BMJ open

Adherence with antiretroviral drug therapy in Ethiopian adult HIV-positive patients

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-003559
Article Type:	Protocol
Date Submitted by the Author:	07-Jul-2013
Complete List of Authors:	Bezabhe, Woldesellassie; University of Tasmania, School of Pharmacy Peterson, Gregory; University of Tasmania, School of Pharmacy Bereznicki, Luke; University of Tasmania, School of Pharmacy Chalmers, Leanne; University of Tasmania, School of Pharmacy Gee, Peter; University of Tasmania, School of Pharmacy
Primary Subject Heading:	HIV/AIDS
Secondary Subject Heading:	Health services research, Infectious diseases, Pharmacology and therapeutics
Keywords:	HIV & AIDS < INFECTIOUS DISEASES, CLINICAL PHARMACOLOGY, Infectious disease/HIV < NEUROLOGY

Adherence with antiretroviral drug therapy in Ethiopian adult HIV-positive patients

Bezabhe, Woldesellassie; Peterson, Gregory; Bereznicki, Luke; Chalmers, Leanne; Gee, Peter

Abstract

Introduction: Achievement of optimal adherence and management of antiretroviral toxicity pose great challenges among Ethiopian patients with HIV/ AIDS. There is currently no long-term follow-up study that identifies the barriers to, and facilitators of adherence to antiretroviral therapy (ART) in the Ethiopian setting. Therefore, we aim to investigate the level of adherence to ART and a wide range of potential facilitators of, and barriers to adherence, including adverse drug reactions (ADRs) occurring with ART.

Methods and analysis: We will conduct a one-year, prospective, longitudinal study involving adult patients with HIV/AIDS commencing on ART between December 2012 and March 2013. Data will be collected on patients' appointment dates in the ART clinics. Adherence to ART will be measured using pill count, medication possession ratio, and patient's self-report methods. The primary outcome of the study will be the proportion of patients who are adherent to ART regimen at 3, 6, 12 months of the study using Pill Count (PC). The optimal level of adherence in this study will be taking 95% or more of the dispensed ART regimen at a point in time. Data will be analysed using the descriptive and inferential statistical procedures.

Ethics and dissemination:

Ethics approval was obtained from the Tasmania Health and Medical Human Research Ethics committee (Approval Number: H0012722); and Bahir-Dar University's Ethics Committee (Approval Number: RCS/567/2004). The result of the study will be reported in peer-reviewed scientific journals, conferences, and seminar presentations.

Article summary

Article focus

- To establish the level of adherence and identify factors that influence adherence to ART in Ethiopian HIV/AIDS patients with cohort study.

Key messages:

- Factors that affect adherence to ART are not still identified in Ethiopia HIV/AIDS with long-term follow-up study.
- Data for this prospective cohort study over the period of at least of 16 months will identify important factors associated long-term adherence to ART that are not still identified in the setting.

Strength and limitations of this study

- This study is the first of its kind conducted in the country to identify factors that affect adherence to ART in the treatment naïve patients who initiated ART.
- Rates of patient drop out; loss to follow up and death are high in this setting, which may challenge the success of the project.

INTRODUCTION

Ethiopia is home to approximately 800,000 patients with HIV/AIDS and the prevalence of HIV/AIDS in the general population is estimated to be 1.5%(1). The introduction of the free antiretroviral therapy (ART) program in Ethiopia, since 2005, decreased mortality and morbidity, and improved the quality of life of patients(2, 3). In the last 8 years, decentralization and scale-up of the HIV care program has occurred, and by the end of 2011, 249,174 adult patients (86% of eligible patients) were on ART(1).

Achievement of optimal adherence, management of antiretroviral drug-related toxicities, and patient retention(4) are becoming the greatest challenges in the management of HIV/ADS in Ethiopia. A cross-sectional study in Ethiopian patients reported adherence rate of 88.1%(5), which is below the near perfect adherence (≥95%) required to maintain the effectiveness of ART(6).

Patient retention in HIV care facilities is low, and averaged 51% to 85% in 55 Ethiopian HIV care facilities in a 2 year patient follow-up study(4). Similarly, a 2011 report from the Ethiopian Ministry of Health indicated that patients dropping out from HIV care was a serious issue, with up to 40% of patients who initiated ART dropping out from treatment in some regions of the country(7). Mortality and drop out from antiretroviral treatment are more common in the first year of patient follow-up than later in Ethiopia(8).

Adherence to medication is a dynamic behaviour affected by factors related to treatment regimen complexity, patient related variables, patient-health care provider relationships, and the quality of health care services(9). Patient adherence to ART is influenced by regimen related factors such as pill burden, frequency of dosing, ADRs, fluid and dietary restrictions(10). Similarly, patient related factors such as lack of transport, shortage of food, use of traditional medicine, alcohol abuse, depression, stigma and discrimination, and lack of social support undermine adherence(11-14). Further, a poor patient-health care provider relationship and low quality services, such as lack of confidentiality and privacy, and drug stock out hamper adherence with ART(12).

JUSTIFICATION FOR THIS STUDY

Adverse effects of ART are common and cause morbidities and mortalities, and have been reported to be a cause of non-adherence. Previous studies were retrospective cross-sectional studies, lacked active surveillance and did not focus on treatment naïve HIV/AIDS patients. While one prospective study has investigated adherence to ART in Ethiopia(15) it was only conducted for three months and also did not focus on treatment naïve patients. A prospective study over a longer period of time focusing on treatment naïve patients is required to assess the level of adherence in this patient group and its barriers and facilitators. There is also a need to conduct a prospective study in Ethiopian patients with HIV/AIDS to assess the emergence of ADRs to ART in clinical practice.

OBJECTIVES

The objectives of this study are to establish the level of adherence and identify factors that influence adherence and assess the incidence of ADRs and associated risk factors in Ethiopian patients with HIV/AIDS initiated on ART.

METHODS AND ANALYSIS:

Study design

This study is a prospective, longitudinal cohort study, in which adult Ethiopian patients with HIV/AIDS initiated on ART will be followed from the time of ART initiation (Month (M) =0) to 12 months of therapy (M=12). ART-initiated patients have an appointment every month for six months and every three months thereafter in ART clinics in Ethiopia; research pharmacists will collect data on appointment dates. The timeline of data collection activities are structured as shown in figure 1. The sequencing and repeating of measures is to observe the time pattern of different predictors on adherence of ART in treatment naïve patients. Depression, stigma, HIV-treatment knowledge, healthcare relationship, and belief about medication, and HIV-symptom index may affect adherence in a time-dependent manner and are measured before and after 6 months of patients' ART. Data's regarding the concomitantly administered medications, comorbidities, ADRs, and laboratory values are collected on every appointment dates. We have also designed a separate qualitative study to be conducted side by side involving patients taking ART, and nurses and peer counsellors working in ART clinics to help to explore the unique factors that affect adherence in these settings.

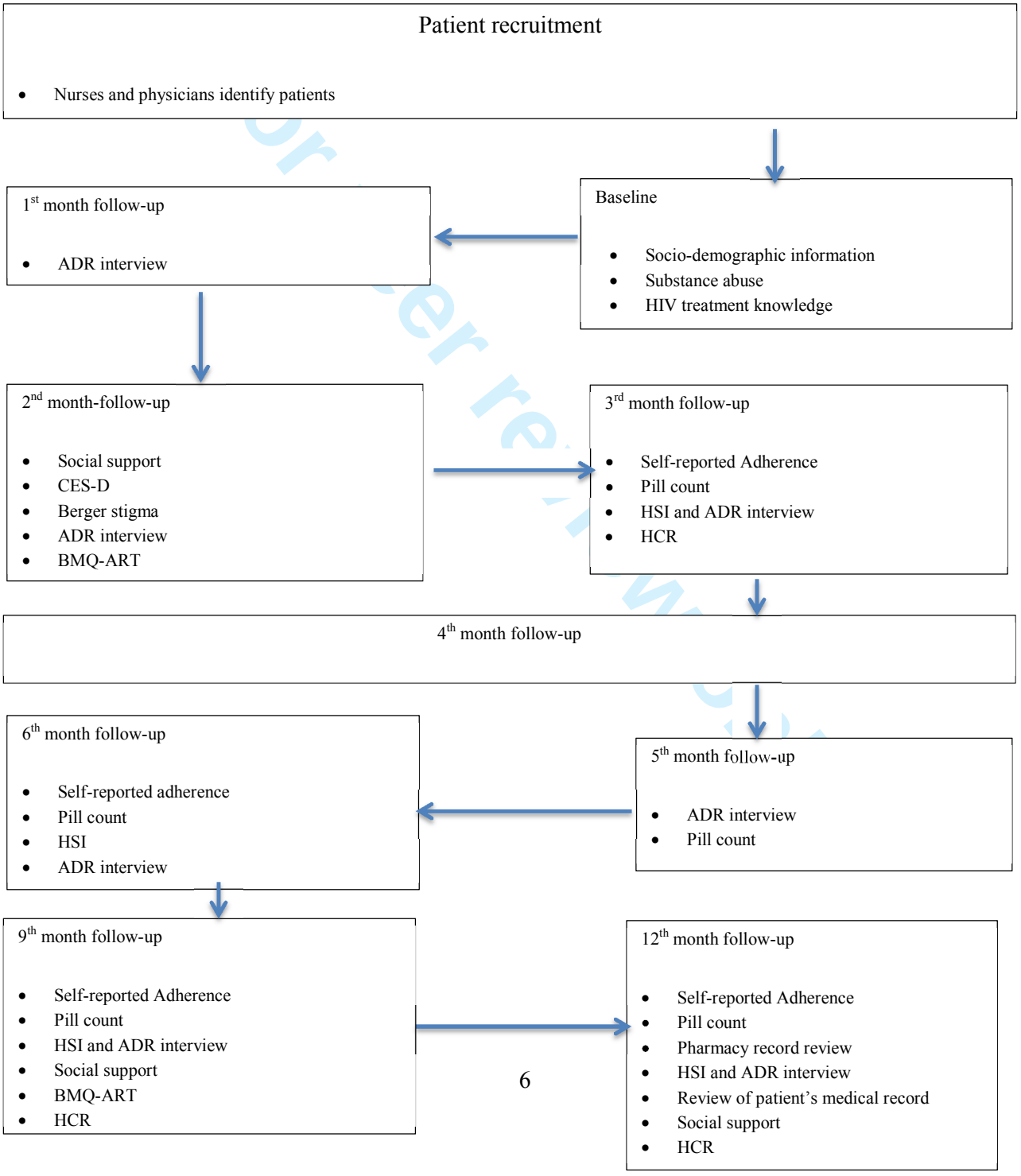


Figure 1 Study design

CES-D=Centre for Epidemiological Studies-Depression

ADR=Adverse Drug Reaction

HSI=HIV-Symptom Index

BMQ=Belief about Medication Questionnaire

HCR=Health Care Relationship

Study setting

The project will be implemented in two hospitals in the North-West Ethiopia: Gondar University Hospital and Felege-Hiwot Hospital. This study will be conducted between December 2012 and March 2014, which will allow a follow-up period of 12 months for each patient.

Inclusion criteria:

- All HIV/AIDS patients at least 18 years old being initiated on ART for the first time.

Exclusion criteria:

- Participants whose follow-up is to be conducted in outlying areas, rather than at the hospital where ART was initiated.

Sample size

The sample size for this study was determined based on a previous study, where 76% of patients had optimal dose, time, and food adherence to ART(15). Taking a 95% confidence level, and precision of 0.07, the sample size was estimated to be 143.

Based on an average of 43 new patients per month, within four months of recruitment in each ART clinics, the pool of patients for recruitment will be 344. Allowing for a non-participation

rate of 23%, and loss to follow-up of up to 30% (Mekides B and Desalew K, July 2012, personal communication), the sample size is achievable.

Recruitment

Between December 2012 and March 2013, participants will be initially invited by their nurses to participate in this study. At the first visit (usually two weeks before ART initiation), nurses will give patients information about the study and invite them to participate. If patients are interested in participating in the study, the research pharmacists to discuss the research will contact them. Informed consent will be obtained from volunteer participants using standard information statement and consent forms. Each of participants will receive $US 3 to reimburse their time and transport cost. The characteristics of patients who declined participation will be collected to determine the representativeness of the sample.

Measures

The questionnaires have been spread to track changes of the different parameters over time as shown in figure 1, while minimizing questionnaire fatigue. Assessment of adherence is a problematic issue as there is no gold standard method of measurement(16). In this study self-report, PC and Medication Possession Ratio (MPR) will be used to measure adherence at month 3, 6, 9, and 12. Use of multiple measures of adherence is recommended in literature as there is no single optimal measure of adherence(16). Adherence to medication found using multiple measures would be converted in to percentage of dose adherence and triangulated. Participants will access both fixed combination and loss combination ART dose. Percentage adherence to each of the pills will be calculated and the lowest dose adherence is taken as the adherence for the given patient.

The primary outcome of the study will be the proportion of patients who are adherent to ART regimen at 3, 6, 12 months of the study using PC. The optimal level of adherence in this study will be taking 95% or more of the dispensed ART regimen at a point in time. Adherence from PCs will be calculated by dividing the difference between current and previous PCs by the number of pills that have to be taken during the same period(5). PCs have been found to be an economic and reliable measure of adherence in resource-limited settings(17).

A modified AIDS Clinical Trial Group (ACTG) self-report adherence questionnaire that asks patients how many doses they missed in the last 7 days will be used to measure dose adherence of patients to ART. In addition, two four-item modified questionnaires from ACTG will be used to measure time and food adherence in the last 7 days(18). Assessing multiple dimensions of adherence by using all items of ACTG self-report adherence questionnaires has provided a strong measure of adherence(19). Self-reported adherence is well correlated with viral load suppression and suitable for resource-limited settings because of its low cost(20).

Patients stating they have missed medications will be asked to indicate reasons why they skipped medication from a list of 16 reasons (e.g. away from home, busy with other things, simply forget). Fourteen of the reasons for non-adherence are taken from ACTG(18) and two reasons associated with traditional medicine and religious treatment, respectively, were obtained from literature review(11).

Pharmacy refill records will be reviewed and the MPR will be calculated by dividing the total number of days covered with the medication dispensed by the number of days between the first fill and the last refill plus the days' supply of the last refill(21). This method is suitable

in our study as HIV-medication is refilled only from the nearby governmental hospital/health centre pharmacy in Ethiopia(1). PC and MPR are superior over self-reported adherence measures and well correlated with virological failure and clinical outcomes(22).

Depression in patients will be evaluated using the seven-item questionnaire of the CES-D scale. This scale has been extensively applied in different settings, including settings to assess depression in HIV/AIDS patients(18). The Revised Berger HIV stigma scale will be used for measurement of stigma. The 10-items of Berger stigma scale have been validated in HIV-positive youth(23). Berger stigma scale was used in Kenyan patients with HIV/AIDS(24). The higher score indicates the existence of greater stigma(25).

Previous studies have suggested that a lack of social support predisposes patients with HIV/AIDS(26). Patients' satisfaction with the social support they get from family members and friends and the help of the support for remembering their medication will be measured using two four-point scale social support questionnaires(18).

The HIV treatment knowledge scale will be used to measure patients' knowledge on adherence, ADRs and drug resistance. This instrument has been developed and validated by Balfour et al(27) in HIV/AIDS patients with ART.

The BMQ will be used to measure patients' belief about ART. The BMQ consists of two five-item scales probing patients' belief about the necessity of the given medication and their concerns about possible ADRs(28, 29).

The trust between the patients and health care providers will be measured using the 13-item HCR trust scale. Items are rated from 0 to 4, the total score ranges from 0 to 52 and a higher score indicates a greater level of trust(30).

The research pharmacist will interview patients and carers, and review patients' medical records for potential ADRs experienced in the preceding four weeks and record the following information using an ADR follow-up documentation form: signs and symptoms of ADRs, interventions, outcomes of interventions, laboratory test results, co-morbidities, concomitant medications (name, start and stop date, dose, route, indication), hospitalisations, reasons for regimen changes and new regimens.

Self-completed HSI will be used to measure patients' concern about 20 possible symptoms associated with ART ADRs. The research pharmacist will interview patient, their caregiver, and physician, and refer patient's medical record and document detail information regarding adverse effect patients diagnosed with. The severity of ADRs will be rated using the WHO ADR severity scale(31). Similarly, a physician and a pharmacist will determine the causality of each ADRs using Naranjo's probability scale(32). The reliability between raters and within raters has improved significantly ($p<0.001$) with the use of Naranjo's probability scale(32).This scale has been widely used in various settings(33). In addition, the Schumock and Thornton scale will be used to rate the preventability of adverse drug events(34).

Socio-demographic and economic variables such as age, gender, marital status, religion, level of education, number of children, employment status, and disclosure of HIV status, average number of meals per day, monthly income, transportation costs to the clinic, and waiting time in the hospital will be collected at the baseline.

Laboratory data such as weight, height, history of ADRs, hepatitis B virus (HBV) and hepatitis C virus (HCV) infection status, WHO stage of HIV/AIDS, CD4 count, haematocrit, white blood cell (WBC) count, absolute neutrophil count, platelet count, liver function tests [alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase

(ALP), and bilirubin direct and total], renal function tests [such as blood urea nitrogen (BUN), serum creatinine, and urea], and ART regimen, date of initiation, dose and frequency of treatment, other concomitant medications and comorbidities will be recorded from patients' on each appointment date from their medical records using a baseline clinical and laboratory data collection sheet.

Loss to follow-up

'Drop out' from ART program is defined as patients not presenting for dispensing of their ART for the last 3 months. Patients' record will be used to calculate the number of days covered by the last dispensed HIV medication and 90 days will be added to determine the date when patients are categorized as 'drop outs'. Study subjects who do not make at least 6 months follow-up will be excluded from the study. Patients lost from the follow-up will be tracked with peer counsellors working in the ART clinics of both hospitals using the registered address and phone number of them or their family member or close friend in their medical record to may help to avoid bias. The reason for being lost from follow-up will be recorded. Analysis of socio-demographic and clinical prognostic characteristics of those who lost from the treatment and those continuing ART will be compared.

Missing items

The percentage of missing items for each scale will be calculated for each participant. If more than 10% items of the scale missed the patient total score of the scale will be excluded from data analysis at that time point. The proportion of missing participants for each variable of interest will be calculated.

Statistical analysis

Descriptive univarate analysis will be conducted for socio-demographic and economic variables. Adherers will be compared with non-adherers with the Pearson chi-squared test for non-numerical variables and independent sample t-tests for numerical variables. Similarly, the characteristics of patients who developed ADRs and did not develop ADRs will be compared with Pearson chi-squared tests for categorical variables and independent samples t-test for continuous variables. Risk factors for adherence will be determined by investigating the influence of socio-demographic, socio-economic variables, and psychosocial variables, healthcare provider relationship, belief on medication and ADRs. Risk factors for ADRs will be determined by investigating the effects of gender, age, body mass index (BMI), CD4 count, history of drug allergy, comorbidities, concomitant medications, and type of regimen. Multiple variable binary logistic regression will be used to evaluate the independent influence of these risk factors on adherence. The exposure and the potential confounders will be modelled in relation with the outcome variable for adjustment using multiple-predicative regression model. The final model will be determined after checking multicollinearity. All statistical calculations will be performed using SPSS Version 20.0. A p-value of <0.05 will be considered as statistically significant.

QUALITY CONTROL AND DATA MANAGEMENT

Bilinguals performed the standard forward-backward translation to make the questionnaires linguistically and conceptually equivalent(35). The English-speaking native researcher made the forward translation of the validated questionnaires into Amharic. Two physicians working in the ART clinics of Ethiopian hospitals reviewed the developed Amharic versions. A professional translator made the backward translation to check the difference between Amharic versions and the original English versions. The differences between the source

version and target version were settled with panel of committee meeting including the forward translator, a physician and the back-translator and final Amharic versions were developed. The Amharic version will be pretested with 60 adult patients receiving ART who will not be included in the main study to check reliability and validity of the questionnaires. Items found to be problematic by patients will be modified.

The collected data will be checked for completeness, accuracy and clarity by the investigators. This quality checking will be performed daily after data collection and amendments will be made before the next data collection measure. Data clean up and crosschecking will be done prior to analysis. Severity(31), causality(32), and preventability(34) of adverse events will be separately assessed by a pharmacist and physician using validated algorithms.

The data will be entered from the two study sites in Ethiopia into a custom-built website housed on a secure server at University of Tasmania. Stored data will be backed up on a daily basis. Access to the information will be only granted to authenticated investigators from anywhere using Internet.

The custom-built website will generate data collection forms for printing. After completion these forms will be scanned and then upload to the website. The form data will be entered onto the website by the research pharmacists. A random sample of the scanned forms will be checked against the website data to ensure accuracy. Additionally, the website has a sophisticated series of checks to ensure that fields are entered and that all fields are within expected values. Researchers at each site will be informed of any incomplete or inconsistent data.

Strength of the study

Several features in the design and planning of the project show the strength of study. First, the study is intended to examine predictors of adherence from different perspectives including patient characteristics, medication regimens, and the health care system. Patients' socio-economic status, level of education, belief and knowledge of HIV medication, social-support and psychosocial variables are mentioned as predictors of adherence elsewhere(36, 37).

Second, the study uses multiple measures of adherence, which is recommended in the literature as there is no gold standard method of adherence measurement(16). Although patients in sub-Saharan Africa have been reported to have comparable rate of adherence with those in the developed countries(38), there is a plausible explanation in the literature that studies in sub-Saharan Africa measure adherence mainly using self-report, which overestimates adherence by as much as 20%(39). Patients refill their HIV-medication in a specific government ART clinic pharmacy; this allows us to use pill count and pharmacy records for adherence measurement(16, 40, 41).

Limitation of the study

Rates of patient drop out, loss to follow up and death are high in this setting(8), which may challenge the success of the project.

The study period may not be sufficient to document long-term ADRs, such as endocrine and metabolic adverse events, which may need more than one year to become apparent. Patients may not show up in ART clinics for treatment of ADRs or may be treated in other nearby clinics, which may underestimate incidence of ADRs.

Conclusion

The study is expected to provide extensive information about adherence, including the barriers and facilitators of adherence, and the ADR profile among a cohort of Ethiopian patients commencing on ART, and will also establish an important foundation for a subsequent intervention study focussing on improving adherence in ART naïve patients with HIV/AIDS.

ETHICS AND DISSEMINATION

Ethics approval was obtained from the Tasmania Health and Medical Human Research Ethics committee (Approval Number: H0012722); and Bahir Dar University's Ethics Committee (RCS/567/2004). The data will be stored in a locked filing cabinet in the Bahir Dar University premises for 5 years; afterwards the data will be shredded and disposed in secure bins. The digital recordings will be erased in accordance with the Tasmanian University regulations. Access to the filing cabinet and custom-built website will only be granted to authenticated investigators. We will disseminate our finding at the public presentation to stakeholders working on HIV/AIDS treatment in Ethiopia. The result of the study will be reported in peer-reviewed scientific journals, conferences, and seminar presentations.

Funding

None

Competing Interests

None

Contributorship

WMB, GMP, LC and LREB have contributed equally to the design of the study. WMB drafted the manuscript. PG developed the custom-built website. All authors revised the manuscript and approved the final copy.

REFERENCES

1. Ethiopian Federal Ministry of Health HIV AIDS Prevention and Control office (HAPCO). Country progress report in HIV/AIDS response2012.

2. Reniers G, Araya T, Davey G, Nagelkerke N, Berhane Y, Coutinho R, et al. Steep declines in population-level AIDS mortality following the introduction of antiretroviral therapy in Addis Ababa, Ethiopia. AIDS. 2009 Feb 20;23(4):511-8.

3. Ethiopian Federal Ministry of Health HIV/AIDS Prevention and Control Office (HAPCO). AIDS in Ethiopia six report. 2010.

4. Assefa Y, Kiflie A, Tesfaye D, Mariam DH, Kloos H, Edwin W, et al. Outcomes of antiretroviral treatment program in Ethiopia: Retention of patients in care is a major challenge and varies across health facilities. BMC Health Serv Res. 2011;11(1):81.

5. Beyene KA, Gedif T, Gebre‐Mariam T, Engidawork E. Highly active antiretroviral therapy adherence and its determinants in selected hospitals from south and central Ethiopia. Pharmacoepidemiol Drug safety. 2009;18(11):1007-15.

6. Carr A, Cooper DA. Adverse effects of antiretroviral therapy. Lancet. 2000;356(9239):1423-30.

7. Ethiopian Federal Ministry of Health HIV AIDS prevention and control office. Multi-sectoral HIV/AIDS response monitoring & evaluation report2011.

8. Wubshet M, Berhane Y, Worku A, Kebede Y, Diro E. High loss to followup and early mortality create substantial reduction in patient retention at antiretroviral treatment program in North-West Ethiopia. ISRN AIDS. 2012;2012.

9. Spire B, Duran S, Souville M, Leport C, Raffi F, Moatti JP. Adherence to highly active antiretroviral therapies (HAART) in HIV-infected patients: from a predictive to a dynamic approach. Soc Sci Med. 2002;54(10):1481-96.

10. Ingersoll KS, Cohen J. The impact of medication regimen factors on adherence to chronic treatment: a review of literature. J Behav Med. 2008 Jun;31(3):213-24.

11. Merten S, Kenter E, McKenzie O, Musheke M, Ntalasha H, Martin-Hilber A. Patient-reported barriers and drivers of adherence to antiretrovirals in sub-Saharan Africa: a meta-ethnography. Trop Med Int Health. 2010 Jun;15 (Suppl 1):16-33.

12. Wasti SP, van Teijlingen E, Simkhada P, Randall J, Baxter S, Kirkpatrick P, et al. Factors influencing adherence to antiretroviral treatment in Asian developing countries: a systematic review. Trop Med Int Health. 2012 Jan;17(1):71-81.

13. Mbuagbaw L, van der Kop ML, Lester RT, Thirumurthy H, Pop-Eleches C, Smieja M, et al. Mobile phone text messages for improving adherence to antiretroviral therapy (ART): a protocol for an individual patient data meta-analysis of randomised trials. BMJ Open. 2013;3(5).

14. van der Kop ML, Ojakaa DI, Patel A, Thabane L, Kinagwi K, Ekstrom AM, et al. The effect of weekly short message service communication on patient retention in care in the first year after HIV diagnosis: study protocol for a randomised controlled trial (WelTel Retain). BMJ Open. 2013;3(6).

15. Amberbir A, Woldemichael K, Getachew S, Girma B, Deribe K. Predictors of adherence to antiretroviral therapy among HIV-infected persons: a prospective study in Southwest Ethiopia. BMC Public Health. 2008;8(1):265.

16. Paterson DL, Potoski B, Capitano B. Measurement of adherence to antiretroviral medications. J Acquir Immune Defic Syndr. 2002 Dec 15;31 (Suppl 3):103-6.

17. Oyugi JH, Byakika-Tusiime J, Charlebois ED, Kityo C, Mugerwa R, Mugyenyi P, et al. Multiple validated measures of adherence indicate high levels of adherence to generic HIV antiretroviral therapy in a resource-limited setting. J Acquir Immune Defic Syndr. 2004 Aug 15;36(5):1100-2.

18. Chesney MA, Ickovics JR, Chambers DB, Gifford AL, Neidig J, Zwickl B, et al. Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG adherence instruments. Patient Care Committee & Adherence Working Group of the Outcomes Committee of the Adult AIDS Clinical Trials Group (AACTG). AIDS Care. 2000 Jun;12(3):255-66.

19. Reynolds NR, Sun J, Nagaraja HN, Gifford AL, Wu AW, Chesney MA. Optimizing measurement of self-reported adherence with the ACTG Adherence Questionnaire: a cross-protocol analysis. J Acquir Immune Defic Syndr. 2007 Dec 1;46(4):402-9.

20. Simoni JM, Kurth AE, Pearson CR, Pantalone DW, Merrill JO, Frick PA. Self-report measures of antiretroviral therapy adherence: A review with recommendations for HIV research and clinical management. AIDS Behav. 2006 May;10(3):227-45.

21. Sikka R, Xia F, Aubert RE. Estimating medication persistency using administrative claims data. Am J Manag Care. 2005 Jul;11(7):449-57.

22. McMahon JH, Jordan MR, Kelley K, Bertagnolio S, Hong SY, Wanke CA, et al. Pharmacy adherence measures to assess adherence to antiretroviral therapy: review of the literature and implications for treatment monitoring. Clin Infect Dis. 2011 Feb 15;52(4):493-506.

23. Wright K, Naar-King S, Lam P, Templin T, Frey M. Stigma scale revised: reliability and validity of a brief measure of stigma for HIV+ youth. J Adolesc Health. 2007 Jan;40(1):96-8.

24. Sarna A, Luchters S, Geibel S, Chersich MF, Munyao P, Kaai S, et al. Short-and long-term efficacy of modified directly observed antiretroviral treatment in Mombasa, Kenya: a randomized trial. J Acquir immune Defic syndrom. 2008;48(5):611-9.

25. Berger BE, Ferrans CE, Lashley FR. Measuring stigma in people with HIV: Psychometric assessment of the HIV stigma scale. Res Nurs Health. 2001;24(6):518-29.

26. Vowles KE, Thompson M. The patient-provider relationship in chronic pain. Curr Pain Headache Rep. 2012 Apr;16(2):133-8.

27. Balfour L, Kowal J, Tasca GA, Cooper CL, Angel JB, Macpherson PA, et al. Development and psychometric validation of the HIV Treatment Knowledge Scale. AIDS Care. 2007 Oct;19(9):1141-8.

28. Horne R, Buick D, Fisher M, Leake H, Cooper V, Weinman J. Doubts about necessity and concerns about adverse effects: identifying the types of beliefs that are associated with non-adherence to HAART. Int J STD AIDS. 2004;15(1):38-44.

29. Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication. Psychol Health. 1999;14(1):1-24.

30. Bova C, Route PS, Fennie K, Ettinger W, Manchester GW, Weinstein B. Measuring patient-provider trust in a primary care population: Refinement of the health care relationship trust scale. Res Nurs Health. 2012 Apr 17.

31. WHO. Monitoring and reporting adverse events: WHO2003.

32. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts E, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239-45.

33. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ. 2004;329(7456):15-9.

34. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. Hosp Pharm. 1992 Jun;27(6):538.

35. de Groot A, Dannenburg L, Van Hell JG. Forward and backward word translation by bilinguals. J Mem Lang. 1994;33(5):600-29.

36. Falagas ME, Zarkadoulia EA, Pliatsika PA, Panos G. Socioeconomic status (SES) as a determinant of adherence to treatment in HIV infected patients: a systematic review of the literature. Retrovirology. 2008;5(1):1-12.

37. Lamb MR, El-Sadr WM, Geng E, Nash D. Association of adherence support and outreach services with total attrition, loss to follow-up, and death among ART patients in Sub-Saharan Africa. PloS one. 2012;7(6):e38443.

38. Mills EJ, Nachega JB, Buchan I, Orbinski J, Attaran A, Singh S, et al. Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. JAMA. 2006 Aug 9;296(6):679-90.

39. Wagner G, Miller LG. Is the influence of social desirability on patients' self-reported adherence overrated? J Acquir Immune Defic Syndr. 2004 Feb 1;35(2):203-4.

40. Miller LG, Hays RD. Measuring adherence to antiretroviral medications in clinical trials. HIV Clin Trials. 2000 Jul-Aug;1(1):36-46.

41. Berg KM, Arnsten JH. Practical and conceptual challenges in measuring antiretroviral adherence. J Acquir immune Defic syndrom. 2006;43(Suppl 1):79.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Method section of the abstract page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Method section of the abstract page 1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction section page 3-4.
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 4
Methods			
Study design	4	Present key elements of study design early in the paper	Page 4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 4-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 4-9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 8-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*Page 8-11*
Bias	9	Describe any efforts to address potential sources of bias	Page 8 (recruitment) and 12 (loss to follow-up)
Study size	10	Explain how the study size was arrived at	Page 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 12-13
		(*b*) Describe any methods used to examine subgroups and interactions	Page 12-13

		(*c*) Explain how missing data were addressed	Page 12
		(*d*) If applicable, explain how loss to follow-up was addressed	Page 12
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 8 and 12
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 12-13
		(b) Indicate number of participants with missing data for each variable of interest	Page 12
		(c) Summarise follow-up time (eg, average and total amount)	Page 12-13
Outcome data	15*	Report numbers of outcome events or summary measures over time	Page 7-11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 2
Limitations			Page 15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 14-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 4-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ open

Adherence to antiretroviral drug therapy in adult HIV-positive patients in Northwest Ethiopia: a study protocol.

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-003559.R1
Article Type:	Protocol
Date Submitted by the Author:	19-Sep-2013
Complete List of Authors:	Bezabhe, Woldesellassie; University of Tasmania, School of Pharmacy Peterson, Gregory; University of Tasmania, School of Pharmacy Bereznicki, Luke; University of Tasmania, School of Pharmacy Chalmers, Leanne; University of Tasmania, School of Pharmacy Gee, Peter; University of Tasmania, School of Pharmacy
Primary Subject Heading:	HIV/AIDS
Secondary Subject Heading:	Infectious diseases, Pharmacology and therapeutics, Health services research
Keywords:	HIV & AIDS < INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES, CLINICAL PHARMACOLOGY

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Method section of the abstract page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Method section of the abstract page 1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction section page 3-4.
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 4
Methods			
Study design	4	Present key elements of study design early in the paper	Page 4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 4-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 4-9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 8-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*Page 8-11*
Bias	9	Describe any efforts to address potential sources of bias	Page 8 (recruitment) and 12 (loss to follow-up)
Study size	10	Explain how the study size was arrived at	Page 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 12-13
		(*b*) Describe any methods used to examine subgroups and interactions	Page 12-13

		(*c*) Explain how missing data were addressed	Page 12
		(*d*) If applicable, explain how loss to follow-up was addressed	Page 12
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 8 and 12
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 12-13
		(b) Indicate number of participants with missing data for each variable of interest	Page 12
		(c) Summarise follow-up time (eg, average and total amount)	Page 12-13
Outcome data	15*	Report numbers of outcome events or summary measures over time	Page 7-11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 2
Limitations			Page 15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 14-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 4-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Adherence to antiretroviral drug therapy in adult HIV-positive patients in Northwest Ethiopia: a study protocol.

Woldesellassie M Bezabhe*[+1,2], Luke Bereznicki[+1], Leanne Chalmers[+1], Peter Gee[+1], Gregory M Peterson[+1]

*Correspondence: mwoldesellassie@yahoo.com;Woldesellassie.Bezabhe@utas.edu.au

+ Contributed equally

[1]School of Pharmacy, University of Tasmania (UTAS), Sandy Bay Campus, Tasmania 7001, Australia

[2]College of Medicine and Health Science, Bahir-Dar University, Bahir-Dar, Gojjam 79, Ethiopia

ABSTRACT

Introduction: Achievement of optimal medication adherence and management of antiretroviral toxicity pose great challenges among Ethiopian patients with HIV/-AIDS. There is currently a lack of ~~no~~ long-term follow-up ~~study~~ studies that ~~identifies~~ identify the barriers to, and facilitators of, adherence to antiretroviral therapy (ART) in the Ethiopian setting. Therefore, we aim to investigate the level of adherence to ART and a wide range of potential ~~facilitators of, and barriers to adherence~~influencing factors, including adverse drug reactions (ADRs) occurring with ART.

Methods and analysis: We ~~have been~~are~~will~~ conducting a one-year ~~,~~ prospective cohort~~, longitudinal~~ study involving adult patients with HIV/AIDS commencing on ART between December 2012 and March 2013. Data ~~have will been~~is being collected on patients' appointment dates in the ART clinics. Adherence to ART ~~has been~~is being ~~will be~~ measured using pill count, medication possession ratio ~~,~~ and patient's self-report ~~methods~~. 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 ~~of the study~~ using p~~P~~ill c~~C~~ount ~~(PC)~~. ~~The optimal level of adherence in this study will be t~~Taking 95% or more of the dispensed ART regimen using pill count at ~~a~~given points ~~in~~ of time will be considered the optimal level of adherence in this study. Data will be analysed using ~~the~~ descriptive and inferential statistical procedures.

Ethics and dissemination:

Ethics approval was obtained from the Tasmania Health and Medical Human Research Ethics ~~committee~~ Committee ~~(Approval Number: H0012722);~~ and Bahir-Dar University's Ethics Committee ~~(Approval Number: RCS/567/2004)~~. The results of the study will be reported in peer-reviewed scientific journals, conferences ~~,~~ and seminar presentations.

ARTICLE SUMMARY

Article focus

- To establish the level of adherence and identify factors that influence adherence to ART in Ethiopian HIV/AIDS patients ~~with~~ in a cohort study.

Key messages:

- Factors that affect adherence to ART ~~are not still~~have not yet been identified in Ethiopian HIV/AIDS patients ~~with~~ in a long-term follow-up study.
- Data ~~for this~~obtained during this prospective cohort study over the period of at least of 12~~6~~ months will identify important factors associated with long-term adherence to ART, that will assist in optimising the outcomes of Ethiopian HIV/AIDS patients ~~that are not still identified in the setting~~.

Strength and limitations of this study

- This study will ~~is the first of its kind conducted in the country to~~ identify factors that affect adherence to ART in ~~the~~ treatment naïve patients who are initiated on ART with long-term follow-up.
- Rates of patient drop out~~;~~, loss to follow up and death are high in this setting, which may challenge the success of the project.

INTRODUCTION

Ethiopia is home to approximately 800,000 patients with HIV/AIDS and the prevalence of HIV/AIDS in the general population is estimated to be 1.5%(1). The ~~introduction of the~~ free antiretroviral therapy (ART) program in Ethiopia, introduced in~~since~~ 2005, has decreased mortality and morbidity ~~,~~ and improved the quality of life of patients(2)~~(2, 3)~~. In the last 8 years, decentralis~~z~~ation and scale-up of the HIV care program has occurred ~~,~~ and by the end of 2011, 249,174 adult patients (86% of eligible patients) were on ART(1).

Achievement of optimal medication adherence, management of antiretroviral drug-related toxicities ~~,~~ and patient retention(3, 4)~~ (5)(5)~~are becoming the greatest challenges in the management of HIV/ADS in Ethiopia. A cross-sectional study ~~in~~ of Ethiopian patients reported an adherence rate of 88.1%(5), which is below the near perfect adherence (≥95%) required to maintain the effectiveness of ART(6).

Patient retention in HIV care facilities is low, ~~and~~ averaged 51% to 85% in 55 Ethiopian HIV care facilities in a 2 ~~-~~year patient follow-up study(3). Similarly, a 2011 report from the Ethiopian Ministry of Health indicated that patients dropping out from HIV care was a serious issue, with up to 40% of patients who ~~initiated~~ commenced ART dropping out from treatment in some regions of the country(7). Mortality and drop out from ~~antiretroviral~~ treatment are ~~more~~ most common in the first year of patient follow-up ~~than later~~ in Ethiopia(8).

Adherence to medication is a dynamic behaviour affected by factors related to treatment regimen complexity, patient-related variables, patient-health care provider relationships, and the quality of health care services(9). Patient adherence to ART is influenced by regimen-related factors such as pill burden, frequency of dosing, adverse drug reactions (ADRs) ~~ADRs~~, and fluid and dietary restrictions(10). Similarly, patient-related factors such as lack of transport, shortage of food, use of traditional medicine, alcohol abuse, depression, stigma and discrimination, and lack of social support undermine adherence(11-14). Further, a poor patient-health care provider relationship and low quality services, such as lack of confidentiality and privacy, and drug stock outs can hamper adherence with ART(12).

JUSTIFICATION FOR THIS STUDY

The sustainable effectiveness of ART depends on patient's ability to adhere with their long-term ART. There is a lack of long-term follow-up studies to identify the various factors altering the medication adherence to ART in Ethiopia. ~~Adverse effects of ART are common and cause morbidities and mortalities, and have been reported to be a cause of non-adherence. Previous studies were retrospective cross-sectional studies, lacked active surveillance and did not focus on treatment naïve HIV/AIDS patients.~~ While one prospective study has investigated adherence to ART in Ethiopia(15) it was only conducted for three months and also did not focus on treatment naïve patients. A prospective study with ~~over~~ a longer follow-up ~~period of time~~ focusing on treatment naïve patients is required to assess the level of adherence in this patient group and its barriers and facilitators. There is also a need to conduct a prospective study in Ethiopian patients with HIV/AIDS to assess the emergence of ADRs to ART in clinical practice, and the potential relationship between ADRs and non-adherence to ART.

OBJECTIVES

The objectives of this study are to establish the level of medication adherence and identify factors that influence medication adherence, and assess the incidence of ADRs and associated risk factors in Ethiopian patients with HIV/AIDS initiated on ART.

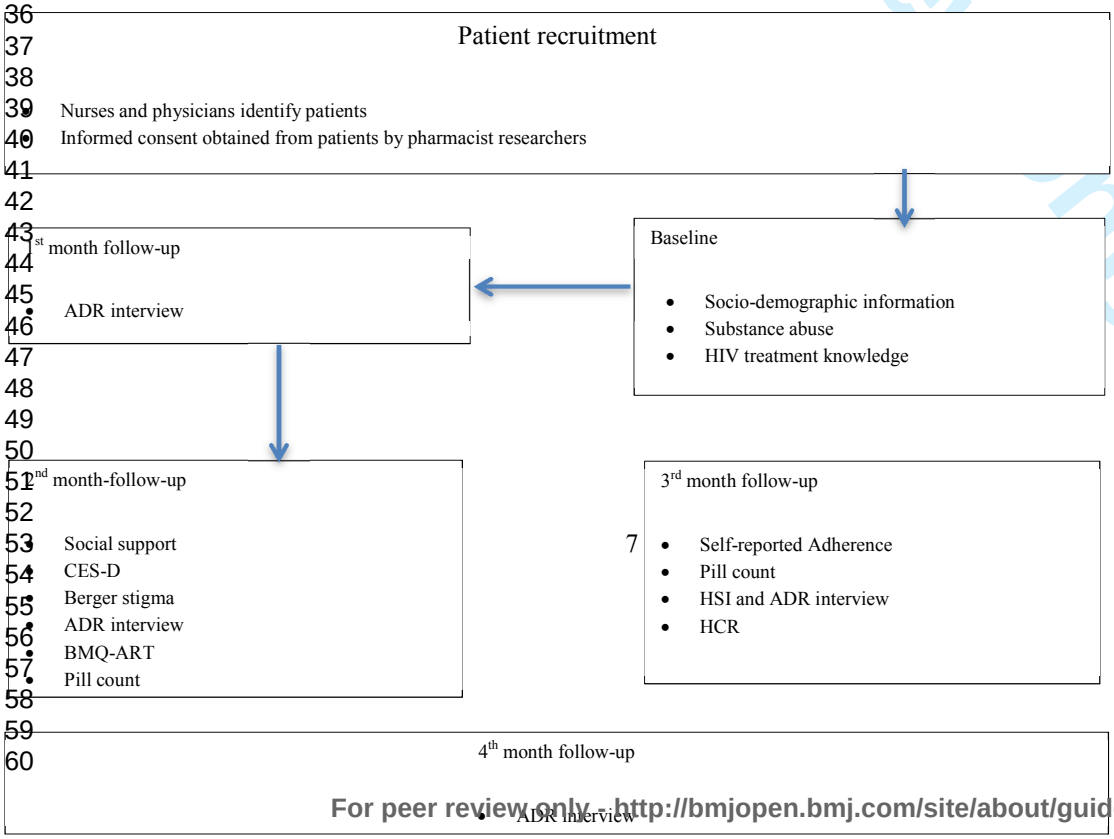
METHODS AND ANALYSIS~~:~~

Formatted: Don't adjust space between Latin and Asian text, Don't adjust space between Asian text and numbers

Study design

This study is a prospective~~, longitudinal~~ cohort study ~~,~~ in which adult Ethiopian patients with HIV/AIDS initiated on ART ~~have~~~~will~~are being~~en~~ ~~will be~~ followed from the time of ART initiation (Month (M) =0) to 12 months of therapy (M=12). ~~qualitative study involving sfurther ,~~ ART-initiated patients have an appointment every month for six months and every three months thereafter in ART clinics in Ethiopia; research pharmacists ~~will~~ are collecting data on appointment dates. The timeline of data collection activities ~~are~~ is structured as shown in figure 1. The data collection points coinciding with the patients' clinic appointments, not representing additional contact with healthcare providers to minimize the Hawthorne effect on adherence. ~~-~~The sequencing and repeating of measures is to observe the time pattern of different predictors on adherence ~~of~~ to ART in treatment naïve patients. Depression, stigma, HIV-treatment knowledge, healthcare relationship, and belief about medication ~~,~~ and HIV-symptom index may affect adherence in a time-dependent manner and are being measured before and after 6 months of patients' ART using validated scales. Data~~'s~~ regarding the concomitantly administered medications, comorbidities, ADRs ~~,~~ and laboratory

values are being collected on every appointment dates. ~~We have also designed a separate qualitative study to be conducted side by side involving patients taking ART, and nurses and peer counsellors working in ART clinics to help to explore the unique factors that affect adherence in these settings.~~



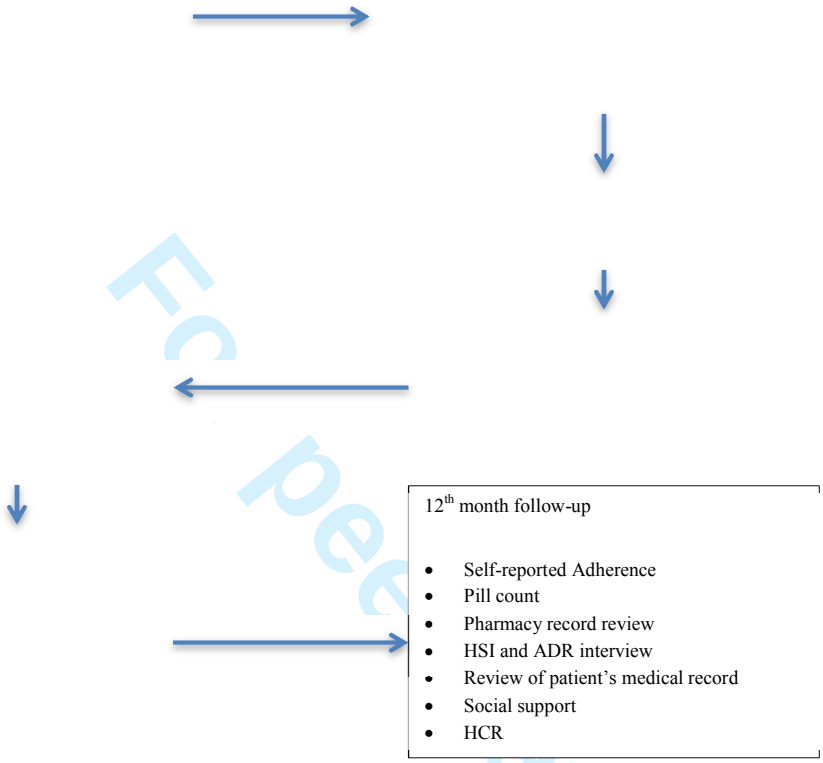


Figure 1 Study design

CES-D=Centre for Epidemiological Studies-Depression

ADR=Adverse Drug Reaction

HSI=HIV-Symptom Index

BMQ=Belief about Medication Questionnaire

HCR=Health Care Relationship

Study setting

The project is being ~~will be~~ carried out ~~implemented~~ in two hospitals in Northwest Ethiopia: Gondar University Hospital and Felege-Hiwot Hospital. Each hospital has 400 beds and serves a catchment area of 5 million people. The total number of HIV/AIDS patients attending each hospital is approximately 7,000 and 10,000 at Gondar University Hospital and Felege-Hiwot Hospital, respectively. Recruitment into the study occurred between ~~This study will be conducted between~~ December 2012 and March 2013. The study will continue ~~up~~ to

and March 2014, which will allow a follow-up period of at least 12 months for each patient.

Inclusion criteria/Exclusion criteria:

- All HIV/AIDS patients at least 18 years old beingold and initiated on ART for the first time,time arewere invited to participate. Participantstients whose follow-up was to be conducted in outlying areas, rather than at the hospital where ART was initiated, arewere not included.

Exclusion criteria:

- Participants whose follow-up is to be conducted in outlying areas, rather than at the hospital where ART was initiated.

Sample size

The sample size for this study was determined based on a previous study, where 76% of patients had optimal dose, time , and food adherence to ART(15). Taking a 95% confidence level , and precision of 0.07, the sample size was estimated to be 143.

Based on an average of 43 new patients per month, within four months of recruitment in each ART clinics, the pool of patients for recruitment will be 344. Allowing for a non-participation rate of 23%, and loss to follow-up of up to 30% (Mekides B and Desalew K, July 2012, personal communication), the sample size is was achievable.

Recruitment

Between December 2012 and March 2013, participants were will be initially invited by their nurses to participate in this study. At the first visit (usually two weeks before ART initiation), nurses will gaive patients information about the study and invited them to participate. If patients werearе interested in participating in the study, the research pharmacists contacted

Formatted: Font: 12 pt
Formatted: Font: 12 pt
Formatted: No bullets or numbering
Formatted: Font: 13 pt, Bold, (Asian) Chinese (PRC), (Other) English (Australia)
Formatted: Indent: Left: 0"
Formatted: Indent: Left: 0.25", No bullets or numbering
Formatted: Font: 12 pt
Formatted: Font: 12 pt

them to discuss the research. Informed consent was ~~will be~~ obtained from volunteer participants using a standard information statement and consent form~~s~~. Each ~~of~~ participant~~s~~ ~~has been will receiver~~is receiving~~res~~ $US 3 to reimburse their time and transport costs. ~~—~~The characteristics of patients who declined participation were ~~will be~~ collected to determine the representativeness of the sample.

Measures

The questionnaires have been spread to track changes of the different parameters over time as shown in figure 1, while ~~minimizing~~ minimising questionnaire fatigue. Assessment of adherence is a problematic issue as there is no gold standard method of measurement(16). In this study self-report, pill count~~PC~~ and Medication Possession Ratio (MPR) ~~will~~ are being used to measure adherence at months 3, 6, 9 ~~,~~ and 12. Use of multiple measures of adherence is recommended in literature as there is no single optimal measure of adherence(16). Adherence to medication found using multiple measures ~~will~~would~~ould~~ be converted in~~-~~to 'percentage ~~of~~ dose adherence' and triangulated. For ~~instance~~example, self-reported percentage adherence over 30 days will be triangulated with percentage dose adherence obtained using pill count ~~of~~over the same duration, which will be useful to estimate ~~the~~patients' true medication adherence ~~of patients.~~ ~~Participants will access to both fixed combination and loss combination ART dose.~~ Percentage adherence to each of the ~~pills~~ medications will be calculated and the lowest dose adherence ~~is~~ taken as the adherence for ~~the~~ a given patient.

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 ~~of the study~~ using pill count~~PC~~. The optimal level of adherence in this study will be considered as taking 95% or more of the dispensed ART

regimen using pill count at a point in time. Adherence from pill count~~PC~~s will be calculated by dividing the difference between current and previous pill count~~PC~~s by the number of pills that have to be taken during the same period(5). Pill count~~C~~s have been found to be an economic and reliable measure of adherence in resource-limited settings(17).

A modified AIDS Clinical Trial Group (ACTG) self-reported adherence questionnaire that asks patients how many doses they missed in the last 7 days is~~will~~ being used to measure patients' dose adherence ~~of patients~~ to ART. In addition, two four-item modified questionnaires from the ACTG ~~will be~~are being used to measure time and food adherence in the last 7 days(18). Assessing multiple dimensions of adherence by using all items of the ACTG self-reported adherence questionnaires has provided a strong measure of adherence(19). Self-reported adherence is well correlated with viral load suppression and is particularly suitable for resource-limited settings because of its low cost(20).

Patients stating they have missed medication~~s~~ ~~have~~will~~will~~ be~~en~~ asked to indicate reasons why ~~they skipped medication~~ from a list of 16 reasons (e.g. away from home, busy with other things, simply ~~forget~~forgot). Fourteen of the reasons for non-adherence are taken from the ACTG(18) and two reasons associated with traditional medicine and religious treatment, respectively, were obtained from literature review(11).

Pharmacy refill records are being~~will be~~ reviewed and the MPR will be calculated by dividing the total number of days covered with the medication dispensed by the number of days between the first fill and the last refill plus the days' supply of the last refill(21). This method is suitable in our study as HIV-medication is refilled only from the nearby governmental hospital/health centre pharmacy in Ethiopia(1). Pill count~~C~~ and MPR are superior ~~over~~ to self-reported adherence measures and well correlated with virological failure

and clinical outcomes(22). Biological surrogate markers such as viral load and CD4 count ~~have~~ correlat~~ion~~e with medication adherence(23). The CD4 count is measured every 6 months in ART clinics; the measures at months 6 and 12 will be used as a biological surrogate marker of adherence. Viral load is not routinely measured in Ethiopian clinical practice, and so has not been included in the trial protocol.

Depression in patients is being~~will be~~ evaluated using the seven-item questionnaire of the CES-D scale. This scale has been extensively applied in different settings, including ~~settings to assess depression~~ in HIV/AIDS patients(18). The Revised Berger HIV stigma scale has ~~will~~ been used for measurement of stigma. The 10- items of the Berger stigma scale have been validated in HIV-positive youth(24). The Berger stigma scale was also used in Kenyan patients with HIV/AIDS(25). ~~The~~ A higher score indicates the existence of greater stigma(26).

Previous studies have suggested that a lack of social support predisposes patients with HIV/AIDS to medication non-adherence~~??~~(27). Patients' satisfaction with the social support they get from family members and friends and the help of the support for remembering their medication is ~~will~~ being measured using two four-point scale social support questionnaires(18).

The HIV treatment knowledge scale ~~will~~ is being~~be~~ used to measure patients' knowledge on adherence, ADRs and drug resistance. This instrument has been developed and validated by Balfour et al(28) in HIV/AIDS patients ~~with~~ taking ART.

The BMQ is being~~will be~~ used to measure patients' beliefs about ART. The BMQ consists of two five-item scales probing patients' beliefs about the necessity of the given medication and their concerns about possible ADRs(29, 30).

The trust between the patients and health care providers is beingwill be measured using the 13-item HCR trust scale. Items are rated from 0 to 4;, the total score ranges from 0 to 52 and a higher score indicates a greater level of trust(31).

The research pharmacist will interview patients and carers, and reviewing patients' medical records for potential ADRs experienced in the preceding four weeks, and recording the following information using an ADR follow-up documentation form: signs and symptoms of ADRs, interventions, outcomes of interventions, laboratory test results, co-morbidities, concomitant medications (name, start and stop date, dose, route, indication), hospitalisations, reasons for regimen changes and new regimens.

Self-completed HSI has will beenis used to measure patients' concern about 20 possible symptoms associated with ART ADRs. The research pharmacists will have beenare interviewing patients, their caregivers, and physicians, and referring to patient's' medical records and documenting detailed information regarding the adverse effects that patients diagnosed withexperience. –The severity of ADRs will is beingsbe rated using the WHO ADR severity scale(32). Similarly, a physician and a pharmacist have beenwill determininge the causality of each ADRs using Naranjo's probability scale(33). The reliability between raters and within raters has been improved significantly ($p<0.001$) with the use of Naranjo's probability scale(33).This scale has been widely used in various settings(34). In addition, the Schumock and Thornton scale haswill been used to rate the preventability of adverse drug events(35).

Socio-demographic and economic variables such as age, gender, marital status, religion, level of education, number of children, employment status, and disclosure of HIV status, average

number of meals per day, monthly income, transportation costs to the clinic ~~,~~ and waiting time in the hospital ~~we~~are ~~will be~~ collected at the baseline.

Laboratory data such as weight, height, history of ADRs, hepatitis B virus (HBV) and hepatitis C virus (HCV) infection status, WHO stage of HIV/AIDS, CD4 count, haematocrit, white blood cell (WBC) count, absolute neutrophil count, platelet count, liver function tests [alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and bilirubin direct and total], renal function tests [such as blood urea nitrogen (BUN), serum creatinine ~~,~~ and urea], and ART regimen, date of initiation, dose and frequency of treatment, other concomitant medications and comorbidities have~~will~~ been recorded from patients~~'~~ on each appointment date from their medical records using a ~~baseline~~ clinical and laboratory data collection sheet.

~~Loss to follow-up~~

~~-~~'Drop out' from ART program is defined as patients not presenting for ~~dispensing~~ refilling of ~~of~~ their ART for the last 3 months. Patients' record ~~will be~~are being used to calculate the number of days covered by the last dispensed HIV medication and 90 days will be added to determine the date when patients are ~~categorized~~ categorised as 'drop outs'. The characteristics of s~~S~~tudy subjects who do not make at least 6 months follow-up (non-persist~~a~~ent patients) will be ~~looked at~~examined separately and compared with those who are persistent~~excluded from the study~~. Patients lost ~~from~~ to the follow-up ~~will be~~are being tracked ~~with~~ by peer counsellors working in the ART clinics of both hospitals using the registered address and phone number of them or their family member or close friend in their medical record which ~~to~~ may help to avoid bias. The reason for being lost ~~from~~ to follow-up has been ~~will be~~ recorded. ~~Analysis of~~ Ssocio-demographic and clinical prognostic

characteristics of those ~~are~~ who are lost from the treatment and those continuing ART will be compared.

~~**Missing items**~~

The percentage of missing items for each scale will be calculated for each participant. If more than 10% of the items of the scale are missed, the patient's total score o~~f the~~n that scale will be excluded from data analysis at that time point. The proportion of missing participants for each variable of interest will be calculated.

Statistical analysis

Descriptive univarate analysis will be conducted for socio-demographic and economic variables. Adherers will be compared with non-adherers with the Pearson chi-squared test for ~~non-numerical~~categorical variables and independent samples t-tests for normally distributed continuous data~~numerical variables~~. Similarly, the characteristics of patients who developed ADRs and did not develop ADRs will be compared ~~with~~ using Pearson chi-squared tests for categorical variables and independent samples t-test for continuous variables. Risk factors for adherence will be determined by investigating the influence of socio-demographic, socio-economic variables, ~~and~~ psychosocial variables, healthcare provider relationship, beliefs ~~on~~ about medications and ADRs. Risk factors for ADRs will be determined by investigating the effects of gender, age, body mass index (BMI), CD4 count, history of drug allergy, comorbidities, concomitant medications, ~~,~~ and type of regimen. Multiple variable binary logistic regression will be used to evaluate the independent influence of these risk factors on adherence. The exposure and the potential confounders will be modelled in relation with the outcome variable for adjustment using a multiple-predicative regression model. The final model will be determined after checking

multicollinearity. All statistical calculations will be performed using SPSS Version 21. A p-value of <0.05 will be considered as statistically significant.

Quality control

~~Bilinguals performed the standard forward-backward translation to make the questionnaires linguistically and conceptually equivalent(37).~~ The English-speaking native researcher made the forward translation of the validated questionnaires into Amharic. Two physicians working in the ART clinics of the Ethiopian hospitals reviewed the developed Amharic versions. A professional translator made the backward translation to check the difference between the Amharic versions and the original English versions. The differences between the source version and target version were settled ~~with~~ by ~~panel of committee~~a meeting ~~including~~ of the forward translator, a physician and the back-translator, and final Amharic versions were developed. The Amharic version was ~~-~~pretested with 4~~6~~0 adult patients receiving ART who would ~~will~~ not be included in the main study to check for reliability and validity of the questionnaires. On average it took about 23 minutes for participants to complete the questionnaires at each appointment date. Items found to be problematic by patients were ~~will be~~ modified.

Data management

The investigators have been checking the ~~The~~ collected data for ~~will be checked for~~ completeness, accuracy and clarity ~~by the investigators~~. These cheacks have been ~~This quality checking will be~~ performed daily after data collection and amendments have~~will~~ been made before the next data collection point ~~measure~~. Data clean up and crosschecking have ~~will~~ also been done prior to data analysis. The research pharmacists have been assessing the

Formatted: Font: 12 pt

Formatted: Font: 12 pt

sSeverity(32), causality(33), and preventability(35) of adverse events will be separately assessed by a pharmacist and physician using validated algorithms.

The data are being will be entereded from the two study sites in Ethiopia into a custom-built website housed on a secure server at the University of Tasmania. Stored data will be backed up on a daily basis. Access to the information iswill be only granted to authenticated investigators from anywhere using the Internet.

The custom-built website will generatgeneratese data collection forms for printing. After completion these forms are being will be scanned and then upload to the website. The form data from the forms are will being entered onto the website by the research pharmacists. A random sample of the scanned forms will have been checked against the website data to ensure accuracy. Additionally, the website has a sophisticated series of checks to ensure that fields are entered and that all fields are within expected values. Researchers at each site have will been informed of any incomplete or inconsistent data.

STRENGTHS OF THE STUDY

Several features in the design and planning of the project show contribute to the strengths of the study. First, the study is intended to examine predictors of adherence from different perspectives including patient characteristics, medication regimens , and the health care system. Patients' socio-economic status, level of education, belief and knowledge of HIV medication, social support and psychosocial variables are mentioned as predictors of adherence elsewhere(36, 37).

Second, the study uses multiple measures of adherence, which is recommended in the literature as there is no gold standard method of adherence measurement(16). Although patients in sub-Saharan Africa have been reported to have a comparable rate of adherence

with those in the developed countries(38), there is a plausible explanation in the literature that studies in sub-Saharan Africa measure adherence mainly using self-report, which overestimates adherence by as much as 20%(39). Patients refill their HIV-medication in a specific government ART clinic pharmacy; this allows us to use pill count and pharmacy records for adherence measurement(16, 40, 41).

LIMITATIONS OF THE STUDY

Rates of patient drop out, loss to follow up and death are high in this setting(8), which may challenge the success of the project. The multiple measures of adherence used in the study may alter patients' ~~behaviour~~behaviour and overestimate ~~their~~ medication adherence (i.e. Hawthorne effect)(42).

The study period may not be sufficient to document long-term ADRs, such as endocrine and metabolic adverse events, which may need more than one year to become apparent. Patients may not show up in ART clinics for treatment of ADRs or may be treated in other nearby clinics, which may underestimate the incidence of ADRs.

~~Conclusion~~

~~The study is expected to provide extensive information about adherence, including the barriers and facilitators of adherence, and the ADR profile among a cohort of Ethiopian patients commencing on ART, and will also establish an important foundation for a subsequent intervention study focussing on improving adherence in ART naïve patients with HIV/AIDS.~~

ETHICS AND DISSEMINATION

Ethics approval was obtained from the Tasmania Health and Medical Human Research Ethics committee (Approval Number: H0012722); and Bahir Dar University's Ethics Committee (RCS/567/2004). Nurses working in the ART clinics familiarised patients with the study; research pharmacists had delivered further information to the interested participants. Participants hadwere given the chance to read and understand the information sheet and to ask any questions before providing written consent. A cCopyies of the information sheet and consent form hadwere handed on to study participants who signconsented. All personally identifying information has been removed from the questionnaires and study documents. Study participants have been identified only using a unique study number. Nurse working in the ART clinics familiarised the study; research pharmacists had delivered further information to the interested participants. Participants had given the opportunitychance to read and understand the information sheet and to ask any questions before obtaining written consent. A copy of information sheet and consent form had handed on to study participants who signed. All personally identifying information has been removed from the questionnaires and study document. Study participants have been identified only using a unique study number.The data will be stored in a locked filing cabinet in the Bahir Dar University premises for 5 years; afterwards the data will be shredded and disposed of in secure bins. The digital recordings will be erased in accordance with the Tasmanian University regulations. Access to the filing cabinet and custom-built website will only be granted to authenticated investigators. We will disseminate our findings at thevia a public presentation to stakeholders working on HIV/AIDS treatment in Ethiopia. The results of the study will be reported in peer-reviewed scientific journals, conferences, and seminar presentations.

CONCLUSION

The study is expected to provide extensive information about adherence, including the barriers to, and facilitators of, adherence, and the ADR profile among a cohort of Ethiopian patients commencing on ART~~, and~~. This will ~~also~~ establish an important foundation for a subsequent intervention study focussing on improving adherence in ART naïve patients with HIV/AIDS.

Author affiliations

[1]School of Pharmacy, University of Tasmania (UTAS), Sandy Bay Campus, Tasmania 7001, Australia

[2]College of Medicine and Health Science, Bahir-Dar University, Bahir-Dar, Gojjam, Ethiopia

Acknowledgements We would like to thank n~~N~~urses working in ART clinics of both hospitals for their participation in the design of the study. We acknowledge Mr Endalkachew Admassie for his contribution during the design of the study.

Contributors WMB, GMP, LC, LREB and PG have contributed equally to the design of the study. WMB drafted the manuscript. PG developed the custom-built website. All authors revised the manuscript and approved the final copy.

Funding: The study was financially supported by Tasmanian School of Pharmacy, University of Tasmania.

Competing interests None

Ethics Approval Tasmania Health and Medical Human Research Ethics Committee and Bahir-Dar University's Ethics Committee

Data sharing statement No additional data are available

Provenance and peer review Not commissioned; externally peer reviewed

REFERENCES

1. Ethiopian Federal Ministry of Health HIV/AIDS Prevention and Control Office. Country progress report in HIV/AIDS response. Addis Ababa: Ethiopian Federal Ministry of Health HIV/AIDS Prevention and Control Office, 2012.

2. Reniers G, Araya T, Davey G, Nagelkerke N, Berhane Y, Coutinho R, et al. Steep declines in population-level AIDS mortality following the introduction of antiretroviral therapy in Addis Ababa, Ethiopia. AIDS. 2009 Feb 20;23(4):511-8.

3. Assefa Y, Kiflie A, Tesfaye D, Mariam DH, Kloos H, Edwin W, et al. Outcomes of antiretroviral treatment program in Ethiopia: Retention of patients in care is a major challenge and varies across health facilities. BMC Health Serv Res. 2011;11(1):81.

4. Assefa Y, Damme WV, Mariam DH, Kloos H. Toward universal access to HIV counseling and testing and antiretroviral treatment in Ethiopia: looking beyond HIV testing and ART initiation. AIDS patient care and STDs. 2010;24(8):521-5.

5. Beyene KA, Gedif T, Gebre - Mariam T, Engidawork E. Highly active antiretroviral therapy adherence and its determinants in selected hospitals from south and central Ethiopia. Pharmacoepidemiol Drug safety. 2009;18(11):1007-15.

6. Carr A, Cooper DA. Adverse effects of antiretroviral therapy. Lancet. 2000;356(9239):1423-30.

7. Assefa Y SE, Alebachew A, Assefa A, Hurely R, Pegurri E, Taye H, Tagessu D, Atnaf Y, Haniko N. Multi-sectoral HIV/AIDS response monitoring & evaluation report. Addis Ababa: Ethiopian Federal Ministry of Health HIV/AIDS Pprevention and Ceontrol Oeffice, 2011.

8. Wubshet M, Berhane Y, Worku A, Kebede Y, Diro E. High loss to followup and early mortality create substantial reduction in patient retention at antiretroviral treatment program in North-West Ethiopia. ISRN AIDS. 2012;2012.

9. Spire B, Duran S, Souville M, Leport C, Raffi F, Moatti JP. Adherence to highly active antiretroviral therapies (HAART) in HIV-infected patients: from a predictive to a dynamic approach. Soc Sci Med. 2002;54(10):1481-96.

10. Ingersoll KS, Cohen J. The impact of medication regimen factors on adherence to chronic treatment: a review of literature. J Behav Med. 2008 Jun;31(3):213-24.

11. Merten S, Kenter E, McKenzie O, Musheke M, Ntalasha H, Martin-Hilber A. Patient-reported barriers and drivers of adherence to antiretrovirals in sub-Saharan Africa: a meta-ethnography. Trop Med Int Health. 2010 Jun;15 (Suppl 1):16-33.

12. Wasti SP, van Teijlingen E, Simkhada P, Randall J, Baxter S, Kirkpatrick P, et al. Factors influencing adherence to antiretroviral treatment in Asian developing countries: a systematic review. Trop Med Int Health. 2012 Jan;17(1):71-81.

13. Mbuagbaw L, van der Kop ML, Lester RT, Thirumurthy H, Pop-Eleches C, Smieja M, et al. Mobile phone text messages for improving adherence to antiretroviral therapy (ART): a protocol for an individual patient data meta-analysis of randomised trials. BMJ Open. 2013;3(5).

14. Van der Kop ML, Ojakaa DI, Patel A, Thabane L, Kinagwi K, Ekstrom AM, et al. The effect of weekly short message service communication on patient retention in care in the first year after HIV diagnosis: study protocol for a randomised controlled trial (WelTel Retain). BMJ Open. 2013;3(6).

15. Amberbir A, Woldemichael K, Getachew S, Girma B, Deribe K. Predictors of adherence to antiretroviral therapy among HIV-infected persons: a prospective study in Southwest Ethiopia. BMC Public Health. 2008;8(1):265.

16. Paterson DL, Potoski B, Capitano B. Measurement of adherence to antiretroviral medications. J Acquir Immune Defic Syndr. 2002 Dec 15;31 (Suppl 3):103-6.

17. Oyugi JH, Byakika-Tusiime J, Charlebois ED, Kityo C, Mugerwa R, Mugyenyi P, et al. Multiple validated measures of adherence indicate high levels of adherence to generic HIV antiretroviral therapy in a resource-limited setting. J Acquir Immune Defic Syndr. 2004 Aug 15;36(5):1100-2.

18. Chesney MA, Ickovics JR, Chambers DB, Gifford AL, Neidig J, Zwickl B, et al. Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG adherence instruments. Patient Care Committee & Adherence Working Group of the Outcomes Committee of the Adult AIDS Clinical Trials Group (AACTG). AIDS Care. 2000 Jun;12(3):255-66.

19. Reynolds NR, Sun J, Nagaraja HN, Gifford AL, Wu AW, Chesney MA. Optimizing measurement of self-reported adherence with the ACTG Adherence Questionnaire: a cross-protocol analysis. J Acquir Immune Defic Syndr. 2007 Dec 1;46(4):402-9.

20. Simoni JM, Kurth AE, Pearson CR, Pantalone DW, Merrill JO, Frick PA. Self-report measures of antiretroviral therapy adherence: A review with recommendations for HIV research and clinical management. AIDS Behav. 2006 May;10(3):227-45.

21. Sikka R, Xia F, Aubert RE. Estimating medication persistency using administrative claims data. Am J Manag Care. 2005 Jul;11(7):449-57.

22. McMahon JH, Jordan MR, Kelley K, Bertagnolio S, Hong SY, Wanke CA, et al. Pharmacy adherence measures to assess adherence to antiretroviral therapy: review of the literature and implications for treatment monitoring. Clin Infect Dis. 2011 Feb 15;52(4):493-506.

23. Gill CJ, Hamer DH, Simon JL, Thea DM, Sabin LL. No room for complacency about adherence to antiretroviral therapy in sub-Saharan Africa. AIDS. 2005 Aug 12;19(12):1243-9.

24. Wright K, Naar-King S, Lam P, Templin T, Frey M. Stigma scale revised: reliability and validity of a brief measure of stigma for HIV+ youth. J Adolesc Health. 2007 Jan;40(1):96-8.

25. Sarna A, Luchters S, Geibel S, Chersich MF, Munyao P, Kaai S, et al. Short-and long-term efficacy of modified directly observed antiretroviral treatment in Mombasa, Kenya: a randomized trial. J Acquir immune Defic syndrom. 2008;48(5):611-9.

26. Berger BE, Ferrans CE, Lashley FR. Measuring stigma in people with HIV: Psychometric assessment of the HIV stigma scale. Res Nurs Health. 2001;24(6):518-29.

27. Vowles KE, Thompson M. The patient-provider relationship in chronic pain. Curr Pain Headache Rep. 2012 Apr;16(2):133-8.

28. Balfour L, Kowal J, Tasca GA, Cooper CL, Angel JB, Macpherson PA, et al. Development and psychometric validation of the HIV Treatment Knowledge Scale. AIDS Care. 2007 Oct;19(9):1141-8.

29. Horne R, Buick D, Fisher M, Leake H, Cooper V, Weinman J. Doubts about necessity and concerns about adverse effects: identifying the types of beliefs that are associated with non-adherence to HAART. Int J STD AIDS. 2004;15(1):38-44.

30. Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication. Psychol Health. 1999;14(1):1-24.

31. Bova C, Route PS, Fennie K, Ettinger W, Manchester GW, Weinstein B. Measuring patient-provider trust in a primary care population: Refinement of the health care relationship trust scale. Res Nurs Health. 2012;35:397-408.

32. WHO. Monitoring and reporting adverse events. Geneva: World Health Organization, 2003.

33. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts E, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239-45.

34. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ. 2004;329(7456):15-9.

35. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. Hosp Pharm. 1992 Jun;27(6):538.

36. Falagas ME, Zarkadoulia EA, Pliatsika PA, Panos G. Socioeconomic status (SES) as a determinant of adherence to treatment in HIV infected patients: a systematic review of the literature. Retrovirology. 2008;5(1):1-12.

37. Lamb MR, El-Sadr WM, Geng E, Nash D. Association of adherence support and outreach services with total attrition, loss to follow-up, and death among ART patients in Sub-Saharan Africa. PloS one. 2012;7(6):e38443.

38. Mills EJ, Nachega JB, Buchan I, Orbinski J, Attaran A, Singh S, et al. Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. JAMA. 2006 Aug 9;296(6):679-90.

39. Wagner G, Miller LG. Is the influence of social desirability on patients' self-reported adherence overrated? J Acquir Immune Defic Syndr. 2004 Feb 1;35(2):203-4.

40. Miller LG, Hays RD. Measuring adherence to antiretroviral medications in clinical trials. HIV Clin Trials. 2000 Jul-Aug;1(1):36-46.

41. Berg KM, Arnsten JH. Practical and conceptual challenges in measuring antiretroviral adherence. J Acquir immune Defic syndrom. 2006;43(Suppl 1):79.

42. Haberer JE, Kiwanuka J, Nansera D, Ragland K, Mellins C, Bangsberg DR. Multiple Measures Reveal Antiretroviral Adherence Successes and Challenges in HIV-Infected Ugandan Children. PloS one. 2012;7(5).