Virological Non-Suppression and Associated Factors Among Adolescents and Youth Living with HIV in Ethiopia: A Facility-Based Case-Control Study

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Abstract

Background: Virological non-suppression remains the major cause of treatment failure and mortality among adolescents and youth living with HIV in low- and middle-income countries (LMICs). Behavioral and mental health disorders affect adherence to antiretroviral therapy (ART) and the underlying virological suppression, but evidence from LMICs is relatively limited. We aimed to assess HIV virological non-suppression and associated factors among adolescents and youth attending ART in Ethiopia.

Methods: A 1:2 matched facility-based case-control study was conducted at ALERT Hospital, Addis Ababa, Ethiopia, among patients with HIV aged 12-24 years who were on ART and with a viral load > (case) or < (control) than 1000 copies/ml after at least six months on ART. The primary outcome was viral load non-suppression: a plasma viral load > 1000 copies/ml based on two consecutive viral load measurements every three months. The primary exposure was depressive symptoms as measured using the PHQ-9 (Patient Health Questionnaire, 9-item version). Other variables include adherence to ART and sociodemographic characteristics of participants. Data were collected using structured, blinded lay interviewer-administered questionnaires, and data extraction forms. Conditional multivariable logistic regression was conducted using STATA version 14.2 to test the main hypotheses.

Results: The study enrolled 192 participants, with a median age of 18 years and 52.1% males. None of the participants reported smoking or chewing Khat (a leaf that stimulates mood). With the PHQ-9 tool, 47%, 28%, and 25% had minimal or no, probable to mild and moderate to severe depression symptoms, respectively. Having depressive symptoms is associated with a higher conditional likelihood of virological failure (odds ratio [OR] = 1.8, $p < 0.001$) and the association was stronger among those who have moderate or severe depressive symptoms (adjusted OR = 5, 95% CI [1.7-14.6]) and unadjusted OR = 6.8, 95% CI [3.1-14.8]). Having moderate and severe depression is associated with non-adherence to ART (adjusted OR = 10.5).

Conclusion: Non-adherence to ART medications, depressive symptoms, advanced WHO stage on ART initiation, poor social support and orphan status were independently associated with virological failure among HIV-infected adolescents and youths on ART. Having moderate and severe depression has higher odds of non-adherence and virological failure. We recommend integration and task-sharing of mental health and HIV care services to reduce virological failure in this group of people.

Background

HIV/AIDS remains a significant contributor to morbidity and mortality in adolescents and youth, especially in sub-Saharan Africa [1, 2, and 33]. According to UNAIDS estimates, 71% of the estimated 2.1 million adolescents and youth living with HIV (AYLHIV) in 2016 lived in nine sub-Saharan African countries and India [15]. Furthermore, 91% of adolescent deaths worldwide were reported in sub-Saharan Africa in 2016. In Ethiopia, HIV prevalence among adolescents and youth aged 10-24 years ranges from less than 0.1 percent in Somali to 1.3 percent in Gambella regional states, while the national figure stands

at 0.2% (CSA and ICF, 2018). Although low, the absolute number of adolescents and young people affected by HIV is high given the Ethiopian population of over 100 million people. Ethiopia's progress towards the UNAIDS 90-90-90 target by 2020 report stands at 79-71-81 [33]. This number might even be overstated as different primary studies done in Ethiopia from primary to tertiary level care indicate a higher burden of viral non suppression, ranging from 22.6% to 26.3% [2, 3, 5, and 14].

The goal of ART is to restrict viral replication in CD4 cells. Achieving viral suppression protects people living with HIV from Acquired Immunodeficiency Syndrome (AIDS)-related illnesses, minimizes ART drug resistance and lowers the risk of transmission to others. Thus virological monitoring through plasma viral load (VL) quantification is an essential part of the monitoring of HIV patients undergoing antiretroviral therapy (ART). Routine VL monitoring allows timely detection of treatment failure, identification of patients in need of more intensive adherence support and protection against unnecessary switching to expensive and limited ART alternative regimen options.

Despite the introduction of the UNAIDS 90-90-90 target with universal testing and treatment to end the HIV epidemic in 2030, viral suppression outcomes remain a major challenge among adolescents and youth living with HIV in LMICs. According to a systematic review done in sub-Saharan countries, when stratified, PLHIV ages 15 to 24 years had lower median achievement in the treatment cascade (60-49-81), compared to PLHIV ≥ 25 years (70-63-91) [15]. Studies have been carried out in a number of countries to investigate factors influencing adherence in these age groups. However, there are inconsistencies and disagreements among studies. In general, Factors that determine viral suppression outcomes are multidimensional and thus understanding the key barriers and outcomes of different factors can help to develop and standardize health service interventions that improve viral load suppression and improve health outcomes for adolescents and youth living with HIV. Factors other than sociodemographic and clinical factors might better explain differences in adherence and/or treatment failure in adolescents. This highlights the need for a more complex study that would look at the entire system which these patients are navigating as well as considering their behavioral and mental health. Of the known risk factors for viral non suppression, the contribution of mental health conditions has been less extensively investigated. While it is the most neglected condition in the HIV care package, according to a recent systematic review and meta-analysis, depression is highly prevalent among people living with HIV in Ethiopia (35.8%) and the odds of non-adherence is high (OR = 3.01) when co-morbid depression is present, Necho et al., 2021 [11].

Thus, this study aimed to assess virological non-suppression and associated factors among 12-24-year-old adolescents taking ART at ALERT Center, Addis Ababa, Ethiopia, 2021. The study is powered to detect the association of virological non-suppression and non-adherence to ART medications with the most neglected mental health condition, depression, using a hypothesis-driven case-control study. The hypothesis was that depressive symptoms have a significant association with virological non-suppression and ART medication non-adherence.

Methods

Study design and setting

A1:2 matched case-control study was conducted among HIV-positive adolescents and youth aged 12-24 who were receiving ART at ALERT Center, Addis Ababa, Ethiopia. We do matching by age and sex to reduce bias and confounding at the design level.

The study was conducted in ALERT center Addis Ababa, Ethiopia. The institution is functioning as a training, research and medical service delivery center. More than 8, 000 people living with HIV are currently enrolled in the ART clinic at ALERT, of which more than 700 are children and youth aged below 24 years. This figure is the second-largest among hospitals that provide ART services in the city. ALERT serves as a referral hospital for the central, western, northwestern and southwestern parts of the city, together with the metropolitan area covering more than 5 million populations. The results obtained from this study may be extrapolated to Addis Ababa city administration and referral hospitals serving adolescent HIV care in the city.

Participants

The study population was HIV-positive adolescents and youth who were attending ART at the ALERT center. The eligibility criteria were as follows:

- Inclusion criteria
 - 12 to 24-year-old adolescents on ART for at least six months and who were receiving follow-up at the ALERT center.
 - Viral load > 1000 copies/ml after at least six months on ART.
- Exclusion criteria
 - No matched control is available.
 - Refused or unable to give assent and/or consent.
 - Presenting with an emergency medical condition.
 - Unable to communicate with research staff (e.g. due to sensory problems, cognitive problems).
- Eligibility criteria for controls
 - Adolescent/young person between 12 and 24 years of age.
 - On antiretroviral therapy for at least six months
 - Age matched to case (+/- 1 year).
 - Sex-matched to case.
 - Viral load < 1000 copies/ml after six months of treatment.

Under 12 years children are excluded from the study as the depression screening tool is less sensitive to detect depression in under 12 years children. In addition consenting of parents was thought to be difficult

during the study period.

Recruitment

Cases and controls were interviewed by two independent, trained general practitioners either on their appointment dates for ART follow-up or when they came for their support group meetings which were conducted on Saturdays every week. Those who did not belong to a support group and who did not come for review during the study period were interviewed by phone. Contact details were found in the VL tests registers. Eligible participants were approached by research staff to provide potential participants with information on the research and invite them to participate.

Sample size calculation

A recent systematic review and meta-analysis found a high burden of depression among people with HIV in Ethiopia (35.8% pooled prevalence) and higher odds of non-adherence (OR = 3.01) in depression compared to those without depression symptoms. Thus, the study is powered by this assumption to assess the association of depression with virological treatment failure in adolescents. The other factors were assessed as contributing factors for treatment failure. Using this study at 95% significance level ($\alpha = 0.05$) and 80% power (delta = 0.8), we assume a 35% exposure rate to depression among control groups and a 2.5 odds ratio of depression exposure in cases relative to the controls. Using STATA for 1:2 matched case-control, the number of cases required is 58. Considering a 10% non-respondent rate, the ratio of cases to control will be 64 to 128. Thus, the total sample size for the cases and the controls is 192.

Outcome measures

We used (1) fully structured, pre-tested, lay interviewer-administered questionnaires, and (2) data extraction forms. The questionnaires were designed in English language and translated into Amharic, the official language in Addis Ababa.

- Primary outcome: viral load suppression
 - Viral non-suppression: elevated VL Ribo Nucleic Acid (RNA) copies of > 1000 copies/ml in plasma in a person with HIV who has been on ART for at least six months. We took the most recent viral load as an outcome measurement.
- Primary exposure: depressive symptoms
 - Depressive symptoms were measured using the Patient Health Questionnaire, 9-item version (PHQ-9) [Kroenke et al, 2011]. Validity of the PHQ-9 tool in Ethiopia was investigated against the gold standard of the Mini International Neuropsychiatric Interview (MINI) diagnostic tool among

cancer patients in Tikur Anbessa hospital, the national referral and teaching hospital, and showed a sensitivity of 88% and specificity of 78.1% to detect major depressive episode (MDE) [43]. Validity of the PHQ-9 for depression screening and the diagnosis was also done against psychiatrist administered semi-structure schedules for clinical assessment in neuropsychiatry (SCAN) interview among 926 Ethiopian adults in 2013 demonstrate good reliability and validity of the tool (sensitivity = 86% and specificity = 67%), Bizu Gelaye et al. [44].

- Other explanatory variables: adherence to antiretroviral medication
 - Adherence was objectively assessed using a physical pill count of dose units taken between the supply date and the review date. Good adherence was defined as adherence necessary to achieve full and durable viral suppression, thus taking ($=$ or $> 95\%$) of the pills. We operationalized the adherence level category as good, fair and poor for analysis as follows:
- Potential confounders: sociodemographic characteristics
 - The demographic characteristics of the study participants were recorded, including age (number of completed years), marital status (married, single, divorced), gender (male or female), occupation (organization employed, self-employed, unemployed), alcohol intake (consumption of alcohol: daily, on weekends, holy days only, not at all), family income (amount in Birr per day), religion (Orthodox, Protestant, Muslim, others), living status (orphanage home, other caregivers, living with a partner, living with parents) orphan Status (double orphan, orphan mother, orphan father, not orphan), support group involvement (always involved, sometimes, rarely or never) and caregiver employment status (employed or not employed). Substance use including chewing khat, (never, sometimes, always), smoking (yes/no). All these data were obtained by face-to-face interviews. First viral load in the hospital (number of viral copies/ μ l). Disclosure status (disclosed HIV status or not), WHO staging (WHO stage at ART initiation, if ART initiation was in other facilities the first WHO stage in the hospital will be taken), CD4 count (CD4 count at ART initiation), Drug S/E (Yes, No) chronic illness (having a chronic disease or not), Current ART regimen (first line second line or third line). These data were extracted from the participants' medical records and viral load records.

Operational definitions

- **Good adherence:** Drug adherence of 95% or ≤ 2 missed drug doses of 30 doses or ≤ 3 missed drug doses of 60 doses.
- **Fair Adherence:** Drug adherence of 85–94% or 3–5 missed drug doses of 30 doses or 3–9 missed drug doses of 60 doses.
- **Poor Adherence:** Drug adherence of $< 85\%$ or ≥ 6 doses of missed ART drug doses of 30 doses or > 9 doses missed ART drug doses of 60 doses.

- **Virological non-suppression:** a plasma viral load above 1000 copies/ ml based on two consecutive viral load measurements after 3 months, with adherence support.

Data collection

Two independent general practitioners with experience in ART follow-up from adult ART (outside the pediatric ART care providers) were assigned for data collection. One of them collected data from the medical records while the other conducted participant interviews and administered the questionnaire. Data collectors were given adequate training on how to administer the questionnaires and how to complete the data extraction tools. Post-training knowledge was assessed using an interactive question and answer discussion on the second day. Pretesting of the questionnaire was performed by data collectors in a small sample of young people who were using ART and in the adult follow-up clinic. Findings were reviewed.

We used structured, pre-tested interviewer-administered questionnaires to collect data. The questionnaires were designed in English language then translated into Amharic language which is the official language in Addis Ababa. A review of the hospital medical records provided baseline pre-ART data before initiation of HIV treatment as well as current treatment and clinical status (see under confounder measurements section). The data collector who was assigned to conduct a face-to-face interview was not aware of whether the respondent is a case or control. To ensure this, the first person who was assigned to recruit eligible participants and to collect necessary data from medical records was also dedicated to remove VL reports and keep these separate until the interview had been completed. Each data entry item was double-checked independently by two data clerks and the entire data set was checked for consistency, and discrepancies were discussed and checked from the primary tool/questionnaire.

Data analysis

Data analysis was performed using STATA version 14.2 to generate frequencies of exposures, means, proportions and odds ratios. Bivariate analysis was conducted to assess associations between different exposures and virological failure. A p-value of < 0.05 was deemed statistically significant in this analysis. Conditional multivariable logistic regression was conducted to test the main hypothesis of an association between depressive symptoms (primary exposure) and non-viral suppression (primary outcome) after adjusting for all pre-specified confounders.

Ethical considerations

Ethical approval to conduct the study was obtained from the Scientific and Ethics Review Committee of the Center for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa), College of Health Sciences, Addis Ababa University, and the Institutional Review Board of the ALERT Center. Written

informed consent was prepared using the American federal regulations consent/assent checklist. Consent was obtained from all study participants who were aged 18 years and above. For adolescents aged 12 to 18 years, assent was obtained. Confidentiality was assured and maintained through no use of names on questionnaires and keeping questionnaires under lock and key.

Results

Overall characteristics

We have approached 66 eligible cases. Of those eligible cases, 1 adolescent was not able to consent and was excluded from the study. One other adolescent didn't get an age match in the study period and was also excluded from the study. All approached eligible controls agreed to participate in the study and were able to consent and were enrolled.

Socio-demographic characteristics

Of the 192 study participants, 52.1% were males. The median age of participants was 18 years. Regarding the educational status of the participants, 61 (31.8%) and 102 (53.1%) of participants were primary and secondary school students, respectively. Despite higher median age of 18, only 19 (9.9%) participants were currently college/university-level students and only 10 participants were college/university graduates. Double orphan status was 26.6% among cases and 9.4% among controls. Only 30% of cases lived with their parents. The mean family daily income in Birr was 116.349. **Table 1** summarizes the sociodemographic and treatment-related information of study participants among cases and controls.

Table 1: Sociodemographic information

Variables		Total (N=192)	Patients with virological failure (N=64)	Participants without virological failure (N=128)
Mean age (years)		17.5	17.5	17.5
Sex	Male	100 (52.1%)	34 (53.1%)	66 (51.6%)
	Female	92 (47.9%)	30 (46.9%)	62 (48.4)
Religion	Orthodox	125 (65.1 %)	48 (75.0%)	77 (60.2%)
	Protestant	43 (22.4 %)	13 (20.3%)	30 (23.4%)
	Muslim	24 (12.5 %0	3 (4.7%)	21 (16.4%)
Employment	Self employed	7 (3.6%)	3 (4.7%)	4 (3.1%)
	Unemployed	172 (89.6%)	52 (81.3%)	120 (93.7%)
	Org. employed	13 (6.8%)	9 (14.1%)	4 (3.1%)
Orphan status	double orphan	29 (15.1%)	17 (26.6%)	12 (9.4%)
	orphan mother	33 (17.2%)	16 (25.0%)	17 (13.3%)
	orphan father	40 (20.8%)	11 (17.2%)	29 (22.6%)
	not orphan	90 (46.9%)	20 (31.3%)	70 (54.7%)
Living status	orphanage home	2 (1%)	1 (1.6%)	1(0.8%)
	other care givers	31 (16.1)	16 (25.0%)	15 (11.7%)
	living with partner	3 (1.6%)	2 (3.1%)	1 (0.9%)

	living with parents	156 (81.3%)	45 (70.3%)	111 (86.7%)
Care giver employment	Not employed	35 (18.2%)	18 (28.1%)	17 (15%)
	Employed	157 (81.8%)	46 (71.9%)	111 (85%)

ART status

The majority (n=115) of participants among controls were taking first-line ART medications and 11 controls took second-line ART whereas 2 controls were taking unclassified regimen line. In comparison, 41 of the case participants were taking second-line ART medications (**Table 2**). However, comparison of results based on regimen lines was not possible due to a programmatic change of ART medications. Dolutegravir based regimen was newly introduced in the country as a first-line ART regimen in adults and adolescents and dolutegravir optimization was made among selected adolescents on second-line art regimen.

Table 2. Treatment status of study participants

Variables		Total Variable Frequency among cases and controls	Variable Frequency among cases	Variable Frequency among controls
WHO Stage during ART initiation	stage 1	35 (18.2%)	1 (1.6%)	34 (26.5%)
	stage 2	99 (51.6%)	37 (57.8%)	62 (48.4%)
	stage 3	50 (26.0%)	21 (32.8%)	29 (22.6%)
	stage 4	8 (4.2%)	5 (7.8%)	3 (2.3%)
Previous history of TB treatment	Yes	49 (25.5%)	26 (40.6%)	23 (17.9%)
	No	143 (74.5%)	38 (59.4%)	105 (82.0%)
Current ART regimen line	first line	135 (70.3%)	20 (31.3%)	115 (89.8%)
	second line	52 (27.1%)	41 (64.1%)	11 (8.6%)
	third line	1 (0.5%)	1 (1.6%)	0 (0%)
	Unclassified	4 (2.1%)	2 (3.6%)	2 (1.5%)

All controls had undetectable current viral load whereas the mean current viral load of cases was 36,107. The mean duration of ART use among cases and controls was not significantly different and the overall mean duration of ART use was 135 months. The baseline viral load had not been determined for any participant, but the mean baseline CD4 count was 490, with no significant difference between cases and controls (**Figure 1**). The mean duration of time since the last/most recent viral load was determined was 111 days. None of the adolescents had recent CD4 counts, with treatment response largely followed by viral load determination every six months. 40% of the case and 18% of controls have a previous history of TB treatment. HIV status had been disclosed to all adolescents and youths.

Depression

Two-way tabulation using fisher's exact test shows significantly different depressive symptoms among cases and controls ($p < 0.001$). **Table 3** shows the PHQ-9 depression screening tool symptom score frequency and severity among cases and controls.

Table 3: depression burden among cases and controls

Viral load category	Burden of depression					
	No (0)	Minimal (1-4)	Mild (5-9)	Moderate (10-14)	Moderately severe (15-19)	Severe (>19)
Control	52	18	43	7	8	0
Case	11	10	11	12	19	1
Total	63	28	54	19	27	1

Depression and adherence to ART

We were also able to notice a higher rate of poor adherence to ART medications among moderate and severely depressed children. Ten out of 11 participants who had poor ART medication adherence had a concomitant moderate to moderately severe depression (**Table 4**).

Table 4: Two-way cross-tabulation of depression and ART medication adherence status

PHQ-9 depression screening score	ART adherence level category			
	Good	Fair	Poor	Total
Mild, minimal or no depression	126	18	11	145
Moderate to severe depression	14	23	10	47
Total	140	41	11	192

We summarized the means and frequencies of PHQ-9 depression screening scores among cases and controls in association with the level of ART adherence. Cases who experienced poor ART adherence had a more advanced depression with, a mean depression score greater than 15 which is moderately severe depression (**Table 5**).

Table 5: Association between depression scores and ART adherence among cases and controls

Variable type	ART adherence level category			
	Good	Fair	Poor	Total
Controls				
Mean	3.53	11.5	0	4.6
Frequency	111	17	-	128
Cases				
Mean	7.6	8.5	15.45	9.23
Frequency	29	24	11	64
Total				
Mean	4.4	9.7	15.45	6.14
Frequency	140	41	11	192

Factors associated with virological non-suppression

We perform conditional logistic regression using STATA version 14.2. On univariate and multivariate conditional logistic regression analysis; orphan status, living status, ART medication adherence, less frequent involvement to monthly adolescent and youth support group, advanced WHO stage during art initiation and depressive symptoms were associated with higher odds of virological failure (**Table 6**). The odds of having virological failure with depressive symptoms was higher when we condition them to minimal and mild depression in one category and moderate and severe depression in another categorical level.

Table 6: A Univariate and Multivariate Conditional (fixed-effects) logistic regression modeling to determine the association of depression and virological failure (n=192).

Virological failure	Univariate analysis			Multivariate analysis		
	OR	P>z	95% CI	OR	P>z	[95% CI]
Depression category level as minimal to mild versus moderate to severe depression	6.8	0.000	[3.1-14.8]	4.974	0.004	[1.7-14.6]
Adherence level as good, fair, and poor	8.0	0.000	[3.5-18.4]	10.90	0.000	[2.4-21.9]
Support group involvement	6.5	0.000	[2.4-17.7]	7.23	0.002	[2.4-48.9]
WHO stage during ART initiation	2.3	0.000	[1.5-3.5]	3.11	0.001	[1.6-6.2]

NB: OR- ods ration; WHO- World Health Organization; Prob > Chi2 = 0.0000

Variables that demonstrate significant association in the univariate conditional regression analysis were adjusted for the multivariate conditional regression analysis of the respective variables. Depressive symptoms were significantly associated with higher odds of ART medication adherence both on the univariate and multivariate logistic regression (crude odds ratio = 11.56, adjusted odds ratio =10.5, p = 0.0001). **Tables 6 and 7** summarizes the univariate and multivariate output results with the respective odds ratio and confidence interval. Though significant association was found between support group involvement and WHO stage during ART initiation to ART adherence, multivariable conditional regression adjusted for depression did not indicate association.

Table 7: Univariate and multivariate logistic regression to determine the association between adherence to ART medications and other independent variables

Univariate conditional logistic regression				
Adherence level	OR	Z	P>z	[95% CI]
Depression category	11.6	4.53	0.000	[4.0-33]
Support group involvement	3.2	2.13	0.033	[1.1-9.5]
WHO stage during ART initiation	1.9	2.30	0.021	[1.1-3.3]
Multivariate conditional logistic regression				
Depression category	10.5	4.23	0.000	[3.5-31]
Support group involvement	2.6	1.31	0.189	[0.6-11]
WHO stage during ART initiation	1.6	1.14	0.254	[0.7-3.5]

Discussion

In this study, we assess HIV virological non-suppression and associated factors among adolescents and youth attending ART in Ethiopia. We found that having depressive symptoms is associated with a higher conditional likelihood of both viral non-suppression and non-adherence to ART medications. The association was stronger among those adolescents who have moderate or severe depressive symptoms (AOR = 5, and Crude OR = 6.8). The findings in our study are supported by several other studies. Psychosocial interventions demonstrate small to moderate effect size on ART medication adherence, Pascale Spaan et al, 2018 [12]. According to data from HIV-infected persons enrolled at a cohort study in Washington DC between January 2011 and June 2014, those with diagnoses of mental health issues or depression have a lower likelihood of sustained viral suppression. This is in agreement with a previous systematic review from 29 studies that included a total of 12,243 participants (Ref).

Data synthesized from these studies revealed that depression treatments and mental health interventions are effective for enhancing adherence to antiretroviral regimens. The odds of a person adhering to ART are 83% better if the patient is treated for depression, and the risk of no adherence is 35% greater among those who do not receive depression treatment. Studies in which participants were diagnosed with clinical depression or had, on average, moderate-to-severe depressive symptoms demonstrated larger effects than studies in which participants had mild depressive symptoms [9]. One study in Ethiopia performed a detailed systematic review to assess the prevalence of depression and the associated factors for the co-occurrence of depression in people living with HIV [11]. Our finding is however is significantly larger with depression prevalence 59.35 and 82% among controls and cases. This difference might be due to study population difference as our study targets only adolescents and youth aged 12-24 years. The figure is also significantly larger than the expected burden in the general population which stands at 17%. This difference might be explained by the most commonly reported additional risk factors among HIV positive patients, according to the systematic review mentioned above, Mogessie Necho, Ethiopia, 2018, presence of perceived HIV stigma, poor social support, poor medication adherence, opportunistic infection and advanced stage of AIDS are most commonly identified risks to depression. The pooled adjusted odds ratio (AOR) of perceived HIV stigma among the indicated studies was 3.75. Six studies reported poor social support as an associated factor for depression in HIV patients and the pooled AOR was found to be 6.22. Moreover, the average odds ratio of poor medication adherence, presence of opportunistic infection, and advanced stages of AIDS were 3.03, 5.5, and 5.43 respectively. Despite this high burden of depression among HIV clients, psychiatric disorders are neither well addressed nor studied in Ethiopia HIV care.

We have assessed possible confounding variables and sociodemographic variables. Of the assessed sociodemographic variables, orphan status and living status were associated significantly with virological failure. Being a double orphan was associated with higher odds of virological failure compared to single orphan or non-orphan (crude OR=1.5, $P < 0.001$). There was also a slightly higher

association between living status and virological failure (crude OR = 0.6, $p < 0.01$). Having a caregiver was associated with a lower conditional likelihood of virological failure and non-adherence (crude OR = 1.6).

This is in agreement with other studies done in Ethiopia and other countries. According to Zvanaka Sithole et al. 2017, Zambia, of the socio-demographic factors assessed, only two of the variables impacted the outcome. Those who had treatment buddies were 0.6 times less likely to have virological failure compared to those who did not (13). Another study on the importance of caregivers in the outcome of pediatric HIV management in Kenya found that treatment failure was associated with not having both parents as caregivers. In Ethiopia, several studies evaluate the association of having caregivers and caregivers being HIV serology positive with viral suppression. Those who had HIV-positive caregivers were 0.5 times less likely to develop Virological failure as compared to those who did not [1, 2, 5, 13]. However, in our study, we do not assess the HIV status of caregivers and families due to ethical reasons.

We also assessed behavioral risk factors including adherence to ART medications, smoking, and alcohol use and chewing khat. However, none of the adolescents/youths smoke or chew khat. Alcohol use rate is also low among adolescents and there is no significant difference among groups. Nonadherence to ART medications as a risk behavior to ART treatment outcome has a strong association with Virological failure on both univariate and multivariate conditional logistic regression (crude OR= 7.97, adOR= 10.95, $p < 0.0001$). This is in agreement with recent study in Ethiopia, poor adherence to ART increased Virological failure by higher odds (AOR =16.09)[2], with similar country-specific findings in Africa (Zimbabwe $n = 102$, 18.5 ; SA $n = 134$, 14.5, Zambia $n= 256$, 18.15) [1, 2, 13, 14, 22]. The good adherence rate, in our study, among the total participants and cases, was 72% and 45%, respectively. This is in agreement with another study by Jeremy L Ross 2019, a prospective cohort study among 250 HIV infected and 59 matched HIV uninfected adolescents in Malaysia, Thailand, and Vietnam from July 2013-March 2017, which found 60% self-reported adherence $\geq 95\%$ at week 144 [8].

Despite the higher odds of Virological failure among non-adherent adolescents, 29 (45%) and 41 (64%) of cases good have good and fair adherence to ART medications respectively. Thus our study found a high burden of virological non suppression among sufficiently adhered adolescents, 45% of all adolescents who did not achieve viral suppression were sufficiently adhered [10]. This clearly indicates the presence of other independent risk factors for viral suppression regardless of adherence status, like depression. Our finding is also supported by several other studies as mentioned in the literature review part. This may also be an important indicator and notification for the necessity in developing a highly sensitive and specific approach to adherence measurement in adolescents and youth. Despite this fact, strict adherence monitoring using available methods is the single most important method of measurement for Virological failure and/or treatment outcome. This study has a limitation in that it was conducted in a single referral hospital and the generalizability of the results could be affected. The study has strengths in that it indicated the association of an important and less understood mental health condition,

depression, and viral suppression among adolescents and youth living with HIV using a hypothesis-driven matched case-control method.

Conclusion

According to the results of our study, non-adherence to ART medications, depressive symptoms, advanced WHO stage on ART initiation and not involving in weekly support group meetings were independently associated with virological failure among adolescents and youths taking ART. The study also found a higher rate of non-adherence among adolescents affected by depression. Having moderate and severe depression has higher odds of non-adherence and virological failure. We recommend integration and task-sharing of mental health and HIV care services to reduce virological failure in this group of people.

Declarations

Funding

This study was supported by the Center for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa), College of Health Sciences, Addis Ababa University, Ethiopia.

Ethics approval and consent to participate

Ethical approval to conduct the study was obtained from the Scientific and Ethics Review Committee of the Center for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa), College of Health Sciences, Addis Ababa University, and the Institutional Review Board of the ALERT Center. For adolescents aged 12 to 18 years, assent was obtained. Confidentiality was assured and maintained through no use of names on questionnaires and keeping questionnaires under lock and key.

Authors' contributions

Study conception, data acquisition, synthesis, and first draft: YM. Data acquisition and synthesis, review the draft: CH, TM. All authors reviewed and approved the final version for publication.

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Competing interests

The authors have declared that no competing interests exist.

Consent for publication

Participants provided informed consent to publish the identified data.

Data availability

Data used for all analyses are included in the manuscript.

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Figures

Figure 1

Baseline CD4 among cases and controls