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Adherence to Antiretroviral Therapy in HIV-Positive Patients in Ethiopia: Review

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Abstract

Background: Highly active antiretroviral therapy (HAART) offered HIV-positive individuals tremendous life-sustaining benefits. The benefits are sustainable only through optimal adherence. This systematic review was conducted to synthesize the available studies in order to determine average adherence, identify variables associated with adherence and shed light on the design and improvement of adherence studies and interventions.

Method: Studies were selected from electronic databases (Pubmed, Hinari, Google scholar) using HAART or Highly active antiretroviral therapy and adherence [Ethiopia] as search terms. Each study was summarized by using format containing: characteristics of the study, sample size, study design and measures of adherence, factors associated with adherence, reasons for missing dose.

Result: A total of 17 studies: 16 cross-sectional and 1 prospective study reporting adherence to HAART in Ethiopian HIV-positive patients were identified in our search items. Almost all of adherence to HAART studies conducted in Ethiopia used cross-sectional study design with self-report as adherence measurement. Though from the lowest evidence design the adherence rate in Ethiopia were higher than many developed countries report. Social support is major positive predictor of adherence to HAART while depression and substance abuse were negative predictors'.

Conclusion: We demonstrated a better self-reported adherence to HAART in Ethiopian HIV-positive patients. However rate and determinants of HAART in Ethiopian HIV-positive patients are poorly defined. The type of study design used and the use of self-report (subjective measure) in adherence assessment made adherence to HAART unexplored in Ethiopia. Further studies should be conducted using prospective cohort and interventional study design using varying methods of adherence measurement.

Keywords: Adherence; HAART; Self report; Pill count; HIV-positive; Ethiopia

Background

Highly active antiretroviral therapy (HAART) is a breakthrough and celebrated in the reduction of mortality and in the improvement of quality of life of people living with HIV/AIDS (PLWHA). On its introduction in 1996, antiretroviral therapy (ART) offered HIV positive individuals tremendous life-sustaining benefits and is most likely the single most dramatic development yet in the treatment of HIV. This evidence has been well-documented in many papers [1-4].

When taken consistently and strictly as directed, the benefits of ART include increased CD4 cell counts [5,6], decreased viral load, and decreased probability of progression to full-blown AIDS and death, and improved quality of life [3,4]. Consistent use of antiretroviral therapy (ART) therefore suppress viral replication and reduce the likelihood of development of drug resistant viral strain and also prevents further viral destruction of the cellular immune system [7,8].

Even though adherence to ART is one of the few potentially alterable factors determining outcomes for patients with HIV, non-adherence to ART is common in all groups of treated individuals [5,9].

Medication adherence, particularly for complex regimens such as HAART, is a complex behavior, requiring patients to remember multiple medications and dosing schedules. Patient failure to follow the ART regimen can lead to the development of treatment-resistant strains of the virus and poorer health outcomes [10,11].

There are multiple factors that influence adherence: patient factors (e.g. socioeconomic, educational status etc.), treatment regimen characteristics, disease characteristics, and patient-provider relationship, patient's clinical, social, psychological, and behavioral variables are among the most important factors that influence adherence and are potentially modifiable variable [12-14]. The search for this potentially modifiable variable correlation with adherence is the main theme in adherence studies. Adherence is a very dynamic varying among many population groups as result of many modifiable variables.

Studies have evaluated adherence to HAART and its associated factors/variables among Ethiopian HIV-positive patients. However these studies reported different adherence rate and determinants. Findings from different studies vary depending on how adherence was measured, the characteristics of the samples, and the remaining variables analyzed. We have learned the importance of having conclusive evidence by combing available studies. A systematic review

identifying and explaining these discrepancies is required for designing further studies and interventional strategies. The objective of this study is to carry out systematic review of HAART adherence in Ethiopian HIV-positive populations and to synthesize studies in order to determine average adherence and identify the variables associated with adherence. This systematic review will also shed light on the design and improvement of adherence to HAART studiesand interventions meant for improving adherence.

Methods

Data search

The studies were searched from electronic databases (Pubmed, Hinari, Google scholar). Words such as [HAART OR highly active antiretroviral therapy] and adherence and[Ethiopia], and antiretroviral therapy and adherence and [Ethiopia] are used as search terms. All studies included in the study are those written in English language. Other search terms that reflect adherence (e.g. compliance, pill counts) are also interchangeably used with adherence. Reference list of originally found article were also searched for eligible article to be included.

Study selection: Inclusion and exclusion criteria

Studies were included in the review if they aimed to evaluate adherence to HAART in a Ethiopian sample, had a cross-sectional or cohort design, measured adherence and/or reported factors associated with adherence and operationally defined adherence as intake of >90% or 95% of the medication prescribed [15,18].

Data extraction

Data extraction was conducted using a standardized format. Data was summarized on format containing characteristics of the study, sample size, study design and measures of adherence, factors associated with adherence, reasons for missing dose. When more than one adherence measurement was used (e.g. unannounced pill count and self -report), data from all methods were collected and compared.

Findings

Characteristics of adherence to HAARRT studies conducted in Ethiopia

Seventeen studies assessing adherence rate and determinates of HAART in Ethiopia in HIV-positive patient were found: Thirteen studies on adults [12,13,15,17,19-26] while four studies were conducted in children [14,18,27,28]. All of these studies have reported either adherence rate and/or determinants' of adherence to antiretroviral therapy. The studies were reported between 2006 to 2014. The sample size extends from the minimum 204 children [27] to a maximum of 510 adults [19]. Four of them are qualitative studies focused on reporting factors associated with adherence [23,24,26,28]. Four studies were conducted in children [14,18,27,28] while 13 studies were conducted in adults which are powered to determine adherence rate and its determinants. One study used prospective study design with 3 months follow up duration. All other studies used cross-sectional study design which is the lowest in the evidence pyramid of studies. Details of the study characteristic were presented in Table 1 and Table 2 below.

The entire studies defined optimal adherence as greater 95% and used this definition in their studies. Adherence was measured across various time periods: the previous day, the previous 3 day and the previous seven day. The previous seven day was however used in estimating of the adherence rate of the studies in the included studies.

Self-report for adults or caregivers report for children was used for the assessment of the entire reviewed studies. However two studies [14,20] used community based unannounced pill count and self-report/ caregivers' report. A very significant difference was observed in both type of measurement in one study [14] that is 93.5% by caregivers report versus 34.8% by community based unannounced pill count.

In most cases adherence was defined whether a dose of a drug is taken or not. However in two of the included studies [15,17] adherence was defined in broader concept considering whether the medication was taken in the right time and the dietary restriction was followed. The two studies have reported dose adherence, time adherence, food adherence and overall adherence. Combined indicator of adherence was made using the three adherence measures taking into account all questions pertaining adherence. This is strict operational definition of adherence used by two of the reviewed studies.

Facilitators and Barriers of adherence in Ethiopian HIV-positive patients

Social support was a positive predictor of adherence in 3 studies [15,17,22]. Other positive predictors of adherence to HAART in Ethiopian HIV-positive patients includes: adherence counseling [27], use of memory aids [17], being on co-trimoxazole medication, for children not knowing one's own sero-status and being unaware caregiver's health problem [18], being married or being married caregivers [14,20], caregiver formal education and caregiver's ability to identify ARV drug correctly [27], initiation while stage III/IV[14], trust in the effects of antiretroviral drugs, and trust in the quality of counseling [23].

Depression was a reported as negative predictor of adherence in 5 studies [12,13,17,22,27]. Substance use in general [27], alcohol drinking[13,20], D4T-3TC-NVP, AZT-3TC-NVP regimens [14,20], Stigma and discrimination[13,18], dosing three times daily regimens[20], Heavy pill burden[18], cost and access to transportation (economic problems) [18,23], lack of nutritional support [18,22], adverse effects [12,16] were negative predictors of adherence to HAART in Ethiopian HIV-positive patients. Details of the facilitators and barriers of adherence to HAART in Ethiopian HIV-positive patients were summarized in Table 2.

Reasons claimed by participants for missing doses include forgetting [14,17,19-21,25], being ill [2], being busy [2,3,21,25] and running out of medication [15,19,22], being away from home [21,23,25] and Lack of transport cost. For details of information refer Table 2.

Discussion

Several important insights have emerged from this study. Adherence improvement interventions and studies can benefit from these insights. Seventeen studies assessing adherence rate and/or determinants to HAART in Ethiopia HIV-Positive patients were identified by electronic and manual search of published literature. Thirteen studies on adults while 4 studies were on children. All of the

studies used homogeneous cut off greater 95% dose taking of monthly medication as operational definition of adherence.

One study used prospective study design while the others used cross-sectional study design. Amberibir and his coworkers used a three month prospective study design, data being collected at the first and third month. The available studies on adherence to HAART from the lowest level (cross-sectional study) design. Limited number and poor quality (cross-sectional) of the studies makes rates and determinants of adherence in Ethiopia unexplored yet. It can be perceived from these facts that adherence and its determinants in Ethiopian HIV-positive population are poorly defined.

	Study	Total no of participant	Study design	Statistical analysis	Adherence measurement
1	Amberbir et al. [17]	400 adult	Prospective cross-sectional	Descriptive, bivariate, and multivariate analyses using SPSS	Self-report
2	Azmeraw [27]	204 children	cross-sectional	Descriptive, bivariate, and multivariate analyses using SPSS	Caregivers' report
3	Beyene et al. [20]	422 adult	Cross-sectional (qualitative and quantitative)	Descriptive, bivariate, and multivariate analyses using SPSS 11.05	Self-report unannounced pill count
4	Biadigilin et al. [18]	390 children respondents	Facility-based cross-sectional	Descriptive, bivariate, and multivariate analyses using SPSS 12.0.1	Caregivers' report
5	Biadigilin et al.	Twelve caregivers and 14 key informants in five hospitals	Qualitative study	NA	NA
6	Giday [19]	510 adults	cross sectional	Descriptive, bivariate, analyses using SPSS 15.0	Self-report
7	Gusdal et al.	79 patients, 17 peer counselors,22provider	Qualitative study	NA	NA
8	Kebede et al.	296 patients	cross-sectional study	Descriptive, bivariate, analyses using SPSS	Self-report
9	Tadios [12]	431 patients	Cross-sectional	Descriptive, bivariate, analyses using SPSS	Self-report
10	Tessema et al. [16]	504 study subjects	Cross-sectional	Descriptive, bivariate, analyses using SPSS	Self-report
11	Tiyou et al. [15]	319 adult PLWHA	Facility based cross-sectional	Descriptive, bivariate, analyses using SPSS 16.0	Self-report
12	Markos et al. [21]	391 adult patients	Cross-sectional survey	Descriptive, multiple logistic rgression, analyses using SPSS 16.0	Interview, pill count, and record review
13	Negash	355 adult patients	Cross-sectional survey		
14	Biressaw et al. [14]	210 children	Quantitative descriptive design	Descriptive, Chi-square test and Multivariate logistic regression analyses using SPSS 16.0	Caregivers report and unannounced home-based pill count
15	Alagaw [22]	357 adults	Cross-sectional survey	Descriptive, bivariate, analyses using SPSS 16.0	Self-report

Table 1: Characteristics of adherence to HAARRT studies conducted in Ethiopia; NA= not applicable.

No	Study	Adherence rate	Determinants of Adherence	Reasons for missing doses
1A	Amberbir et al. [17]	DA=94.3% TA=97.2% FA=84.5% OA= 75.7%	Social support was positive predictors while depression was negative predictors	Forgetting, feeling sick or ill, being busy and running out of medication
1B	Amberbir et al.[17]	DA= 92.3%, TA=97.4% FA=83.3% OA=72.7%	Social support and use of memory aids were positive predictors while depression was negative predictors	forgetting, feeling sick or ill, being busy and running out of medication
2	Azmeraw et al. [27]	OA= 80.9%	Adherence counseling, caregiver formal education, and caregiver's ability to identify ARV drug correctly were positive predictors while care giver substance use and depression were negative predictors.	Not reported
3	Beyene et al. [20]	AS=93.1% AUPC=88.1%	Being unmarried, unemployment; failure to disclose HIV status, lack of support from family, alcohol drinking, treatment regimen D4&-3TC-NVP and AZT-3TC-NVP, and dosing three times daily regimens were negative predictors	Transport cost and lack of food
4	Biadgilign et al. [18]	OA=91%	Not paying a fee for treatment, children who had ever received any nutritional support from the clinic were less likely to adhere. Being on co-trimoxazole medication, not knowing one's own sero-status, and children who were not aware of their caregiver's health problem were more likely to adhere	Not reported
5	Biadgilign et al.[28]	NA	Heavy pill burden, fear of stigma and discrimination, cost and access to transportation, lack of understanding of the benefit of taking the medication, economic problems in the household, and lack of nutritional support were the barriers	-
6	Giday et al. [19]	OA=88.2%	Inadequate adherence counseling, low level of knowledge, and absence of job were negative predictors	Running out of medication, forgetting, gastrointestinal symptoms, giving priority for praying, being hopeless
7	Gusdal et al. [23]	NR	Difficulties in supporting themselves, transport cost, opportunistic infection treatment, and expensive referrals to other hospitals were barriers while trust in the effects of ARV and in the quality of counseling were facilitators	NR
8	Kebede et al. [25]	OA=95.8%	Good educational status were positive predictor	lack of money for transport, and forgetting

9	Tadios et al. [12]	OA=81.2%	Regular follow-up, not being depressed having no side effects, regimen fitting daily routine and satisfaction with the relationship with doctors were positive predictors	Being too busy, forgetting and being away from home
10	Tessema et al. [16]	OA=82.7%	Adverse effects, unwillingness to disclose HIV status	-
11	Tiyou et al. [15]	DA= 95% FA=89.7% TA= 95% OA=72.4%	Family support were an independent predictor	Running out of medication, being away from home and being busy
12	Markos et al.[21]	OA=74.2%	Presence of symptoms in the past month, distance of residence, and presence of dependents	Being busy, Forgetting, change in daily routine and being away from home
13	Negashet al. [13]	NR	Stigma, discrimination, depression, and alcohol use negatively affected	
14	Biressaw et al. [14]	ACR=93.5%, AUPC=34.8%	Married caregivers and stage III/IV are positive predictors while D4T+3TC+EFV regimen negative predictor	Forgetfulness and Child refusal
15	Alagaw et al. [22]	74.4%	Living with supporter was positive predictor while depression and Inadequate diet were negative predictors	Toxicity, forgetting, illness, Running out of medication, Lack of transport cost, and lack of food

Table 2: Rate and determinants of Adherence to HAART studies conducted in HIV-positive patients in Ethiopia; DA= dose adherence, TA= Time adherence, FA= food adherence, OA= Overall adherence, UAPC= unannounced pill count, ACR=, NR= not reported

Discrepant finding were observed among and within studies in adherence rate measurement. Within study variation occurs when a study uses more than outcome (adherence) measurement methods. Self-report measured adherence were 93.1% while unannounced pill count were 88.1% in study conducted in selected hospitals in south and central Ethiopia[20] and caregivers report adherence rate was 93.5% while unannounced pill count was 34.8% in children adherence study [14]. It is clear from this studies that adherence measures vary with method of adherence measurement used.

Self-reported adherences to HAART in Ethiopian HIV-positive patients were greater than some of developed countries report [29,30]. Adherence rate to HAART in Ethiopia vary from the lowest 34.8% [14] to the highest 95.8% [25]. The major distinction between the two is that the former used objective adherence measurement (unannounced community based pill count) while the latter used caregivers report (a subjective measure). All most all adherence studies in Ethiopia used subjective measure of adherence measurement: self-report for adults while caregivers report for children. This method has been shown to overestimate adherence both in the HIV setting and non-HIV setting and non-consistent results were found when compared to more objective measures [14, 31].

The level of adherence varies not only with patient but also with the type of adherence measurement used. The methods of adherence measurement includes: pharmacy refill record, pill counts, medication event monitoring (MEMs), viral load measurement, CD4 count and self-report. Because of their low cost and easy implementation self-report and pill counts are widely used in developing country [32]. However self-report is prone to recall biases and sometimes may report exaggerated adherence and heavily depends on how the interview was made. Yet, self-reported adherence correlates with both viral load and clinical outcomes in some studies [33,34]. Except two studies [15,17] all other studies have measured adherence using only dose adherence.

Best adherence measurement has to assess whether or not dose is skipped, maintaining the scheduled time and food or dietary instructions agreed with the health provider to get the overall adherence rate. Therefore most of the studies conducted in Ethiopian HIV-positive patients narrowed adherence definition into taking a dose of medication or not. This kind of adherence definition lacks practical significance: for example not following dietary restriction which may decrease the blood concentration of the drug [35].

Social support was most commonly cited facilitator of adherence in most of the reviewed studies while failure to disclose sero-status was cited as negative predictor of adherence. The two parameters are linked as if one cannot disclose his/her sero-status it is impossible for him/her to get social support. It is very crucial during initiation to encourage the patients to disclose their sero-status to relatives.

Depression was negative predictor of adherence in five reviewed studies. This can be avoided by providing necessary knowledge of how to live with HIV/AIDS. Encouragement and providing social support

through community worker can alleviate the depression problem and finally improve adherence [36]. Antidepressants medications are also used in most studies to alleviate the depression and this treatment has increased the adherence to HAART [37-39]. In some studies no such association has been elucidated [40].

No interventional study had been conducted in Ethiopia setting. A prospective study design was used only by one study [17] which has one month duration. Because of this rate and determinants of HAART adherence in Ethiopia is yet poorly defined. We are looking forward for the evidence from one study which is powered to determine predictors of adherence using prospective study design of one year duration. The study protocol was published which has the aim to investigate the level of adherence to ART and a wide range of potential influencing factors, including adverse drug reactions occurring with ART. The primary outcome of the study will be the proportion of patients who are adherent to their ART regimen at 3, 6 and 12 months using pill count [41].

Conclusion and Recommendation

Almost all of adherence to HAART studies conducted in Ethiopia used cross-sectional study design with self-report as adherence measurement. Though from poor evidence study design, adherence rate to HAART in Ethiopian HIV-positive patients were better than some developed countries report. Positive predictors of adherence in Ethiopia include Social support, adherence counseling, and use of memory aids while negative predictors' include: depression, substance use, alcohol drinking, stigma and discrimination, dosing three times daily regimens, heavy pill burden, cost and access to transportation (economic problems), lack of nutritional support, and adverse effects.

Adherence rate and its determinants in Ethiopian HIV-positive population was explained/ studied poorly. Further studies have to be conducted which uses prospective cohort Interventional study design and varying methods of adherence measurement. The interventional study design has to test the effectiveness of the use of reminder devices (pillbox, alarms, mobile phone, text messages, peer support, treatment with antidepressants, counseling, food rations, delivering ART in to communities, and income generating activities.

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