Psychosocial Factors Affecting Medication Adherence Among HIV-1 Infected Adults Receiving Combination Antiretroviral Therapy (cART) in Botswana

Natalie T. Do,¹ Kelesitse Phiri,² Hermann Bussmann,^{1,2} Tendani Gaolathe,^{1,3}
Richard G. Marlink,^{1,2} and C. William Wester^{1,2,4,5}

Abstract

As increasing numbers of persons are placed on potentially life-saving combination antiretroviral therapy (cART) in sub-Saharan Africa, it is imperative to identify the psychosocial and social factors that may influence antiretroviral (ARV) medication adherence. Using an 87 question survey, the following data were collected from patients on cART in Botswana: demographics, performance (Karnofsky) score, perceived stigma and level of HIV disclosure, attitudes and beliefs concerning HIV/AIDS, substance and/or drug use, depression, and pharmacy and healthcare provider-related factors. Overall adherence rates were determined by patient self-report, institutional adherence, and a culturally modified Morisky scale. Three hundred adult patients were recruited between April and May 2005. The overall cART adherence rate was 81.3% based on 4 day and 1 month patient recall and on clinic attendance for ARV medication refills during the previous 3 months. Adults receiving cART for 1–6 months were the least adherent (77%) followed by those receiving cART for greater than 12 months (79%). Alcohol use, depression, and nondisclosure of positive HIV status to their partner were predictive of poor adherence rates (p value <0.02). A significant proportion (81.3%) of cART-treated adults were adherent to their prescribed treatment, with rates superior to those reported in resource-rich settings. Adherence rates were poorest among those just starting cART, most likely due to the presence of ARV-related toxicity. Adherence was lower among those who have been treated for longer periods of time (greater than 1 year), suggesting complacency, which may become a significant problem, especially among these long-term cART-treated patients who return to improved physical and mental functioning and may be less motivated to adhere to their ARV medications. Healthcare providers should encourage HIV disclosure to “at-risk” partners and provide ongoing counseling and education to help patients recognize and overcome HIV-associated stigma, alcohol abuse, and depression.

Introduction

ACCORDING TO RECENT UNAIDS DATA, an estimated 33 million people are infected with HIV-1.¹ Unless these individuals receive appropriate treatment, the majority will die prematurely.

Sub-Saharan Africa alone accounts for 22.1 million HIV-1-infected individuals. Botswana, located in the center of southern Africa, has one of the highest documented HIV-1 seroprevalence rates in the world. The Botswana 2005 National

Sentinel Surveillance documented 33.6% HIV-1 seroprevalence among pregnant women presenting for routine antenatal care.²

Due to the limited distribution sites and economic considerations, HIV-1-infected persons in Botswana initially had difficulty obtaining antiretroviral medications (ARVs). Since the inception of Botswana’s public National ARV Treatment Program in January 2002, however, more than 110,000 persons have received this potentially life-saving treatment.

Access to ARV medications, however, is not the sole solution. A key component to the success of combination

¹Botswana-Harvard School of Public Health AIDS Initiative Partnership for HIV Research and Education (BHP), Gaborone, Botswana.

²Harvard School of Public Health, Boston, Massachusetts 02115.

³Ministry of Health, Gaborone, Botswana.

⁴Vanderbilt Institute of Global Health, Nashville, Tennessee 37232.

⁵Vanderbilt University School of Medicine, Division of Infectious Diseases, Nashville, Tennessee 37232.

antiretroviral therapy (cART) is how well HIV-1-infected persons adhere to these complex treatment regimens, as poor adherence negatively impacts both the individual and the community. Consequences of poor adherence or non-adherence include reduced CD4⁺ cell counts, higher plasma HIV-1 RNA levels, delayed immunologic recovery, disease progression and death,³⁻⁵ and the development of ARV drug resistance.⁶⁻⁸ The impact of HIV/AIDS is also felt at a societal level. HIV/AIDS-related death can lead to a decrease in the work force population and increased orphanage. Thus, the social and economic burden can be staggering.

Medication nonadherence can be defined as the number of doses not taken or taken incorrectly.⁹ Current estimates of nonadherence rates among cART-treated persons can range from 50% to 70%, depending on the patient's social and cultural environment.¹⁰ The development of interventions to improve adherence relies on both an in-depth understanding of potential barriers to adherence and knowledge of current adherence counseling practices.¹¹ Previous studies have suggested that depression and substance abuse are important factors that negatively impact medication adherence rates in the West.¹²

Previous studies in the sub-Saharan African region have concluded that pill burden is a significant factor influencing overall medication adherence rates. The fewer the pills and the simpler the dosing requirements, the better the adherence for the majority of treated patients.^{7,11-13} Studies have also suggested that patients who understand their ARV regimen are more likely to be adherent.¹³ Proper patient education strategies focusing on the correct dosing of medications, however, rely heavily on healthcare providers.¹⁴ In Botswana, the current standard of care requires nurses to provide the majority of ARV adherence counseling. Patients do, however, receive adherence counseling from a variety of sources, including physicians and nurses during routine examinations, as well as pharmacy staff members during medication refills.

There is a paucity of evidence-based data evaluating adherence and the factors associated with poor adherence among cART-treated adults in sub-Saharan Africa. Based on the published literature,¹⁵ we hypothesized that the following factors would be predictive of poor cART adherence: (1) longer duration on ARV treatment, (2) reduced levels of formal education, (3) difficulty in getting to the clinic, (4) reduced levels of physical functioning, (5) lower quality of life scores, (6) poor social support, (7) lack of HIV disclosure due to stigmatization, (8) poor knowledge of ARV medications, (9) the presence of active or recent ARV-associated toxicity, and (10) higher pill burden.

Our study was designed to evaluate a large group of cART-treated adults in urban Botswana who had been receiving treatment for (1) less than 6 months, (2) 6–12 months, or (3) greater than 12 months to determine which factors were negatively correlated with overall ARV medication adherence. We anticipate that such information would enable the identification of adults at risk for poor adherence and, in the future, improve the overall quantity and quality of life among the rapidly increasing numbers of HIV-1-infected adults receiving cART in the region.

Materials and Methods

Study design

The study involved a cross-sectional prospective survey among a large group ($n = 300$) of HIV-1-infected adults at-

tending the outpatient adult Infectious Disease Care Clinic (IDCC) on the grounds of Princess Marina Hospital (PMH) in Gaborone, Botswana between April and May 2005. This study was approved by the Ministry of Health, Botswana's Health Research Development Unit, and the Harvard School of Public Health's Human Subjects Committee.

Study site

The adult PMH IDCC was the first national ARV treatment site and is the largest outpatient ARV treatment clinic in Botswana. This clinic has provided longitudinal outpatient medical care to greater than 16,000 HIV-1-infected adults since its inception over 7 years ago. On an average clinic day, staff members provide care to approximately 100–150 patients. All stable adult IDCC patients see their physician every 3 months but come monthly for ARV refill visits where they are attended by pharmacy staff only and given a 30–35 day supply of ARV medications. The adult PMH IDCC was, therefore, an ideal site to evaluate the factors associated with short-term and long-term adherence among cART-treated patients in Botswana.

Participant selection and recruitment

Patients are referred for cART initiation from CD4⁺ cell count screening clinics. During the first clinic visit, all patients undergo laboratory blood draws for baseline functioning and screening for general medical conditions such as anemia or renal and hepatic impairment. Patients also receive an adherence educational session in a group format, followed by individual counseling and education. Patients are instructed to identify an adherence assistant who will assist the patient with maintaining cART adherence via encouragement and/or reminders. The patients are also screened by a physician for HIV/AIDS-related opportunistic infections. Chest x-rays are obtained and patients are initiated on PCP prophylaxis with oral cotrimoxazole (or dapsone if they are sulfa allergic). Patients are then instructed to return to the clinic in 2 weeks at which time their laboratory and chest x-ray results are reviewed. In addition, at this visit, all patients are required to return to the clinic with a self-nominated adherence assistant. The patient is started on cART if the following criteria are met: the laboratory work is within normal limits, the patient has shown motivation for treatment through the identification of an adherence assistant, and the patient does not have active opportunistic infections that would preclude initiating cART that day. Once the patient is started on cART, adherence counseling occurs at every longitudinal visit and is done in the consulting room, when the patient is scheduled to see the doctor and nurse, and in the pharmacy area during every ARV medication refill visit. Throughout the entire process, trained adherence counselors, social workers, support groups, and family welfare educators are available to patients. Scheduled reinforcements, however, are done only on an "as needed" case-by-case basis.

Every morning during study enrollment, all patients aggregating in the waiting area were read a brief study recruitment script by a study member or IDCC nurse outlining the objectives of the study, the risks and benefits of participation, and where to obtain more information about the study. Interested patients were given a copy of the informed consent,

available in English and Setswana, to read. Trained staff members fully reviewed the study consent forms with each potentially eligible and interested patient. Translators were available for participants who had difficulty reading or understanding the forms. Consenting patients were provided a private room to complete the survey.

All participants were enrolled on a “first come, first serve” basis, with a maximum of 20 persons completing the survey on any individual study enrollment day. If more than the maximum number of patients were interested in enrolling in the study, these persons were told that the desired target for the day had been reached, and they were thanked for their interest. Once the target number ($n=100$) in each ARV treatment group was reached, no additional patients were enrolled for that group.

Study inclusion criteria

All HIV-1-infected adults (greater than 18 years of age) presenting for care at the PMH IDCC who were on cART for at least 1 month were potentially eligible for this study. Patients were excluded if they (1) did not provide informed consent, (2) were less than 18 years of age, or (3) were on cART for less than 1 month.

Survey instrument

The 87-question study survey was available in both Setswana and English. All participants required between 30 and 45 min to complete the survey. The surveys were anonymous and patients were informed that their responses were private and would not be disclosed to anyone, including IDCC healthcare providers.

The survey collected information on patient demographics (gender, age, marital status, employment status), individual cART regimens, performance (Karnofsky and European Quality of Life) score, perceived stigma and level/extent of HIV disclosure, attitudes and beliefs concerning HIV/AIDS, substance use and abuse, tobacco use, depression, and pharmacy and healthcare provider-related factors. Copies of the survey instrument are available on request.

The level of physical functioning (performance) was assessed using the Karnofsky Performance Scale and the European Quality of Life score.^{16–21} To assess for the presence of active substance abuse, which has been shown in prior studies to be a significant predictor of poor adherence,²² participants were asked if they regularly consumed alcohol, tobacco, or illicit substances using four-point Likert-style response options. Specifically, questions regarding alcohol use focused on quantity, frequency of use of (daily, three to four times per week, weekends only, or one weekend per month), and whether the patient continued their ARV medications when consuming alcohol.

Depression was assessed using (1) three questions created for this study, (2) one question from the European Quality of Life (EQ-5D)¹⁹ instrument, and (3) 21 questions from the Beck Depression Inventory, which has been used in prior studies to determine the level of depression in HIV-1-infected adults.^{23,24} All questions in this section were graded using four-point Likert-style responses. The following total point scales were used to assess depression: mild (10–15), moderate (16–23), and severe (24–62).² For this study, a cut-off score of 14 was used to distinguish between “depressed” and “nonde-

pressed” patients,² with higher scores being indicative of greater levels of depressive symptomatology.

Patients were asked additional questions pertaining to pharmacy-related factors, including duration and extent of pharmacy staff interaction, interaction with pharmacy staff (amount of time counseled, content of counseling sessions), individual preferences for duration and extent of counseling, and overall attitude toward their healthcare provider.

Overall medication adherence rates were ascertained using (1) patient 4 day recall, (2) patient 1 month recall, and (3) institutional adherence, defined as self-reported attendance rates at the adult IDCC pharmacy for scheduled ARV medication refills during the prior consecutive 3 months.^{25–27} To aid in our overall adherence assessment, a culturally sensitive and modified version of the Morisky score for adherence^{28,29} was also incorporated into the survey.

Adherence definition

For this study, patients were defined as “adherent” if they met all three of the following criteria: (1) self-report of no missed ARV medication doses in the past 4 days, (2) self-report of no missed ARV medication doses in the past 1 month, and (3) self-report of no missed ARV medication refill visits during the past 3 months.

Statistical considerations

Patient demographics, psychological indices, and medication adherence information were analyzed using SAS statistical software, version 8.0 (Cary, NC). All variables were categorical (ordinal) and frequency distributions were used to describe variables of interest. Specifically, two-way tables with a Chi-square distribution were used to assess the association of adherence with sociodemographic, psychological, and clinical variables. Fisher exact tests were employed where table cells had expected counts of less than five. All p -values were two tailed, and a p -value of less than 0.05 was considered statistically significant.

Results

During April–May 2005, 300 consenting adults presenting for care at the adult PMH IDCC completed our survey. The sample included 100 adults receiving cART for 1–6 months, 100 adults receiving cART for 6–12 months, and 100 adults receiving cART for greater than 12 months.

Most of the respondents were female (76.3%), which reflects the demographics of patients currently receiving HIV/AIDS care and treatment in Botswana (Table 1). Most respondents (60.4%) were between 24 and 35 years of age. The majority (77%) of respondents were either cohabiting (30%) and/or single (47%), with only 14% reporting being married. In terms of educational level, 55.7% had completed secondary schooling and another 17.7% had completed some level of tertiary education. Only 55.3% were actively employed. Of the respondents, 44.6% reported being domiciled with one to three other persons, 29.6% lived with four to six other persons, and 12% reported living with seven or more other persons. One-third of persons (34%) spent, on average, between 30 and 60 min traveling to the clinic, 26.3% required only 15–30 min, 18% required more than 1–2 h, with 9.6% needing greater than 2 h to get to the clinic. Of the 9.6% that required greater than

TABLE 1. BASELINE CHARACTERISTICS OF THE STUDY POPULATION ($n = 300$)

	n (%)
Gender	
Male	71 (23.7%)
Female	229 (76.3%)
Age (years)	
18–29	83 (27.7%)
30–35	98 (32.7%)
>36	66 (22%)
cART regimen	
CBV/NVP	198 (66.0%)
CBV/EFV	77 (25.7%)
Marital status	
Single	141 (47%)
Cohabiting	90 (30%)
Married	42 (14%)
Employment status	
Actively employed	166 (55.3%)
Unemployed	133 (44.3%)
No answer	1 (0.33%)
Educational level	
Primary	75 (25%)
Secondary	167 (55.7%)
Tertiary	53 (17.7%)
Karnofsky performance score and EuroQoL	
Score of 100	260 (86.7)
Score of 90	26 (8.7%)
Score of 80	7 (2.3%)
Score of 70	5 (1.7%)
Score of <70	2 (0.7%)
European Quality of Life [EQ-5d (EuroQoL)]	
Score of 5	212 (70.7%)
Score of 6	59 (19.7%)
Score of 7	15 (5%)
Score >7	29 (4.7%)

2 h of travel to the clinic, 3.4% were in the group receiving treatment for less than 1 month, and 3.1% were in the group receiving treatment for greater than 12 months. Travel times did not statistically significantly affect adherence rates.

The majority of respondents (66.0%) were being treated with zidovudine (ZDV) and lamivudine (3TC) (coformulated as *Combivir* or *Lamizid*) plus nevirapine, which was consistent with the 2005 Botswana National ARV Treatment Guidelines³⁰ that recommend the first-line regimen of ZDV + 3TC + nevirapine (NVP) for all women of reproductive potential. Of the remaining respondents, 25.6% were receiving ZDV + 3TC plus efavirenz (EFV) and 5.6% were receiving stavudine (d4T) plus 3TC and NVP, which was also in accordance to existing National ARV Treatment Guidelines.³⁰

The majority of study participants had excellent performance scores, with 86.7% having a Karnofsky performance score of 100%. Performance was also assessed using EQ-5d (EuroQoL), a five question survey that assesses mobility, self-care, ability to engage in daily activities, pain/discomfort, and anxiety/depression. Each of the five questions in the EQ-5d (EuroQoL) had a point value of 1 to 3 (with 1 indicating no difficulties and 3 indicating the worst performance). The majority of our study participants (90.3%) had a favorable EQ-5d (EuroQoL) performance score of 5 (70.6%) or 6 (19.7%).

Only one patient reported very poor quality of life measures at the time of survey completion and had a categorized quality of life of 15, the lowest possible score.

Seventy-two percent of all respondents reported disclosing their positive HIV-1 status to their partner, with 16% deciding not to answer this question.

The majority of respondents (91.3%) believed in the efficacy of antiretroviral medications and, specifically, that ARVs significantly prolong one's life compared to 6% who did not. Just over 75% of the respondents viewed their HIV status as "very serious" prior to initiating their ARV treatment and this same percentage of respondents also viewed their HIV status as "very serious" while receiving public cART. In addition, 81% viewed ARV medications as the best treatment for HIV/AIDS, whereas 11.3% felt that "no treatment" was the best approach and 4.7% believed that religion was the best treatment for their HIV/AIDS.

In addition, 9.9% of respondents reported active and consistent alcohol use (either daily use or at least three times a week) and, of these, 7.3% reported moderate alcohol consumption and 2.6% reported heavy alcohol use. None of the survey participants reported using illicit drugs, although 6.0% reported moderate tobacco use and 5.6% reported heavy tobacco use.

The Beck Depression Inventory (BDI) portion of the survey revealed that 85 (28.3%) of the 300 respondents had some level of depression. Of these 85, 46.9% had "mild" depression, 31.8% had "moderate" depression, and 21.2% had scores categorizing them as "severely" depressed.

Among respondents, 26.7% reported active or very recent ARV-associated toxicity, most commonly gastrointestinal intolerance or peripheral neuropathy. The majority of these toxicities (40.4%) were mild/moderate nausea and/or emesis, with the majority of these gastrointestinal symptoms occurring among adults who had been on cART only for 1–6 months.

In terms of study participant views pertaining to their own individual healthcare provider relationships, 94% were comfortable in openly discussing HIV/AIDS with their current healthcare provider. Forty-two percent felt that nurses provided the most effective adherence counseling. Time of medication counseling with pharmacy staff was not statistically significantly correlated with adherence, although the respondents favored having additional counseling on ARV-related toxicities (33.3%), HIV-1 disease progression (19.7%), and proper ARV medication storage (15.3%).

In assessing pill burden, we found that 67% of study participants were taking only their prescribed ARV medications, whereas 21.7% were also actively taking one or two other medications, and 8.3% reported actively taking three or more additional medications to treat comorbidities. When respondents were asked specific reasons for why they missed ARV medication doses, most reported that they "forgot" (20.6%), "felt healthy" and therefore no longer needed their ARV medications (7.6%), or that they were experiencing active toxicities that made them "feel worse" (3.3%). When asked specific reasons for why they missed refill appointments, most reported "other" with "could not miss work" and being "too sick to come to the clinic" as the most frequently cited reasons.

Using our study's definition of adherence, 81.3% of respondents were deemed "adherent." Twenty-two (7.3%) of 300 respondents reported missing a dose within the past 4 days,

TABLE 2. MEDICATION ADHERENCE ASSESSMENTS

	n (%)
Adherent based on study definition	
On cART for 1–6 months (<i>n</i> = 100)	77 (25.7%)
On cART for 6–12 months (<i>n</i> = 100)	88 (29.3%)
On cART for >12 months (<i>n</i> = 100)	79 (26.3%)
Missed any ARV doses within the past 4 days	
No	277 (92.4%)
Yes	22 (7.3%)
Unsure	1 (0.3%)
Missed any ARV doses within the past 1 month	
No	269 (89.7%)
Yes	28 (9.3%)
Unsure	2 (0.7%)
Did not answer	1 (0.3%)
Missed any ARV treatment clinic visits within the past 3 months	
No	287 (95.7%)
Yes	9 (3.0%)
Unsure	2 (0.7%)
Did not answer	2 (0.6%)

28 (9.3%) reported missing a dose within the past month, and only 9 (3.0%) respondents self-reported missing a clinic refill appointment within the past 3 months (Table 2). Patients receiving cART for 1–6 months were the least adherent (77%), followed closely by those receiving treatment greater than 12 months (79%). Patients receiving cART for 6–12 months had the best adherence rates (88%) of our three cART-treated populations (Table 2).

Our multivariate analysis suggested no differences (all *p*-values >0.10) between the “adherent” and “nonadherent” populations when evaluated by age, gender, level of education, employment status, travel time required to arrive at the clinic/dispensary, duration of ARV treatment, number of persons actively residing with the participant, and pill burden. However, the presence of depression, active alcohol use, and the failure to disclose one’s positive HIV-1 status to a partner were all statistically significant predictors of non-adherence (all *p*-values <0.02) (Table 2).

Discussion

Our study strongly suggests that adult cART-treated adults in this urban Botswana setting have excellent overall ARV medication adherence rates.

The cART-treated group with the poorest medication adherence rate (77% overall) was the group of patients who had been receiving cART for the shortest duration of time, namely 1–6 total months. Of note, approximately one-quarter (26.7%) of these patients did report active or very recent ARV-associated toxicities, with almost all of the reported toxicities occurring in this particular cART-treated group. Among those with poor adherence, a significant proportion reported that the primary reason for missing their ARV medication doses was that they “felt healthy” and “no longer needed their ARV medications,” with the majority of these patients (56.5%) receiving cART for more than 1 year. It could be hypothesized, therefore, that there may be two main reasons, other than forgetfulness, for poor adherence: (1) ARV medication toxicity, which most often occurs early in a patient’s ARV treatment course and (2)

complacency, which is typically a long-term issue and is a direct consequence of cART-treated patients returning to improved physical and mental functioning, who then may be less motivated to adhere to their ARV medications. Such information should be used to bolster existing adherence educational messages administered by healthcare personnel as they interact with cART-treated adults in the outpatient setting, focusing especially on the first 6 months and on patients on treatment for longer than 1 year. For patients in the early stages of cART treatment, clinics should consider providing incentives or intensive group counseling during which cART-treated persons living with HIV/AIDS could tell their story (testimonials), which may help motivate patients. For patients who have been on cART for greater than 1 year, clinics should consider instituting a “refresher” course on the importance of adherence as well as individualized therapy in which the patient is asked to reflect on significant events of the past year and how being adherent to cART treatment has both prolonged and improved their overall quality of life.

Our findings also highlight the significant role that the lack of disclosing positive HIV-1 status to partners has in determining overall medication adherence rate. Patients who failed to disclose to their partner were significantly more likely to be poorly adherent. Healthcare providers caring for HIV-1-infected outpatients need to address this issue, both to improve medication adherence rates and to identify others “at risk.” Patients who have not disclosed their HIV status to their partners are more likely to miss doses than other patients, probably due to the fear of having their positive HIV status revealed.^{31,32} Thus, stigmatization has a pivotal role in a patient’s ability to be adherent with medications, because lack of disclosure can cause patients to skip dose(s) if privacy cannot be ensured. Additional reasons for nondisclosure include privacy, self-blame, fear of rejection, and not wanting to be a burden to their partner.³³ Healthcare providers in the region should strongly encourage HIV disclosure to partners by providing ongoing counseling and education to help patients recognize and overcome HIV-associated stigma, alcohol use or abuse, and depression. Other studies have also shown that “treatment supporters/assistants” can also improve treatment outcomes.³⁴ Treatment supporters are nonfamilial assistants whose duty is to constantly remind the patient of scheduled dosing times.

Our study population was predominantly female (76.3%) and it is possible that the threat of emotional or physical abuse to women by their male partners was a contributing reason for nondisclosure. Previous studies from Tanzania, South Africa, and Kenya reported that between 16% and 51% of women chose not to disclose their status due to fear of violence.³⁵ Existing education and counseling programs for women should include discussions involving gender and HIV, roles and expectations in relationships, the risk of physical and sexual violence, and violence associated with the disclosure of HIV status. Strategies to address intimate partner violence include behavioral changes via television, radio, and print such as brochures, counseling from healthcare workers on how to recognize and leave potentially dangerous situations, and strengthening statutes and policies regarding domestic violence. Other strategies can focus on empowering women financially through microfinance and microcredit programs. By empowering women to establish small businesses, women can improve their decision making capacity within the

household and the financial means to access nutrition, child health, and contraceptives. Microcredit interventions in rural parts of other countries such as Bangladesh have been shown to reduce partner violence.³⁶

Consistent with other studies, alcohol use and the presence of depression were found to be predictive of poor adherence. Depression in persons living with HIV/AIDS in a resource-limited settings range from 21% to 57%.³⁷ Poverty can limit the ability of those living with HIV/AIDS to adopt healthy behaviors such as medication adherence, avoiding breastfeeding, and practicing safe sex. Currently, screening for depression at Princess Marina Hospital is targeted toward individuals who have been identified by other healthcare professionals as being “high risk” for underlying depression. Our findings have been presented locally and we are sharing the results of our study with the Botswana Ministry of Health as well as the Principal Investigator the President’s Emergency Plan for AIDS Relief (PEPFAR) Master Trainer program in Botswana. It is our hope that the results of this study will lead to the establishment of routine screening for depression in all newly enrolled IDCC patients across the country. The current protocol for those who have been identified as being depressed is a psychiatric referral so that long-term counseling and medical treatment (i.e., prescription of antidepressants) can take place.

Pill burden did not appear to adversely influence adherence rates in our cART-treated population. Our population as a whole was self-reportedly very adherent and appeared committed to taking their medications, even with the additional burden of other medications to treat comorbidities among approximately 22% of patients. Advances in technology can further decrease pill burden by providing easier and more convenient dosing formulations (i.e., once daily and the use of coformulated/combination tablets) and the utilization of ARV medications that have longer half lives.

Because travel time to and from the clinic represents time absent from work, it is possible this may have affected the adherence rate. Travel time to the clinic, however, was not significantly associated with adherence rates in our study population. Travel time to the clinic could also possibly account for why our study population was predominantly female. In various cultures, males are the main contributors to the family income and possibly could not afford to take the time off that is necessary for a medical visit to the clinic.

Our study is limited by its reliance on self-reported adherence patterns. Adherence rates were assessed using only two methodologies: patient 4 day and 1 month recall and institutional pharmacy refill attendance, which was also self-reported. These measures are prone to “reporting” and “social desirability” biases. Another possible limitation is selection bias. Our study consisted only of patients who volunteered to participate, thus potentially skewing the results as perhaps only those who are confident of achieving survey high marks may be comfortable participating. Other established methodologies, which include pill counts, electronic event monitoring (“MEMS caps”), and plasma HIV-1 RNA level determination may have significantly improved the reliability of our findings. Of note, two large retrospective studies^{38,39} conducted among HIV-1-infected adults presenting for care at the adult PMH IDCC at or around the same time that our study was conducted showed comparable virological success rates, with 82–91% of cART-treated patients obtaining unde-

tectable plasma HIV-1 RNA levels following 1 year of ARV treatment. These studies were conducted among 310 TB/HIV-1 coinfect³⁸ and 429 ARV treatment-naïve adults³⁹ receiving similar first-line cART combinations. Another limitation is that no further information is available regarding longer-term adherence and clinical outcomes once depression was recognized and treated, as this was not a longitudinal study. Additional studies evaluating long-term outcomes among patients with HIV and comorbid psychiatric illnesses such as depression are warranted. In addition, because of possible loss to follow-up, this study is limited by the potential bias of better retention of more adherent patients, thus complicating the interpretation of change in adherence rates over time.

In summary, a significant proportion (81.3%) of our cART-treated adults were adherent to their prescribed treatment, with rates superior to those reported in resource-rich settings.³³ Adherence rates were poorest among those just starting cART, most likely due to the presence of ARV-related toxicity, and among those who have been treated for longer than 1 year, suggesting complacency. Lack of HIV disclosure, alcohol use or abuse, and the presence of depression correlate with poor medication adherence and will need to be continually screened for in cART-treated populations in the region to ensure early intervention and better patient outcomes.

Acknowledgments

We first want to acknowledge and thank all of the study participants who completed this survey. We also want to personally acknowledge and thank Kgalalelo Foya for her assistance with data collection. We would also like to thank Margaret Magodiello, Tlamelelo Kapaletswe, and the entire Princess Marina Hospital adult Infectious Disease Care Clinic (IDCC) and “Tshepo” study teams for their assistance in conducting this study. Lastly, we would like to acknowledge and personally thank Erika Färdig and Danae Roumis for administrative oversight, review of this manuscript, and overall technical assistance and expertise.

Author Disclosure Statement

No competing financial interests exist.

References

- UNAIDS 2008 Report on the global AIDS epidemic, 2008; data.unaids.org/pub/GlobalReport/2008/jc1510_2008_global_report_en.pdf; accessed 17 January 2009.
- 2005 Botswana National HIV-1 Sentinel Surveillance report, Ministry of Health, Gaborone, Botswana.
- Erwin J: Adherence and its implications for antiretroviral therapy. *Int Antiviral News* 1998;6:12–14.
- Hogg RS, Heath K, Bangsberg D, *et al.*: Intermittent use of triple-combination therapy is predictive of mortality at baseline and after 1 year of follow-up. *AIDS* 2002;16:1051–1058.
- Stephenson J: AIDS researchers target poor adherence. *JAMA* 1999;281:1069.
- Lange J: Issues for the future of antiretroviral therapy. *Antiviral Ther* 1997;2 (Suppl):71–83.
- Williams A and Friedland G: Adherence, compliance, and HAART. *AIDS Clin Care* 1997;7:51–58.
- Veenstra J, Schuurman R, Cornelissen M, *et al.*: Transmission of zidovudine-resistant HIV-1 following deliberate injection

- of blood from a patient with AIDS: Characteristics and natural history of the virus. *Clin Infect Dis* 1995;21:556–560.
9. Smith DL: Patient compliance: An educational mandate. McLean, VA: Norwich Eaton Pharmaceutical, Inc. and Consumer Health Information Corp., 1989.
 10. Chesney MA, Ickovics J, Hecht FM, Sikipa G, Rabkin J. Adherence: A necessity for successful HIV combination therapy. *AIDS* 1999;13(Suppl A):S271–278.
 11. Golin C, Liu H, Hayes R, *et al.*: A prospective study of predictors of adherence to combination antiretroviral medication. *J Gen Int Med* 2002;17:756–765.
 12. Gordillo V, del Amo J, Soriano V, and Gonzalez-Lahoz J: Sociodemographic and psychological variables influencing adherence to antiretroviral therapy. *AIDS* 1999;13:1763–1769.
 13. Miller LG, Liu H, Hayes RD, *et al.*: Knowledge of antiretroviral dosing and adherence: A longitudinal study. *Clin Infect Dis* 2003;36:514–518.
 14. Ickovics JR and Meisler AW: Adherence in AIDS clinical trials: A framework for clinical research and clinical care. *J Clin Epidemiol* 1997;50(4):385–391.
 15. Ware N, Idoko J, Kaaya S, *et al.*: Explaining adherence success in sub-Saharan Africa: An ethnographic study. *PLoS* 2009;6(1):0039–0047.
 16. Karnofsky DA and Burchenal JH: The clinical evaluation of chemotherapeutic agents in cancer. In: *Evaluation of Chemotherapeutic Agents* (MacLeod CM, ed.). Columbia University Press, New York, 1949, p. 196.
 17. Karnofsky D, Abelman W, Craver L, and Burchenal J: The use of nitrogen mustards in the palliative treatment of carcinoma. *Cancer* 1948;1:634–656.
 18. Schag CC, Heinrich RL, and Ganz PA: Karnofsky performance status revisited: Reliability, validity, and guidelines. *J Clin Oncol* 1984;2:187–193.
 19. Johnson JA, *et al.*: Valuation of EuroQOL (EQ-5D) health states in an adult US sample. *Pharmacoeconomics* 1998;13:421–433.
 20. Kind P: The EuroQol instrument: An index of health-related quality of life. In: *Quality of Life and Pharmacoeconomics in Clinical Trials*, 2nd ed. (Spilker B, ed.). Lippincott-Raven Publishers, Philadelphia, 1996, pp. 191–201.
 21. Sapin C, Fantino B, Nowicki ML, and Kind P: Usefulness of EQ-5D in assessing health status in primary care patients with major depressive disorder. *Health Quality Life Outcomes* 2004;2:20.
 22. Tucker J, Orlando M, *et al.*: Psychosocial indicators of antiretroviral non-adherence in HIV-positive adults with substance use and mental health problems. *Health Psych* 2004;23:363–370.
 23. Judd F and Mijch A: Depressive symptoms in patients with HIV infection. *Aust NZ J Psychiatry* 1996;30:104–109.
 24. Beck AT, Ward CH, and Mendelson M: An inventory for measuring depression. *Arch Gen Psychiatry* 1961;6:561–571.
 25. Bangsberg D, Hecht F, Charlebois E, Zolopa AR, *et al.*: Adherence to protease inhibitors, HIV-1 viral load and development of drug resistance in an indigent population. *AIDS* 2000;14:357–366.
 26. Bangsberg DR, Perry S, Charlebois ED, *et al.*: Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. *AIDS* 2001;15:1–2.
 27. Stone V: Strategies for optimizing adherence to highly active antiretroviral therapy: Lessons from research and clinical practice. *Clin Infect Dis* 2001;33:865–872.
 28. Morisky DE, Green LW, and Levine DM: Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care* 1986;24(1):67–74.
 29. Shalansky SJ, Levy AR, and Ignaszewski AP: Self-reported Morisky score for identifying non-adherence with cardiovascular medications. *Ann Pharmacother* 2004;38(9):1363–1368.
 30. Anabwani G and Jimbo W, eds. *Botswana Guidelines on Antiretroviral Treatment*. Botswana Ministry of Health, Gaborone, 2005.
 31. Hardon A, Davey S, Gerrits T, *et al.*: From access to adherence: The challenges of antiretroviral treatment. Studies from Botswana, Tanzania, and Uganda. World Health Organization, Geneva, 2006.
 32. Hardon AP, Akurut D, Comoro C, *et al.*: Hunger, waiting time and transport costs: Time to confront challenges to ART adherence in Africa. *AIDS Care* 2007;19:658–665.
 33. Derlega VJ, Winstead BA, Greene K, *et al.*: Reasons for HIV disclosure/nondisclosure in close relationships: Testing a model of HIV-disclosure decision making. *J Social Clin Psychol* 2004;23(6):747–767.
 34. Nachega JB, Knowlton AR, Deluca A, *et al.*: Treatment supporter to improve adherence to antiretroviral therapy in HIV-infected South African adults: A qualitative study. *J Acquir Immune Defic Syndr* 2006(Suppl 1):S127–S133.
 35. Medley A, Garcia-Moreno C, McGill S, *et al.*: Rates, barriers, and outcomes of HIV sero-disclosure among women in developing countries: Implications for prevention of mother-to-child transmission programmes. *Bull WHO* 2004;82(4):299–307.
 36. Schuler SR, Hashemi SM, Riley AP, *et al.*: Credit programs, patriarchy, and men's violence against women in rural Bangladesh. *Social Sci Med* 1996;43(12):1729–1742.
 37. Ying Wu D, *et al.*: Burden of depression among impoverished HIV positive women in Peru. *J Acquir Immune Defic Syndr* 2008;48:500–504.
 38. Shipton LK, Wester CW, Stock S, *et al.*: Safety and efficacy of nevirapine and efavirenz based antiretroviral therapy in adults treated for HIV and tuberculosis co-infection in Botswana. *Int J Tuberculosis Lung Dis* 2009;13(3):360–363.
 39. Bisson GP, Gross R, Strom JB, *et al.*: Diagnostic accuracy of CD4 cell count increase for virologic response after initiating highly active antiretroviral therapy. *AIDS* 2006;20:1613–1619.

Address correspondence to:

C. William Wester
Vanderbilt University School of Medicine
Vanderbilt Institute of Global Health (VIGH)
1161 21st Avenue South
A-2200, Medical Center North
Nashville, Tennessee 37232-2582

E-mail: william.wester@vanderbilt.edu
(or cwwester@gmail.com)