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Patient-initiated Repackaging of Antiretroviral Therapy, Virological Failure and Drug Resistance

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Abstract

Patient-initiated repackaging of antiretroviral therapy (ART) refers to removal of ART medications from their original manufacturer's containers, and putting them into alternative containers. This behavior may be triggered by stigma associated with HIV infection, and may be associated with negative patient outcomes. We assessed association between patient initiated repackaging of ART and virological failure (VF) in a sample of 450 HIV-infected patients. VF was defined as a plasma HIV RNA level ≥ 400 copies/mL. A total of 197 (43.7%) of the interviewed patients reported repackaging their ART medications. One hundred ninety-one patients (43%) had VF, and VF was associated with medication repackaging (adjusted prevalence ratio [APR], 1.5; 95% CI, 1.2–1.9). Continued support, health education and counselling on matters related to stigma in HIV infected patients is critical as such information may influence individual behavior and improve patient adherence, a core component in preventing VF and ART drug resistance.

Keywords

HIV; Repackaging of Anti-Retro-Viral; Virological failure; Stigma; ART Resistance mutations

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INTRODUCTION

Patient-initiated repackaging of antiretroviral therapy (ART) refers to removal of ART medications from their original manufacturer's containers, and putting them into alternative containers such as paper or plastic bags. Unlike adherence aids, which are intended to simplify patient's complex and confusing regimen(1), patient-initiated repackaging may be related to stigma that is associated with HIV infection. While these aids are reported to improve patient adherence(2), patients-initiated repackaging may have negative consequences if related to underlying stigma associated with HIV infection.

The main benefit of manufacturer's original packaging includes protection of drug effectivity(1, 3). The effectivity of medications may be compromised with these alternative repackaging materials if stored over a long duration. For example, if the use of other repackaging materials allows air penetration(1), it is likely that the amount of moisture in alternative packaging will be higher than manufacturer's original packaging, potentially impairing the drug's effectivity. Despite the benefits associated with manufacturer's original packaging, patient-initiated repackaging continues, and HIV-associated stigma may be the main reason for patient-initiated repackaging. Since HIV-related stigma is associated with poor patient outcomes(4–6), it is possible that patients who repack their ART may be less likely to take their medications appropriately. Whether patient-initiated repackaging is associated with virological failure and subsequent resistance to ART is unknown. We evaluated the association between patient-initiated repackaging of ART, virological failure and ART drug resistance among a cohort of HIV-infected adults attending five infectious disease clinics in Northern Tanzania.

METHODS

Study design and population

We used a cross-sectional study design to evaluate the association between patient-initiated repackaging of ART and virological failure and ART drug resistance. The study population included HIV-infected adolescent and adult patients attending Care and Treatment Centers (CTC) at the Kilimanjaro Christian Medical Center (KCMC), Mawenzi Regional Hospital (MRH), Kibosho, and Kilema District Hospitals, and Majengo Health Center in Northern Tanzania between January 2004 and May 2015. These CTCs offer treatment according to the Tanzanian Ministry of Health Treatment Guidelines for the provision of ART. Each patient is typically seen on a monthly basis and their prescriptions refilled.

Data collection

After obtaining informed consent, standardized questionnaires translated into Kiswahili were administered to participating patients by trained research nurses. Among other things, questionnaire addressed demographic characteristics, and patient repacking behaviors. Blood samples were collected from all participants for viral load testing at Kilimanjaro Christian Medical Center Biotechnology Laboratory and resistance testing at National Health Laboratory Quality And Training Centre (NHL-AATC). KCMC laboratory has participated in the ACTG Virology Quality Assurance Program for RNA measurement and UKNEQAS

for flow cytometry quality assurance. Key mutations were identified according to the March 2015 revision of the Stanford HIV drug resistance Mutations in HIV document(7)

As part of routine HIV clinical care, all patient data including demographics, medication use, opportunistic infections, adherence indicators (adherent = fewer than 2 missed days per month/non-adherent = 2 or more missed days per month), and laboratory values were collected on standardized forms, and entered into a database designed and funded by the Tanzanian National AIDS Control Program (NACP) in collaboration with Elizabeth Glaser Pediatric AIDS Foundation (EGPAF). This database was searched for other clinical data, and when information was missing, it was abstracted from their respective medical files.

Definition of Variables

The primary outcome was the virological failure defined as an HIV RNA level ≥ 400 copies/mL. Exposure of interest is patient-initiated repackaging of ART categorized as binary variable (yes/no). Other variables were evaluated including age, gender, duration on first-line ART, treatment sites, marital status, education, adherence to ART and CD4 cell count at the time of the interview. The presence of one or more major resistance mutation among patients whose HIV RNA levels were ≥ 1000 copies/mL was also evaluated.

Analysis

We wanted to assess whether patient-initiated repackaging of ART was associated with virological failure. Frequencies of categorical variables were calculated as the proportions of patients sampled. Multivariate binomial regression model was used to assess the association between patient-initiated repackaging of ART and virological failure. Bivariate binomial regression models were used to assess for potential confounders. All biologically plausible variables and those that changed the estimate by 20% on bivariable analyses were included in the final multivariate model. All associations were presented as adjusted prevalence ratios (APRs) with 95% confidence intervals (CIs). Estimates whose CIs excluded 1 were considered statistically significant.

Ethical review

Institutional Review Board approval was obtained from the Kilimanjaro Christian Medical University College (KCMU-Co) and Duke University Health System (DUHS).

RESULTS

We surveyed 450 HIV-infected patients receiving treatment between January 2004 and May 2015. Most were female (302, 67.1%), the majority were between 30 and 55 years old (332; 73.8%), had less than a primary school education (364; 80.1%), and 204 (45.5%) were either divorced/separated or widowed; (Table 1). The greatest proportion of patients came from Mawenzi Regional Hospital (223; 49.5%). Approximately half of patients had been on first-line ART for longer than 5 years (236; 52.4%), and most patients were not aware that future treatment options were limited (301; 66.9%). Two hundred fifty-nine (57.6%) had plasma HIV RNA levels <400 copies/mL, and the most recent CD4+ cell count was less than 350 c/mm^3 for 275 participants (61.1%).

Virological failure and association

One hundred and ninety-one patients (43%) met the definition of virological failure. Patients who reported to be repackaging their ART medications were more likely to have virological failure than those who did not repackaged their medications (prevalence ratio [PR], 1.4; 95% CI, 1.1–1.7) (Table 2). In bivariable analysis compared to patients who were less than 30 years, those who were between 30 and 55 were less likely to have virological failure. Other significant factors associated with virological failure include female vs male (PR, 0.8; 95% CI, 0.6–1.0), being aware on limited availability of future treatment options (PR, 0.8; 95% CI, 0.6–1.0) and being adherent to ART (PR, 0.6; 95% CI, 0.5–0.7).

After adjusting for age, gender, education, marital status, CD4 cell count, duration on treatment, adherence to ART, awareness of limited treatment options and CTC sites, the association between patient-initiated repackaging of ART and virological failure persisted (APR, 1.5; 95% CI, 1.2–1.9) (Table 2). Several other factors that were associated with virological failure on multivariate analysis include CTC site (Mawenzi vs KCMC; APR, 1.5; 95% CI, 1.2–1.9), being aware on limited availability of future treatment options (APR, 0.8; 95% CI, 0.7–1.0) and adherence to ART (APR, 0.6; 95% CI, 0.4–0.8).

Antiretroviral drug resistance mutations and HIV subtypes

Among the 191 subjects with plasma HIV RNA levels > 400 copies/mL, 48 (25%) had plasma HIV RNA levels 1000 copies/mL and had sequencing of their isolates attempted. Of these 48 subjects, 44 (91.7%) had successful HIV genotyping in which 11 subjects (25.0%) were infected with HIV type 1 subtype A, 8 (18.2%) were infected with HIV type 1 subtype C, 8 (18.2%) were infected with HIV type 1 subtype D and 17 (38.6%) were infected with circulating recombinant forms CRF01_AE. Of the 44 subjects, 35 (79.5%) had isolates with at least one major resistance mutations while 9 had wild type virus. Two subjects had virus with only 1 major antiretroviral drug resistance mutation; in both cases, these were non-nucleoside reverse transcriptase inhibitor (NNRTI)-associated mutations (K103N in one and E138A in the other) (Table 3). One subject had two major resistance mutations, and these were one nucleoside reverse transcriptase inhibitor (NRTI)-associated mutation (M184V) and the other NNRTI-associated mutations (K103N). The remaining 32 (91.4%) patients had three or more major NRTI- and/or NNRTI-associated mutations. Of those who had three or more major resistance mutations, two had minor PI-associated mutations and these were K20KM, T74ST and L33F. On bivariable analysis patient-initiated repackaging of ART medications was marginally associated with resistance mutations (PR, 1.1; 95% CI, 0.9–1.4).

DISCUSSION

We demonstrated high prevalence of patient-initiated repackaging of ART with 43.8% of the interviewed participants reported to repackaging their drugs. Virological failure was also high with 42.4% of participants having plasma HIV RNA levels 400 copies/mL. The high level of virological failure in this population may be due to the different risk factors observed; for example, over half of the study participants had adherence less than 95% and two-thirds weren't aware that future ART treatment options are limited. Among those who reported

repackaging, a quarter reported stigma being the main reason for repackaging. These data have important public health message suggesting the need to constantly offer health education to patients in order to reduce stigma.

The main strengths of this study are that, to our knowledge, it is the first study that assesses the association between patient-initiated repackaging of ART medication and virological failure. We showed that patient-initiated repackaging of ART is associated with virological failure with those repackaging their medications having a 50% increased chance of virological failure. It is likely that patients who repack their medications are likely to experience HIV-associated stigma and less likely to take their medications as prescribed or even failing to attend clinic regularly for prescription refill. In areas where HIV is highly stigmatized such as in resource limited settings, repackaging of ART becomes an alternative way of coping with stigma as repackaged medications are hardly identifiable by others as HIV medicines. The importance of HIV-associated stigma has been extensively documented and has shown to negatively impact HIV care and treatment(8–10). As scaling up of ART continues, more strategies to reduce stigma are warranted.

We demonstrated a high level of resistance mutations with approximately 80% of those with HIV RNA > 1000 copies/mL having at least one or more major resistance mutations. Although majority had NRTI- and NNRTI-associated resistance mutations, a few had minor PI-associated resistance mutations. PI is the final salvage regimen in many parts of resource limited settings(11, 12). Given limited availability of future treatment options in resource-limited settings, such an observation serves as a wakeup call to health care workers in these settings. Of note is the high proportion of patients with circulating recombinant forms. Approximately 39% of the study participants had circulating CRF01_AE. These circulating recombinants have been documented to be associated with negative outcomes such as high viral load(13), shorter patient survival(14) and faster disease progression to AIDS(15).

Evaluation of patient-initiated repackaging and self-reported adherence revealed that those who were repackaging tended to be less likely to be adherent. Implementing strategies to reduce HIV-associated stigma in order to improve adherence and reduce the development of resistance mutations is critical.

Although we were able to show association between patient-initiated repackaging of ART and virological failure, our study is not without limitations. This association was evaluated using a cross-sectional study design, thereby limiting our ability to establish temporal relationship. In addition, the adherence assessments relied on self-reports, and the latter is subject to biases including recall bias(11, 16). However, self-reported adherence has been used extensively and noted to be associated with clinical outcomes such as virological failure(6, 17, 18). Despite the limitations, the use of reliable laboratory measures for virological failure and testing for drug resistance make this study stronger.

Conclusion

The study reports that patient-initiated repackaging of ART medications is important predictor of virological failure; patients who repackaged their medications were more likely

to experience virological failure. It is critical for the health care providers in resource-limited settings to constantly provide education on ART and counseling on matters related to stigma. The provision of such information may influence individual behavior and improve patient adherence, a core component in preventing virological failure and ART drug resistance.

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Table 1

Demographic and Clinical Characteristics of HIV-Infected Patients Receiving Care at 5 Care and Treatment Centers in Kilimanjaro Region, Moshi, Tanzania 2004 – 2015

Characteristics	All Patients n = 450	Repackaging n = 197	Not repackaging n = 253
Age			
< 30	22 (4.9)	5 (2.5)	17 (6.7)
30 – 55	332 (73.8)	145 (73.6)	187 (73.9)
> 55	96 (21.3)	47 (23.9)	49 (19.4)
Gender			
Female	302 (67.1)	135 (68.5)	167 (66.0)
Male	148 (32.9)	62 (31.5)	86 (34.0)
Education			
primary school education	364 (80.1)	152 (77.2)	212 (83.8)
> primary school education	86 (19.9)	45 (22.8)	41 (16.2)
Marital			
Not married	62 (13.8)	22 (11.2)	40 (15.8)
Married	184 (40.9)	86 (43.7)	98 (38.7)
Divorced/Separated/Widowed	204 (45.3)	89 (45.2)	115 (45.5)
CD4 at the time of interview			
< 350 cells/mm ³	275 (61.1)	128 (64.9)	147 (58.9)
350 cells/mm ³	175 (38.9)	69 (35.1)	106 (41.1)
Duration on treatment			
< 36 months	132 (29.3)	52 (26.4)	80 (31.6)
36 – 60 months	82 (18.2)	30 (15.2)	52 (20.6)
> 60 months	236 (52.4)	115 (58.4)	121 (47.8)
Reasons for repackaging			
Easier to carry	N/A	148 (75.1)	N/A
Stigma	N/A	48 (24.4)	N/A
HIV-RNA			
< 400 c/mL	259 (57.6)	98 (49.8)	161 (63.6)
400 c/mL	191 (42.4)	99 (50.2)	92 (36.4)
Adherence			
Non adherence	239 (53.1)	41 (20.8)	198 (78.2)
Adherence	211 (46.9)	156 (78.2)	55 (21.7)
Sites			
KCMC	75 (16.7)	52 (26.4)	23 (9.1)
Mawenzi	223 (49.5)	69 (35.0)	154 (60.9)
Others	152 (33.8)	76 (38.6)	76 (30.0)
Aware of limited drug options			

Characteristics	All Patients n = 450	Repackaging n = 197	Not repackaging n = 253
No	301 (66.9)	130 (66.0)	171 (67.6)
Yes	149 (33.1)	67 (34.0)	82 (32.4)

Abbreviations: KCMC, Kilimanjaro Christian Medical Center; N/A, Not applicable; HIV-RNA, Human Immune Deficiency Virus Ribonucleic Acid.

Table 2

Crude and Adjusted Risk Factors of Virological failure to First and Second Line ART among HIV-Infected Adults Receiving Care at five Care and Treatment Centers in Kilimanjaro Region, Moshi, Tanzania 2004 – 2015

Characteristics	Bivariable Analysis Prevalence Ratio 95% CI	Multivariable Analysis Prevalence Ratio 95% CI
Age		
< 30	1	1
30 – 55	0.7 (0.5 – 1.0)	0.8 (0.6 – 1.3)
> 55	0.7 (0.5 – 1.1)	0.8 (0.5 – 1.4)
Gender		
Male	1	
Female	0.8 (0.6 – 1.0)	0.9 (0.7 – 1.1)
Education		
primary school education	1	1
> primary school education	1.1 (0.8 – 1.4)	1.0 (0.8 – 1.3)
Marital		
Not married	1	1
Married	0.8 (0.6 – 1.1)	1.0 (0.7 – 1.4)
Divorced/Separated/Widowed	0.8 (0.6 – 1.1)	0.9 (0.6 – 1.2)
Repackaging		
No	1	1
Yes	1.4 (1.1 – 1.7)	1.5 (1.2 – 1.9)
Duration on treatment		
< 36 months	1	1
36 – 60 months	0.8 (0.6 – 1.2)	0.9 (0.6 – 1.2)
> 60 months	0.8 (0.7 – 1.1)	0.9 (0.7 – 1.1)
CD4 at the time of interview		
< 350 cells/mm ³	1	1
350 cells/mm ³	1.1 (0.9 – 1.3)	1.2 (0.9 – 1.5)
Sites		
KCMC	1	1
Mawenzi	1.3 (0.9 – 1.8)	1.4 (1.0 – 2.1)
Others	1.1 (0.8 – 1.5)	1.2 (0.8 – 1.8)
Aware of limited drug options		
No		
Yes	0.8 (0.6 – 1.0)	0.8 (0.7 – 1.0)
Adherence		
Non adherence	1	1
Adherence	0.6 (0.5 – 0.7)	0.6 (0.4 – 0.8)

Abbreviations: KCMC, Kilimanjaro Christian Medical Center; HIV-RNA, Human Immune Deficiency Virus Ribonucleic Acid.

Table 3

Summary of genotypic antiviral drug–resistance mutations in isolates obtained from HIV-infected Adults Receiving Care at five Care and Treatment Centers in Kilimanjaro Region, Moshi, Tanzania 2004 – 2015

Number of mutations	Number of isolates (%)	Antiretroviral drug–resistance mutation(s) (no. of isolates), by class of antiviral drug		
		PI-Minor	NRTI	NNRTI
1	2 (5.7)	–	–	K103(1), E138A (1)
2	1 (2.9)	–	M184V (1)	K103N (1)
			A62V(2); D67G(4); D67N (12); F77L (1); K219E (4); K219Q (9); K65R (5); K70E (1); K70H (1); K70R (13); L210W (5); M184V (32); M41L (6); T215FI (1); T215FI (1); T215FV (1); T215IT (1); T215IV (1); T215Y (6); T69D (2); T69DELETION (1); T69INSERTION (1); T69G (1)	A98G (3); E138A (2); E138Q (5); F227L (1); G190A (11); G190G (1); G190EG (1); G190T (1); H221Y (5); K101AP (1); K101E (3); K101H (2); K103N (16); K103NS (1); K103S (1); K238KN (1); K238T (1); L100I (1); M108IV (1); M230L (1); P225H (3); P225HP (1); V106I (4); V106M (3); V108I (2); V179D (1); V179T (5); Y181C (9); Y188H (2); Y188L (2).
3	32 (91.4)	K20KM (1); T74ST (1); L33F (1).	T69N (4); T69NT (3); V75I (2); V75M (2); Y115E (2); Y69N (1);	

Abbreviations: PI, protease inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; NNRTI, nonnucleoside reverse-transcriptase inhibitor