USAID
FROM THE AMERICAN PEOPLE

FACTORS ASSOCIATED WITH ADHERENCE TO ANTIRETROVIRAL THERAPY IN RWANDA

QUALITY ASSURANCE PROJECT

OPERATIONS RESEARCH RESULTS

SEPTEMBER 2008

This publication was produced for review by the United States Agency for International Development. It was prepared by Rachel Jean-Baptiste.

OPERATIONS RESEARCH RESULTS

FACTORS ASSOCIATED WITH ADHERENCE TO ANTIRETROVIRAL THERAPY IN RWANDA: A MULTI-SITE STUDY

September 2008

Rachel Jean-Baptiste

The Quality Assurance Project (QAP) is funded by the U.S. Agency for International Development (USAID) under Contract Number GPH-C-00-02-00004-00. The Project serves developing countries eligible for USAID assistance, USAID Missions and Bureaus, and other agencies and nongovernmental organizations that cooperate with USAID. The Project offers technical assistance in the management of quality assurance and workforce development in health care, helping develop feasible, affordable approaches to comprehensive change in health service delivery. The QAP team includes prime contractor University Research Co., LLC (URC), Initiatives Inc., and Joint Commission Resources, Inc.

Recommended citation: Jean-Baptiste R. 2008. Factors Associated with Adherence to Antiretroviral Therapy in Rwanda: A Multi-site Study. *Operations Research Results.* Published for the U.S. Agency for International Development (USAID) by the Quality Assurance Project. Bethesda, MD: University Research Co., LLC.

About this series: The *Operations Research Results* series presents the results of country or area research that QAP is circulating to encourage discussion and comment within the international development community. Please visit www.qaproject.org for more information on other QAP operations research studies.

Acknowledgments: This study was conducted by Dr. Rachel Jean-Baptiste, with assistance from Rwandan colleagues Dr. Claude Sekabaraga and Dr. Joseph Ntaganira, who provided oversight and support at study development stage; Mr. George Gahenda and Dr. Horatius Munyampundu, who supported the data collection and management process; and Ms. Larissa Jennings, who supported with parts of the data analysis. Special acknowledgement is due to Dr. Nigel Livesley and Dr. Lynne Miller Franco, whose critical review appreciably enriched the report. Most important was the full cooperation of the leaders of the Rwandan study hospitals, the healthcare providers, and all of the patients who participated.

TABLE OF CONTENTS

LIST OF TABLES

ABBREVIATIONS

3TC	Lamivudine
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
ARV	Antiretroviral
AZT	Zidovudine
CI	Confidence interval
D4T	Stavudine
HIV	Human immunodeficiency virus
NVP	Nevirapine
OR	Odds ratio
PEPFAR	President's Emergency Plan for AIDS Support

EXECUTIVE SUMMARY

Few studies in Africa have evaluated the difference in antiretroviral (ARV) therapy adherence rates between patients taking different first line triple ARV therapy prescriptions. Furthermore, while many adherence studies rely on self-report as a means for data collection on adherence, they mostly focus on capturing the number of tablets the patient has taken and often do not assess whether those tablets were taken on schedule or with required food restrictions, despite the fact that these elements of adherence also can affect the therapeutic effects of ARVs. The first objective of this study was to evaluate adherent behavior between patients on fixed-dose antiretroviral therapy Triommune and those taking multiple drug combination antiretroviral regimens. The second was to evaluate differences between patients who were adherent by the pills-taken-only criterion and those who took their tablets with the correct dosage, on schedule, and with any food restrictions ("correct use" criteria).

Of patients seen at four health facilities (one urban and three non-urban) in Rwanda between October 2004 and February 2005, 720 were invited to participate in in-person interviews. A detailed questionnaire assessed current ARV prescription, dosage, and food restrictions; four-day adherence recall; side effects; psychosocial factors, including patient satisfaction, depression, and social support; and socio-demographic factors. Patients who reported having taken 95–100% of prescribed pills were considered adherent by the pills-taken criterion, while those who took 95–100% of pills as prescribed, on schedule, and with the recommended food restrictions were considered adherent by the correct use criteria. (Patients who took less than 95% or more than 100% of pills prescribed were considered non-adherent.) Multivariate analyses were performed to identify factors most associated with adherence by either set of criteria.

Complete data were collected and analyzed for 653 participants. Close to 43% were on Triommune (a branded, fixed-dose combination of Stavudine [D4T], Lamivudine [3TC], and Nevirapine [NVP]); 26% on Stavudine (D4T) + Lamivudine (3TC) + Nevirapine (Combination 1a); 13% on D4T + 3TC + Efavirenz (Combination 1b); 3% on Combivir (a branded, fixed-dose combination of Zidovudine [AZT] and Lamivudine in a single pill) + Nevirapine (Combination 2a); and 15% on Combivir + Efavirenz (Combination 2b). Most patients (95%) were treatment naïve at the start of their then-current therapy. Using the proportion of pills taken as the criterion for measuring adherence, 92% of patients reported taking at least 95% of their pills, and 98% of all prescribed pills had been taken. Adherence rates were higher among patients who were on fixed-dose Triommune than among those on multiple drug regimens. However, a greater proportion of patients on Combinations 1a, 1b, and Triommune were adherent compared to patients on Combinations 2a and 2b, which contain AZT ($p < 0.0001$), suggesting that combination type as opposed to pill burden was more closely associated with adherence. When adherence was measured not only as the proportion of pills taken but also as the proportion taken on schedule and following food instructions, only 69% of patients were adherent, and overall adherence rates fell to 73%. Multivariate analyses revealed that compared to patients on Triommune, those on Combination 1a were significantly more likely to take at least 95% of prescribed pills (odds ratio [OR] = 2.9; 95% confidence interval [CI] = 1.1 – 7.7; $p < 0.05$), while those on Combination 2b were significantly less likely to do so (OR = 0.26; 95% CI = 0.1 – 0.5; $p < 0.0001$) in a model that controlled for social support, length of time one has known of one's HIV-positive status, and whether or not care is received in an urban setting. Similarly, multivariate analyses of factors associated with adherence to ARVs using the correct use criteria revealed big differences in the odds of being adherent, depending on the prescription type: Compared to those on Triommune, patients on Combination 1a had more than 10 times the odds of being adherent, while those on Combinations 1b and 2b, which contains Efavirenz, had 93–99% lower odds of being adherent in a model that controlled for employment status and whether or not one was receiving care in an urban setting.

Whether on fixed-dose or multiple drug combinations, the vast majority of patients reported taking at least 95% of prescribed ARVs. However, regimens containing AZT were associated with lower

adherence than those containing D4T. Furthermore, adherence was lower when correct timing and recommended food restrictions were taken into account.

I. BACKGROUND

Adherence to medicines for chronic health conditions in general is not well documented in developing countries, and what is known is far from encouraging. Results of research on adherence to long-term medicines in Malaysia revealed that only 44% of patients were adherent, and the issues of overdosing, underdosing, and wastage were very prevalent[1]. Studies of hypertensive medications in China, Gambia, and the Seychelles revealed that only 43%, 27%, and 26%, respectively, of patients were adherent[2–4].

However, adherence rates to antiretroviral (ARV) medicines for patients with acquired immunodeficiency syndrome (AIDS) appear to be a different story. Particularly in Africa, studies have reported very high levels of adherence, from 85–99%[5–11]. Adherence to antiretrovirals is contained within a continuum of total doses, frequency, and timing[12]. Good adherence is defined as taking one's medicine as prescribed and agreed between the patient and provider. Poor adherence includes missing doses completely, as well as taking drugs inappropriately (taking doses at the wrong times or not adhering to dietary requirements associated with a drug)[13,14]. Studies have established a clear association between viral suppression and the percentage of antiretroviral doses taken as prescribed. Specifically, greater adherence is associated with better viral suppression[15–19]. Reviews of numerous studies revealed that 95% or greater adherence is necessary in order to achieve and maintain undetectable viral loads among most patients treated with highly active antiretroviral therapy (HAART)[18,20–22]. Among patients who do achieve this level of adherence, the virus is suppressed in 78%–100% after six to ten months of therapy[18,21,22]. The likelihood of virologic failure increases sharply for patients with adherence rates lower than 90%, although some patients do reach undetectable viral loads with much lower adherence rates[18].

Most studies of ARV adherence in Africa report data from small sample sizes, clinical trials, or other highly controlled patient environments, such as pilot programs providing antiretroviral therapy (ART). Few studies have reported on adherence within "normal" clinical settings. As ARVs become available to more patients, the importance of understanding differences in levels of adherence within the context of the normal clinical setting becomes more apparent. Additionally, most studies of adherence to ARVs in Africa that relied on self-report have restricted the definition of adherence to the number of pills taken versus the number prescribed ("pills-taken adherence")[5,7–9,11]. Not taken into consideration is whether ARVs were taken inappropriately (wrong times, not adhering to dietary requirements, etc.), all of which affect the absorption and blood levels of the drug. This report uses the term "correct use adherence" to refer to adherence where pills are taken appropriately. Clay (2005) describes the therapeutic range as the amount of the drug needed in the body to produce a good therapeutic effect without toxicity[22]. The desired therapeutic effect of ART results in increases in CD4, viral load suppression, and prevention of opportunistic infections[22].

For some regimens, such as fixed-dose, triple combination Triommune, where a patient simply takes one pill twice daily and there are no food restrictions, an assessment of pills taken is a relatively comprehensive measure of adherence. However, for those on a more complex first line regimen that may require multiple pills several times a day with certain food restrictions, solely assessing pills taken does not give a full picture of adherent behavior. Few studies of patients receiving antiretroviral treatment in Africa have evaluated the difference in adherence between patients on Triommune compared to those on more complex triple antiretroviral regimes. Similarly, little is known in Africa about socio-demographic and psychosocial differences between patients who are adherent compared to those who are not. This is particularly true in Rwanda, where 3.1% of the population is HIV (human immunodeficiency virus) - positive and where the Ministry of Health has scaled up provision of ART in all parts of the country with great speed since 2004[23].

II. OBJECTIVES

The first objective of this study was to evaluate adherent behavior between patients on fixed-dose antiretroviral therapy Triommune, compared to patients taking multiple drug combination antiretroviral regimens. The second was to evaluate differences between patients who were adherent by the "pills-taken" only criterion compared to those who took their tablets with the correct dosage, on schedule, and with any food restrictions ("correct use").

III. METHODOLOGY

This study took place in four Rwandan health facilities, representing one district hospital, a public health center, a public/private health center, and a university hospital, and located in urban (one) and non-urban (three) settings. All four had been providing ARVs for at least one year and were active participants in the Rwandan Ministry of Health's plan to expand access to ARVs for greater population coverage.

The study examined adherence to five ARV drug combinations (Table 1) that were in use in Rwanda during the period of study implementation.

Table 1: Antiretroviral regimens examined by the study

Regimen name	Drugs included	Pills per dose	Doses per day	Total pills per day
Triommune	Fixed-dose combination of Stavudine* (D4T) + Lamiduvine** (3TC) + Nevaripine (NVP)	1	2	2
Combination 1a	D4T + 3TC + NVP	3	2	6
Combination 1b	D4T + 3TC + Efavirenz*** (EFV)	2 in am 3 in pm	2	5
Combination 2a	Fixed-dose combination of Zidovudine (AZT) and 3TC, known by brand name Combivir, + NVP	2	2	4
Combination 2b	Combivir (AZT + 3TC) + EFV	1 in am 2 in pm	2	3

*Also known by the brand name Zerit; **Also known by the brand name Epivir; ***Also known by the brand name Stocrin.

A. Patient Recruitment

At each study facility, clinicians who treat HIV-positive patients were asked to evaluate each of their patients for inclusion in this study. Specifically, patients met eligibility criteria if they were:

- HIV-positive,
- Currently taking ARVs,
- Had been taking ARVs for at least three months,
- Were either outpatients or hospitalized patients of the health facility on the day of recruitment, and
- Were able to provide informed consent.

Attempts were made to approach all patients who met inclusion criteria and were seen at the hospital between the months of October 2004 and February 2005. All reasonable efforts were made to accommodate the participant, including scheduling or rescheduling the interview up to three times at their convenience.

Study aims, interviewing procedures, and methods for maintaining confidentiality were explained to each potential participant. The interviewer read a prepared script that provided an overview of the study aims and the risks and benefits to each patient approached for participation. After hearing the script, the patient was asked to voice any questions and whether or not he/she would consent to participate. Patients were asked to sign the informed consent form if they agreed to participate in the study. Each questionnaire and its matching informed consent form were assigned a unique four digit identifier. To protect patient confidentiality, this number, as opposed to the patient's name, was used in further analyses.

Once informed consent was obtained, the interviewer proceeded to conduct a structured interview in a private location at the health facility. All interviews were conducted by a sensitive, well-trained interviewer using a semi-structured questionnaire. Interviews were conducted in Kinyarwanda, the local language of Rwandans. Answers to open-ended questions were later translated back to English to accommodate appropriate analysis.

B. Data Collection

The types of data collected included socio-demographic information such as age, sex, marital status, education, employment status, length of time since tested HIV-positive, length of time since first started ARV treatment, and length of time since receiving care at the facility where the interview occurred. Participants were also asked to describe their current treatment prescription and whether they were treatment naïve at the start of this treatment. To assess ARV adherence, patients were asked about all prescribed ARVs, the number of doses missed, the number of doses not taken on schedule, and the number of doses not taken with the required food restrictions over the past four days. They were also asked in general about the number of doses missed per week, the last time they missed a dose, and about difficulties they may have with taking the medications on time. This questionnaire built on work done by the New York AIDS Institute and the United States Veterans Administration[24,25] and was modified to fit Rwanda norms. The pills-taken criterion for adherence was defined as having taken 95–100% of prescribed ARVs during the past four days. The "correct use" criterion was defined as having taken 95–100% of prescribed ARVs on schedule and with food restrictions, if any, during the past four days.

Participants who reported having missed at least one dose within the past 30 days were asked about several commonly known reasons for missing doses and to comment on how often these reasons caused them to miss their treatment. Common reasons included forgetting to take the medicine, being too tired or too sick to do so, wanting to avoid the medicine's side effects, and not being at home when scheduled to take the medicine, among others.

Several psychosocial factors, found to be of importance in relationship with adherence to ARVs among some HIV/AIDS populations, were explored in this study. They include patient satisfaction with provider care[26–28], depression[29,30], and perceived social support from family and friends[28,31–33]. To assess patient satisfaction with the healthcare provider, data were collected on each participant's perception of the quality of care provided by his/her doctor. Specifically, participants were asked if the doctor had adequately explained the progression of the AIDS disease and their prescribed medication, as well as whether they believed that the doctor treated him/her with respect and maintained confidentiality about his/her HIV status.

Depression was assessed using seven questions that relate to feeling as if one could not shake off the blues even with help from family and friends; having trouble keeping one's mind on what one is doing; feeling as if everything one did was an effort; having trouble sleeping; feeling lonely; feeling sad; and feeling as if one just could not get going. For each question, participants were asked to say whether or not they experienced each situation never, rarely, sometimes, or always within the past week.

Social support was assessed using three questions on: whether or not one's family was aware of one's HIV status, how satisfied one feels with the support from family and friends, and the extent to which

family and friends reminded one to take the medicines. For each question, participants were provided a range of answer choices.

Because the literature suggests a relationship between symptoms experienced and medication adherence[34], participants were asked about their experience with side effects and symptoms that are common among patients on ARVs. Symptoms explored included fatigue, fever, nausea, dizziness or lightheadedness, skin problems, diarrhea, and nervousness/anxiety, among others.

1. Pilot testing the questionnaire

The questionnaire was pilot tested in two phases. During the first phase, its content was evaluated for content validity by five HIV/AIDS clinical experts in Kigali. Suggestions were discussed and incorporated as necessary. During the second phase of pilot testing, the proposed process for identifying and interviewing patients was evaluated. Two providers identified five eligible patients. These patients were then approached by the appropriate research staff for interviews. Based on lessons learned from this exercise, the data collection process was modified. Any additional necessary changes on the data collection questionnaire that became evident were also made at the end of this phase. The revised questionnaire and data collection process were used in subsequent data collection efforts as described.

2. Data management

To ensure data integrity during the data collection phase, efforts were made to streamline the process and to maintain confidentiality. All forms necessary for a particular interview (i.e., participant identification, consent form, data collection tools) were collated and placed in envelops so that interviewers could easily pick up full and complete interviewing packages. The interviewers were trained to understand the importance of maintaining confidentiality and were sensitized to the local cultural response to HIV/AIDS. They used this understanding as appropriate throughout the interviewing process to establish rapport and help participants feel safe to respond to questions. Interviewers were trained to ensure that each study participant was asked every question in the questionnaire. Thus, before leaving each interview, the interviewer double-checked the questionnaire for any accidental omissions. Whenever possible, an attempt was made to obtain any data that were omitted during the interview from the relevant participants. The research manager periodically (every two or three days) reviewed data tools from interviews for completion.

Answers to open-ended questions from the survey instrument were translated from Kinyarwanda into English. A sub-sample of responses was used to develop codes for open-ended questions, and necessary additions were made as needed. The data were entered into EPI Info 2000 and stored as an ASCII file that was later uploaded into secured SPSS master files. To ensure accuracy, the data were double-entered and hand-checked. In addition, the data were closely monitored for missing data lines, blanks, outliers, inappropriate or impossible values, and illogical values for logical combinations of variables by evaluating frequency distributions. Data entry was concurrent with data collection, so that to the extent possible and necessary, interviewers could be briefed on any noted patterns of data collection errors.

C. Data Analysis

Both sets of criteria for measuring adherence (pills taken and correct use) were analyzed using descriptive statistics. T tests and F tests were used for comparing continuous variables that followed the normal distribution, while the Median Test was used for continuous variables that did not. Chi-squared was used for bivariate analyses of categorical or dichotomous variables.

Descriptive analyses were used to describe the most common reasons for non-adherence and to describe the sample of participants in terms of socio-demographics, psychosocial factors, and symptoms as described above.

In addition, scales were created that numerically summarized the extent to which individuals experienced each psychosocial factor. Coefficient alpha, mean, and standard deviation were also evaluated for

acceptability. Differences between adherent and non-adherent participants were evaluated using T tests for independent samples. Where the scale was found to not follow a normal distribution, the median was used as a measure of central tendency, and the two populations were evaluated using the Median Test.

Multivariate logistic regression models were constructed to calculate adjusted odd ratios and 95% confidence intervals for factors associated with pills-taken and correct use adherence. All first-order socio-demographic variables that were found to be significantly associated with adherence in bivariate analyses were selected for inclusion, as well as all psychosocial factors and the symptoms scale. The method used was backwards conditional logistic regression. A variable could remain in the model as long as its adjusted p value (once in the model with all other significant variables) was equal to or less than 0.05. Variables not meeting this criterion were removed from the model one at a time, using the p value of least significance as a guide. Variables continued to be removed from the model until all factors remaining in the model had a p value of 0.05 or less. Once a factor was removed from the model, it was not re-entered. Adjusted odds ratios and 95% confidence intervals were calculated for each factor within the final model.

IV. RESULTS

A. Demographic Characteristics of the Sample

Of the patients seen at the four facilities during the study period, 670 (93%) consented to be interviewed. Those not interviewed came from two facilities and either refused outright or were not contacted by the interviewer. After data cleaning, another 17 participants were dropped from analysis because of incomplete prescription data, leaving a total of 653 interviews for the analysis.

Of the patient data analyzed, almost three-quarters (72%) were female, and the average age of respondents was 38.7 years +/- 7.9 years. The youngest participant was 19 years old, while the oldest was 73. Only 27.9% of participants were educated beyond primary level. Slightly more than a third were married or living with a partner common law, and most (65.7%) were employed. Participants had known of their HIV status for a median of 36 months (three years), had been on ARV for a median of six months, and had been seeking care at the current facility for a median of 10 months. On the day they were interviewed, most participants had come to the health facility to pick up their ARV refills (87.6%), though some had also come for counseling (7.4%). Very few were there because of illness (4.5%) or side effects (0.5%). Almost half were on Triommune (42.8%), while a quarter were on D4T + 3TC + NVP first line treatment (hereafter, Combination 1a); 13.1% were on D4T + 3TC + EFV first line treatment (Combination 1b); 3.4% were on Combivir + NVP first line treatment (Combination 2a); and 14.9% were on Combivir + EFV first line treatment (Combination 2b).

These prescriptions were five of the potential antiretroviral triple therapy prescriptions for first line treatment of AIDS in Rwanda as per Ministry of Health guidelines at the time. About 41 participants (6.3% of the original 653 participants) reported being on non-specific ARV combinations and were excluded from further analyses. Ninety-five percent of all participants were ARV treatment-naïve at the start of their current treatment.

A little more than 25% of participants were receiving care within Kigali (urban), while 75% were receiving care outside the capital (non-urban). These two populations were similar in terms of marital status and employment status. Both urban and non-urban patients had been receiving care at the facility where their interview took place for a median of 10 months, and their reasons for the visit did not differ significantly, as the vast majority came to pick up their periodic supply of ARVs. However, there were some significant differences between the two groups. The proportion of women receiving services in Kigali was significantly greater than that of women receiving services outside the capital ($p = 0.02$). Additionally, a greater proportion of those receiving care outside of Kigali had secondary education or higher, compared to those receiving care in the capital ($p < 0.001$). On average, patients receiving care in the urban setting had known of their HIV status almost a year longer than those receiving care in non-

urban settings (52.3 months versus 41.6 months; $p < 0.002$). Significant differences were noted among patients with regard to their length of time on ARV: Those receiving care in Kigali had been on ARVs for a median 10 months (3–60), while those outside Kigali had been on ARVs for a median six months (3–48) ($p < 0.0001$).

All patients on Triommune were receiving care in non-urban health facilities, while most patients on another combination were receiving services in Kigali ($p < 0.0001$). It should be noted that Triommune was not provided at facilities supported by the President's Emergency Plan for AIDS Support (PEPFAR) at the time of data collection, but it was supported by other donors such as the World Bank and the Global Fund to Fight AIDS, Tuberculosis and Malaria, whose programs were then mostly outside Kigali. A larger proportion of patients in non-urban facilities, compared to those in Kigali, was treatment naïve ($p = 0.007$). These data are shown in Table 2.

Table 2: Demographic characteristics of the population interviewed

Patient characteristics	Total (n = 653)	Receiving care		p value
		In Kigali (n = 164; 25.1%)	Outside Kigali (n = 489; 74.9%)	
Gender*				0.02
Male	183 (28%)	35 (21.3%)	148 (30.3%)	
Female	470 (72%)	129 (78.7%)	341 (69.7%)	
Mean age (year +/- SD)	38.7+/-7.9	38.6+/-8.4	38.6 +/- 7.8	0.1
Range (years)	19–73	19–60	19–73	
Highest education achieved***				<0.001
Secondary level or higher	182 (27.9%)	20 (11.9%)	162 (33.1%)	
Lower than secondary	471 (72.1%)	144 (88.1%)	327 (66.9%)	
Marital status				0.52
Yes (married or common law)	232 (35.5%)	58 (35.4%)	174 (35.6%)	
No	421 (64.5%0	106 (64.6%)	315 (64.4%)	
Work status				0.50
Employed	429 (65.7%)	104 (63.4%)	325 (66.5%)	
Unemployed	224 (34.3%)	60 (36.6%)	164 (33.5%)	
Length of time since tested HIV-positive Mean months** Range (months)	 3–216	 52.3 (43.4) 3–144	 41.6 (35.4) 3–216	0.002
Length of time on ART (median months)*** Range (months)	 6 3–60	 10 3–60	 6 3–48	0.000
Time seeking care at current facility (median months) Range (months)	 10 1–180	 10 1–132	 10 1-180	0.37
Reason for today's visit				0.40
Counseling	48 (7.4%)	17 (10.3%)	31 (6.3%)	
Illness	29 (4.5%)	7 (4.3%)	22 (4.5%)	
Picking up ARVs	569 (87.6%)	139 (84.8%)	430 (87.8%)	
Side effects	3 (0.5%)	1 (0.6%)	2 (0.4%)	
Current ARV treatment***	612†	141	471	<0.0001
Triommune Combination 1a: D4T + 3TC + NVP Combination 1b: D4T + 3TC + EFV Combination 2a: Combivir + NVP Combination 2b: Combivir + EVF	263 (42.8%) 157 (25.7%) 80 (13.1%) 21 (3.4%) 91 (14.9%)	0 (0%) 73 (46.5%) 36 (45%) 15 (71.4%) 17 (12.1%)	263 (55.6%) 84 (53.5%) 44 (55%) 6 (28.8) 74 (15.7%)	
Treatment naïve at start of current ARV treatment?**				0.007
Yes No	583 (95.5%) 30 (4.9%)	124 (90.5%) 13 (9.5%)	459 (96.4%) 17 (3.6%)	

SD = standard deviation.

*p<0.05; **p<0.01; ***p<0.001; †41 patients with non-descript antiretroviral prescriptions not included.

B. Assessment of Adherence

Adherence rates were calculated using two criteria: the pills-taken criterion, for which the ratio of the total number of pills prescribed versus total number of pills taken within the past four days was calculated, and correct use criteria, which focused on how closely patients followed their ARV prescription and calculated adherence as 95% pills taken on the recommended schedule and following any food instructions. (As noted 41 patients reported taking ARV combinations that were not triple therapy combinations and were excluded from these analyses, leaving 612 patients whose data were analyzed.)

1. Pills-taken adherence

A patient was considered adherent to the pills-taken criterion if he/she reported taking 95–100% of prescribed ARV tablets during the past four days. Patients who reported taking less than 95% or more than 100% of prescribed pills were deemed non-adherent.

Overall 92%, or 566 patients, reported being adherent as measured by this criterion. Of the 8%, or 46 patients, who were found to be non-adherent, overdosing (taking 100–150% of prescribed medicines) was reported by 16; the remainder took less than 95% of the pills prescribed. It is important to note that while underdosing occurred among all prescription types, only patients on Combinations 2a or 2b reported overdosing.

Bivariate analyses were conducted to evaluate adherent behavior between patients on fixed-dose antiretroviral Triommune and those on multiple drug combination ARV. Results (Table 3) show that a greater proportion of patients on Triommune were adherent than those on other drug regimens ($p = 0.004$).

Table 3: Adherence among patients on fixed-dose versus combination ARV therapy

	Adherent (>/= 95% of pills taken)	**Non-adherent (< 95% of pills taken)**	**p value**
			0.004
Fixed-dose ARV (Triommune)	252 (95.8%)	11 (4.2%)	
Free drug ARV combination (Combinations 1a, 1b, 2a, 2b)	314 (89.5%)	37 (10.5%)	

Further analysis elucidated these results and showed that adherence was similar among patients taking Triommune or Combinations 1a or 1b, but rates were significantly lower among those on Combinations 2a and 2b. Almost 30% of those taking Combination 2a and 20.9% of those on Combination 2b took less than 95% of their prescribed pills, compared to 3.8% of patients on Combination 1a, 5% on Combination 1b, and 4.2% on Triommune ($p < 0.0001$). Among those who took less than 95% of pills prescribed, the adherence rate was 77%. These results are in Table 4.

Table 4: Bivariate analysis of patient adherence by ARV prescription type

	Adherent (95–100% of pills taken)	Non-adherent (< 95% or > 100% of pills taken)	p value
TOTAL	566 (92.5%)	46 (7.5%)	< 0.0001
Combination 1a: D4T + 3TC + NVP	151 (96.2%)	6 (3.8%)	
Combination 1b: D4T + 3TC + EFV	76 (95%)	4 (5%)	
Fixed-dose Triommune	252 (95.8%)	11 (4.2%)	
Combination 2a: Combivir + NVP	15 (71.4%)	6 (28.8%)	
Combination 2b: Combivir + EFV	72 (79.1%)	(20.9%)	
Cumulative adherence rates (overall adherence = 98.7%)	99.9%	77%	

Other significant differences between adherent and non-adherent patients were revealed in descriptive analyses of the sample. Adherent patients had known of their HIV status for a shorter period of time than non-adherent patients (median 36 months versus 48 months, $p = 0.02$). Differences between facilities were also significant, with a larger proportion of adherent patients receiving care in non-urban settings ($p = 0.002$). Adherent patients tended to be younger and not as well educated as non-adherent patients. A greater proportion of adherent patients was treatment naïve at the start of their current ARV regimen and also had been on ART for less time. These differences, though important, only approached statistical significance with p values below 0.1. These results are in Table 5.

Table 5: Descriptive characteristics of adherent and non-adherent patients by pills-taken criterion

Patient characteristics	Patient adherent by pills taken		p value
Total	Yes (n = 566; 92%)	No (n = 48; 8%)	
Gender			0.34
Male	155 (27.4%)	15 (31.3%)	
Female	411 (72.6%)	33 (68.7%)	
Mean age (Yrs +/- SD)~ Range (years)	38.6+/-7.9 19–73	40.9+/-8.6 23–64	0.06
Highest education achieved~			0.07
Secondary education or higher	167 (29.5%)	39 (81.3%)	
Less than secondary education	399 (70.5%)	9 (18.8%)	
Marital status			0.45
Yes (officially married or common law)	201	16	
No	365	32	
Work status~			0.09
Employed	380 (67.1%)	27 (56.3%)	
Unemployed	186 (32.9%)	21 (43.8%)	
Length of time since tested HIV-positive (median months)* Range (months)	36 3–216	48 6–180	0.02
Length of time on ART (median months)~ Range (months)	6 3–60	7 3–48	0.058
Length of time seeking care at current facility (median months) Range (months)	10 1–180	10 1–132	0.94
Treatment naïve at start of current ARV treatment?~			0.08
Yes	541 (95.6%)	43 (89.6%)	
No	25 (4.4%)	5 (10.4%)	
Facility**			0.002
Urban (inside Kigali)	121 (85.8%)	20 (14.2%)	
Non-urban (outside Kigali)	445 (94.1%)	28 (5.9%)	

~$p < 0.1$, approaches significance; *$p \leq 0.05$; **$p \leq 0.01$.

2. Correct use adherence

Using the correct use criteria to define adherence to ARVs, a patient was considered to be adherent if he/she took 95–100% of prescribed ARVs in correct doses, as scheduled, and with recommended food restrictions, if any, during the previous four days. Percentage of prescribed pills taken was calculated as follows:

$$\frac{\text{[\# pills x \# taken on schedule x \# taken with required food restrictions]}}{\text{[\# pills prescribed x \# to be taken on schedule x \# to be taken with food restrictions]}} \times 100$$

When adherence was thus analyzed, the proportion of patients adherent to ARV treatment dropped considerably. Only 68.6%, or 420 patients, reported taking their ARVs on schedule and following recommended food restrictions. Overall adherence rates were 73%. The most adherent patients were on Combination 1a, followed closely by those on Triommune. Only 67% of patients on Combination 2a were adherent, and adherence was worse for those on Combinations 1b and 2b: Only 23% and 8.5% of patients with those prescriptions, respectively, took all prescribed pills on schedule and with food restrictions. These low proportions largely reflect the fact that Combinations 1b and 2b include Efavirenz, an ARV that has specific food instructions. These results are shown in Table 6.

Table 6: Bivariate analysis of patient adherence by *correct use* for patients on fixed-dose Triommune versus free-drug combination ART

	95–100% of pills			
	Taken	On schedule	Following food instructions	**Number (%) correct use**
TOTAL	566 (92.5%)	550 (89.9%)	24 (14%)	420 (68.6%)
Combination 1a: D4T + 3TC + NVP	151 (96.2%)	148 (3.8%)	N/A	148 (94.3%)
Combination 1b: D4T + 3TC + EFV	76 (95%)	75 (96.3%)	18 (23%)	18 (23%)
Fixed-dose Triommune	252 (95.8%)	242 (92%)	N/A	234 (88.9%)
Combination 2a: Combivir + NVP	15 (71.4%)	14 (67%)	N/A	14 (67%)
Combination 2b: Combivir + EFV	72 (79.1%)	71 (78.8%)	6 (8.5%)	6 (8.5%)

N/A = Not applicable.

Descriptive analyses revealed that those who took their medicines correctly were more likely to be female ($p < 0.0001$), younger ($p = 0.02$), and treatment naïve at the start of their current treatment regimen ($p = 0.04$). In addition, a greater proportion had been on ARVs longer ($p = 0.002$) and were receiving care in non-urban settings ($p < 0.0001$). Education level, marital status, employment status, length of time since tested HIV-positive, and length of time since receiving care at the facility where interviews took place were not significantly associated with taking medicines correctly. These results are shown in Table 7.

Table 7: Descriptive characteristics of adherent and non-adherent patients by correct use adherence criteria

Patient characteristics	95% of doses taken correctly		p value
	Yes (n = 420; 68.6%)	No (n = 192; 31.4%)	
Gender***			<0.0001
Male	96	75	
Female	324	117	
Mean age (years +/- SD)*	37.8 +/- 7.3	40.1 +/- 8.5	0.03
Highest education achieved			0.84
Secondary education or higher	121	57	
Lower than secondary education	297	135	
Marital status			0.49
Yes (married or common law)	148	69	
No	272	123	
Work status			0.26
Employed	282	123	
Unemployed	138	69	
Treatment naïve*			0.04
Yes	405	177	
No	15	15	
Length of time since tested HIV-positive (median months, range)	36 (3–216)	36 (3–192)	0.16
Length of time on ART (median months, range)**	6 (3–60)	6 (3–48)	0.002
Length of time since receiving care at this facility (median months, range)	10 (1–180)	10 (1–132)	0.75
Facility***			<0.0001
Urban	74	62	
Non-urban	346	130	

*p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001.

C. Reasons for Non-adherence

1. Missing doses

All patients who either missed doses within the past four or 30 days were asked why; 26.5%, or 163 patients, fell in this category. The top three reasons for missing doses were forgetting (30%), being away from home (25%), and being busy with other things (11%). Less commonly mentioned reasons were that the patient ran out of pills (8%), felt sick or ill (7%), or had a change in daily routine (5%). No patient said he/she missed taking medicines due to having too many pills to take. No one reported missing doses because of lack of money to buy drugs, unavailability of medicines at the pharmacy, or not wanting others to notice their taking the medicine.

2. Following the schedule

Participants who took the correct number of doses but not according to schedule within the past four days were asked for a reason. Almost 6% (5.7%, n = 35) of participants fell in this category. The most common reason for taking doses off schedule was simply forgetting (44%). The data were analyzed to see which doses patients were more likely to miss: Evening doses made up the majority of doses missed (59%), although a quarter (26%) of participants reported missing morning doses. Two patients who did not provide a reason for not taking doses as scheduled, and three did not tell when they were most likely to take a dose off schedule.

3. Following food restrictions

There are no food restrictions with Triommune and Combinations 1a and 2a, but patients taking Combination 1b or 2b with EFV are advised to avoid oily or fatty foods when taking their medicines[35–37]. Approximately 171 patients interviewed were on Combination 1b or 2b. Of those, 81% reported not following any food restrictions while taking their ARVs. A small minority (9.8% or 43 patients) whose prescription did not require food restrictions, such as those on Triommune or Combinations 1a or 2a, reported following food restrictions, but this was not included in the analysis. While most patients (92%) took the correct number of pills, resulting in overall proportion of pills taken to be 98%, these rates dropped dramatically to 73% when schedule and food restrictions were taken into consideration as part of the definition and calculation of adherence rates. The percentage of patients who were adherent also dropped—to 68.6%—when these criteria for calculating adherence were applied.

D. Physical and Psychosocial Factors Associated with Adherence to Antiretrovirals

1. Symptoms burden

Patients were asked to describe how bothered they were by each of 20 possible symptoms they might have experienced within the past four weeks. Answers to these items were summarized to create a symptoms scale and obtain a symptoms burden score for each patient. The correlation matrix alpha for the scale was 0.74. Overall scores ranged from 0–51, with a mean score of 12.7 +/- 9.3. As the scores did not follow the normal distribution, the mean could not be used as a measure of central tendency, and the median was relied upon instead (median = 11). This scale was subsequently evaluated for differences by adherence status for both pills-taken and correct use criteria for measuring adherence in bivariate analyses. No significant differences were found in scores between patients who took 95–100% pills versus those who did not. However, patients who took their medicines in accordance with the correct use criteria also had a significantly higher burden of symptoms compared to those who did not (median score = 12 versus 9, p = 0.002).

2. Patient satisfaction

In order to identify the role, if any, of patient satisfaction and adherence status, all of the responses to the patient satisfaction questions were used to create a patient satisfaction scale. The alpha correlation of this scale was 0.70. Scores on this scale ranged from 0–12, with 0 being not satisfied at all, and 12 being very satisfied. The mean and standard deviation were 11.3 +/- 1.5. The F test was used in bivariate analyses to compare satisfaction levels for adherent and non-adherent patients. For both adherence criteria, patients who were non-adherent reported slightly greater satisfaction with their provider than to those who were adherent. This was statistically significant with the correct use criteria (p = 0.01), but not for the proportion of pills-taken criterion.

3. Depression

Depression was measured using a seven-question scale that explored patients' experiences and feelings in the past week, such as feeling blue, having trouble concentrating, feeling that everything one did was an effort, having trouble sleeping, feeling lonely, sad or just couldn't "get going." Answers to the depression

items were summarized to create a depression scale and obtain a depression score for each patient. The correlation matrix alpha was 0.70. The mean depression score was 2.96 +/- 3.7, and scores ranged from 0 to 19, with 0 being "not depressed at all" and 19 being "very depressed." The scores did not follow the normal distribution, so the mean could not be used as a measure of central tendency. Thus, comparisons for adherent versus non-adherent patients for both pills-taken and correct use adherence were done using the Median Test. Results indicate that patients who were adherent by the pills-taken criterion or by correct use criteria had a significantly higher median depression score compared to patients who were not adherent by either measure ($p = 0.04$ for pills taken; $p = 0.002$ for correct use).

4. Social support

Three questions were asked to assess participants' perception of their social support. They related to: (1) whether one's family was aware of one's HIV status, (2) feeling satisfied with support obtained from family and friends, and (3) whether family and friends remind them to take their medicines. "Good social support" was defined as saying "yes" to all three questions. Results show that a significantly greater proportion of patients who took at least 95% of their prescribed ARVs had good social support compared to those who did not (64% versus 48%, $p = 0.03$). However, this difference is washed out when the correct use criteria are used to establish adherence status; close to two-thirds of both adherent and non-adherent patients reported good social support, and no significant differences were noted. These results are shown in Table 8.

Table 8: Physical and psychosocial factors associated with adherence to ARVs

Factor	Pills taken			Correct use		
	Adherent	Non-adherent	p value	Adherent	Non-Adherent	p value
Symptoms burden (median, range)	11 (0–51)	10 (0–29)	0.30	12.0 (0–51)	9.0 (0–39)	< 0.002
Patient satisfaction (mean, SD)	11.3 +/- 1.6	11.5 +/- 0.9	0.06	11.2 +/- 1.6	11.4 +/- 1.1	< 0.01
Depression (median, range)	2.0 (0–19)	1.0 (0–10)	0.04	2.0 (0-19)	1.0 (0-15)	< 0.002
Good social support (% yes)	64.0%	48%	0.03	62.4%	65.1%	0.53

E. Multivariate Models of Adherence

Multivariate logistic regression models were used to identify all factors significantly related to adherence as defined firstly by the pills-taken criterion and secondly by correct use criteria. All potentially important variables were evaluated, including demographic variables, ARV prescription type, and psychosocial factors. Of note, Triommune was used as the comparison group for the other ARV combinations and was therefore not included in the model. Thus, odds ratios (ORs) obtained for the drug combinations are in comparison to Triommune. Two such models were created: one that evaluated factors associated with proportion of the pills-taken criterion and the other that evaluated factors associated with correct use criteria.

Table 9 displays the best multivariate model of factors associated with taking 95–100% pills. Factors that significantly enhanced patients' odds of being adherent were being on Combination 1a (OR = 2.88; 95% confidence interval [CI] = 1.08–7.69; $p = 0.04$) and having good social support (OR = 1.94; 95% CI = 1.02–3.60; $p = 0.04$). Factors that significantly decreased one's odds of being adherent were being on Combination 2b (OR = 0.26; 95% CI = 0.13–0.53; $p < 0.0001$), receiving care in an urban setting (OR =

0.31; 95% CI = 0.16–0.63; p = 0.001), and having known of one's HIV status for longer (OR = 0.99; 95% CI = 0.98–0.99; p = 0.02).

Table 9: Multivariate logistic regression model of factors associated with taking 95–100% of prescribed ARVs

Factor	Adjusted OR	95% CI	p value
Combination 1a	2.88	1.08–7.69	0.04
Combination 2b	0.26	0.13–0.53	< 0.0001
Receiving care in urban setting	0.31	0.16–0.63	0.001
Months HIV-positive	0.99	0.98–0.99	0.02
Good social support	1.94	1.02–3.60	0.04

Similarly, Table 10 displays the best multivariate model of factors associated with taking 95–100% of pills on schedule and following food instructions. Factors that significantly enhanced patients' odds of being adherent were being on Combination 1a (OR = 10.49; 95% CI = 3.95–27.89; p < 0.0001) and being employed (OR = 1.7; 95% CI = 0.99–2.7), though this only approached statistical significance (p = 0.05). Factors that significantly decreased one's odds of being adherent were being on Combination 1b (OR = 0.07; 95% CI = 0.04–0.15; p < 0.0001) or Combination 2b (OR = 0.01; 95% CI = 0.01–0.03; p < 0.0001) and receiving care in an urban setting (OR = 0.31; 95% CI = 0.16–0.63; p = 0.001). None of the physical and psychosocial variables remained in this final model.

Table 10: Multivariate logistic regression model of factors associated with taking 95–100% of prescribed ARVs on schedule and following food instructions

Factor	Adjusted OR	95% CI	p value
Combination 1a	10.49	3.95–27.89	< 0.0001
Combination 1b	0.07	0.04–0.15	< 0.0001
Combination 2b	0.01	0.01–0.03	< 0.0001
Employed	1.7	0.99–2.7	0.05
Receiving care in urban setting	0.12	0.05–0.25	< 0.0001

V. DISCUSSION

When this study took place, Rwanda was in the beginning stages of its expansion of ARVs. Within a year, the Rwandan Government and international donors ensured a five-fold increase in the number of facilities providing ARVs, from four mostly urban facilities in 2003 to 20 countrywide in 2004. Triommune also became available in 2004 through the World Bank Multi-Country HIV/AIDS Program for Africa (MAP). This study captures the early stages of this expansion and was the first to compare ARV adherence rates between urban and non-urban populations in Rwanda. As such, it captures a good cross-section of people on ART at the time. However, it should be stressed that the data reported here, while a good reflection of the situation in 2004, may not be a good reflection of what is happening now.

Participants came from four types of facilities: a district hospital, a public health center, a public/private health center, and a university hospital. Three were located outside the capital city of Kigali and one

within it. While significant differences were noted in several demographic factors, of most interest is the fact that there were no patients on Triommune in the urban health facility. ART was being provided in these facilities by PEPFAR, and at that time Triommune was not FDA-approved and was therefore not part of the regimen offered to clients receiving ART through PEPFAR programs. Most of these patients were instead on ARV combination D4T + 3TC + (Efavirenz or Nevirapine) (Combinations 1a or 1b). Patients on ARV combination Combivir + (Efavirenz or Nevirapine) (Combinations 2a or 2b) were well spread throughout the four institutions.

This study is also one of the first to evaluate adherence both in terms of the ratio of pills taken versus prescribed ("pills-taken" adherence) as well as the ratio of pills taken exactly as prescribed versus not ("correct use" adherence) in a developing country setting. Most other studies of ARV adherence in such countries have defined adherence only within the context of pills taken[5–11]. Yet ARVs are required to be taken on a specific schedule. Failure to do so can have pharmacokinetic implications, because the amount of drug in the body must remain constant at all times to most successfully fight off the virus and prevent the development of resistance[38]. Also, food can either enhance or inhibit ARV efficacy by affecting absorption, metabolism, distribution, and excretion[39]. One study found that the half-life can be reduced by as much as 25% in patients who do not follow dietary restrictions with certain ARVs[40]. Patients who take their medicines off schedule or without required food restrictions may not be getting the full benefits of the medicine and could experience treatment failure[39]. Triommune is the simplest triple antiretroviral therapy, as it minimizes pill burden and has no food restrictions. As such, it is promoted as first line therapy in many developing countries for treatment-naïve patients.

Similar to other studies of adherence to antiretroviral therapy in Africa, a high proportion of the sample (92%) reported taking at least 95% of prescribed ARVs, and overall adherence rates were also very high. Using this criterion, adherence rates were extremely high for patients who were adherent (99.9% pills taken) and relatively poor for patients who reported missing pills (77% pills taken). Demographic factors most strongly associated with adherence were whether or not care was received in urban versus non-urban settings, with a greater proportion of patients seen in non-urban settings adherent ($p = 0.002$), and knowing one's HIV-positive status for a shorter period of time (median 36 versus 48 months, $p = 0.02$).

The literature shows that fixed-dosed combinations significantly decrease the risk of non-compliance with medicines for other chronic conditions such as hypertension and diabetes. In a recently published meta-analysis, where nine studies were reviewed by Bangalore et al. (2007), including one HIV/AIDS study, the risk for non-compliance was found to be 24% lower among patients on fixed-dose regimens[41]. Results of this study indicate that 95.8% of those on Triommune reported having taken at least 95% of prescribed pills. Yet similar proportions of patients on triple therapy combinations, D4T + 3TC + NVP or EFV (Combinations 1a or 1b), were adherent by this criterion as well. Furthermore, multivariate results suggest significantly greater odds of taking at least 95% of prescribed ARVs if patients are on Combination 1a, compared to those taking Triommune (OR = 2.88; 95% CI = 1.08–7.69; $p = 0.04$), despite the fact that patients on Combination 1a have three times the pill burden, when factors such as social support and urban care setting are controlled in the analysis. In comparison, a lower proportion of patients on Combivir (AZT + Lamivudine) + NVP or EFV (Combinations 2a or 2b) were found to be adherent, yet the pill burden for patients on these combinations is less than that for patients on Combinations 1a or 1b. This finding clearly suggests that specific regimens, such as those containing AZT, and not pill burden, are more important in predicting adherence to ARVs.

Concern is growing over the long-term adverse events associated with D4T, particularly metabolic abnormalities and lipoatrophy. A recent study in Rwanda showed a three-fold increase in the prevalence of lipoatrophy among patients taking D4T versus those on AZT-containing regimens[42]. However, results from this study suggests that adherence to AZT-containing regimens might be harder for patients, which could lead to treatment failure. While current thought is to recommend AZT instead of D4T as part of first therapy, results here suggest that both potential complications and potential for adherence must be weighed if such a strategy is adopted. The majority of patients in this study had been on ARVs for a short

period, and other data show that AZT is less well tolerated in the short term[43]. Additional studies to assess adherence to these combinations over longer periods are required.

The results here further demonstrate that while most patients reported missing very few ARV tablets, they were not necessarily taking them as scheduled or following specified food restrictions. We find that when adherence is measured using the correct use criteria, this population reported taking only 73% of their ARV tablets correctly. Almost a third (31.4%) of study participants was non-adherent by these criteria. Lower proportions of patients on Combinations 1b, 2a, and 2b were adherent, compared to those on other combination therapy. The data here highlight the fact that correctly taking one's ARVs may have less to do with pill burden than with following specific additional instructions, such as taking them on a specified schedule and with certain food restrictions. Patients whose ARV combination included Efavirenz should be avoiding fatty or oily foods before taking this drug, but the results indicate that 86% of patients on ART combinations with EFV were not following these instructions. The data from this study do not help explain reasons why patients might have been unaware of this aspect of their treatment.

Within a few months to a few years, many patients who start with Triommune will be put on alternative first line therapies or may even start second line therapies that are not as simple to take. A study by Richard et al. (2004) reported that up to 52% of ARV-experienced individuals in Uganda developed resistance within eight months of treatment initiation[43]. A more recent study by Shekelle et al. (2007) on a worldwide ART resistance surveillance program reported that 5.5% of treatment-naïve patients in Africa had developed resistance to at least one drug during a relatively short period after starting treatment[44]. Depending on the type of resistance developed, patients are either switched to alternative first line therapies that are not fixed-dose combinations or moved on to second line treatments that also contain multiple tablets. Particularly in East Africa, the demand for second line ART is noted in the literature[45]. Such combination antiretroviral therapies can include some nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors that have specific food restrictions. These restrictions, when followed appropriately, can play a major role in ensuring the therapeutic range that will produce the greatest therapeutic effect[39]. Thus, following food restrictions becomes a particularly important aspect of adherence to ARVs as the treatment becomes more complicated. Results of this study highlight a potential adherence problem that is currently receiving limited attention.

This study is one of the few to clearly identify factors associated with good versus poor adherence. Results of the multivariate analyses show that compared to those on Triommune, being on Combination 1a enhanced one's odds of taking at least 95% of ARVs, while being on Combination 2b decreased such odds. Furthermore, results highlight the fact that patients in urban areas have lower odds of being adherent that those in non-urban areas. This finding is particularly interesting, as it begs the question. Patients receiving care outside Kigali were more likely to be male, to be better educated, to have been on ART for less time, to be on different ARV prescriptions, and to be treatment naïve. However, none of these other factors remained in the multivariate model, and it is not clear whether or how much they contribute to the overall relationship between receiving care in an urban setting and resulting adherence rates.

This study suffers from the same weakness as many others that have evaluated adherence in Africa: It relied on self-report alone and did not compare self-report adherence to more objective measures, such as viral load and CD4 counts. Literature has reported that patients tend to overestimate their adherence in self-reports. By comparing urine assays with self-reports for short-term assessment of adherence to AZT, Demas et al. found that 29% of participants had not taken the last dose that they reported taking[32]. Furthermore, it has been suggested that patients in developing countries may feel unable to tell a provider that they have not been taking all of their ARVs[45]. Even taking this into consideration, the data here suggest that patients are taking a high percentage of their pills, and this is in line with other studies that have evaluated patient adherence to ARVs in Africa. While these results are encouraging, they do highlight potential problems with patients taking more complicated regimens correctly. Inevitably, a

great number of patients now on first line therapy will need more complex regimens within two years. These more complex regimens will have to be taken correctly to ensure good therapeutic effect. Thus, a major conclusion is that as patients in Africa move from uncomplicated first line ARV therapies such as Triommune to alternate therapies that require specific food and dosing schedule restrictions, providers will need to be more vigilant in ensuring good adherence.

VI. REFERENCES

1. Aziz AMA, Ibrahim MIM. Medication noncompliance: A thriving problem. *Medical Journal of Malaysia* 54(2) June 1999.
2. World Health Organization (WHO). Adherence to Long-term Therapies, Evidence for Action. Geneva: WHO, 2003.
3. Grave JW. Management of difficult to control hypertension. *Mayo Clinic Hypertension Proceedings* 75:278–84, 2000.
4. Bovet P, Burnier M, Madeleine G, Waeber B, Paccaud F. Monitoring one-year compliance to antihypertension medication in the Seychelles. *Bulletin of the World Health Organization* 80(1):33–9, 2002.
5. Laurent C, Diakhate N, Gueye NF et al. The Senegalese government's highly active antiretroviral therapy initiative: An 18-month follow-up study. *AIDS* 16(10):1363–70, 2002.
6. Laniece I, Ciss M, Desclaux A, Diop K, Mbodj F, Ndiaye B, Sylla O, Delaporte E, Ndove I. Adherence to HAART and its principle determinants in a cohort of Senegalese adults. *AIDS* 17 Suppl. 3:S103–108, 2005.
7. Orrell C, Bangsberg DR, Badri M, Wood R. Adherence is not a barrier to successful antiretroviral therapy in South Africa. *AIDS* 17:1369–75, 2003.
8. Nachega JB, Stein DM, Lehman DA, et al. Adherence to antiretroviral therapy in HIV-infected adults in Soweto, South Africa. *AIDS Research and Human Retroviruses* 20:1053–56, 2004.
9. Idigbe EO, Adewole TA, Eisen G, et al. Management of HIV-1 infection with a combination of Nevirapine, Stavudine, and Lamivudine. *Journal of Acquired Immune Deficiency Syndrome* 40:65–69, 2005.
10. Byakika-Tusiime J, Oyugi JH, Tumwikirize WA, et al. Adherence to HIV antiretroviral therapy in HIV+ Ugandan patients purchasing therapy. *International Journal of STD & AIDS* 16:38–41, 2005.
11. Laurent C, Kouanfack C, Koulla-Shiro S, et al. Effectiveness and safety of a generic fixed-dose combination of Nevirapine, Stavudine, and Lamivudine in HIV-1-infected adults in Cameroon. *Lancet* 364:29–34, 2004.
12. Fauci A, Bartlet J, Goosby E. Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents. 2000. Available at: http://www.hivatis.org and accessed August 20, 2003.
13. Knobel H, Carmona A, Grau S, Pedro-Botet J, Diez A. Adherence effectiveness of HAART. *Archives of Internal Medicine* 158:1953, 1998.
14. Waters L, Nelson M. Why do patients fail HIV therapy? *International Journal of Clinical Practice* 61(6):983–90, 2007.
15. Descamps D, Flandre P, Calvez V, et al. Mechanisms of virologic failure in previously untreated HIV-infected patients from a trial of induction-maintenance therapy. Trilege [Agence Nationale de Recherches sur le SIDA 072] Study Team. *Journal of the American Medical Association* 283:205–211, 2000.
16. Gifford AL, Bormann JE, Shively MJ, Wright BC, Richman DD, Bozzette SA. Predictors of self-reported adherence and plasma HIV concentrations in patients on multidrug antiretroviral regimens. *Journal of Acquired Immune Deficiency Syndrome* 23:386–95, 2000.

17. Haubrich RH, Little SJ, Currier JS, et al. The value of patient-reported adherence to antiretroviral therapy in predicting virologic and immunologic response. California Collaborative Treatment Group. *AIDS* 13:1099–1107, 1999.
18. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Annals of Internal Medicine* 133:21–30, 2000.
19. Bangsberg DR, Hecht FM, Charlebois ED, et al. Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. *AIDS* 14:357–66, 2000.
20. Low-Beer S, Yip B, O'Shaughnessy MV, Hogg RS, Montaner JS. Adherence to triple therapy and viral load response. *Journal of Acquired Immune Deficiency Syndrome* 23:360–1, 2000.
21. Pradier C, Carrieri P, Bentz L, Spire B, Dellamonica P, Moreau J, Moatti JP, MANIF 2000 Study Group. Impact of short-term adherence on virological and immunological success of HAART: A case study among French HIV-infected IDUs. *International Journal of STD & AIDS* 12:324–28, 2001.
22. Clay P.G. The Body: The Complete HIV/AIDS Resource. Supplement introduction. Available at www.thebody.com/content/treat/art877.html and accessed 10/29/08. Winter 2005.
23. United Nations Programme on HIV/AIDS. Country and regional responses to AIDS: Rwanda. Available at http://www.unaids.org/en/CountryResponses/Countries/rwanda.asp and accessed February 2008.
24. AIDS Institute, New York State Department of Health. Promoting Adherence to HIV Antiretroviral Therapy. AIDS Institute, New York State Department of Health. Not dated.
25. Justice A, Rabanec L. ATCG [AIDS Trinical Trials Group] Adherence Baseline Questionnaire. Available at http://www.caps.ucsf.edu/tools/surveys/pdf/2098.4186.pdf and accessed October 30, 2008.
26. Södergård B, Halvarsson M, Tully MP, Mindouri S, Nordström ML, Lindbäck S, Sönnerborg A, Lindblad AK. Adherence to treatment in Swedish HIV-infected patients. *Journal of Clinical Pharmacy and Therapeutic* 31(6):605–16, 2006.
27. Beach MC, Keruly J, Moore RD. Is the quality of the patient-provider relationship associated with better adherence and health outcomes for patients with HIV? *Journal of General Internal Medicine* 21(6):661–65, 2006.
28. van Servellen G, Lombardi E. Supportive relationships and medication adherence in HIV-infected, low-income Latinos. *Western Journal of Nursing Research* 27(8):1023–39, 2005.
29. Turner BJ, Laine C, Cosler L, Hauck WW. Relationship of gender, depression, and health care delivery with antiretroviral adherence in HIV-infected drug users. *Journal of General Internal Medicine* 18(4):248–57, 2003.
30. Tadios Y, Davey G. Antiretroviral treatment adherence and its correlates in Addis Ababa, Ethiopia. *Ethiopian Medical Journal* 44(3):237–44, 2006.
31. Edwards LV. Perceived social support and HIV/AIDS medication adherence among African American women. *Qualitative Health Research* 16(5):679–91, 2006.
32. Demas PA, Thea DM, Weedon J, McWayne J, Bamji M, Lambert G, Schoenbaum EE. Adherence to zidovudine for the prevention of perinatal transmission in HIV-infected pregnant women: the impact of social network factors, side effects, and perceived treatment efficacy. *Women and Health* 42(1):99–115, 2005.
33. Kumarasamy N, Safren SA, Raminani SR, Pickard R, James R, Krishnan AK, Solomon S, Mayer KH. Barriers and facilitators to antiretroviral medication adherence among patients with HIV in Chennai, India: A qualitative study. *AIDS Patient Care and STDS* 19(8):526–37, 2005.

34. Ammassari A, Murri R, Pezzotti P, Trotta MP, Ravasio L, De Longis P, Lo Caputo S, Narciso P, Pauluzzi S, Carosi G, Nappa S, Piano P, Izzo CM, Lichtner M, Rezza G, Monforte A, Ippolito G, d'Arminio Moroni M, Wu AW, Antinori A; AdICONA Study Group. Self-reported symptoms and medication side effects influence adherence to highly active antiretroviral therapy in persons with HIV infection *Journal of Acquired Immune Deficiency Syndrome* 28(5):445–49, 2001.
35. American Society of Health System Pharmacists. Available at http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=medmaster.chapter.a699004 and accessed 10/29/08.
36. http://www.poz.com/search/index.shtml?cx=000236603529059451265%3Afh6x-u-ygwo&cof= FORID%3A9&sa=Search%23942&startDate=&endDate=&query=sustiva (accessed October 2008).
37. Sustiva, Clinical Pharmacology. http://www.rxlist.com/cgi/generic/efaviren_cp.htm (accessed October 2008).
38. CRY: Coalition on Rights and Responsibilities of Youth Street A-14, Ittehad Colony, Peshawar City, Pakistan. Access to treatment: ARVs do not destroy HIV but they can reduce its effects and help a person to live a longer life. Accessed 10/2/2008 and available at http://www.hivcollaborativefund.org/fileadmin/HIVCDocs/CRY_TreatmentMaterials_061906.pdf.
39. Castleman T, Seumo-Fosso E, Cogill B. Food and Nutrition Implications of Antiretroviral Therapy in Resource Limited Settings. *Technical Notes No 7*, Food and Nutrition Technical Assistance (FANTA), Academy for Educational Development, Washington, DC, August 2003.
40. Damle BD, Yan JH, Behr D, O'Mara E, Nichola P, Kaul S, Knupp C. Effect of food on the oral bioavailability of Didanosine from encapsulated enteric-coated beads. *Journal of Clinical Pharmacology* 42(4):419–27, 2002.
41. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: A meta-analysis. *American Journal of Medicine* 120(8):713–19, 2007.
42. van Griensven J, De Naeyer L, Mushi T, Ubarijoro S, Gashumba D, Gazille C, Zacharia R. High prevalence of lipoatrophy among patients on Stavudine: Containing first line antiretroviral therapy regimens in Rwanda. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 101(8):793–98, 2007.
43. Hawkins D et al. Randomised comparative study of patients' tolerance of and adherence to Combivir and Tenofovir versus Stavudine, Lamivudine and Tenofovir as post-exposure prophylaxis (PEP). Fourth International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, Sydney, abstract MOPDC02, 2007.
44. Richard N, Juntilla M, Abraha A, Demers K, Paxinos E, Galovich J, Petropoulos C, Whalen CC, Kyeyune F, Atwine D, Kityo C, Mugyenyi P, Arts EJ. High prevalence of antiretroviral resistance in treated Ugandans infected with non-subtype B human immunodeficiency virus type 1. *AIDS Research and Human Retroviruses* 20(4):355–64, 2004.
45. Shekelle P, Maglione M, Geotz MB, Wagner G, Wang Z, Hilton L, Carter J, Chen S, Ringlet C, Mojica W, Newberry S. Antiretroviral (ARV) Drug Resistance in the Developing World. Evidence Report/Technology Assessment. Rockville, MD: Agency for Healthcare Research and Quality, 2007.
46. Hardon AP, Akurut D, Comoro C, Ekezie C, Irunde HF, Gerrits T, Kglatwane J, Kinsman J, Kwasa R, Maridadi J, Moroka TM, Moyo S, Nakiyemba A, Nsimba S, Ogenyi R, Oyabba T, Temu F, Laing R. Hunger, waiting time and transport costs: Time to confront challenges to ART adherence in Africa. *AIDS Care* 19(5):658–65, 2007.
47. Safren SA, Kumarasamy N, James R, Raminani S, Solomon S, Mayer KH. ART adherence, demographic variables and CD4 outcome among HIV-positive patients on antiretroviral therapy in Chennai, India. *AIDS Care* 17(7):853–62, 2005.

QUALITY ASSURANCE PROJECT
University Research Co., LLC
7200 Wisconsin Avenue, Suite 600
Bethesda, MD 20814

Tel: (301) 654-8338
Fax: (301) 941-8427
www.qaproject.org