Cohort Event Monitoring of Antiretrovirals in Addis Ababa, Ethiopia

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Abbreviations and acronyms

3TC	Lamivudine
ADE	Adverse Drug Event
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretroviral Drugs
AZT	Zidovudine
D4T	Stavudine
DDI	Didanosine
EFV	Efavirenz
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
IR	Incidence Rate
LPV/RTV	Lopinavir-Ritonavir
NVP	Nevirapine
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
STG	Standard Treatment Guideline
TDF	Tenofovir
WHO	World Health Organization

1. Summary

Ethiopia is one of the countries with a highest prevalence of HIV/AIDS in sub-Saharan Africa with a prevalence of 2.4% (7.7% urban, 0.9% rural) among the age group 15-49 and with an overlapping co-morbidity. Numbers of people currently on Antiretroviral Therapy (ART) are about 400,000. Taking these and those who will be on ART into account, it would be necessary to follow upon the safety profile of the drugs and maintain the safety of the people who are using it. Thus, this study was proposed to carry out Cohort Event Monitoring (CEM) analysis among well characterized cohort of newly HIV infected individuals and on antiretroviral drugs prospectively in Addis Ababa aiming at evaluating the safety use of ART. In this cohort event monitoring (CEM), 2,505 people living with HIV (PLHIV) and started HAART were involved and followed for a minimum of 24 months. Female PLHIV represent for 59.13% (n=1412) while males correspond to 40.87% (n=976). Majority of the PLHIV (51.11%, n=1238) were in the age group that ranges from 35 to 39 years followed by the age range 15-34 years (42.07%, n=1,019). Children under the age of 14 years represent for 2.85% (n=69) whereas those above the age of 60 years accounts for 3.96% (n=96). In this CEM, anteretrovial drugs (ARV) related adverse events were reported at four different time points in 24 months [at 6, 12, 18 and 24 months of HAART intitation]. For the first time point [in 6 months after intiation of HAART], a quarter of the pateints [25.54%, n=637) had one ore more type of adverse events. Most of the adverse events (16.52, n=412) were related to dermatological /allergic reaction followed by Central Nervous System-CNS /neuropsychiatric manifestations (4.41%, n=110). Gastrointestinal manifestations accounted for 2.37% (n=59) of the adverse events reported. Majority (66.80%, n=1666) of the adverse events were observed in individuals who are taking tenofovir based regimens [TDF-3TC-EFV or TDF-3TC-NVP]. Overall death was observed in 111(4.43%) of the individuals of which 45(4.61%) were females and no death was observed in under 5 children. The estimates of ADEs observed in this study is relatively low compared to data from resource limited countries on ART for a period of 24 months but also highlighted significant gaps in program and guideline implementation. It is therefore important that MOH shall integrate CEM to the routine patient care and management system.

2. Background

Antiretroviral drugs have well-documented evidence-based favourable benefit–risk ratios. Although various studies both from developed and developing countries have investigated and well characterized the safety profile of antiretroviral drugs, there are a limited number of studies evaluating the safety of particularly first and second -line antiretroviral therapy (ART) in areas where co-morbidity is common. Ethiopia is one of the countries with a high prevalence of HIV/AIDS in sub-Saharan Africa with a prevalence of 2.4% (7.7% urban, 0.9% rural) among the age group 15-49 and with an overlapping co-morbidity. Number of people tested positive with the disease is 1,216,908 and those currently on Antiretroviral Therapy (ART) are about 300,000. In addition 397,818 people are in need of the drug (1, 6).

Taking into account the number of people who are and will be on ART, it would be necessary to follow upon the safety profile of the drugs and maintain the safety of the people who are using it. This follow up has been carried out in the country by the National Pharmacovigilance Center situated at the Food, Medicine and Health Care Administration and Control Authority (EFDA) in line with the mandate given to it by the proclamation no 661/2002.

According to a summary of this spontaneous report sent to the Pharmacovigilance Center from 2001-2003 E.C. (205, 77%) of the adverse drug events were caused by drugs of ART followed by antitubercular drugs (37.14%). The most observed reactions as reported by the health providers were: lipodystrophy (65, 32%), various skin reactions (41, 20%), anemia (31, 15%), peripheral neuropathy (27, 13%). Also current reports showed similar patterns for the years 2005-2007 E.C with specific drug reactions of tenofovir (renal tubulopathy) and ZDV based fixed dose combination (2).

It can be clearly observed from the above preliminary report that the safety of the public using these drugs should be monitored actively. Moreover, the

primary data obtained through this system needs to be strengthened by an active follow up in the form of Cohort Event Monitoring (CEM) and the obtained data shall be translated for the better and safer use of the ART drugs by the public. CEM is a time-limited, targeted programme and a prospective, observational, study of adverse events associated with one or more monitored drugs.

The Ethiopian Food and Drug Administration (EFDA) in collaboration with AHRI has planned to carry out Cohort Event Monitoring (CEM) study among well characterized cohort of newly HIV infected individuals and on antiretroviral drugs prospectively in Addis Ababa aiming at evaluating the safety use of ART in Ethiopian population and come up with specific intervention strategies for establishing the safe use of the available drugs.

3. Objectives

General objective: To determine the incidence and severity of any adverse drug events (ADEs) among different population groups (adult, children, pregnant women) with and without co morbidity on ART

Specific objectives: The specific objectives of the proposed research are as follows:

- To assess possible risk factors and covariates for the development of ADEs on ART
- To determine the clinical characteristics, management and outcomes of ADEs on ART

4. Research Methods

The whole process of CEM on antiretroviral involves structures (Hospitals and Health Centers), functions (collecting events, assessing and evaluating the data and communication), the people involved (the patients, health providers at facility, data manager, advisory committee and other experts) and the tools (Data abstraction forms, CEM flow data base from WHO). From the selected sites, adverse events occurring on a HIV/AIDS patient as a result of the use of background antiretroviral and others [if any] was recorded on the data abstraction forms. Collected data on the event was verified and entered into a RedCap database. Analysis and evaluation for signal and causality assessment was carried out using pre existing tools.

Study design: The selected design was a prospective, descriptive, observational longitudinal study on selected patients who are ARV-naive from selected ART sites in Addis Ababa with calculated sample size of 3000.

The study was intended to be undertaken over a period of three years from April 2018 to March 2021. Participants were to be followed up from enrollment into end of the study and since participants were enrolled at different stages, the follow-up time for each participant was expected to be different. Thus, events were rounded to the nearest time point.

Study population: According to WHO, generally, in establishing a CEM, several events are needed to alert to a signal or help evaluate a problem. Hence, enrolling a cohort of 3000 patients would give a 95% chance of identifying a single event with an incidence of 1:1000 (3). The study population for this purpose was all HIV/AIDS patients at the selected 20 sites who are naïve to ART and are willing to participate in the study.

Site selection: Initially, EFDA planned to carry out a National CEM study in 53 facilities. However, it is a known fact that in any study the beginning of the activity is usually tried by a pilot programme. So for the sake of convenience, facilities from Addis Ababa region were selected for this phase one programme.

Using the experiences obtained from this, the CEM will be scaled up to other regions. Accordingly, facilities at Addis Ababa were selected based on the number of patients in each facility i.e.: choosing sites with patient number above 1000 to be included (Table 1). This data was obtained from the latest month patient uptake report obtained from MSH/SIAPS (5).

Table 1: List of selected Health care facilities in Addis Ababa*

Hospitals	Health Centers
ALERT Hospital	Addis Ketema Health Center
Black Lion Specialized Hospital	Arada Health Center
Federal Police Hospital	Bole 17/19 Health Center
Gandhi Memorial Hospital	Kaliti Health Center
Menelik II Hospital	Kazanchis Health Center
Ras Desta Hospital	Kolfe Health Center
St Peter General Hospital	Kotebe Health Center
St. Paul Millennium College Hospital	Saris Health Center
Yekatit 12 Hospital	Wereda 23 Health Center
Zewditu Memorial Hospital	

** Woreda 19 Health Center was excluded because of facility inconvenience and lack of support from facility management, respectively*

Inclusion/Exclusion criteria: All patients with a confirmed diagnosis of HIV, who are naïve and have agreed to start antiretroviral therapy, were included in the study. There was no exclusion criteria based on age, sex, presence of other disease conditions or use of other medications. Patients not seen at the beginning of their ARV treatments or those who have experience with ARV treatment, those who are not willing to participate and those who discontinue taking the ART during the study period was excluded from the study. Also those patients or parents/legal guardians who are not willing to provide signed

informed consent or those with a history of mental illness or prisoner status were included in the study.

Sample size calculation: In order to obtain the total sample size for the study (3000), from each facility it is necessary to categorize the facilities according to their current HIV patient number size as obtained from MSH/SIAPS patient uptake report of the month (5). Accordingly, we had three groups as indicated below:

Group I: Facilities with patient number <1700 and included Kolfe Health Center, Kaliti Health Center, Wereda 23 Health Center, Addis Ketema Health Center, Arada Health Center, Bole 17/19 Health Center, Kotebe Health Center , Saris Health Center and Kazanchis Health Center.

Group II: Facilities with patient number between 1701-3700 and included Gandhi Memorial Hospital, Ras Desta Damtew Hospital, Yekatit 12 Hospital, Menelik II Hospital, St Peter General Hospital, and Federal Police Hospital.

Group III: Facilities with patient number >3701 and included Zewditu Memorial Hospital, ALERT Hospital, St Paul Millennium College Hospital, and Black Lion Specialized Hospital.

To fairly distribute the total sample size (3000) between the three groups, the first group is assigned to take 40% out of the total, the second 35% and the last group 25%. Upon calculation this gives 1198 for the nine facilities of group I (133 each), 1050 for the six facilities of group II (175 each) and 752 for the 4 facilities of group III (188 each). Enrollment of this number of patients was continuing consecutively each day at each facility until the required target number is obtained. However, during the real time data collection period the numbers were readjusted.

Data collection and analysis: Data was collected by data collectors at each health facility (one from dispenser and the other from the prescriber and one from laboratory) who was trained on the CEM protocol, data collection and the tools prepared for the purpose. Data collecting tools were pretested and the

comments have been included for final use. Data quality control including checking for completeness and errors was performed by the CEM focal person at each facility and by the coordinator. The following information was captured at enrolment for ART naïve patients (adults and pediatrics): Date of enrollment, demographic data, past medical history and medication, baseline clinical assessment-WHO staging, reproduction health, TB and nutritional screening, physical examination and clinical evaluation for HAART including laboratory assessments, concomitant illness and medication, complementary/traditional medications [if any], ART medication.

The following data was required to be captured on follow-up assessments: Clinical examination, reproductive health (for adults), TB status, laboratory investigations-viral load, CD4, CBC, organ function test [creatinine clearance, fasting cholesterol, triglycerides, glucose] whenever available, HIV conditions and opportunistic infections and new complementary medicines. The ART summary data are collected as information becomes available or relevant. They include the baseline clinical status of patients when they start ART; regimen changes and other status changes thereafter; and interruptions with stop or lost and restart dates and reasons.

An ADE was defined as the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not it was considered causally related to the product. An undesirable medical condition could be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). The term ADE was used to include both serious and non-serious AEs. Adverse events were required to be diagnosed by the clinician on site as per case definition, or be classified as "to be determined" in the case of uncertainty. Each ADE was required to be validated by independent experts.

A serious ADE is one that fulfils one or more of the following criteria: Results in death, is immediately life-threatening, requires in-patient hospitalization or existing hospitalization prolonged, results in persistent or significant disability or incapacity, is a congenital abnormality or birth defect and is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

Ethical considerations: This is a routine clinical evaluation of patients for the use and events from the use of medicines to improve drug use and practices in the country which are the mandates of EFDA. It poses no risk to the participants since there is no intervention in the process. Consenting patients was conducted to return on their routine appointment dates where they will be asked if they had any adverse events after taking their medicines. However, individual consent form is required for this programme. Every eligible patient is required to sign the informed consent form before enrollment and after read the information sheet. In case of pediatric patients, the parent/guardian was required to sign on the patients behalf. Furthermore, a CEM study team read to patients who are not literate before they sign the consent form. All information collected on the questionnaires was handled under strict confidentiality.

Training: Training for this study included taking informed consent, as well as general data collection, documenting and was provided study staffs involved in the process.

Monitoring and Evaluation: Progress of the CEM activities at all sites was monitored monthly by the field coordinators. Monitoring was carried out using a checklist and review meetings was carried out with the established task force, field coordinator and data manager and site coordinators to evaluate progress of programme and findings.

Patient database: All data that was captured manually were entered and stored on RedCap at AHRI secured central server to prevent tampering and to ensure security.

5. Results and Discussions

Socio-demographic and clinical characteristics: In this cohort event monitoring (CEM), 2,505 people living with HIV (PLHIV) and started HAART were involved and followed for a minimum of 24 months with a response rate of 84%. Female PLHIV represent for 59.1% (n=1481) while males correspond to 40.9% (n=1024). Majority of the PLHIV (49.4%, n=1238) were in the age group that ranges from 35 to 39 years followed by the age range 15-34 years (40.7%, n=1,019). Children under the age of 14 years represent for 2.8% (n=69) whereas those above the age of 60 years accounts for 3.8% (n=96). The age and sex distribution of this CEM mirrors the national HIV epidemiology. It also shows that HIV is still major public health problem and special attention and tailored intervention need also be given to children, adolescents and older ages (Figure 1).

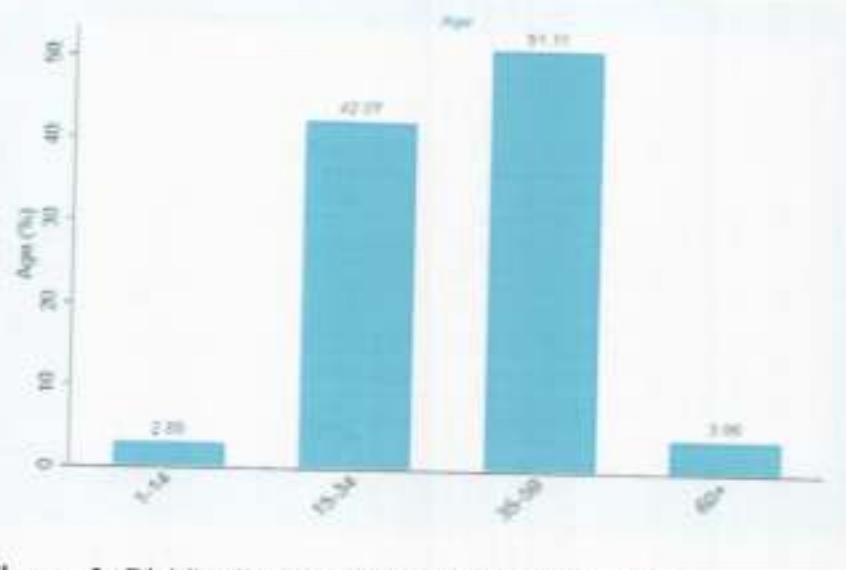

Figure 1: Distribution of participants with age

At baseline following the routine patients management protocol, WHO clinical staging of PLHIV was assessed and majority (61.2%, n=1534) of them were categorized as WHO clinical stage I. WHO clinical stage II, III and IV represents for 13.2% (n=331), 17.5% (n=437) and 8.1% (n=203), respectively (Table 2). Accordingly, 22.3% (n=560) PLHIV were reported to have one or more type of comorbidity and/or co infection. Tuberculosis was the most common

coinfection observed in 31.6% (n= 177) of the individuals. Clinical bacterial infections and malnutrition are equally observed in 18.4% (n=103). Anemia as defined by the level of heamatocrit and/or heamoglobin value [depending of age and sex] was seen in 8.9% (n=50) of the individual. From non-communicable diseases, depression and hypertension was the most frequent diseases observed in 7.5% (n=42) and 4.8% (n=27) of the PLHIV, respectively. Measurement of nutritional status [based on BMI] was also conducted at baseline before the initiation of HAART and more than half of the individuals (56.2%, n=1407) were found to have normal weight while 20.6% (n=516) were under weight. One tenth (13.3%, n=338) of the PLHIV in this CEM were found to be overweight and those obese PLHIV represent for 9.7% (n=244).

The presence of advanced WHO clinical staging and the rate of concomitant coinfection indicated that many PLHIV still present to health facilities late in the course of HIV infection. This evidence reveals that the health system need to work more in reaching PLHIV with enhancing testing and treatment service.

The 2017 National ART Treatment guideline recommends the use of a simplified, less toxic and more convenient regimens as fixed-dose combinations as first-line ART comprising NRTI backbone (TDF + 3TC) and one NNRTI (EFV) and are maintained as the preferred choices in adults, adolescents and children older than ten years (8). However, the revised protocol which was endorsed in 2018 recommended TDF+3TC+DTG or TDF+3TC+EFV as a preferred first-line regimen for adults and adolescents (9). But, availability of the FDC DTG containing regimen was variable and was practiced late in 2019. Thus, in this CEM study patients with the previous [2017] protocol was considered. Accordingly, first line tenofovir-based (TDF-3TC-EFV/NVP) and AZT containing alternative regimens [AZT-3TC-EFV/NVP] were most common used drugs (92.5%, n=2304) and (6%, n=150), respectively.

Table 2: Clinical characteristics of the patients

Characteristics	n	%
WHO clinical stage		
I	1534	61.2
II	331	13.2
III	437	17.4
IV	203	8.1
Comorbidity		
Liver disease	13	2.3
Diabetes	13	2.3
Renal disease	15	2.7
Hypertension	27	4.8
Depression	42	7.5
Anemia	50	8.9
Malnutrition	103	18.4
Bacterial infection	103	18.4
Tuberculosis	177	31.6
Others	17	3.0
Nutritional status		
Under weight	516	20.6
Normal weight	1,407	56.2
Over weight	338	13.5
Obese	244	9.7

Adverse events: In this CEM, anteretrovial drugs (ARV) related adverse events were reported at four different time points in 24 months follow up time [at 6, 12, 18 and 24 months of HAART intitation]. For the first time point [6 months after the intiation of HAART], three-fouth of PLHIV (74.1%, n=1857) doesn't reported any adverse event. However, in the remaining quarter of the PLHIV (25.4%, n=637) various type of adverse events were reported. Most of the adverse events (64.7%, n=412) were related to dermatological /allergic reaction such as skin rash/reaction followed by Central Nervous System-CNS /neuropsychiatric manifestations (17.3%, n=110) including dizziness, bad dreams and sleep disturbances. Gastrointestinal manifestations like nausea, vomiting and diarrhea

accounts for 9.3% (n=59) of the adverse events reported. Majority (66.8%, n=1666) of the adverse events were observed in individuals who are taking tenofovir based regimens [TDF-3TC-EFV/NVP].

Following observed adverse effets treatment changes [shifting and substitution] was observed in 16.2% (n=103) of the cases. Gastrointestinal manifestations were more common among female PLHIV (71.9%, n= 41) than male PLHIV (28.1%, n=16). Occurrence of neuropsychiatric manifestations were comparable between male (48.6%, n=52) and female PLHIV (51.4%, n=55). Allergic manifestations were more pronounced in female PLHIV (59.1%, n=234) than male PLHIV (40.9%, n=162). Similar trend was also observed for male to female variation of an absence of adverse events, 40.9% (n=721) and 59.1% (n=1043), respectively. Overall, adverse events were more common among female PLHIV (59.0%, n=1404) than their male counterparts (40.93%, n=973). Other side effects like numbness of the hand, leg swelling, and red eye take less than 2% of the proportion of side effects.

With regards to age, most adverse events were among PLHIV in the age group of 35-49% (43.2%, n= 1043) and 25-34 (33.4%, n= 805) (Figure 2). Similar trends were also observed for the common adverse events. For instance, gastrointestinal adverse events were more common among PLHIV in the age groups of 35-49 years (46.6%, n= 27) and 24-34 years (29.1%, n= 17). Likewise, neuropsychiatric manifestations were highest among PLHIV in the age groups of 35-49 years (50.5%, n= 53) and 25-34 years (28.6%, n= 30). Allergic reactions were also common among PLHIV who were in the age group 35-49 years (45.7%, n= 183) and 25-34 years (32.5%, n= 130).

Figure 2: Pattern of adverse effects by age category

In general adverse events were more common among PLHIV with normal BMI (56.2%, n= 1401) and those who were under weight (20.5%, n= 511) (Figure 3). Similar trends also observed for gastrointestinal and neuropsychiatric related adverse events and allergic reactions. For instance, 49.2% (n= 29) gastrointestinal related adverse events were among PLHIV with normal BMI while PLHIV who were under weight and obese contribute for 28.8% (n= 17) and 13.6% (n= 8) of the gastrointestinal adverse events, respectively. The remaining 8.5% (n= 5) of the gastrointestinal adverse events were among PLHIV who were overweight. Similarly, 61.8% (n= 68) of the neuropsychiatric related adverse events were among PLHIV of normal BMI whereas underweight PLHIV's contributed for 18.18% (n= 20) of the neuropsychiatric adverse events. Allergic reaction were also more common among PLHIV with normal BMI (51.9%, n= 214) and those underweights (23.5%, n= 97).

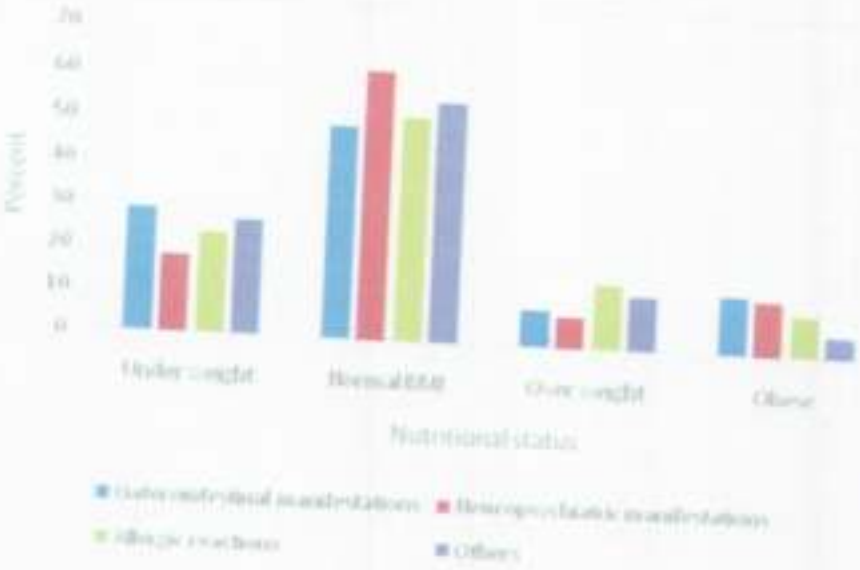

Figure 3: Pattern of adverse effects by nutritional status

Of the 560 PLHIV with comorbidities or co infections, 40.5% (n= 227) had adverse events (Figure 4). Gastrointestinal manifestations were highest among PLHIV with tuberculosis (40%, n= 10) followed by PLHIV with bacterial infection (28%, n= 7). Neuropsychiatric manifestations were highest among PLHIV with depression (21.7%, n= 10), tuberculosis (21.7%, n= 10), bacterial infection (19.6%, n=9) and malnutrition (13.0%, n= 6). Allergic reaction were more pronounced among PLHIV with tuberculosis (32.3%, n= 44), bacterial infections (25%, n= 34), malnutrition (12.5%, n= 17) and anemia (6.6%, n= 9).

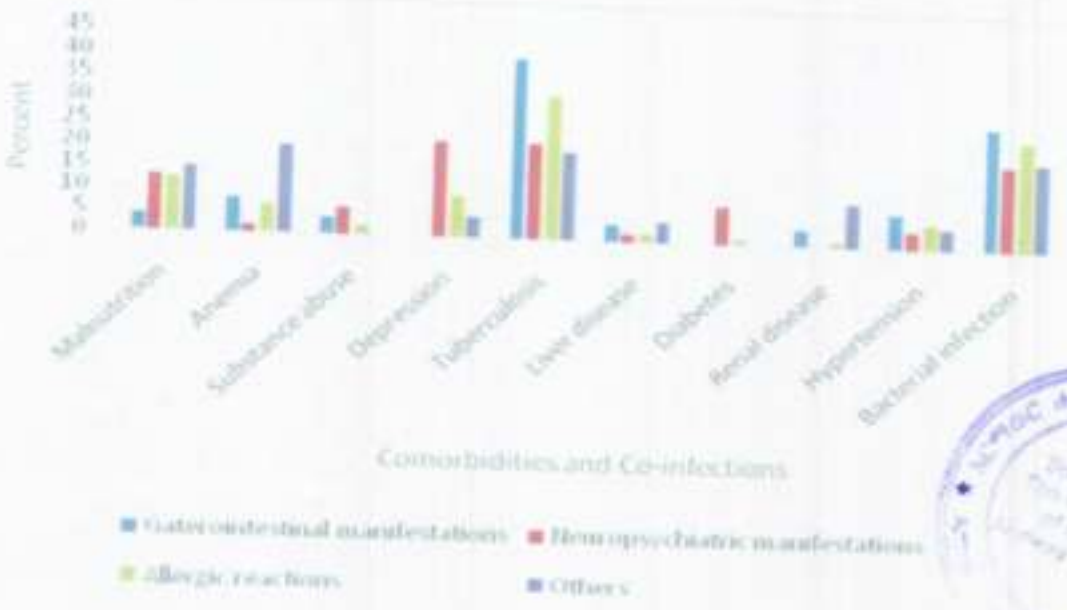

Figure 4: Pattern of adverse effects by baseline comorbidity/infections

Lost to follow up: Of the 2505 PLHIV, 8.7% (n=218) were lost to follow up in a period of two years. Majority of individuals were lost during the first 6 months of HAART. Female PLHIV represent for 59.2% (n=129) of lost to follow up case while male PLHIV accounts for 40.8% (n=89) of the lost to follow ups. More than half (52.4%, n= 120) of the PLHIV who were lost to follow up had normal weight at base line. On the other hand, about a quarter (23.6%, n=54) of the lost to follow up cases were under weight. Nearly half (48.2%, n=105) of the lost to follow up cases were in WHO clinical staging I followed by WHO clinical stage III (26.5%, n=58). Similarly, malnutrition was the most important comorbidity associated with lost to follow up (10.1%, n=22). TB follows as the second important co infection associated with lost to follow up (5.5%, n=12). Comorbidity and coinfection status of 157 (72%) lost to follow up individuals were either none or unknown.

Death: Among 2,505 study participants in all study periods, overall death was observed in 4.4% (n=111) of the PLHIV in a period of three years. Most of these deaths had occurred in the first six month follow up period (71.2%, n=79). Male PLHIV corresponds to 53.2% (n=59) while female PLHIV represent for 40.5% (n=45) of the deaths. The genders of seven deaths were not known. Surprisingly, 30.6%

(n=34) of the deaths were under WHO clinical stage I while those PLHIV on WHO clinical stage III accounted for 26.1% (n=29), of the deaths. Interestingly, no death was observed in under 5 children. Higher frequency of death was seen in age group of 35-49 years (43.2%, n=48). Moreover, 15.32% (n=17) of the deaths were among PLHIV with malnutrition. Those PLHIV with TB corresponds for 9.00% (n=10) of the deaths. Anemia was the third (6.31%, n=7) important comorbidity associated with death. Comorbidity and co infection status of 64 PLHIV (57.7%) were either none or unknown. Unexpectedly, the reported death was minimal among PLHIV with adverse event and shows the need to understand the cause of death among people on HAART.

6. Limitations of the study

The study has obvious limitations. The study planned to enroll 3.000 patients over a period of 24 months however the final number enrolled was 2760, of whom only 2.505 patients were eligible for analysis. Many factors contributed to this. one health facilities failed to participate. The study was originally initiated by EFDA and later transferred to AHRI and had created some delay and administration gaps and required repeated trainings which took more time than expected. Due to limited human resources and high burden of patients, staff at health facilities did not have enough time to recruit the expected numbers of patients, and to successfully follow up patients and fill all required data as per protocol. This resulted in incomplete data. However, during monitoring it was possible to recollect the missed data. This indeed extended result delivery time and impacted logistic issues.

Despite persistence provision of information about the study and explaining the benefits of participating in such the study, reluctance and refusal of patients to participate in the study was observed. This again extended duration of the study period. Limited laboratory facilities and dependence on existing health facility staffs were also other factors contributing for extended study period. The high staff turnover would have required continuous training on the protocol and was

difficult to create functional teams at the health facility level that shared the same vision as the central study team. In some health facilities staffs did not take full ownership of the study and the level of commitment was very low. Finally, in house infrastructure problem [failure of the RedCap database system] created delay on data entry and analysis. The change in ART treatment protocol and the COVID-19 pandemic were also additional factors that impacted our study and created unnecessary delay.

7. Conclusion

The estimates of ADEs observed in this study is relatively low compared to data from resource limited countries among 2505 subjects on ART for a period of 24 months but also highlighted significant gaps in program and guideline implementation. Cohort event monitoring is basically a valuable method for gathering information on ADEs to ARVs. However, it is also a very resource intensive method. It is therefore important that MOH shall integrate CEM to the routine patient care and management system. ADEs related to alternative first and second line ART is minimal but could be interpreted cautiously. Periodical laboratory investigation is found to be low and hence it is somehow challenging to associate observed ADEs with physiological and/or pathological values.

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