-up of patients on ART needs to be strengthened to reduce lost follow up. Moreover, for sites with migrant workers and daily laborers, additional strategies to retain patients either at the site or offsite of treatment needs to be devised.

6.3.3. Early Warning Indicator-3a. Patient retention on first-line ART at 12 months

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.

Suggested target: ≥ 70%

Findings:

In the surveyed ART sites the percentage of health institutions with >=70% achievement were 55.6% in 2008 (ranged: 54%-94%), 77.6% in 2009 (ranged: 38.3%-95%) and 79.6% (Ranged: 42.4%-93.9%) in 2010. The percentage EWI-3a in hospitals and health center was comparable (71.5% hospitals Vs 71% in health centers). However, 44.4%, 22.4% and 20.4% of the 2008, 2009 and 2010, respectively of the ART sites did not meet the WHO recommendations, which shows the failure to retain patients on their first line drugs at the end of at least 12 months period.

Conclusion

The retention of the patients on the prescribed first line drugs could show the presence of potent ARVs to improve the quality of life in the treatment program. However, the rate of retention in 2008 was lower (only half of the patients) and

improved in 2009 and 2010 with about 20% of the patients were not retained on the first line regimens. Therefore, as seen from the data the rate of retention on the first line regimens is improving and reasonable number of sites are attaining the recommendation of WHO.

6.3.4. Early Warning Indicator-5b. ART clinic appointment keeping

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.

Suggested target: ≥ 80%

Findings: In all the health facilities the percentage of patients with ART clinic appointment went very good. The indicator was found to be varied 69%-100% (2008), 78%-100% (2009) and 71%-100% (2010). However 13.3%, 2.0% and 4.1% of the health institutions in 2008, 2009 and 2010 did not meet the WHO cutoff values, respectively. After 2008, there was marked improvement in the number of sites that achieved the WHO target. At least one site did not reach this target during all the three rounds.

Conclusion

In this indicator, the overall achievement seems good. However, need to be strengthened by adherence counselors. Indicator -2 and Indicator -5 seem have relationships for that indicator-2 needs strong adherence counseling not to be lost. In similar fashion, Indicator-5 needs strong adherence counseling not to lose

their appointments dates so that they can pick their drugs on time with clinical appointments like in Ethiopian setting (appointment with the physician for clinical care means they will pick drugs for their treatment.).

6.3.5. Early Warning Indicator-6b. ARV drug supply continuity

Percentage of months in a designated year in which there were no ARV drug stock-outs.

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

Denominator: 12 months.

Suggested target: 100%

Findings:

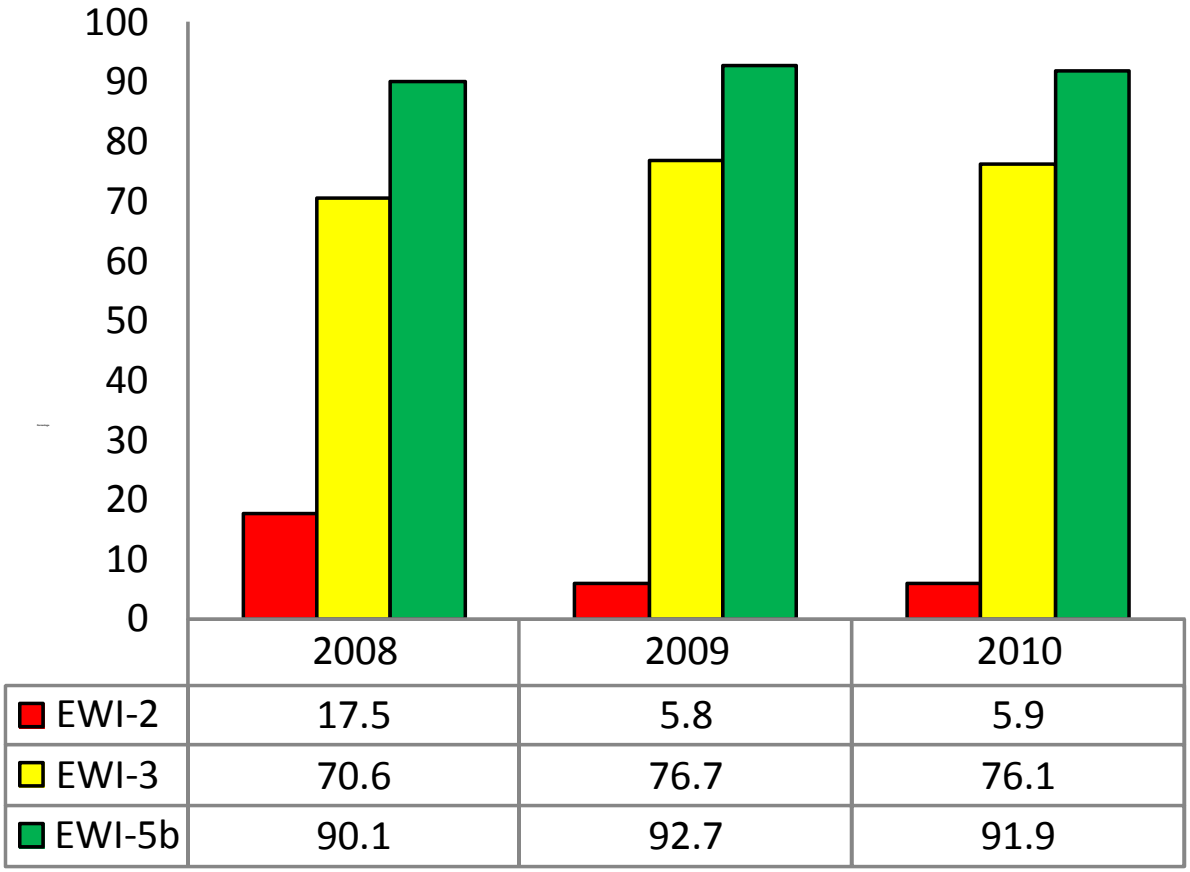
For the years 2008, 2009 and 2010 there were no drug supply shortages both at the health facility level and at the regional levels. In some health facilities, from different documents, we observed even they try to shift the overstocks to other health institutions within their districts or regions**.** However, some health facilities complained about the shortage of drugs for their review period of stocks. They reported that sometimes they prescribed from 15 days to one month, while the usual trend of ART prescription period for the country is an average of 2 months.

Conclusion

*The supply of drugs for ART showed in the year 2008, 2009 and 2010 was not having any problem. However, proper documentation related to pharmacy sections need more effort to clarify it, which might help for the head of the institutions and the programmers to use the data for future plan. Moreover, few sites were mentioning the presence of lower stocks of some drugs such as Neverapine and they were obliged to prescribe the drugs for some shorter periods like for two weeks until they got additional drugs from the main stores at a national level. To solve all these problems, intensive collaborative effort of the pharmacy versus clinical records is required***.**

Table-4. Summarized determined EWIs for each health facility in 2008, 2009 and 2010.

Sites	available for the	Region	SITE	EWI-1 (%)			EWI-2 (%)			EWI-3a (%)			EWI-5b (%)			EWI-6b (%)		
				2008	2009	2010	2008	2009	2010	2008	2009	2010	2008	2009	2010	2008	2009	2010
Adama	2009/2010	Oromiya	HOSP		100	100		0	0		76.5	74.9		90	87		100	100
Addis Zemen	2008	Amhara	HC	100			23			60.2			93			100		
Adigrat	08/2009/20	Tigray	HOSP	100	100	100	27	10	10	63.2	64.12	76.4	93	95	80	100	100	100
Akaki	2009/2010	AA	HC		100	100		0	2		90.4	92.5		96	99		100	100
Alamata	08/2009/20	Tigray	HC	100	100	100	35	18	7	57.9	62.4	88.1	79	87	96	100	100	100
Alert	08/2009/20	AA	HOSP	100	100	100	2	0	2	92.5	74.5	86.2	80	82	89	100	100	100
Ambo	08/2009/20	Oromiya	HOSP	100	100	100	27	7	0	68.7	85.3	77.9	94	90	90	100	100	100
Arbaminch	08/2009/20	SNNPRG	HOSP	100	100	100	19	19	7	73.5	94.7	85.3	98	95	96	100	100	100
Assosa	08/2009/20	BENS	HOSP	100	100	100	16	0	0	69.4	71.7	74	100	98	97	100	100	100
Awash	2009/2010	Afar	HC		100	100		8	0		38.3	53.7		97	81		100	100
Axum	08/2009/20	Tigray	HOSP	100	100	100	32	30	29	63.1	69.1	63.4	92	96	93	100	100	100
Bambasi	08/2009/20	BENS	HC	100	100	100	7	13	22	72.2	73.1	57.9	87	92	100	100	100	100
Bedelle	08/2009/20	Oromiya	HC	100	100	100	9	0	0	76.1	64.9	42.9	100	98	94	100	100	100
Betzatha	08/2009/20	AA	HOSP	100	100	100	0	0	2	72.7	95.4	91.9	90	92	93	100	100	100
Bole 17	2009/2010	AA	HC		100	100		2	0		79.1	74.8		100	96		100	100
Dangla	2008	Amhara	HC	100			6			71.7			89			100		
D/ Tabor	08/2009/20	Amhara	HOSP	100	100	100	18	16	19	71	76.5	69.5	89	94	91.9	100	100	100
D/ Brihan	2008	Amhara	HOSP	100			15			67.9			92			100		
D/Markos	2009/2010	Amhara	HOSP		100	100		9	6		75.9	75.9		88	86		100	100
Dessie	08/2009/20	Amhara	HOSP	100	100	100	11	4	6	76.7	71.6	70.7	90	91	83	100	100	100
Dilechora	08/2009/20	DD	HOSP	100	100	100	23	0	0	71.3	67.9	66.1	97	99	99	100	100	100
Dilla	08/2009/20	SNNPRG	HOSP	100	100	100	22	0	0	72.7	70.3	74.5	99	92	97	100	100	100
Dupti	2009/2010	Afar	HOSP		100	100		0	0		88.7	74.5		96	97		100	100
Este	2008	Amhara	HC	100			5			84.6			78			100		
Felege Hiwot	08/2009/20	Amhara	HOSP	100	100	100	21	16	19	64.5	76.5	69.5	87	94	99	100	100	100
Finoteselam	08/2009/20	Amhara	HOSP	100	100	100	20	4	22	72.4	89.5	74.5	76	87	93	100	100	100
Gebreguracha	2008	Oromiya	HC	100			0			76.9			87			100		
Ghandi	2009/2010	AA	HOSP		100	100		0	0		89.5	80.2		94	95		100	100
Gonder	08/2009/20	Amhara	HOSP	100	100	100	21	10	4	65.1	88.7	85.2	88	96	92	100	100	100
Hiwotfana	08/2009/20	HARAR	HOSP	100	100	100	20	0	12	63.2	51.1	66.6	80	96	97	100	100	100
Jimma	08/2009/20	Oromiya	HOSP	100	100	100	18	1	1	70	78.8	79.3	94	95	96	100	100	100
Karamara	08/2009/20	SOMALI	HOSP	100	100	100	16	0	0	71.1	68.8	60.7	85	96	87	100	100	100
Kazanches	08/2009/20	AA	HC	100	100	100	1	2	2	88.3	61.5	77.9	69	89	97	100	100	100
Kemisie	08/2009/20	Amhara	HC	100	100	100	30	11	5	59.4	69	76.5	93	99	96	100	100	100
Kombolcha	08/2009/20	Amhara	HC	100	100	100	11	11	9	78.1	76.5	79.3	74	83	80	100	100	100
Kotebe	2009/2010	AA	HC		100	100		2	0		79.4	84.8		97	94		100	100
Lageharie	08/2009/20	DD	HC	100	100	100	29	29	2	57.3	57.4	77.6	98	98	95	100	100	100
Lalibela	08/2009/20	Amhara	HOSP	100	100	100	27	10	15	63.5	75.8	70.1	97	99	96	100	100	100
Maychew	08/2009/20	Tigray	HOSP	100	100	100	17	7	14	75.9	73.2	77.2	96	96	87	100	100	100
Mekele	08/2009/20	Tigray	HC	100	100	100	32	16	18	62.6	74.1	76.9	97	91	99	100	100	100
Mekele	08/2009/20	Tigray	HOSP	100	100	100	22	10	13	71.9	70.5	79.6	89	97	96	100	100	100
Metema	2008	Amhara	HOSP	100			33			57.8			85			100		
Mettu	08/2009/20	Oromiya	HOSP	100	100	100	19	0	1	65	73.6	70.2	83	85	94	100	100	100
Minilik II	08/2009/20	AA	HOSP	100	100	100	2	1	1	74.5	86.8	84.1	72	78	71	100	100	100
Modjo	2008	Oromiya	HC	100			19			66.2			95			100		
N/S/ Lafto	2009/2010	AA	HC		100	100		1	0		82.2	70.1		87	84		100	100
Nekemet	08/2009/20	Oromiya	HOSP	100	100	100	32	0	2	63.9	90.9	82.2	98	89	93	100	100	100
Police	2009/2010	AA	HOSP		100	100		1	0		78.1	89.8		80	77		100	100
Rasdesta	08/2009/20	AA	HOSP	100	100	100	4	3	0	73.6	80	93.9	94	90	84	100	100	100
Sawla	08/2009/20	SNNPRG	HC	100	100	100	9	5	0	73.9	75	65.6	97	96	93	100	100	100
Shiromeda	08/2009/20	AA	HC	100	100	100	1	1	2	76.8	90.7	83	99	98	97	100	100	100
Shoarobit	08/2009/20	Amhara	HC	100	100	100	25	1	9	66.4	73.2	78.8	96	90	86	100	100	100
St Paul	2009/2010	AA	HOSP		100	100		0	0		89.2	82.2		97	94		100	100
Tepi	2008	SNNPRG	HC	100			11			73.4			98			100		
Woldia	08/2009/20	Amhara	HOSP	100	100	100	28	4	19	65.2	92.9	72.9	91	98	99	100	100	100
Yekatit	08/2009/20	AA	HOSP	100	100	100	2	1	4	93.7	80.4	77.5	98	93	99	100	100	100
Zewditu	2009/2010	AA	HOSP		100	100		1	3		95	92		88	86		100	100
			Average	100.0	100.0	100.0	17.0	5.8	5.9	70.6	76.7	76.1	90.1	92.7	91.9	100.0	100.0	100.0



	2008	2009	2010
EWI-2	17.5	5.8	5.9
EWI-3	70.6	76.7	76.1
EWI-5b	90.1	92.7	91.9

Figure-3. Average percentages of three EWIs in the years 2008, 2009 and 2010

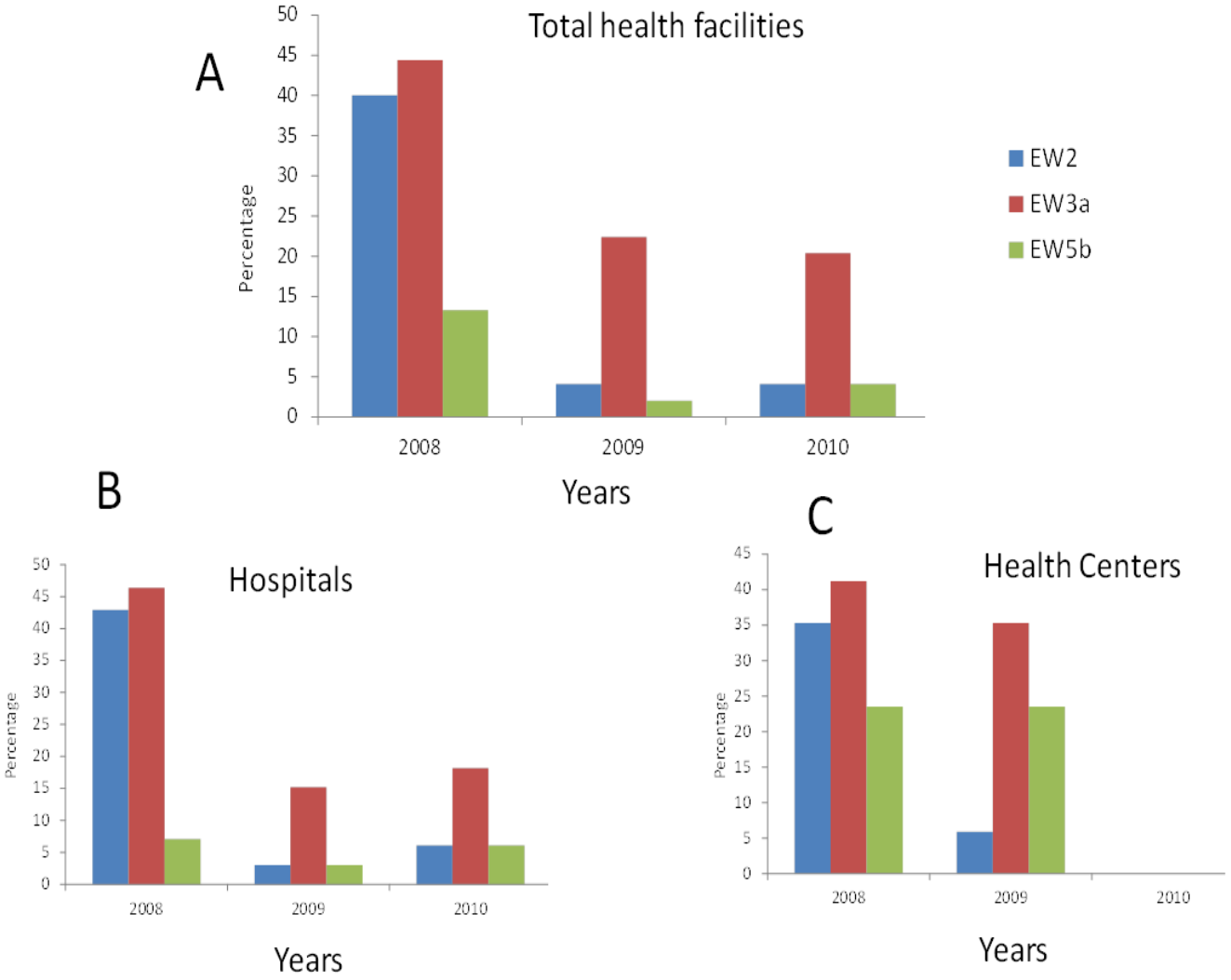


Figure-4. Percentage of health facilities (A- All Health institutions included in the survey, B. Hospitals, C: Health Centers) which did not meet WHO criteria for the three EWIs in the survey years

6.3.6. Transfer outs and deaths

In 2008, in the assessed sites we observed 605(9.6%) transfer outs and 383(6.1%) deaths documented. Unlike the rate of death which was higher in health centers than hospitals (8.2% versus 5.4%), the rate of transfer out was higher in hospitals (10.1%) compared to in health centers (7.9%). This could be due to the tendency to transfer an improving patients or increased access to their respective areas from hospital to health center to avoid overload in the hospitals.

7. CONCLUSIONS

In these rounds of the EWI survey, the total numbers of health institution to be surveyed were planned to be 70. From the site selection, these sites were representatives in all over the country. In every region of the country, at least one hospital and one health center were included. However, due to logistic reasons and the problems related to the tool (since the dates should be changed from GC to EC), the number of health institutions covered were 45(64.3% in 2008) and 70% in 2009 and 2010. By patient load, the Hospital-health center representation was planned to be 70:30 which was based on patient load on the time of the survey and was nearly attained (77:23). Of the overall new patients enrolled in the country for the year 2008, 2009 and 2010 nearly 49%, 44% and 48% of them were in the selected health institutions for the survey, respectively.

Of those assessed sites in the year 2008, about half of the health institutions had higher level of lost-to-follow-up rate, which decreases overtime. This might be due to either poor recording system of real situation such as tracking mechanisms, like in Metema Hospital in 2008. However, the overall LTFP rate is averaged at less than 20% for the survey periods. If all deaths were accounted for with proper documentation, this figure could be lower. The

reduction of LTF after 2008 could be the result of improvements in such a tracking system.

The percentage of transfer outs and death were 9.6% and 6.1% in the health institutions we assessed especially in the year 2008. The transfer out rate was slightly higher in hospitals than health centers (10% versus 8%), which is in agreement to the decentralization of the service to the health centers. The paper based documentation system was found to be uniform in all assessed sites including the patient charts. In all hospitals and some health centers, an electronic data base system was available. However, patient tracking, as used in the health centers by HIV positive expert patients, needs to be strengthened in the hospitals.

8. GENERAL RECOMMENDATIONS

Based on the assessment made in these rounds of the survey the following recommendations were made

1. Records of the pharmacy and the clinics should read the same for planning and monitoring of patients
2. In some of the health institutions the types of the patients served are heterogeneous. Even though it will be difficult to devise a strategy for each kind of patient, an approach should be there for daily laborers to reduce lost follow-ups and increase intakes in the refereed/transferred in sites
3. Since surveys need more logistic and human resource, reporting of the indictors through the routine reporting system for ART should be devised which increase the participation of health institutions in the country.
4. The use of the survey tool for data collection need to be further verified for its appropriateness especially for dates of different calendar system

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Annex-1. Early Warning Indicators (EWIs)

1. EARLY WARNING INDICATOR-1. ART PRESCRIBING PRACTICES

a. ***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).***

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%

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

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%

c. ***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)[15].***

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%

2. EARLY WARNING INDICATOR-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)

Numerator: number of patients initiating ART at the site in the selected time period who were not seen at the clinic, or pharmacy, ≥ 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: ≤ 20%

3. EARLY WARNING INDICATOR-3. PATIENT RETENTION ON FIRST-LINE ART AT 12 MONTHS

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)

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: ≥ 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*).

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. EARLY WARNING INDICATOR-4. ON-TIME ARV DRUG PICK-UP

a. Percentage of patients picking up all prescribed antiretroviral (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.

Suggested target: ≥ 90%

Note

Patients who die, 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, or who are transferred out, between the first and second drug pick-ups 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*).

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%

5. EARLY WARNING INDICATOR-5. ART CLINIC APPOINTMENT KEEPING

a. Percentage of ART patients attending 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.

Suggested target: ≥ 80%

***Exclusion**: Patients who die 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 or who are transferred out between the first and second clinic 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*).

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%

6. EARLY WARNING INDICATOR-6. ARV DRUG SUPPLY CONTINUITY

a. 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*

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%

b. 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*).

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%

c. Percentage of months in a designated year in which there were no ARV drug stock-outs (*cross-sectional*).

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

Denominator: 12 months.

Suggested target: 100%

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

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.

Suggested target: ≤ 2%

7. OPTIONAL EARLY WARNING INDICATORS-7

a. Pill Count or Standardized Adherence Measure

*Optional EWIs should **only** be used if physical pill counts or standardized adherence measurements are systematically performed for all patients who pick up drugs. Provider estimates and patient self-reports, that are not based on pill counts or a standardized measurement tool, **should not** 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.*

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

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.

Suggested target: ≥ 80%

c. Percentage of patients who, during a selected time period, demonstrate ≥ 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.

Suggested target: ≥ 80%

8. EARLY WARNING INDICATOR-8.

a. 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) .

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%