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Health Outcomes and Cost-Effectiveness of Treating Depression in People with HIV in Sub-Saharan Africa: A Model-Based Analysis

Huaiyang Zhong, BS¹, Isabel K. Arjmand, MS¹, Margaret L. Brandeau, PhD¹, Eran Bendavid, MD, MS^{2,3}

¹Department of Management Science and Engineering, Stanford University, Stanford, CA

²Division of General Medical Disciplines, Department of Medicine, Stanford University, Stanford, CA

³Center for Health Policy and the Center for Primary Care and Outcomes Research, Stanford University, Stanford, CA

Abstract

High prevalence of depression among people living with HIV (PLHIV) impedes antiretroviral therapy (ART) adherence and viral suppression. We estimate the effectiveness and cost-effectiveness of strategies to treat depression among PLHIV in Sub-Saharan Africa (SSA). We developed a microsimulation model of HIV disease and care in Uganda which captured individuals' depression status and the relationship between depression and HIV behaviors. We consider a strategy of screening for depression and providing antidepressant therapy with fluoxetine at ART initiation or re-initiation (if a patient has dropped out). We estimate that over 10 years this strategy would reduce prevalence of depression among PLHIV by 16.0% [95% uncertainty bounds 15.8%, 16.1%] from a baseline prevalence of 28%, increase adherence to ART by 1.0% [1.0%, 1.0%], and decrease rates of loss to followup by 3.7% [3.4%, 4.1%]. This would decrease first-line ART failure rates by 2.5% [2.3%, 2.8%] and increase viral suppression rates by 1.0% [1.0%, 1.0%]. This strategy costs \$15/QALY compared to the status quo, and was highly cost-effective over a broad range of sensitivity analyses. We conclude that screening for and treating depression among PLHIV in SSA with fluoxetine would be effective in improving HIV treatment outcomes and would be highly cost-effective.

Corresponding author: Eran Bendavid, Associate Professor of Medicine, Primary Care and Population Health, Department of Medicine, Stanford University. Telephone: 650.723.2363 ebd@stanford.edu.

Author Contributions:

Huaiyang Zhong is responsible for all of the modeling and data analysis in this study.

Study concept and design: Zhong, Arjmand, Brandeau and Bendavid

Acquisition of data: Zhong and Bendavid

Analysis and interpretation of data: Zhong, Brandeau and Bendavid

Drafting of the manuscript: Zhong, Brandeau and Bendavid

Critical revision of the manuscript for important intellectual content: Zhong, Brandeau and Bendavid

Statistical analysis: Zhong and Bendavid

Study supervision: Brandeau and Bendavid

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Keywords

HIV; Mental health; Depression; Cost-Effectiveness

INTRODUCTION

Despite considerable efforts devoted to improving antiretroviral therapy (ART) coverage and viral suppression in Sub-Saharan Africa (SSA) (Tanser, Barnighausen, Grapsa, Zaidi, & Newell, 2013), HIV care falls short of UNAIDS 90-90-90 goals in most SSA countries (Joint United Nations Programme on HIV/AIDS, 2017). Two key targets for improving HIV care are reducing loss from care and increasing adherence to ART (Gupta, Dabla, Joshi, & Chakraborty, 2014; Joint United Nations Programme on HIV/AIDS, 2017; McCreesh et al., 2017). Developing effective and cost-effective approaches to attain these goals is central to many HIV control programs. Here, we assess the outcomes and cost-effectiveness of screening for, and treating, depression among people living with HIV (PLHIV) to improve population health.

Increasing evidence points to a high prevalence of depression among PLHIV. A meta-analysis found that 9-32% of PLHIV in SSA suffer from depression (Bernard, Dabis, & de Rekeneire, 2017). Compared to uninfected individuals, PLHIV have nearly twice the risk of depression (D. H. Akena, Musisi, & Kinyanda, 2010; Ciesla & Roberts, 2001; Spirig, 1998). Depression jeopardizes ART effectiveness and viral suppression by decreasing adherence, and reducing patient engagement (Bangsberg et al., 2000; Byakika-Tusiime et al., 2009; Cholera et al., 2017; Gonzalez, Batchelder, Psaros, & Safren, 2011; Horberg et al., 2008; Glenn J Wagner et al., 2014). Treatment of depression has been found to improve ART adherence and clinic attendance (Sin & DiMatteo, 2014; G. J. Wagner et al., 2017). Treatment approaches include pharmacological therapy and group and individual psychotherapy (Honagodu, Krishna, Sundarachar, & Lepping, 2013; Nakimuli-Mpungu et al., 2015).

We focus on a pharmacological intervention, fluoxetine, that is inexpensive and has good evidence of effectiveness in reducing depressive symptoms (Cipriani et al., 2016). Using data for Uganda, we assess the impact on HIV care cascade endpoints, clinical indicators, and cost-effectiveness of using fluoxetine to treat depression among PLHIV.

METHODS

We used a microsimulation model (Bendavid et al., 2008) that captures HIV transmission, HIV disease course, depression, and the benefits from treatment of both HIV and depression (Figure 1; Supplement). We consider a strategy of screening for depression and providing antidepressant therapy (ADT) with fluoxetine at ART initiation. Key data and sources are shown in Table 1 and Supplemental Tables S1 and S2.

Each individual is characterized by demographic features (age and gender), HIV-related features (HIV status, CD4 cell counts, viral load, and opportunistic infections), treatment features (treatment regimen and adherence), depression status (with or without depression),

and depression treatment status. We track HIV care, including pre-ART loss from care (leakage), post-ART loss to follow-up (LTFU), and ART failure. Uninfected individuals can become infected through sexual contact with infected individuals.

The base case assumes individuals with depression suffer from depression until receiving ADT. Depression prevalence is stratified by gender, HIV infection status, and CD4 count. Individuals without depression may become depressed following either an HIV-positive test result or a decline in CD4 cell count below 50 cells/ μ L (Table 1). Depression lowers ART adherence rates, increases leakage, and increases LTFU (Tables 1, S2). ART adherence changes when depression status changes (Table 1).

We assume a depression screening tool with characteristics similar to the Patient Health Questionnaire-9 (PHQ-9) (D. Akena, Joska, Obuku, & Stein, 2013; Glenn J Wagner et al., 2014), a simple diagnostic questionnaire with estimated 91.6% sensitivity and 81.3% specificity for depression in Uganda (D. Akena et al., 2013; Kroenke, Spitzer, & Williams, 2001). We model ADT based on the cost and effectiveness of fluoxetine at a dosage of 40 mg/day. Our treatment algorithm (Figure 1, details in Supplement) is based on the clinical experience of long-term ADT that provide 6-month, 12-month, and long-term relapse and remission rates with 42% overall long-term remission (Table 1).

We used the model to assess costs and health outcomes measured in quality-adjusted life years (QALYs), discounted at 3%, and cost-effectiveness of providing ADT. We took a healthcare system perspective (Sanders, Neumann, Basu, & et al., 2016). Outcomes measured include prevalence of depression, annual rates of leakage and LTFU, percent of patients adherent to ART, percent of patients with virologic suppression, costs (2017 USD), life years, and QALYs. We measured the costs of fluoxetine, CD4 tests, viral load tests, ART (first-line and second-line), HIV tests, HIV-related inpatient and outpatient care, and non-HIV healthcare for each individual (Table S1). QALY weights were stratified based on HIV infection and depression status.

We performed one-way and two-way sensitivity analyses to examine critical assumptions; probabilistic sensitivity analysis varying all model parameters (distributions in Tables 1 and S1); and structural sensitivity analysis using a model that includes natural rates of developing and recovering from depression (details in Supplement).

We calibrated our model to data for Uganda (Figures S1-S4).

RESULTS

Base Case Analysis

The ADT intervention yields an additional 0.02 QALYs per person compared to the status quo (Table 2). The benefits of providing ADT accrue mainly from relief of depression leading to higher quality of life, improvements in retention and adherence, and reduction in new HIV infections. Compared to the status quo, providing ADT reduces depression prevalence among HIV-infected individuals by 16.0% [95% uncertainty bounds 15.8%,

16.1%] from a baseline prevalence of 28% (Table 3). All changes are percent change relative to the status quo.

Relief of depression improves several HIV care outcomes (Table 3). Rates of LTFU after ART initiation are reduced by 3.7% [3.4%, 4.1%]. ART adherence increases by a modest 1.0% [1.0%, 1.0%] and failure of first-line ART is reduced by 2.5% [2.3%, 2.8%]. Compared to the status quo, an additional 1.0% [1.0%, 1.0%] of the HIV-infected population is virologically suppressed.

The intervention costs \$15/QALY gained compared to the status quo and thus would be considered very cost-effective by any criteria (Laxminarayan et al., 2006; Murray & Lopez, 2002; World Health Organization, 2009). Extrapolated to the population level, we estimate that the intervention would cost \$12.13 million and gain 790,000 QALYs over the analytic time horizon (Table 3).

Sensitivity Analyses

At \$2.52, the highest reported price (for Botswana) (World Health Organization, 2014), the ICER is \$22/QALY. At the lowest reported effectiveness (32% in remission at 6 months), depression prevalence is reduced by 7.3% [7.2%, 7.4%] and the ICER is \$42/QALY. If the long-term relapse rate is 50% (vs. 42% in the base case), the ICER is \$18/QALY. If ADT uptake is only 50%, the ICER is \$36/QALY.

The improvement in quality of life from ADT contributes significantly to the health benefits. If there is no quality-of-life improvement from treating individuals with depression, the ICER is \$292/QALY. If we remove the quality-of-life benefits from treating depression and increase antidepressant cost to the upper bound of \$2.52, the ICER is \$419/QALY.

We performed one-way sensitivity analyses on the parameters characterizing the relationship between depression, ART adherence, and viral failure. In the base case, the OR for adherence among those depressed is 0.32, and the OR for viral failure is 9.9 with ART non-adherence. Changing the ORs to their bounds, 0.93 and 3.2, respectively, increases the ICER to \$29/QALY.

In probabilistic sensitivity analysis, the ADT intervention was very cost-effective for all model parameter realizations when using the Uganda GDP per capita (\$631)(The World Bank, 2019) as the willingness-to-pay reference value (Figure 2).

In structural sensitivity analysis, using a model that incorporates natural development of and remission from depression, the ICER was \$28/QALY.

DISCUSSION

Our analysis indicates that screening PLHIV for depression and providing fluoxetine or a similar antidepressant is an effective and highly cost-effective strategy for improving HIV-related outcomes in Uganda, and likely throughout other regions of SSA with a generalized HIV epidemic. Beyond reducing depressive symptoms among PLHIV, ADT improves adherence and reduces virologic failure rates, thereby improving suppressions rates and

reducing HIV transmission. Such a strategy is likely to be highly cost-effective, especially where the prices of generic antidepressant medications are low. At an estimated cost of \$1.16 per month and an ICER of \$15/QALY gained, provision of ADT to PLHIV with depression falls well below commonly accepted thresholds, and is more cost-effective than interventions such as home care treatment (Laxminarayan et al., 2006).

Treatment of depression in PLHIV in SSA has been limited to date. International funding agencies frequently focus on physical illnesses (such as HIV) rather than mental illness. Country ministries also provide few funds for mental health services. In 2010, Uganda devoted only 1% of public health expenditures to mental health care (Kigozi, Ssebunnya, Kizza, Cooper, & Ndyabangi, 2010). Additionally, Uganda and other countries in SSA have very few trained mental health providers (Kigozi et al., 2010). Providing ADT can be accomplished as part of routine HIV care and thus would be practical to implement in settings with few trained mental health professionals.

Our analysis has several limitations. First, our model is instantiated with data from Uganda and therefore is most applicable to countries with a similar HIV context. Second, there is relatively little data on the natural course of depression in PLHIV and in lower-income countries (Stegenga, Kamphuis, King, Nazareth, & Geerlings, 2012). We made simplifying assumptions that match the existing evidence available from similar populations and interventions. While additional granularity about depression could be added, such detail is unlikely to impact our population-level outcomes. Third, we assumed that PLHIV on ART receive no depression treatment under the status quo. To the extent that PLHIV already receive depression treatment, our analysis may overstate the intervention benefits. Fourth, we did not consider side effects of fluoxetine such as sexual dysfunction (Ferguson et al., 2005). Our analysis may thus overestimate the health benefits of ADT. However, given the low fluoxetine cost and the significant improvement in QALYs among treated individuals, our conclusions regarding cost-effectiveness are unlikely to change. Fifth, our analysis assumes that ADT will improve ART adherence. Recent evidence suggests that adding another pill to ART treatment could reduce adherence (Hosseinipour et al., 2016). To the extent that this occurs, our analysis may overestimate the health benefits of ADT. Lastly, we only examined the cost-effectiveness of a pharmacological intervention for depression treatment. A promising area for depression treatment is group or interpersonal therapy, which may impact the appeal of pharmacological ADT (Chibanda et al., 2015; Hosseinipour et al., 2016).

We conclude that ADT for treatment of depression among PLHIV in Uganda and similar countries in SSA is likely both highly effective and cost-effective when judged by common criteria (Goldie et al., 2006; Murray & Lopez, 2002; World Health Organization, 2001). Use of available HIV funding to help alleviate depression in PLHIV would be strongly leveraged by the direct and indirect benefits from resulting improvements in the HIV care cascade, will generate both individual and population benefits, and compares favorably to other investments in HIV and other diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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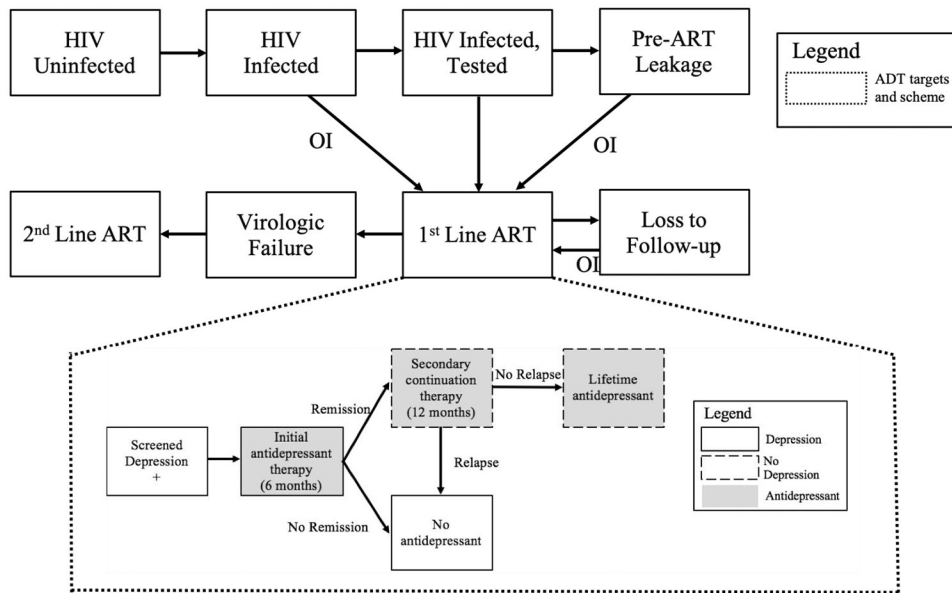


Figure 1. Schematic representation of HIV natural history model and antidepressant treatment scheme. In each state and each time period, an individual can die, remain in the same state, or transition to another state following the direction of the arrows. Individuals enter the population during the various stages of HIV natural history (HIV uninfected, HIV infected and tested, etc.) and leave the population via death. ADT: antidepressant treatment; ART: antiretroviral therapy; Pre-ART Leakage: patients are identified for ART but do not start ART; OI: opportunistic infection.

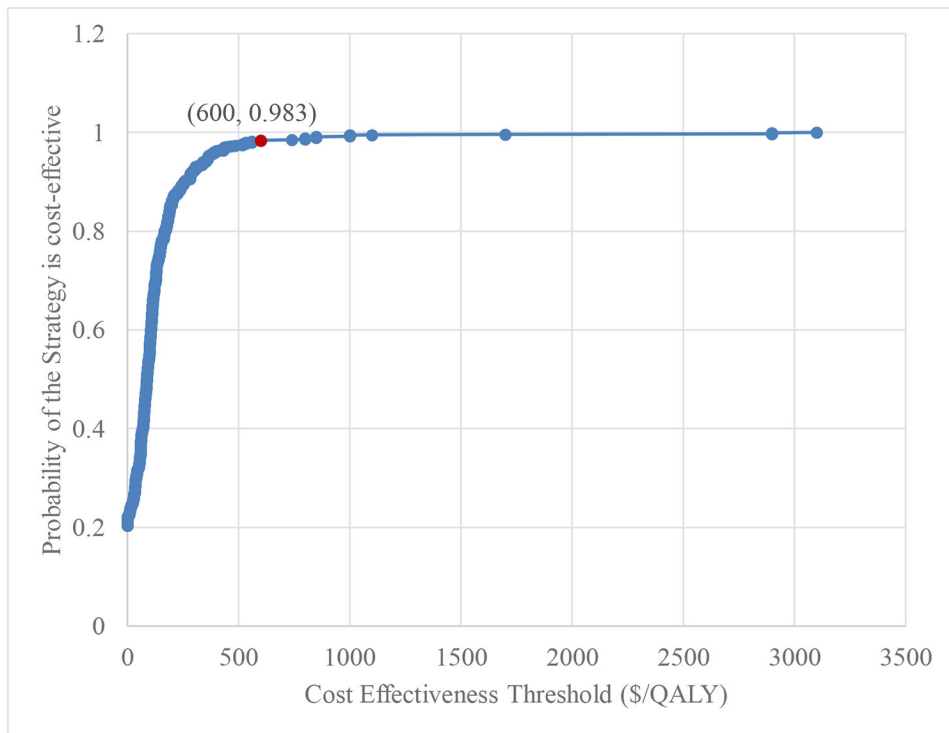


Figure 2.
Cost-effectiveness acceptability curve

Table 1.

Data and Sources: Depression

Parameter	Value	Range	Type of Probability Distribution Used in PSA	Sources
Depression prevalence (%)				
HIV negative	17.0	(12.0, 23.0)	Beta	(Ovuga, Boardman, & Wasserman, 2005)
HIV positive	28.0	(23.0, 33.0)	Beta	(Breuer, Myer, Struthers, & Joska, 2011)
Odds ratios for depression				
HIV positive, status known	1.99	(1.32, 3.00)	Lognormal	(Dickens Akena, Musisi, Joska, & Stein, 2012; Ciesla & Roberts, 2001)
CD4 <50	2.34	(1.39, 3.93)	Lognormal	(Kaharuza et al., 2006)
Female	1.85	(1.24, 2.44)	Lognormal	(Kaharuza et al., 2006; Kinyanda, Hoskins, Nakkui, Nawaz, & Patel, 2011)
Adherence prevalence (%)	80.0	(72.0, 88.0)	Beta	(Mills et al., 2006)
Odds ratios for HIV-infected individuals with depression				
Adherence	0.32	(0.11, 0.93)	Lognormal	(Byakika-Tusiime et al., 2009)
No leakage	0.32	(0.11, 0.93)	Lognormal	Assumed
No LTFU	0.32	(0.11, 0.93)	Lognormal	Assumed
Odds ratio for viral failure due to non-adherence	9.90	(3.20, 45.10)	Lognormal	(Obirikorang, Selieh, Abledu, & Fofie, 2013; Weidle et al., 2006)
PHQ-9 diagnostic test				
Sensitivity	0.92	(0.83, 1.00)	Beta	(D. Akena et al., 2013)
Specificity	0.81	(0.73, 0.89)	Beta	(D. Akena et al., 2013)
Treatment effects				
Probability of remission at month 6 of initial therapy	0.70	(0.32, 0.79)	Beta	(Ngo et al., 2014; Patel et al., 2003)
Probability of remission at month 12 of continuation therapy	0.40	(0.36, 0.50)	Beta	(Hollon, Stewart, & Strunk, 2006)

ART: antiretroviral therapy; LTFU: loss to followup; PHQ-9: Patient Health Questionnaire-9; PSA: probabilistic sensitivity analysis.

Base Case Results: Costs, Life Years, Quality-Adjusted Life Years, and Incremental Cost-Effectiveness Ratio

Table 2.

Strategy	LYs	Incremental LYs	QALYs	Incremental QALYs	Costs (\$)	Incremental Costs (\$)	ICER (\$/QALY gained)
Status Quo	16.93		16.41	--	2153.28	--	--
ADT Provision	16.94	0.001	16.43	0.02	2153.52	0.25	15.43
Population Level							
Status Quo	831.34 M		805.67 M	--	105,687.20 M	--	--
ADT Provision	831.38 M	0.04 M	806.45 M	0.79 M	105,699.36 M	12.13 M	15.43

M: million; ADT: antidepressant therapy; LY: life year; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio, compared to the status quo

Table 3.

Base Case Results: Relative Percentage Changes (vs. Status Quo) in Care Cascade Parameters and 95% Uncertainty Bounds

Strategy	Reduction in Depression Prevalence	Reduction in Pre-ART Leakage	Reduction in LTFU	Increase in Adherence to ART	Reduction in First Line ART Failure	Increase in Virologic Suppression
ADT Provision	15.981 (15.841, 16.111)	-0.510 (-0.756, 0.349)	3.722 (3.352, 4.092)	1.014 (1.014, 1.015)	2.526 (2.276, 2.775)	1.005 (1.004, 1.006)

ADT: antidepressant therapy; ART: antiretroviral therapy; LTFU: loss to followup.