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RESEARCH ARTICLE

# Reasons for Missing Antiretroviral Therapy: Results from a Multi-Country Study in Tanzania, Uganda, and Zambia

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**Data Availability Statement:** The authors confirm that, for approved reasons, some access restrictions apply to the data underlying the findings. Although the patient-level data do not include patient names, this IRB decision is in the interest of ensuring patient confidentiality. An individual may email the lead author ([olivier.koole@lshtm.ac.uk](mailto:olivier.koole@lshtm.ac.uk)) or the CDC division of Global HIV/AIDS science office ([gapmts@cdc.gov](mailto:gapmts@cdc.gov)) to request the data.

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## Abstract

### Objectives

To identify the reasons patients miss taking their antiretroviral therapy (ART) and the proportion who miss their ART because of symptoms; and to explore the association between symptoms and incomplete adherence.

### Methods

Secondary analysis of data collected during a cross-sectional study that examined ART adherence among adults from 18 purposefully selected sites in Tanzania, Uganda, and Zambia. We interviewed 250 systematically selected patients per facility ( $\geq 18$  years) on reasons for missing ART and symptoms they had experienced (using the HIV Symptom Index). We abstracted clinical data from the patients' medical, pharmacy, and laboratory records. Incomplete adherence was defined as having missed ART for at least 48 consecutive hours during the past 3 months.

### Results

Twenty-nine percent of participants reported at least one reason for having ever missed ART (1278/4425). The most frequent reason was simply forgetting (681/1278 or 53%), followed by ART-related hunger or not having enough food (30%), and symptoms (12%). The median number of symptoms reported by participants was 4 (IQR: 2–7). Every additional

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symptom increased the odds of incomplete adherence by 12% (OR: 1.1, 95% CI: 1.1–1.2). Female participants and participants initiated on a regimen containing stavudine were more likely to report greater numbers of symptoms.

## Conclusions

Symptoms were a common reason for missing ART, together with simply forgetting and food insecurity. A combination of ART regimens with fewer side effects, use of mobile phone text message reminders, and integration of food supplementation and livelihood programmes into HIV programmes, have the potential to decrease missed ART and hence to improve adherence and the outcomes of ART programmes.

## Introduction

At the end of 2013 two-thirds of the estimated 35 million people globally living with HIV lived in sub-Saharan Africa.[1] The number of people receiving antiretroviral treatment (ART) reached about 13 million. Sub-Saharan Africa achieved the greatest increase in ART coverage by reaching 9 million people, corresponding to about 37% coverage among people living with HIV in that region.[1,2] The goal of ART is to achieve and sustain viral suppression to achieve the full clinical and prevention benefits of HIV treatment.[3,4] A systematic review of studies from low-and middle income countries reported a pooled estimate of viral suppression (<1000 copies/ml) of 78% (95% confidence interval (95% CI):68%-86%) at 12 months after ART initiation.[5]

Achieving viral suppression requires consistent adherence to ART.[6] Factors identified in the literature as affecting ART adherence include patient characteristics (socio-demographic and psychosocial factors), patient/provider aspects (patient-provider interactions, trust, and confidentiality), health-system related factors (waiting time at the clinic, transport), disease characteristics (HIV-related symptoms), and therapy-related factors (number of pills, medication side effects).[7,8]

In order to develop effective adherence interventions, it is important to identify the common reasons people report for not taking their ART. We used data collected during a cross-sectional study conducted in 2011 that examined adherence to ART among adults in three countries in sub-Saharan Africa: Tanzania, Uganda, and Zambia.[9] In the primary paper we examined individual and programmatic factors associated with incomplete adherence. We found that 3% of participants missed two or more consecutive days of their ART in the past three months, and that having greater versus less self-reported HIV-related symptoms (a dichotomized variable based on the country-specific median number of symptoms) was significantly associated with incomplete adherence. In this secondary analysis we focused on self-reported reasons for ever missing ART and investigated the role of symptoms in missing ART. We also explored the association between having experienced specific symptoms and incomplete adherence.

## Methods

### Design and study setting

From May to October 2011, a cross-sectional study was conducted among ART patients from 18 purposively selected study sites in Tanzania, Uganda, and Zambia. Site selection has been

described in an earlier publication [10] and included clinics from different levels in the health system (ranging from rural health centres to referral hospitals), from different types of health facilities (public sector, non-governmental organizations (NGOs), or faith-based organizations), and with different ART provision experiences and adherence strategies.

### Inclusion criteria

Patients attending the study sites who were at least 18 years of age at ART initiation, who initiated ART at least six months prior to the interview, and who spoke one of the study languages were eligible for inclusion.

### Data collection and sampling

Based on clinic client flow, participants were selected using a systematic sampling approach with every fifth patient selected at the larger facilities and every third patient at the smaller clinics. After selection, potential participants were screened for eligibility by trained research interviewers, and, if they consented, interviewed until we obtained a sample of 250 eligible patients from each facility (4500 patients in total).

### Measures

The survey was designed in English and then translated into 10 languages (Swahili for Tanzania; Acholi, Luganda, Lumasaaba, Lunyankore for Uganda; and Bemba, Chewa, Lozi, Nyanja and Tonga for Zambia) and pretested during the training of the fieldworkers and piloting of the study-instruments.

The survey contained several measures on self-reported adherence, and questions on psychosocial factors including stigma (Internalized Stigma Scale [11]), depression (Hopkins Symptoms Checklist [12]), social support (Duke University Functional Social Support questionnaire [13]), and alcohol abuse (CAGE [14]).

The survey also included a list of 16 reasons for ever missing ART (based on the AACTG questionnaire) [15] and on symptoms experienced in the four weeks prior to the interview. Symptoms were collected using a modified HIV Symptom Index that has 20 items scored on a five point Likert scale.[16] During translation and pre-testing the team modified the responses from a five point to a four point Likert scale, with 0 representing the absence of that symptom and 3 indicating that the patient did have the symptom and it bothered them “a lot” resulting in an index that ranges from 0 to 60. The participant was also asked if they attributed the symptom to their ART.

Based on previous evidence of the importance of treatment interruptions as a predictor of viral load failure and resistance [17,18], and because missing ART for at least 48 consecutive hours was the strongest measure related to virological failure during our primary analysis, we constructed a missed at least 48 consecutive hours measure from two questions about missed tablets in the past 3 months to define incomplete adherence.[9]

Data regarding ART initiation (ART start dates and regimens, and pre-ART characteristics) were abstracted from the patient’s medical, pharmacy, and laboratory records using structured data abstraction forms.

### Data management and analysis

All data were double entered in a study database using EpiData Entry 3.1 (EpiData Association, Odense, Denmark) at the in-country research organizations, and then transferred to the central

data office at Family Health International 360 (FHI 360) for further cleaning and consistency checks.

For data analysis, the proportions of reasons for ever missing one's ART and experiences of symptoms in the past four weeks are reported. Because of the dependency on self-reported symptoms, we investigated the relationship between symptoms and incomplete adherence in the past three months as a purely explorative objective, and therefore limited this analysis to univariate analysis only. We also explored the association between specific antiretroviral drugs (nevirapine versus efavirenz, and stavudine versus zidovudine) and symptom burden (expressed as the HIV Symptom Index score) using multiple linear regression, with backwards stepwise elimination, including site as a fixed effect. Variables associated with symptom burden with a  $p$ -value  $<0.10$  were considered for multivariable analysis, and variables with a  $p$ -value  $<0.05$  in the multivariable analysis were considered significant.

### Ethics statement

The study was reviewed and approved by the institutional review board (IRB) of the U.S. Centers for Disease Control and Prevention (CDC) and the six partner and national ethical review committees. The Partners Healthcare IRB ceded review to FHI 360.

### Results

A total of 6825 patients were screened for eligibility at the participating sites. Of these 1848 patients were ineligible, and 482 did not provide informed consent. An additional 70 patients with no data on missed ART for at least 48 consecutive hours were excluded, leaving 4425 patients for the final analysis.

### Characteristics of study population

Characteristics at the time of the interview and at ART initiation, stratified by country, are presented in [Table 1](#). Participants were predominantly female (68%) and had started ART between 2002 and 2011. At ART initiation the median age was 40 years (inter quartile range (IQR): 34–47 years) and the median CD4 cell count was 145 cells/ $\mu$ l (IQR: 75–217). At the time of the interview, the median time on ART was 4 years (IQR: 2–5 years) and about 45% of participants had changed their ART regimen since initiation. Twenty-three percent changed from an initial stavudine (d4T) containing regimen, 13% from an initial nevirapine (NVP) containing regimen and 7% from an initial efavirenz (EFV) containing regimen. One-third of patients (32%) were receiving AZT/3TC/NVP, 17% AZT/3TC/EFV, and 16% d4T/3TC/NVP or TDF/3TC-FTC/EFV at the time of data collection. About 3% of patients were receiving a second-line regimen that contained a protease inhibitor.

### Incomplete adherence (defined as missed ART for at least 48 consecutive hours during the past 3 months)

About 3% (141/4425) of our study participants had missed taking their ART for at least 48 consecutive hours during the past 3 months.

### Reasons for ever missing one's ART

Among all ART patients, 29% of participants reported at least one reason for having ever missed ART (1278/4425), with only 0.2% (9/4425) missing responses to these questions. About half of patients who reported ever missing ART (53% or 681/1278) reported they simply forgot, followed by having too much hunger because of ART or not having enough food (30%), and

**Table 1. Characteristics at interview and at ART initiation of study population in multi-country (Tanzania, Uganda, and Zambia) adherence study, 2011.**

Characteristic	Tanzania (n = 1469)	Uganda (n = 1474)	Zambia (n = 1482)	Total number of patients (n = 4425)
<b>Gender: n (%)</b>				
Male	394 (26.8)	505 (34.3)	520 (35.1)	1419 (32.1)
Female	1075 (73.2)	969 (65.7)	962 (64.9)	3006 (67.9)
<b>At interview</b>				
Age (years): median (IQR)	41 (35–47)	39 (34–46)	40 (34–47)	40 (34–47)
Years on ART: median (IQR)	3.2 (2.0–4.6)	3.6 (2.2–5.4)	4.2 (2.5–5.7)	3.6 (2.2–5.3)
CD4 (cells/ $\mu$ L): median (IQR)	372 (243–548)	368 (245–524)	427 (291–588)	391 (255–560)
Missing: n (%)	701 (47.7)	803 (54.5)	700 (47.2)	2204 (49.8)
<b>ART regimen: n (%)</b>				
d4T-3TC-NVP	549 (37.4)	11 (0.7)	158 (10.7)	718 (16.2)
AZT-3TC-EFV	389 (26.5)	296 (20.1)	76 (5.1)	761 (17.2)
AZT-3TC-NVP	258 (17.6)	898 (60.9)	253 (17.1)	1409 (31.8)
TDF-3TC/FTC-EFV	114 (7.8)	83 (5.6)	493 (33.3)	690 (15.6)
PI-containing	31 (2.1)	39 (2.6)	66 (4.5)	136 (3.1)
Other	38 (2.6)	134 (9.1)	369 (24.9)	541 (12.2)
Missing	90 (6.1)	13 (0.9)	67 (4.5)	170 (3.8)
<b>Regimen containing: n (%)</b>				
EFV	517 (35.2)	382 (25.9)	641 (43.3)	1540 (34.8)
NVP	823 (56.0)	1036 (70.3)	708 (47.8)	2567 (58.0)
d4T	575 (39.1)	23 (1.6)	207 (14.0)	805 (18.2)
AZT	660 (44.9)	1217 (82.6)	347 (23.4)	2224 (50.3)
TDF	123 (8.4)	221 (15.0)	787 (53.1)	1131 (25.6)
<b>Regimen change since ART initiation: n (%)</b>				
Yes	663 (45.1)	667 (45.3)	670 (45.2)	2000 (45.2)
No	806 (54.9)	807 (54.7)	812 (54.8)	2425 (54.8)
<b>Change from NVP at initiation: n (%)</b>				
Yes	246 (16.7)	141 (9.6)	197 (13.3)	584 (13.2)
No	708 (48.2)	924 (62.7)	504 (34.0)	2136 (48.3)
Not applicable	515 (35.1)	409 (27.7)	781 (52.7)	1705 (38.5)
<b>Change from EFV at initiation: n (%)</b>				
Yes	165 (11.2)	59 (4.0)	64 (4.3)	288 (6.5)
No	342 (23.3)	259 (17.6)	495 (33.4)	1096 (24.8)
Not applicable	962 (65.5)	1156 (78.4)	923 (62.3)	3041 (68.7)
<b>Change from d4T at initiation: n (%)</b>				
Yes	345 (23.5)	400 (27.1)	256 (17.3)	1001 (22.6)
No	442 (30.1)	6 (0.4)	183 (12.3)	631 (14.3)
Not applicable	682 (46.4)	1068 (72.5)	1043 (70.4)	2793 (63.1)
<b>Change from AZT at initiation: n (%)</b>				
Yes	212 (14.4)	82 (5.6)	110 (7.4)	404 (9.1)
No	427 (29.1)	840 (57.0)	256 (17.3)	1523 (34.4)
Not applicable	830 (56.5)	552 (37.4)	1116 (75.3)	2498 (56.5)
<b>At ART initiation</b>				
<b>Year of ART initiation: n (%)</b>				
2002–2004	10 (0.7)	60 (4.1)	97 (6.5)	167 (3.8)
2005	123 (8.4)	180 (12.2)	192 (13.0)	495 (11.2)
2006	155 (10.6)	152 (10.3)	209 (14.1)	516 (11.7)

(Continued)

Table 1. (Continued)

Characteristic	Tanzania (n = 1469)	Uganda (n = 1474)	Zambia (n = 1482)	Total number of patients (n = 4425)
2007	198 (13.5)	224 (15.2)	254 (17.1)	676 (15.3)
2008	272 (18.5)	219 (14.9)	241 (16.3)	732 (16.5)
2009	315 (21.4)	280 (19.0)	235 (15.9)	830 (18.8)
2010	356 (24.2)	313 (21.2)	240 (16.2)	909 (20.5)
2011	36 (2.5)	43 (2.9)	11 (0.7)	90 (2.0)
Missing	4 (0.2)	3 (0.2)	3 (0.2)	10 (0.2)
<b>WHO clinical stage: n (%)</b>				
Stage 1 and 2	414 (28.2)	704 (47.8)	567 (38.3)	1685 (38.1)
Stage 3	659 (44.9)	512 (34.7)	671 (45.3)	1842 (41.6)
Stage 4	274 (18.6)	151 (10.2)	92 (6.2)	517 (11.7)
Missing	122 (8.3)	107 (7.3)	152 (10.2)	381 (8.6)
<b>CD4 (cells/μL): median (IQR)</b>				
Missing: n (%)	281 (19.3)	296 (20.1)	312 (21.1)	889 (20.1)
<b>ART regimen: n (%)</b>				
d4T-3TC-NVP	736 (50.1)	394 (26.7)	396 (26.7)	1526 (34.5)
AZT-3TC-EFV	421 (28.7)	251 (17.0)	77 (5.2)	749 (16.9)
AZT-3TC-NVP	218 (14.8)	668 (45.3)	288 (19.5)	1174 (26.5)
TDF-3TC/FTC-EFV	36 (2.5)	54 (3.7)	403 (27.2)	493 (11.1)
PI-containing	5 (0.3)	16 (1.1)	12 (0.8)	33 (0.8)
Other	51 (3.5)	13 (0.9)	95 (6.4)	159 (3.6)
Missing	2 (0.1)	78 (5.3)	211 (14.2)	291 (6.6)
<b>Regimen containing: n (%)</b>				
EFV	507 (34.5)	318 (21.6)	559 (37.7)	1384 (31.3)
NVP	954 (64.9)	1065 (72.3)	701 (47.3)	2720 (61.5)
d4T	787 (53.6)	406 (27.5)	439 (29.6)	1632 (36.9)
AZT	639 (43.5)	922 (62.6)	366 (24.7)	1927 (43.6)
TDF	36 (2.5)	63 (4.3)	409 (27.6)	508 (11.5)

d4T: stavudine; 3TC: lamivudine; NVP: nevirapine; EFV: efavirenz; AZT: zidovudine; TDF: tenofovir; FTC: emtricitabine; PI: protease inhibitor.

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feeling sick or uncomfortable because of the ART (12%) (Fig 1). Other frequently cited reasons included no transport to the pharmacy (11%) and being away from home (3%).

A small number of patients (about 2% of those who ever missed ART or less than 1% of all patients in the study) have ever missed taking their ART because they were told to stop taking the drugs by a traditional healer. Of the 4,425 patients in this study, 257 (6%) ever consulted a traditional healer or herbalist because of HIV, the majority of whom were from Tanzania (76%).

### HIV Symptom Index Score (symptom burden)

Eighty-eight percent of participants reported experiencing at least one symptom during the past four weeks (Table 2), with responses missing for only a small proportion of participants (5/4425). The median number of symptoms reported was 4 (IQR: 2–7) with a median HIV Symptom Index score of 8 (IQR: 3–14). Women reported significantly more symptoms (median of 4 among women versus 3 among men) and a higher symptom burden (median HIV Symptom Index score of 8 among women versus 7 among men). More symptoms [5 (IQR: 3–8)] and a higher median HIV Symptom Index score [11 (IQR: 5–17)] were reported in Uganda (Kruskal Wallis p-value<0.001 for both comparisons).

Female gender and being initiated on a d4T—or NVP—containing ART regimens were associated with having more symptoms during univariate analysis (Table 3). During multivariable analysis, females (coefficient: +1.6, 95%CI: +1.0, +2.2) and participants taking ART regimens containing d4T at initiation (coefficient: +0.9, 95% CI: +0.3, +1.4) remained significantly associated with a greater symptom burden.

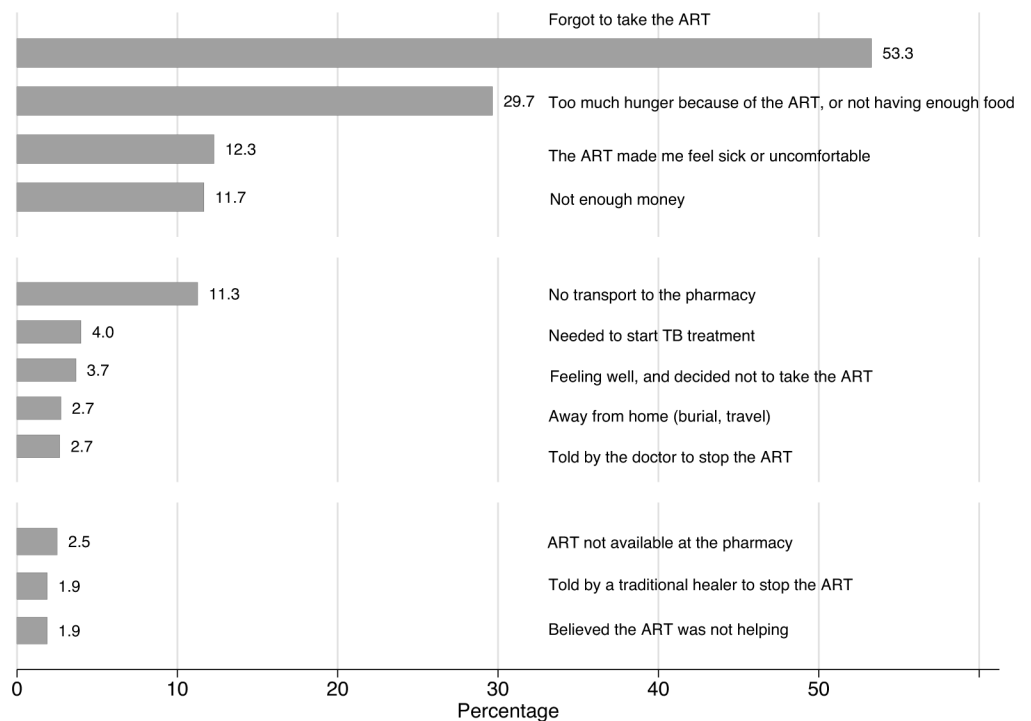
### Types of symptoms

Fatigue or loss of energy was the most cited symptom (37%), followed by pain, numbness, or tingling in the hands or feet (35%), and headache (34%). Feeling sad, down, or depressed was reported by 30% of participants (Table 2). Of these most frequently reported symptoms, only pain, numbness, or tingling in the hands or feet was attributed to ART by a substantial proportion of participants with this symptom (33%). Other symptoms that were not as common but more frequently attributed to ART by at least 30% of participants with that symptom included trouble remembering (37%), hair loss or changes in hair (35%), nausea or vomiting (34%), problems with having sex (31%), and skin problems (30%).

Men reported significantly more diarrhoea, skin problems, and problems with having sex while women reported significantly more fatigue or loss of energy; headache; loss of appetite or change in the taste of food; fever, chills, or sweats; feeling dizzy or lightheaded; troubles remembering; nausea or vomiting; feeling sad, down, or depressed; weight loss or wasting; hair loss or hair change; bloating, pain, or gas; and muscle aches or joint pains (data not shown).

### Association between symptoms and incomplete adherence

Every additional symptom increased the odds of incomplete adherence by 10% (odds ratio (OR): 1.10, 95% CI: 1.05–1.15) (data not shown). Patients who reported at least one symptom



**Fig 1. Reasons for patients who ever missed ART in multi-country (Tanzania, Uganda, and Zambia) adherence study (N = 1278), 2011.**

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**Table 2. Reported symptoms in the past four weeks in multi-country (Tanzania, Uganda, and Zambia) adherence study, 2011.**

	Tanzania (n = 1469)	Uganda (n = 1474)	Zambia (n = 1482)	Total (n = 4425)	Attributed to ARVs by patient (n, %)	Severe symptoms ("It bothers me a lot") (n, %)
Reporting at least one symptom, n (%)	1193 (81.2)	1389 (94.2)	1325 (89.4)	3907 (88.3)		
Number of symptoms reported, median (IQR)	3 (1–6)	5 (3–8)	4 (2–6)	4 (2–7)		
HIV Symptom Index score, median (IQR)	6 (2–12)	11 (5–17)	7 (3–13)	8 (3–14)		
<b>Symptom, n (%)</b>						
Fatigue or loss of energy	360 (24.5)	754 (51.2)	514 (34.7)	1628 (36.8)	308 (18.9)	534 (32.8)
Pain, numbness, or tingling in the hands or feet	462 (31.4)	662 (44.9)	436 (29.4)	1560 (35.3)	512 (32.8)	583 (37.4)
Headache	394 (26.8)	610 (41.4)	515 (34.8)	1519 (34.3)	233 (15.3)	415 (27.3)
Felt sad, down or depressed	451 (30.7)	518 (35.1)	340 (22.9)	1309 (29.6)	140 (10.7)	467 (35.7)
Muscle aches or joint pains	382 (26.0)	524 (35.5)	284 (19.2)	1190 (26.9)	314 (26.4)	435 (36.6)
Fat deposits or weight gain	378 (25.7)	289 (19.6)	480 (32.4)	1147 (25.9)	326 (28.4)	145 (12.6)
Fevers, chills, or sweats	237 (16.1)	524 (35.5)	374 (25.2)	1135 (25.6)	178 (15.7)	333 (29.3)
Trouble remembering	220 (15.0)	470 (31.9)	419 (28.3)	1109 (25.1)	405 (36.5)	400 (36.1)
Cough or breathing difficulties	208 (14.2)	488 (33.1)	330 (22.3)	1026 (23.2)	128 (12.5)	326 (31.8)
Problems with having sex (such as loss of interest or a lack of satisfaction)	316 (21.5)	388 (26.3)	312 (21.1)	1016 (23.0)	317 (31.2)	423 (41.6)
Weight loss or wasting	278 (18.9)	411 (27.9)	321 (21.7)	1010 (22.8)	167 (16.5)	267 (26.4)
Dizzy or lightheaded	250 (17.0)	429 (29.1)	320 (21.6)	999 (22.6)	287 (28.7)	267 (26.7)
Loss of appetite or change in taste of food	267 (18.2)	341 (23.1)	307 (20.7)	915 (20.7)	252 (27.5)	318 (34.8)
Skin problems (rash, dryness, or itching)	257 (17.5)	381 (25.8)	205 (13.8)	843 (19.1)	255 (30.2)	369 (43.8)
Difficulty falling or staying asleep	259 (17.6)	327 (22.2)	251 (16.9)	837 (18.9)	204 (24.4)	306 (36.6)
Felt nervous or anxious	248 (16.9)	373 (25.3)	191 (12.9)	812 (18.4)	117 (14.4)	271 (33.4)
Bloating, stomach pain, or gas	249 (17.0)	353 (23.9)	194 (13.1)	796 (18.0)	219 (27.5)	265 (33.3)
Nausea or vomiting	132 (9.0)	203 (13.8)	189 (12.8)	524 (11.8)	176 (33.6)	147 (28.1)
Diarrhea or loose bowl movements	148 (10.1)	146 (9.9)	181 (12.2)	475 (10.7)	100 (21.1)	122 (25.7)
Hair loss or hair change	36 (2.5)	101 (6.9)	42 (2.8)	179 (4.0)	63 (35.2)	60 (33.5)

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were more likely to have incomplete adherence (OR: 3.0, 95% CI: 1.2–7.4) (Table 4). About half of the symptoms from the HIV Symptom Index Score (9/20) were associated with incomplete adherence: fatigue or loss of energy (OR: 1.5, 95% CI: 1.0–2.1), fevers, chills, or sweats (OR: 1.7, 95% CI: 1.2–2.4), nausea or vomiting (OR: 1.7, 95% CI: 1.1–2.7), diarrhoea or loose bowl movements (OR: 2.2, 95% CI: 1.5–3.4), feeling sad, down, or depressed (OR: 1.5, 95% CI: 1.1–2.1), skin problems (OR: 2.0, 95% CI: 1.4–2.8), cough or breathing difficulties (OR: 1.8, 95% CI: 1.3–2.6), loss of appetite or change in the taste of food (OR: 2.1, 95% CI: 1.4–3.0), and abdominal pains (OR: 1.6, 95% CI: 1.1–2.3).

Patients who reported feeling sick and uncomfortable because of ART were also more likely to have incomplete adherence (OR: 3.7, 95% CI: 2.1–6.6).

## Discussion

This is the first study to our knowledge to interview more than 4000 patients on their reasons for ever missing ART and their current experiences with HIV-related symptoms using a

**Table 3. Regression coefficients of factors associated with symptom burden (expressed as HIV Symptom Index Score) in multi-country (Tanzania, Uganda, and Zambia) adherence study, 2011.**

Risk factor	Single regression*		Multiple regression*	
	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value
Male (versus female)	-1.6 (-2.2, -1.0)	<0.001	-1.6 (-2.2, -1.0)	<0.001
WHO clinical stage at ART initiation (versus WHO stage 1 and 2)		0.138		
Stage 3	+0.7 (+0.1, +1.4)			
Stage 4	+0.6 (-0.3, +1.6)			
Missing	+0.7 (-0.3, +1.8)			
CD4 cell count at ART initiation (versus $\geq 250$ cells/ $\mu$ L)		0.495		
< 250 cells/ $\mu$ L	-0.1 (-1.4, +0.4)			
Missing	-0.5 (-1.6, +0.5)			
Regimen at ART initiation containing				
NVP (versus EFV)	+1.0 (+0.3, +1.6)	0.006		NS
d4T (versus AZT)	+0.9 (+0.3, +1.4)	0.003	+0.9 (+0.3, +1.4)	0.004
Current age (per 10 years)	-0.1 (-0.4, +0.2)	0.479		
Duration on ART (per year)	+0.1 (-0.1, +0.2)	0.400		
CD4 cell count (versus $\geq 250$ cells/ $\mu$ L)		0.367		
< 250 cells/ $\mu$ L	+0.6 (-0.3, +1.5)			
Missing	-0.1 (-0.7, +0.6)			
Current regimen containing				
NVP (versus EFV)	+0.6 (-0.1, +1.3)	0.115		
d4T (versus AZT)	+0.7 (-0.2, +1.5)	0.109		

\*Regression coefficients and P-values calculated using linear regression with site as a fixed effect.

Factors with negative coefficients are associated with a reduced symptom burden; those with a positive coefficient with an increased symptom burden.

d4T: stavudine; NVP: nevirapine; EFV: efavirenz; AZT: zidovudine; CI: confidence interval.

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consistent data collection tool across 18 study sites in 3 countries in sub-Saharan Africa. This paper builds on the study’s primary analysis that found that 3% of participants missed two or more consecutive days of their ART in the past three months and that having greater numbers of self-reported symptoms, (defined as more than the country-specific median), was significantly related to this measure of incomplete adherence.[9] In this secondary analysis we focused on specific symptoms and their association with incomplete adherence, and on reasons for ever missing ART.

This analysis found that about one third of participants (29%) reported ever missing ART. Simply forgetting was cited as the most common reason for ever missing ART, a result which concurs with findings from other studies.[19–21] Advances in mHealth technologies are emerging as an option to address forgetting to take ART. For example, several studies have found that patients who received text messages have better levels of ART adherence and clinical indicators, such as lower viral loads and higher CD4 cell counts, compared to patients who did not receive text messages.[22–24] However, in their network meta-analysis examining direct and indirect evidence from randomized trials, Mills and colleagues found a large benefit for weekly but not for daily SMS messages [25], emphasizing the need for tailored mHealth interventions.[26] Such findings support the inclusion of mobile phone text messaging in the package of adherence intervention tools, as recommended by the World Health Organization in their latest guidelines, as well as the need for more research on how to optimize the use of text messaging.[27] However, the potential of unwanted disclosure if the message is intercepted by

**Table 4. Analysis of individual symptoms with incomplete adherence as outcome (defined as missed ART for at least 48 consecutive hours during the past 3 months) in multi-country (Tanzania, Uganda, and Zambia) adherence study, 2011.**

	Total (n = 4425)	Incomplete adherence (n = 141)	Crude Odds Ratio (OR) (95% CI) *	P- value*
Reporting at least one symptom, n (%)	3907 (88.3)	136 (96.5)	2.95 (1.19–7.35)	0.007
<b>Symptom, n (%)</b>				
Fatigue or loss of energy	1628 (36.8)	67 (47.5)	1.45 (1.01–2.06)	0.042
Pain, numbness, or tingling in the hands or feet	1560 (35.3)	57 (40.4)	1.11 (0.78–1.58)	0.562
Headache	1519 (34.3)	61 (43.3)	1.29 (0.91–1.83)	0.162
Felt sad, down or depressed	1309 (29.6)	63 (44.7)	1.49 (1.05–2.12)	0.029
Muscle aches or joint pains	1190 (26.9)	49 (34.8)	1.25 (0.87–1.80)	0.240
Fat deposits or weight gain	1147 (25.9)	37 (26.2)	0.99 (0.66–1.47)	0.950
Fevers, chills, or sweats	1135 (25.6)	52 (36.9)	1.67 (1.16–2.41)	0.007
Trouble remembering	1109 (25.1)	37 (26.2)	1.02 (0.69–1.52)	0.906
Cough or breathing difficulties	1026 (23.2)	51 (36.2)	1.80 (1.25–2.61)	0.002
Problems with having sex (such as loss of interest or a lack of satisfaction)	1016 (23.0)	39 (27.7)	1.13 (0.76–1.66)	0.554
Weight loss or wasting	1010 (22.8)	39 (27.7)	1.20 (0.81–1.77)	0.362
Dizzy or lightheaded	999 (22.6)	45 (31.9)	1.42 (0.98–2.06)	0.071
Loss of appetite or change in taste of food	915 (20.7)	53 (37.6)	2.05 (1.43–2.95)	<0.001
Skin problems (rash, dryness, or itching)	843 (19.1)	48 (34.0)	1.95 (1.35–2.81)	<0.001
Difficulty falling or staying asleep	837 (18.9)	38 (27.0)	1.35 (0.91–1.99)	0.145
Felt nervous or anxious	812 (18.4)	38 (27.0)	1.27 (0.85–1.89)	0.256
Bloating, stomach pain, or gas	796 (18.0)	40 (28.4)	1.59 (1.08–2.34)	0.022
Nausea or vomiting	524 (11.8)	28 (19.9)	1.72 (1.11–2.67)	0.020
Diarrhoea or loose bowl movements	475 (10.7)	31 (22.0)	2.24 (1.47–3.43)	<0.001
Hair loss or hair change	179 (4.0)	6 (4.3)	1.01 (0.43–2.36)	0.975

\*OR and P-value calculated using logistic regression with site as a fixed effect.

OR: odds ratio; CI: confidence interval.

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others, and the cost and sustainability of these mHealth interventions in the absence of external funding, remain important issues.[28]

Having too much hunger because of ART or not having enough food was experienced by about one-third of participants who reported ever missing ART. The mechanism of ART-related hunger is unclear, but the possibility of immunological phenomena may play a role.[29] Food insecurity has been described as an important barrier to adherence and subsequent mortality in impoverished populations.[30–35] The integration of food supplementation into HIV care programmes has been shown to improve adherence [36], and to have clinical and immunological benefits.[37] In order to address the underlying causes of food insecurity, organizations are looking for more sustainable long-term solutions to address this issue in the form of livelihood programmes.[38] The lack of evidence and research on the integration of livelihood programmes into HIV programmes [38] could be one of the reasons why these programmes have not been more widely implemented. Further implementation research on how these programmes should be evaluated, and subsequent cost-effectiveness studies are needed.

Previous studies [19,20] have also found that being away from home for funerals and travelling (and running out of ART while travelling) were common reasons for missing ART. In our study about 1% of all participants included, or 3% of participants ever missing ART, reported this as a reason for missing ART. Currently cities and urban areas bear a major part of the

global HIV burden—in sub-Saharan Africa, nearly half (45%) of people living with HIV reside in urban areas.[39] Travelling and migration in and out of cities can be a challenge for retention in care and adherence but also an important factor linking different networks of HIV transmission.[40] Interventions to provide patients with an adequate supply of ART are critical to minimizing treatment interruptions during travel.

Lack of money for transport was mentioned by 12% of the participants who ever reported missing ART and no transport to the pharmacy by 11%. This has also been cited in other studies as a risk factor for missed medical appointments at the health facility for follow-up and refill because of competing demands between transport costs and other necessities such as food, housing, and school fees.[30,41] Further decentralization of ART services, thereby bringing ART services closer to the patients [42], and involving patients and their families as the model of Community ART Groups (peer support) has the potential to further reduce transport costs and thus minimize out-of-pocket payments.[43] In addition, reducing the frequency of follow-up visits for refills or for routine clinical monitoring may also contribute to reducing the cost burden of transportation.

A large majority of patients (88%) in this study reported experiencing at least one symptom from the HIV Symptom Index, and, not surprisingly, the odds of incomplete adherence increased significantly with each additional symptom, as similarly described elsewhere.[44] Patients who reported feeling sick and uncomfortable because of ART were about 4 times more likely to have incomplete adherence, also confirming findings from other studies.[19,45] We also found that women reported a significantly greater symptom burden (both more symptoms and severity), as described elsewhere.[46]

Fatigue or loss of energy was the most reported symptom (37%), twice as much as reported by Bhatt et. al in South Africa [19], but only attributed to ART by 19% of patients with fatigue. On the other hand, pain, numbness, or tingling in the hands or feet was reported by 35% of patients, and about one third of the patients who reported this symptom attributed it to ART. This is comparable with findings from Thailand where 10% and 28% of probable and possible HIV-associated neuropathy was reported.[47] Peripheral neuropathies are expected to be more prevalent in settings where d4T is part of the first-line regimen.[48] Fortunately, the latest WHO recommendations call for the phasing out of d4T-containing regimens and their replacement by preferably tenofovir-containing regimens.[27] In this study, there was already clear evidence of this change with the proportion of d4T-containing regimens decreasing from 37% at baseline to 18% at the time of the interview, and tenofovir-containing regimens increasing from 11% (at baseline) to 26% (at the time of the interview).

About one third of the patients (30%) reported feeling sad, down, or depressed in the previous four weeks based on the HIV Symptom Index. While we cannot conclude that a patient is suffering from depression based on just one question, this number is surprisingly high and is consistent with the report of moderate to severe depression symptom severity among people living with HIV in sub-Saharan Africa. A systematic review, including 23 studies in sub-Saharan Africa, found prevalence estimates of 18% for major depression and 30% for depression symptoms among HIV-positive patients on ART.[49] In their analysis, patients who reported depression symptoms were 55% less likely to achieve good adherence compared to those not reporting depression symptoms. Similarly, in our univariate analysis, participants who reported feeling sad, down, or depressed were about 50% more likely to report incomplete adherence. This finding supports the screening for depression among patients with HIV.[49] However the region's health system capacity to detect and treat depression is limited.[50] Dietary protein supplementation has been suggested as a specific strategy to further reduce depression in patients on ART, in settings with food insecurity.[29]

Only one-third of participants reported ever missing ART, which may be low given that other studies have found up to 20% of participants missed taking their ART over just the past week alone.[51] It is well-established that self-report surveys tend to overestimate actual adherence.[52] However, this overestimate may also introduce a bias by not capturing the reasons for missed ART among both people willing to disclose, as well as among people unwilling to disclose incomplete adherence behaviors.

This study was conducted in 2011 before the WHO guidelines to replace d4T-containing regimens with tenofovir-containing regimens were introduced. [27] As such the factors related to missing ART may differ among patients on tenofovir-containing regimens.

We found some variability in the proportion of symptoms attributed to ART by patients: symptoms of peripheral neuropathy, troubles with remembering, nausea and vomiting, skin problems and problems with having sex were mostly attributed to ART. This could potentially lead to some bias with less adherent individuals more likely to report symptoms and attribute them to their ART. The cross-sectional design of the study limits the causal inference of whether it is incomplete adherence that leads to symptoms or whether it is the symptoms that are leading to incomplete adherence. Another limitation of the study is the difficulty in attributing symptoms to ART; some of these symptoms may also arise from the HIV infection itself, or arise from co- morbidities frequently associated with HIV infection (diabetes, hepatitis C infection).[53] We were also unable to assess whether ART clients who declined to participate differed from those participating in the study.

## Conclusions

Symptoms were a common reason for missing ART, together with simply forgetting and food insecurity. Women and participants taking ART regimens containing d4T at initiation experienced greater symptom burden. A combination of ART regimens with fewer side effects, use of mobile phone text messaging, and integration of food supplementation and livelihood programmes into HIV programmes, have the potential to decrease missed doses of ART and hence to improve adherence and the outcomes of ART programmes.

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### Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC, HRSA or any other federal agency or office.

## Author Contributions

Conceived and designed the experiments: OK JAD JM ST FWM GK MM AA SA YDM EVP KT SW JK AZ DRB RC. Analyzed the data: OK JAD JM ST. Wrote the paper: OK JAD JM ST FWM GK MM AA SA YDM EVP KT SW JK AZ DRB RC.

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