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The Role of Depression in Work-Related Outcomes of HIV Treatment in Uganda

Glenn J. Wagner¹, Bonnie Ghosh-Dastidar¹, Mary Slaughter¹, Akena Dickens², Noeline Nakasujja², Elialilia Okello², and Seggane Musisi²

¹RAND Corporation, 1776 Main St., Santa Monica, CA, USA 90407 ²Department of Psychiatry, Makerere University, College of Health Sciences, P.O. Box 7072, Mulago Hill, Kampala, Uganda

Abstract

Purpose—The primary goal of this analysis was to examine the influence of depression above and beyond the effects of HIV treatment on work activity and function.

Methods—We combined data from three longitudinal studies of patients starting antiretroviral therapy (ART) and/or entering HIV care in Uganda. Assessments were conducted at baseline and months 6 and 12. The 9-item Patient Health Questionnaire (PHQ-9) was used to assess depressive symptoms, as well as Major (scores > 9) and Minor (scores 5–9) Depression status; work functioning was assessed using a sub-scale of the Medical Outcomes Study HIV Health Survey (MOS-HIV). Multivariate random-effects logistic regression models for longitudinal data were used to examine the impact of treatment on work status and optimal work functioning, with measures of both baseline and change in physical health functioning, cognitive functioning and depression in the models, controlling for baseline demographics and CD4 cell count.

Results—The sample of 1,731 participants consisted of 1,204 starting ART and 527 not yet eligible for ART. At baseline, 35% were not working and 37% had sub-optimal work functioning. Intention-to-treat analyses revealed that those on ART experienced greater improvement in both work outcomes over 12 months relative to non-ART patients, and that baseline and change in physical health functioning, continuous and categorical depression were all independently associated with improvement in both work outcomes, even after accounting for the direct effect of ART.

Conclusions—Improvement in physical and mental health plays a key role in the positive impact of HIV treatment on work activity and function, suggesting potential economic benefits of integrating depression treatment into HIV care.

With the necessary investment of billions of dollars to sustain scale-up of HIV antiretroviral therapy (ART) in sub-Saharan Africa (SSA), evaluation of the downstream effects of HIV treatment on key social and economic outcomes has greater relevance for public health policy. Aside from its obvious effects on physical health [1,2], ART may also benefit the economic well-being of individuals and households by enabling persons living with HIV/

AIDS (PLHA) to work productively and provide for themselves and their families [3–5]. However, depression and poor mental health may impede individuals from experiencing the full potential benefit of ART and HIV care on work functioning and income generation [6,7]. Understanding how depression may influence economic well-being has implications for policy and funding regarding integration of mental health services into HIV care programs that are largely void of such services in SSA.

HIV disease and its harmful effects on physical health can impair work functioning and productivity, and even render some individuals bed-ridden and unable to work [8]. Deleterious economic effects of HIV/AIDS on individuals and households include reduced income [9,10], reallocation and consumption of assets, savings and resources [11], and diversion of productive labor to care giving, particularly in the latter phases of the disease [12–14]. The few studies that have examined the effects of ART on work functioning in SSA have mostly involved employed tea farmers, with findings showing that ART is associated with reduced absenteeism and increased work productivity and hours worked [15,16]. However, these studies compared ART patients with a comparison group of peer workers with unknown HIV status. A more recent study by Thirumurthy et al. followed cohorts of pre-ART and ART clients and found that the ART group experienced a significant increase in employment levels and hours worked [17]. While these studies suggest a benefit of ART on work functioning, there has been little investigation into potential moderating factors that may influence whether treatment has more or less benefit on work-related outcomes.

While physical health functioning is central to work and productivity, the psychological components of living with HIV can also affect work and income generation. Drawing from Social Cognitive Theory [18], and in the context of HIV, we posit that physical and mental health are both key to a person's self-efficacy and expected outcomes regarding work-related behavior and ability to earn income. When a person is physically healthy and functioning well, they feel optimistic, confident and motivated to act on their goals and needs, including finding work and being productive. Conversely, physical deterioration or depression can result in fatigue, physical impairment, and loss of motivation and self-confidence to engage in food and income generating activity. Scholars such as Warr [19] have highlighted the interconnections between work performance and context and aspects of psychological well-being and mental health. Similarly, studies of PLHA in the West have demonstrated associations between employment, work functioning and aspects of quality of life as well as both physical and mental health [20,21]. In addition to physical health functioning, poor cognitive functioning (e.g., difficulty concentrating) is associated with depression [22], may influence work performance [23], and can benefit from ART [24], and therefore should be accounted for as well in understanding the effects of HIV treatment on work outcomes.

In our previous research with PLHA who had just initiated HIV care in Uganda, 34% of depressed participants were working (defined as activity that contributes to income or food generation) compared to 64% of those not depressed, and depression was independently associated with work status after controlling for demographics, physical health functioning and social support [25]. This analysis did not, however, examine the longitudinal changes in

work status of patients receiving HIV treatment, and how simultaneous changes in depression may influence change in work functioning. With research showing that 10–20% of PLHA in SSA have Major Depression [26–28], and another 20–30% have sub-clinical but elevated depressive symptoms [26,27,29–31], the role of depression in the economic well-being and functioning of PLHA needs to be further explored.

We have conducted three longitudinal studies of PLHA entering HIV care or starting ART in Uganda over the past five years, with the primary goal of examining social and economic benefits of HIV treatment. In the analysis reported here, we combined data from these studies to examine the effects of ART and HIV care on work status and functioning, and the role of depression as an influential determinant of these outcomes. More specifically, we assessed whether the influence of depression varied by depression severity (Minor vs. Major Depression), and whether change in depression was related to corresponding changes in the work-related outcomes after accounting for the direct impact of ART. If depression is found to play a role in the change in economic outcomes affected by HIV treatment, this research will have policy implications suggesting the need for integrating depression treatment into HIV care in SSA, and the importance of diagnosis and treatment of depression to maximize the cost-effectiveness and sustainability of ART scale-up.

METHODS

Study Design

Data from three longitudinal studies were merged for the analysis. Participants in Studies A and B enrolled in studies of ART impact on multiple health outcomes and involved patients just entering HIV care and included patients starting ART and those not yet eligible for ART. Enrolment for Study A was between January and September 2008, while Study B enrolled patients from July 2008 to August 2009. Participants in Study C had been in HIV care for different lengths of time but were about to start ART at study enrollment (between January 2010 and February 2011). Study C was designed specifically to examine the role of depression and antidepressant therapy on the socioeconomic outcomes of ART; in addition to depression being assessed at each time point, antidepressants were prescribed to those who were clinically depressed. Thus, the analysis for this paper included all participants in Studies A and B, but only the participants in Study C not receiving antidepressant therapy. Depression treatment was not available as part of usual care at any of the participating sites in each of the three studies. In all three studies, participants completed assessments at baseline and months 6 and 12.

Setting

Study A was conducted at two HIV clinics operated by Joint Clinical Research Center in Kampala and Kakira. Study B was conducted at two HIV clinics in Kampala, one operated by Reach Out Mbuya and one by Mulago-Mbarara Teaching Hospitals Joint AIDS Program (MJAP). Study C was conducted at four HIV clinics operated by Mildmay Uganda, in Kampala and the rural towns of Mityana, Naggalama and Mukono. All sites are located in the relatively stable eastern region of the country. This region offers increased economic advantages relative to the rest of Uganda, because of its close proximity to the capital city

Kampala, which has the most opportunities for work in the formal labor market, and to Lake Victoria with opportunities for employment in the fishing industry. Also, the town of Kakira is the location of a large sugar cane plantation. These clinics generally serve clients in the lower socioeconomic strata who work in the informal labor market (*e.g.*, commercial or subsistence farming; selling goods or employed in microenterprises). Data collection across the three studies occurred in the years 2008 through 2011, during which time no dramatic changes in economic conditions were evident in the study settings.

Sample

Eligibility criteria for Studies A and B included being age 18 years or older, just started receiving care at the clinic and completed evaluation for ART eligibility, and if not yet eligible for ART than $CD4 < 400$ cells/mm³ (which signifies some immune suppression). In Study C, participants needed to be 18 years of age or older and just been prescribed ART. In all studies, the primary eligibility criteria for initiation of ART was having a CD4 cell count 250 cells/mm³ or a WHO HIV disease stage III or IV (AIDS diagnosis). Eligible patients were enrolled consecutively in each study. Providers referred eligible patients who were interested in participating to the study coordinator for consent procedures, screening and scheduling of baseline interviews. All participants were required to provide written informed consent. Data on patient refusals to participate were not maintained, but the study coordinators reported that very few (<5%) eligible patients refused to participate. The study protocol was approved by IRBs at RAND, Makerere University (Studies B and C), and JCRC (Study A), as well as the Uganda National Council of Science and Technology.

Measures

All measures were interviewer-administered by trained interviewers (Masters level graduate students) in Luganda, the predominant language in this region of Uganda. The questionnaire was translated from English using standard translation and back-translation methodology. All measures were administered at each of the three assessment time points.

Work status—We assessed impact of HIV on work activity by first asking respondents if they had to stop or cut down on the work they normally do since learning of their HIV diagnosis. To assess current work status, respondents were asked whether or not they engaged in work activity that generated income or food in the last 7 days. Work could include a range of jobs from salaried employment, running a small business (*e.g.*, selling things) or working on the family farm or in the family business. House chores or homemaking were not considered work.

Work functioning—Participants were asked how often their health had affected their ability to work over the past month, with response options being ‘never’, ‘rarely’, ‘sometimes’ and ‘most of the time’. To further assess the impact of health on work functioning we used the 2-item role functioning subscale of the Medical Outcomes Study HIV Health Survey (MOS-HIV), a measure that has been validated in Uganda with the use of a Lugandan translation [32]. These two items ask the respondent to indicate whether their health 1) keeps them from working, or 2) renders them unable to do certain kinds or amounts of work, either at their job or at home or school; response options are Yes or No,

and as with all MOS-HIV subscales, the scores were summed and transformed to a standardized score of 0–100. Given that this subscale only has 2 items, and each item has only two response options, standardized scores for an individual were either 0, 50 or 100; therefore, in our multivariate analysis we used a binary variable that represented optimal work functioning and was defined as having a score of 100.

Depression—The 9-item Patient Health Questionnaire (PHQ-9) [33] was used to measure the presence of depressive symptoms over the past 2 weeks. Each of the 9 items corresponds to the symptoms used to diagnose depression according to DSM-IV (Diagnostic and Statistics Manual of Mental Disorders, 4th Edition) criteria [34]; responses to each item range from 0 ‘not at all’ to 3 ‘nearly every day’. Items were summed with a possible range of 0–27, with scores < 5 representing no depression, 5–9 representing ‘mild’ depression, 10–14 ‘moderate’, 15–19 ‘moderately severe’ and 20–27 ‘severe’ depression. Scores > 9 correspond highly to Major Depression (88% specificity and sensitivity) when compared with a diagnostic clinical interview [33]. For our analysis, scores of 5–9 represented “Minor Depression” and scores greater than 9 represented “Major Depression”. The PHQ-9 has been used successfully with HIV-infected individuals in other studies within sub-Saharan Africa [35].

Physical health—CD4 count and WHO HIV disease stage (stages I to IV, with III and IV representing an AIDS diagnosis) were abstracted from the client’s medical chart. Physical health functioning was assessed with the 6-item MOS-HIV subscale of the same name [32], which asks the respondent to indicate whether their current health limits their ability to engage in activities of daily life ranging from eating, dressing and bathing to more vigorous activities such as running or lifting heavy objects. The response options include 1 “yes, limited a lot”, 2 “yes, limited a little” and 3 “no”; items were summed and the scale score was transformed to a standardized score of 0–100 with higher scores representing better functioning.

Cognitive functioning was assessed using a subscale of the MOS-HIV, which asks about the frequency of 4 cognitive impairment symptoms in the past 4 weeks (e.g., difficulty keeping attention; forgetting things that happened recently) using a 1 “all of the time” to 6 “none of the time” response format. Items were summed and the scale score was transformed to a standardized score of 0–100 with higher scores representing better functioning.

Demographic characteristics included age, gender, and education level (classified as a binary indicator of having at least some secondary education).

Data Analysis

We computed mean and standard deviation for the continuous measures and frequency and percentage for the binary measures, and conducted bivariate tests (two-tailed t-tests, chi square tests) to assess for sample differences across the three studies and by treatment assignment. Multivariate random-effects logistic regression models were used to examine the effects of ART and HIV care on the two primary outcomes (work status and optimal work functioning) measured across the three assessments; this approach assumes a linear trend in the outcome between baseline and Month 6, and Month 6 and Month 12, which

limits our ability to describe how the rate of change may vary between these two times intervals, but enables us to address the primary questions of our analysis in a more parsimonious model. We assumed a hierarchical structure with multiple assessments nested within participants, and with participants nested within their study site. The model specification included a random intercept for each study site and participant to allow for baseline differences in the outcome across sites, as well as a different intercept for each participant. This approach also produced adjusted standard errors to account for correlations among multiple assessments conducted with each person, and due to clustering within study site.

All analyses included weights. To account for baseline differences between the ART and non-ART groups, we used propensity score weighting [36]. The propensity score is the probability that a member of the population receives treatment rather than the comparison condition and thus helps to provide an unbiased estimate of treatment effects. To account for dropout between baseline and Month 12, we developed attrition weights to adjust or re-weight the sample of study completers. To estimate the propensity scores and attrition weights, we used non-linear generalized boosting models (GBM) [37], both of which required us to specify an inclusive list of predictors (demographic, medical and psychosocial measures) that may be correlated with treatment assignment (or study completion) and/or the primary work-related outcomes. All of the random effects models with weights were fit using a maximum likelihood approach in XTMELOGIT in Stata [38].

Model Specification—Three models were estimated for each of the two primary work-related outcomes, with the goal of examining the effect of ART on change in the outcome over 12 months of treatment, and the potential role of depression in explaining these changes. The dependent variable in the models was change in the outcome measure across the three study assessments. All three models included the following core set of independent variables: 1) ART status (representing whether or not there is a group difference in the dependent variable at baseline), 2) time [ordinal variable representing the change in the dependent variable for each additional unit of time (i.e., 6 months) over the three time periods, and which is attributed to HIV care or the non-ART group], 3) the interaction of ART status by time (representing the additional change in the dependent variable with each unit of time among patients in the ART group relative to the non-ART group, 4) baseline measures of physical health and cognitive functioning, as well as variables measuring change in physical health and cognitive functioning from baseline to Month 12 (to control for the direct influence of physical health and cognitive functioning on the change in work outcomes), and 5) covariates including age, male gender, any secondary education, and baseline CD4 count.

What differed across the 3 models were the depression-related independent variables to assess the influence of global depressive symptoms versus categorical depression severity. The regression effects for each measure of depression over time were decomposed into two parts: (i) a baseline value for the respective measure, and (ii) change from baseline in that measure. The main effect of the first term determined the cross-sectional association between baseline depression and the outcome, while the second term determined whether changes in depression over time are associated prospectively with changes in the outcome.

The first model included baseline depressive symptoms (as measured by the continuous PHQ-9 total score) and the interaction of time and change in depressive symptoms from baseline to Month 12. The second model included separate baseline indicators of having Major Depression (PHQ-9 score > 9) and Minor Depression (PHQ-9 score between 5–9), and the interaction of time and change in depression symptoms (as measured by PHQ-9 total score). The last model included baseline indicators of Major and Minor Depression, as well as separate interaction terms for time by improvement in depression severity category (with the three categories being none, Minor or Major Depression) and time by worsening of depressive severity category.

Sensitivity analysis—The primary analysis used an intention-to-treat (ITT) approach, which included all participants in the ART and non-ART groups according to their ART status at baseline, regardless of any change in ART status thereafter. This produced a conservative estimate of the effects of ART given that 127 non-ART patients started ART during the study period (66 at Month 6 and 61 by Month 12); note that 9 ART stopped taking ART during the study (4 by Month 6 and 5 by Month 12). We evaluated the robustness of the ITT analysis with a sensitivity analysis in which we excluded the 136 participants who switched treatment assignments during the course of the study. We also conducted a second sensitivity analysis in which non-ART patients who started ART at Month 6 were assigned to the ART arm starting at Month 6. In this analysis, we used a time-lag effect model to assess the effect of baseline treatment assignment on change between baseline and Month 6, and the “true” rather than baseline Month 6 treatment assignment on the change between Month 12 and Month 6. Both sensitivity analyses were performed for each of the two primary outcomes; in each case, the findings remained unchanged from the original ITT models. Hence, we chose not to present the data from the sensitivity analyses.

RESULTS

Sample Characteristics

The merged sample consisted of 1,731 participants, 602 from Study A, 482 from Study B, and 647 from Study C. The baseline characteristics of the total sample, as well as by study, are presented in Table 1. The samples drawn from the three studies differed significantly on several variables. Mean age was higher in Study C compared to Study B (36.4 years vs. 34.6; $t = 3.3$, $p = .005$), and mean CD4 count varied significantly across studies, with the average CD4 cell count (sickest patients) in Study C (158 cells/mm³) being significantly lower than that in both Study A (216 cells/mm³; $t = 6.9$, $p < .001$) and Study B (273 cells/mm³; $t = 12.5$, $p < .001$), which was expected given that all participants in Study C were ART eligible. With regard to the work-related measures, a significantly lower proportion of participants from Study A (60%) was currently working compared to Studies B (69%; $t = 3.0$, $p = .01$) and C (67%; $t = 2.5$, $p = .05$), but there were no differences with regard to optimal work functioning. There were between-study differences on all depression measures, with the highest level of depression observed among participants of Study A, followed by Study B, and the lowest level of depression in Study C due to clinically depressed patients being given antidepressant therapy, and as a result being excluded from this analysis of ART effects alone (see Table 1 for statistics).

The ART and non-ART samples did not differ on demographics, but the ART group had a significantly lower mean CD4 cell count (150 cells/mm³ vs. 344 cells/mm³; $t = 23.7$, $p < .001$) and physical health functioning (72.4 vs. 79.1; $t = 5.1$, $p < .001$) compared to the non-ART group (see Table 1), as expected. Perhaps as a consequence of these physical health differences, the two groups differed significantly with regard to work status and functioning, and depression, as described below.

Work status and functioning—Average time between HIV diagnosis and study baseline was 19.5 months (median = 8.4 months), and 59% were diagnosed at least 6 months prior to study enrollment. When asked about the impact of HIV on their work activity, 18% had to stop working at least temporarily because of HIV [with 83% of this group not working at study baseline], another 38% had to cut down on their work or perform less physically demanding work, while the remaining participants (44%) had experienced little change in their work life since testing HIV positive. Two-thirds of the sample (65%) reported working over the past 7 days, with a greater proportion of the non-ART group working relative to the ART group (72% vs. 62%; $p < .001$). Among those working, a sizeable minority had jobs in the formal labor market (e.g., skilled labor such as mechanic or carpenter, clerical work or professional such as teacher or policeman) and earned salaries (37%), while most others either sold things as part of a microenterprise or were part of the service industry (e.g., waitress, worked at retail shop) (27%), or worked in farming or fishing (24%) (the remaining 12% were engaged in other types of work); the proportions of each these categories of work did not differ significantly between the ART and non-ART group participants who were working at baseline.

Among those currently working, 59% stated that their health affected their ability to work some or most of the past month, and another 5% reported being unable to work at all in the past month because of health limitations. Nearly two-thirds (63%) reported optimal work functioning (score of 100 on the role functioning subscale; no limitations or impairment in ability to work or perform daily responsibilities at work or home), while 30% said their health kept them from working and that they were unable to perform some activities (score of 0); the other 7% reported either unable to work or unable to perform some activities, but not both. The proportion of non-ART participants (75%) with optimal work functioning was significantly greater compared to that of the ART patients (58%; $p < .001$).

Depression—The mean PHQ-9 at baseline was 4.0 (SD = 3.8), with 9% having Major Depression (scored > 9 on PHQ-9) and 28% having Minor Depression (scored between 5–9 on PHQ-9). The ART group had higher rates of Major Depression (10% vs. 6%; $p = .02$) and higher PHQ-9 total scores (mean = 4.17 vs. 3.63; $p = .005$) (see Table 1).

Change in Work Status and Functioning Over Time—We used bivariate and multivariate analyses to examine change in work-related outcomes across the three time point assessments in the ART and non-ART groups. Overall retention at Month 12 was 77%; retention differed across the studies [highest in Study A (94%) and lowest in Study B (63%); $p < .001$], and was greater in the non-ART group compared to those in the ART group (81% vs. 75%; $p = .004$). The use of attrition weights in the multivariate models enabled us to control for these differences.

Work status: While a higher proportion of the non-ART group (72%) was working at baseline compared to the ART group (62%), rates did not differ between the groups at Month 6 (75% vs. 76%, $p = .72$) or Month 12 (77% vs. 79%, $p = .27$). However, examining change over time among those working and not working at baseline, separately, revealed a significant pattern of change. Of the ART respondents who were working at baseline, the vast majority continued to be working at Month 6 (85%) and Month 12 (87%) among those who completed all follow-up assessments; in contrast, there was considerable change among those not working at baseline, with over half (60%) working at Month 6 ($p < .001$), and two-thirds (66%) at Month 12 ($p < .001$). Findings were very similar in the non-ART group: of those who were working at baseline, 88% were working at Month 6 and 84% at Month 12, while 41% of those not working at baseline were now working at Month 6 ($p < .001$) and 58% were working at Month 12 ($p = .004$).

In the multivariate analysis of work status, each of the three models revealed a significant baseline difference between the ART and non-ART groups, with a higher percentage of the non-ART group working. In each model the overall time trend for the sample was not significant. However, the interaction of time and ART status was significant, indicating that the improvement in work status in the ART group was significantly greater than that in the non-ART group (see Table 2). Each of the 3 models examined different aspects of how baseline depression and change in depression may relate to change in work status. In model 1, greater baseline depressive symptoms (PHQ-9 total score) was associated with significantly lower odds of working over the 12-month study, while greater reduction in depressive symptoms from baseline to Month 12 was associated with greater odds of working. Similarly, models 2 and 3 both showed that having either Major or Minor Depression at baseline was associated with lower odds of working, while greater change in depressive symptoms (model 2) or category of depression severity (model 3) were associated with the likelihood of working (symptom reduction or moving to a lower severity category was associated with greater odds of working, while increased symptoms or moving to a higher severity category was associated with lower odds). Covariates that predicted improved work status over time were baseline measures of male gender, better physical health functioning and being older (see Table 2), as well as greater improvement in physical functioning from baseline to Month 12.

Work functioning: The proportion of non-ART patients with optimal work functioning was significantly greater than that of the ART group at baseline (75% vs. 58%; $p < .001$) and Month 6 (90% vs. 84%; $p = .001$), but slightly less than the ART group at Month 12 (89% vs. 93%; $p = .006$). Among the participants who completed all assessments, the rate of non-ART patients with optimal work functioning increased from 76% at baseline to 90% at Month 6 ($p < .001$), but there was no further change at Month 12 (89%; $p = .08$); the rate of optimal work functioning in the ART group increased significantly from baseline (59%) to Month 6 (84%; $p < .0001$), and continued to increase at Month 12 (93%; $p < .001$).

In the multivariate analysis of optimal work functioning, each of the three models revealed: 1) greater work functioning at baseline in the non-ART group compared to the ART patients, 2) a significant time trend indicating that the sample as a whole experienced significant improvement in work functioning over time, and 3) a significant interaction

between ART status and time, indicating that the ART group experienced a greater improvement in work functioning compared to the non-ART group (see Table 3). In model 1, greater depressive symptoms at baseline was associated with lower odds of optimal work functioning over the 12-month study, and greater reduction in depressive symptoms from baseline to Month 12 was associated with greater odds of optimal work functioning. Models 2 and 3 showed that having either Major or Minor Depression at baseline was associated with lower odds of optimal work functioning, and greater change in depressive symptoms (model 2) or category of depression severity (model 3) were associated with the likelihood of achieving optimal work functioning (symptom reduction or moving to a lower severity category was associated with greater odds of optimal functioning, while increased symptoms or moving to a higher severity category was associated with lower odds). Covariates that predicted achievement of optimal work functioning over time were having a secondary education, better physical health functioning at baseline, and greater improved physical health functioning over time (see Table 3).

DISCUSSION

In this analysis of data from three studies of HIV clients who were starting ART and/or entering HIV care, our findings suggest that HIV care in general, and ART even more so, improves both work status and functioning. Work-related benefits of HIV treatment are arguably expected given that treatment improves physical health functioning [39]; however, what is particularly noteworthy are the findings that document a clear harmful influence of depression on work status and functioning.

Participants in our study reported a significant negative impact of HIV on their work life, with many having to stop work following their diagnosis, and continuing to not work at the time they entered HIV care or started ART. Consistent with other studies [15–17,40], we observed that HIV care and ART are associated with a greater likelihood of working and improved work functioning. The impact of HIV treatment on work activity was most apparent among those not working at baseline. Of those who were not working at baseline, roughly half to two-thirds reported working at Months 6 and 12. Work functioning also improved significantly. These benefits were experienced by both ART and non-ART patients, but our data revealed a significantly greater improvement in the ART group, with regard to both work-related outcomes. Similar to the research reviewed by Beard et al. [5], most of the work benefits were observed in the first 6 months of treatment. Given the intent-to-treat nature of our analysis, and with some of the non-ART patients having started ART during the course of the study, our results are conservative and likely underestimate the effects of ART during this period.

While it's clear that HIV treatment has a beneficial effect on work activity and function, it's important to also understand the mechanisms that underlie this effect. Our multivariate results support the presumption that improved physical health and functioning associated with HIV treatment would be central to an effect on work outcomes. As a result, we saw that physical health functioning at baseline as well as change in physical health functioning over time were independently associated with change in work status and functioning. Perhaps more noteworthy is the strong evidence provided by our data for the influence of depression

on work-related outcomes. Having depression at the onset of treatment was predictive of worse work outcomes, whether depression was defined by global symptomatology, a clinical disorder (Major Depression) or as sub-threshold Minor Depression. The fact that a broad range of depressive severity is significantly related to work-related outcomes suggests the importance of more aggressive approaches to depression screening, diagnosis and treatment so that work-related complications associated with depressive symptoms can be mitigated. Also, change in depression, whether heightened or alleviated, corresponded to like changes in work status and functioning. These findings reveal the significance of both physical and mental health, which may affect work through physical functional capacity, specific depressive symptoms (e.g., fatigue, loss of interest or motivation, poor concentration), and self-efficacy and expected outcomes regarding work-related behavior as suggested by Social Cognitive Theory [18]. Accordingly, future research is needed to better understand the mechanisms by which physical and mental health influence work outcomes.

While our data suggest that physical and mental health are likely key mechanisms by which HIV treatment affects work activity and functioning, the fact that the ART group continued to show an advantage in these work outcomes even after controlling for change in physical health and depression, as well as other covariates, suggests that there are other aspects of ART that we have not measured that influence work status. One possible explanation is the greater exposure to social support at the clinic setting (from both providers and peers) for ART versus non-ART patients, since ART patients may have to go to the clinic more often (monthly versus every 6 months) and for longer visits compared to non-ART patients. This increased support could lead to greater reduction in internalized HIV stigma and increased empowerment and self-efficacy regarding work functioning.

The study has a number of limitations. With widespread access to ART in Uganda at the time of study enrollment, we could not ethically randomly assign ART to matching groups in Studies A and B. This resulted in a non-randomized comparison group with clear differences, as there were indications that the non-ART group had better health at baseline than the ART group, although the non-ART group did have evidence of immune suppression ($CD4 < 400$). While having a non-ART group enabled us to control for other time trends in the context of receipt of HIV care, we are not able to account for natural changes in the outcomes in the complete absence of HIV care. Nonetheless, our comparison group is favorable to several previous studies [15,16,40], which compared the outcomes of ART clients with those in a sample of the general population (regardless of HIV status). The clientele at the study sites is predominantly in the lower socioeconomic strata, so our data cannot address whether similar effects and relationships would be observed among clients in higher economic strata. Additionally, our evaluation is limited by our reliance on a self-report rather than diagnostic interview to assess depressive disorders and to distinguish between Minor and Major Depression. As a result, our rates of these depressive conditions are likely to be over-estimated, although the PHQ-9 has been shown to have good criterion validity [33]. Our measure of work also has limitations, as it is a relatively crude measure and had a short time frame (past 7 days); future research should examine a longer time frame and a more nuanced breakdown of work in terms of number of hours worked, absenteeism and productivity level while at work. Lastly, we did not assess for presence of

comorbid conditions such as dementia, cardiovascular disease or tuberculosis, which could impact depression as well as work functioning.

In conclusion, our findings revealed a significant beneficial effect of HIV care in general, and especially ART, on work status and functioning, and that changes in both physical health and depression during the first year of care or treatment play key roles in these work-related outcomes. Physical health functioning has an obvious direct influence on ability to work and the level of work functioning, but our findings show that psychological well-being may be just as important. HIV treatment more than adequately addresses the need for improved physical health [1,2], and studies suggest it also may benefit mental health [41], but our results imply a need to consider the additional value of integrating depression treatment into HIV care programs in SSA. Furthermore, the fact that Minor Depression, as well as Major Depression, was associated with impairment in work outcomes suggests the importance of early, aggressive management of depression. Effective diagnosis and treatment of depression, in conjunction with HIV primary care, could have significant economic benefits for individual patients and their households, and contribute to maximizing the cost-effectiveness and sustainability of ART scale-up in the region.

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Table 1

Baseline Characteristics by Study, ART Status and in Combined Sample

	Study			Baseline ART Status		Combined (N=1731)
	A (N=602)	B (N=482)	C (N=647)	Non-ART (N=527)	ART (N=1204)	
Age (mean years)	35.7 ^b	34.6 ^b	36.4 ^b	35.1	35.9	35.6
Male	32%	36%	36%	29% ^b	37% ^b	35%
Secondary education or more	14%	13%	17%	13%	16%	15%
In a committed relationship	46%	48%	46%	45%	47%	46%
CD4 count (mean cells/mm ³)	216 ^c	273 ^c	158 ^c	344 ^c	150 ^c	209
Cognitive functioning	77.4	78.0	92.1	84.0	82.5	8.30
Physical health functioning	71.8 ^c	71.9 ^c	79.1 ^c	79.1 ^c	72.4 ^c	74.5
Worked in the past 7 days	60% ^b	69% ^b	67% ^b	72% ^c	62% ^c	65%
Optimal work functioning	66%	62%	61%	75% ^c	58% ^c	63%
In a committed relationship	46%	48%	46%	45%	47%	46%
Major Depression	13% ^c	8% ^c	5% ^c	6% ^a	10% ^a	9%
Minor Depression	39% ^c	29% ^c	16% ^c	26%	28%	28%
Depression symptoms (mean PHQ-9)	5.22 ^c	4.11 ^c	2.80 ^c	3.63 ^b	4.17 ^b	4.01

^a p < .05,^b p < .01,^c p < .001

Table 2

Multivariate Analysis of Impact of ART and Change in Depression on Work Status over 12 Months of HIV Treatment

	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
ART status	0.42(0.26, 0.70)	0.42(0.25, 0.69)	0.41(0.25, 0.68)
Time	1.08(0.87, 1.34)	1.10(0.89, 1.36)	1.14(0.91, 1.44)
Time × ART status	1.38(1.06, 1.78)	1.40(1.08, 1.82)	1.40(1.08, 1.81)
Cross-Sectional			
Baseline depressive symptoms	0.88(0.84, 0.93)		
Baseline Major Depression		0.36(0.20, 0.65)	0.38(0.21, 0.67)
Baseline Minor Depression		0.53(0.37, 0.76)	0.44(0.30, 0.65)
Prospective (change over time)			
Time × change in depressive symptoms	1.07(1.04, 1.10)	1.06(1.04, 1.09)	
Time × improved depression status			1.59(1.25, 2.03)
Time × worsened depression status			0.54(0.35, 0.82)
Covariates			
Age	1.03(1.01, 1.04)	1.03(1.01, 1.04)	1.03(1.01, 1.04)
Male gender	2.27(1.65, 3.13)	2.28(1.65, 3.14)	2.28(1.65, 3.14)
Any secondary education	1.27(0.85, 1.91)	1.27(0.85, 1.91)	1.28(0.85, 1.92)
Baseline CD4 count	1.00(1.00, 1.00)	1.00(1.00, 1.00)	1.00(1.00, 1.00)
Baseline cognitive functioning	1.00(0.99, 1.02)	1.01(0.99, 1.02)	1.01(0.99, 1.02)
Change in cognitive functioning	1.00(0.98, 1.01)	1.00(0.99, 1.02)	1.00(0.99, 1.02)
Baseline physical health functioning	1.03(1.02, 1.04)	1.03(1.02, 1.05)	1.03(1.02, 1.05)
Change in physical health functioning	1.02(1.01, 1.03)	1.02(1.01, 1.03)	1.02(1.01, 1.03)

Table 3

Multivariate Analysis of Impact of ART and Change in Depression on Optimal Work Functioning over 12 Months of HIV Treatment

	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
ART status	0.56(0.38, 0.82)	0.56(0.38, 0.82)	0.55(0.37, 0.80)
Time	1.91(1.50, 2.44)	1.93(1.51, 2.46)	2.18(1.67, 2.84)
Time × ART status	1.51(1.12, 2.05)	1.57(1.16, 2.11)	1.57(1.16, 2.12)
Cross-sectional			
Baseline depressive symptoms	0.89(0.86, 0.93)		
Major Depression at baseline		0.45(0.30, 0.68)	0.48(0.32, 0.73)
Minor Depression at baseline		0.55(0.43, 0.71)	0.49(0.37, 0.65)
Prospective (change over time)			
Time × change in depressive symptoms	1.12(1.09, 1.15)	1.11(1.08, 1.14)	
Time × improved depression status			1.83(1.39, 2.41)
Time × worsened depression status			0.39(0.28, 0.55)
Covariates			
Age	0.99(0.98, 1.01)	0.99(0.98, 1.01)	0.99(0.98, 1.01)
Male gender	0.81(0.65, 1.01)	0.82(0.66, 1.02)	0.81(0.65, 1.01)
Any secondary education	1.54(1.14, 2.09)	1.54(1.14, 2.08)	1.55(1.15, 2.10)
Baseline CD4 count	1.00(1.00, 1.00)	1.00(1.00, 1.00)	1.00(1.00, 1.00)
Baseline in cognitive functioning	1.00(0.99, 1.01)	1.01(0.99, 1.02)	1.00(0.99, 1.02)
Change in cognitive functioning	1.00(0.99, 1.01)	1.00(0.99, 1.01)	1.00(0.99, 1.02)
Baseline physical health functioning	1.05(1.04, 1.06)	1.05(1.05, 1.06)	1.05(1.05, 1.06)
Change in physical health functioning	1.02(1.01, 1.03)	1.02(1.02, 1.03)	1.02(1.02, 1.03)