Patient-Reported Adverse Effects Associated with Combination Antiretroviral Therapy and Coadministered Enzyme-Inducing Antiepileptic Drugs

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Abstract. Concurrent treatment with combination antiretroviral therapy (cART) and an enzyme-inducing antiepileptic drug (EI-AED) is common in resource-limited settings; however, the incidence and impact of adverse effects in cotreated patients is largely unknown. Symptoms of adverse effects were assessed by both spontaneous report and checklist for 145 human immunodeficiency virus (HIV)-infected Zambian adults initiating various treatment combinations, such as cART with an EI-AED ($N = 20$), cART only ($N = 43$), or neither drug (untreated; $N = 82$). At study baseline, the cART + EI-AED group reported more headache, generalized fatigue, problems with concentration, and depression than the untreated group ($P < 0.01$ for all). At 2 weeks, a greater proportion of cART + EI-AED participants reported increased nausea or vomiting compared with baseline ($P < 0.05$). Adverse effects did not appear to impact self-reported adherence at 2 weeks as 100% cART adherence was reported in 19 of 20 (95%) and 42 of 43 (98%) cART + EI-AED and cART-only participants, respectively; 100% EI-AED adherence was reported in 19 of 20 (95%) participants. However, adherence at 6 months was suboptimal in both groups with 18 of 33 (56%) participants on cART experiencing greater than 1-week lapse in pharmacy-reported medication supply. Our results highlight the need to educate patients about the increased potential for nausea and vomiting with cART + EI-AED cotreatment. Although adherence was high early during treatment, adherence should be reinforced overtime to minimize the potential for HIV and/or epilepsy treatment failure.

INTRODUCTION

Side effects associated with combination antiretroviral therapy (cART) remain a common cause of suboptimal medication adherence and therapeutic failure among human immunodeficiency virus (HIV)-infected individuals.^{1–3} The World Health Organization (WHO) recommends a symptom-directed approach to manage cART toxicity⁴ and multiple instruments have been developed to assess self-report of adverse effects.^{5,6} Unfortunately, adverse effects are often underreported in routine clinical settings^{7,8} and are challenging to distinguish from HIV-related symptoms.⁹ Identifying adverse effects in routine clinical settings will become increasingly important as life expectancy in those with HIV infection continues to improve and more individuals require medication for comorbid conditions.¹⁰

The concurrent use of enzyme-inducing antiepileptic drugs (EI-AEDs) may alter the adverse effects reported by individuals taking cART due to induction of cytochrome P450 (CYP450) liver enzymes.^{11,12} This interaction may also manifest as decreased cART blood levels and increased HIV viral replication, leading to the development of drug resistance.^{13–15} In low-income settings where HIV is most prevalent, the EI-AEDs carbamazepine and phenobarbital are often the only antiseizure medications available.^{15–17} Antiepileptic drugs, particularly EI-AEDs, are commonly

associated with adverse effects that persist even after seizures are controlled.^{18–20}

The potential for co-usage of cART and EI-AEDs is considerable.^{13,16,17} Seizure disorders are relatively common in HIV-infected individuals, with new-onset seizures reported in greater than 10% of participants in several HIV cohorts.^{21,22} Antiepileptic drugs are prescribed to prevent recurrent seizures and are also used to treat other common comorbidities in HIV-infected persons, including peripheral neuropathy and psychiatric conditions like bipolar disorder.²³ Joint American Academy of Neurology/International League Against Epilepsy guidelines recommend pharmacokinetic monitoring of cART blood levels among patients also taking EI-AEDs to ensure HIV treatment efficacy as it is unclear whether dose adjustment is necessary when combining these medications.¹³ However, in resource-limited settings where concurrent cART and EI-AED use is most likely, pharmacokinetic monitoring, when available, is often cost prohibitive and dose adjustments may be limited by fixed-dose cART combination pills. In these patients, self-reported adverse effects may be the first indication of an interaction between these therapies. To date, there are limited data regarding patient-reported adverse effects in the setting of cART and EI-AED co-usage.

We examined patient-reported adverse effects among HIV-infected adults taking an EI-AED with cART as part of routine clinical care in Lusaka, Zambia. Since medication adherence is essential for effective HIV virologic suppression and may decline with greater pill burden, we also evaluated adherence to cART for those with and without concurrent EI-AED use and, in a subset of participants, examined HIV viral load (VL) response 6 months after cART initiation.

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MATERIALS AND METHODS

Participants were recruited between January 18, 2013 and February 13, 2014 from the Cohort of HIV-Associated Seizures and Epilepsy study and the University of Zambia's University Teaching Hospital Adult Infectious Disease Center of Excellence (AIDC) in Lusaka, Zambia. Patients with AIDC clinic file numbers ending in four randomly preselected numbers were assessed for eligibility. Eligibility criteria included nonpregnant patients greater than 18 years of age with documented HIV infection. A score of greater than 17/24 on the Zambian Mini-Mental Status examination, indicating mild or no cognitive impairment, was also required to ensure accurate self-report of symptoms.²⁴ Other medications commonly required in our study population include fluconazole to prevent recurrent cryptococcal meningitis or rifampin-based antituberculosis treatment (ATT). To mitigate the potential for overlapping adverse effects of these medications with EI-AEDs or cART, participants were eligible for study inclusion only if they had been taking fluconazole or ATT for greater than 1 month. Those prescribed trimethoprim/sulfamethoxazole (TMP/SMX) for prophylaxis were eligible if they were taking this medication for greater than 2 weeks.

To investigate the adverse effects associated with cART and EI-AED co-usage, eligible study participants were divided into three groups based on prescribed treatments. The first group included individuals initiating cotreatment with cART and an EI-AED (either carbamazepine or phenobarbital). This cART + EI-AED group included 1) individuals taking an EI-AED for a preexisting seizure disorder and initiating cART, 2) individuals taking cART who were initiating an EI-AED, and 3) individuals initiating both an EI-AED and cART simultaneously. The second group (cART-only) included individuals who had not experienced a seizure and were initiating cART for the first time. The third group included HIV-positive individuals with no seizure history who had not yet initiated cART (untreated). In all cases, participants were eligible to initiate cART per national treatment guidelines that include a CD4 count < 350 cells/mm³ and an EI-AED was prescribed if they had a history of untreated seizures.²⁵

A trained Zambian nurse obtained written, informed consent in English or a local language (Nyanja or Bemba). Participants in the untreated group were interviewed once, whereas participants in the cART + EI-AED and cART-only groups were interviewed before initiating treatment and again 2 weeks later to assess changes in patient-reported symptoms and medication adherence. A 2-week interval was selected as all patients starting medications at AIDC attend a routine 2-week follow-up appointment. A subset of study participants also participated in a 6-month interview to assess medication adherence and virologic suppression. At the end of each interview, participants were reimbursed 20 Kwacha (~4 USD) for the cost of transportation.

The University of Zambia's Biomedical Research Ethics Committee and Michigan State University's Biomedical Institutional Review Board provided ethical approval of this study prior to initiation. This study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2000.

Instruments. Study participant demographics, reported adverse effects, and simultaneous medication usage (other

than cART and EI-AEDs) were collected via a structured interview. WHO HIV staging⁴ and laboratory results were abstracted from medical records. For participants in the cART + EI-AED group already on cART for at least 6 months, VL determinations were performed to rule out baseline cART treatment failure (defined as VL greater than 1,000 copies/mL). VL assessment was also performed at 6 months for those initiating either cART only or cART with an EI-AED.

Symptoms and adverse effects were ascertained in two ways. First, participants were asked an open-ended question regarding any general medical or neurological problems they experienced in the past 2 weeks, similar to how adverse effects are assessed as part of routine clinical care. Second, participants were asked about the occurrence of 16 specific symptoms in the previous 2 weeks. These adverse effects were compiled from existing instruments designed to assess adverse events frequently reported for cART (non-nucleosidase reverse transcriptase inhibitors and protease inhibitors) and EI-AEDs.^{18,26–35} Responses were graded as mild, moderate, and severe using preestablished criteria based on limitations imposed and treatment sought by the participant.

To assess medication adherence, participants in the cART + EI-AED and cART-only groups were asked about problems taking their medications, the number of doses missed during the previous week, and to rank the number of pills they had taken on a visual analog scale. These measures have been used previously in this setting³⁶ and have been shown to be consistent with electronic and virologic measures.^{37,38} Adherence was assessed at 2-week follow-up by interview and was reported as the percent of doses taken as prescribed in the prior week. For the subset of individuals with available 6-month data, adherence data was obtained by clinic records for cART pharmacy pill collection and health-care provider records.

Statistical analysis. One-way analysis of variance (ANOVA) and χ^2 tests were used, as appropriate, to compare participant demographics and clinical characteristics between the treatment groups as well as the severity of symptoms across groups. Frequencies were obtained for symptoms that were spontaneously reported by participants, both at baseline and at follow-up, and for medication adherence. The 16 adverse effects assessed via checklist were analyzed independently using one-way ANOVA to compare the severity of symptoms across groups. For participants in the cART + EI-AED and cART-only groups, the change in symptom severity was assessed by comparing adverse effects reported at baseline and at follow-up using paired *t*-tests. All statistical analyses were performed in SAS (version 9.4; SAS Institute, Inc., Cary, NC). A *P* value < 0.05 was considered significant.

RESULTS

Demographic and clinical characteristics. A total of 145 participants were interviewed to assess patient-reported adverse effects (20 cART + EI-AED, 43 cART-only, 82 untreated). As shown in Table 1, participants in the cART + EI-AED group had a higher mean CD4 cell count (297 cells/mm³) than participants in the cART-only (158 cells/mm³) and untreated groups (212 cells/mm³ *P* = 0.028). Participants in

TABLE 1
Demographic and clinical characteristics of study participants

	cART + EI-AED (N = 20)	cART-only (N = 43)	Untreated (N = 82)	P value
Gender, female (%)	9 (45)	23 (53)	44 (54)	0.798
Age, mean (SD)	34.7 (9.4)	37.6 (8.6)	37.7 (9.8)	0.421
CD4 cell count (cells/mm ³), mean (SD)	297 (259)	158 (118)	212 (200)	0.028
CD4 count > 350 cells/mm ³ (%)	6 (30)	1 (2)	16 (20)	
ALT, mean (SD)	40.7 (60.8)	35.9 (53.6)	35.2 (37.7)	0.890
Missing	0	2	1	
WHO Stage (%)				0.107
I	6 (30)	15 (35)	22 (28)	
II	1 (5)	0 (0)	9 (12)	
III	5 (25)	20 (47)	29 (37)	
IV	8 (40)	8 (18)	18 (23)	
Missing	0	0	2	
cART regimen (%)				
First-line			—	
Efavirenz (600 mg daily) + NRTIs	16 (80)	40 (93)		
Nevirapine (200 mg twice daily) + NRTIs	2 (10)	1 (2)		
Second-line				
Lopinavir/ritonavir (400/100 mg twice daily) + NRTIs	2 (10)	2 (5)		
EI-AED treatment (%)		—	—	
Carbamazepine (200 mg twice daily)	19 (95)			
Phenobarbital (90 mg daily)	1 (5)			
Other coadministered medications (%)				
Trimethoprim/sulfamethoxazole	11 (55)	35 (81)	42 (51)	0.004
Antituberculosis treatment	6 (30)	12 (29)	23 (28)	0.985
Fluconazole	0 (0)	3 (7)	4 (5)	0.559
Baseline VL, n (%) (copies/mL) (N = 8)		—	—	
< 40	3 (38)			
41–999	4 (50)			
≥ 1,000	1 (6)			

ALT = alanine aminotransferase; cART = combination antiretroviral therapy; EI-AED = cytochrome P450 enzyme-inducing antiepileptic drug; mg = milligrams; NRTI = nucleoside reverse transcriptase inhibitor; SD = standard deviation; VL = viral load; WHO = World Health Organization.

the cART-only group (N = 35, 81%) were more likely to be taking TMP/SMX than participants in the cART + EI-AED (N = 11, 55%) or untreated group (N = 42, 51%; *P* = 0.004).

Of the 20 participants in the cART + EI-AED group, 10 participants were already taking cART and initiating an EI-AED, nine participants were prescribed an EI-AED and initiating cART, and one participant was starting both drugs simultaneously. Eight of the 10 participants on cART had baseline VL determinations as they were taking cART for at least 6 months. All participants initiating an EI-AED had experienced a seizure in the previous 24 hours. Of those in the cART + EI-AED group already on cART, the VL was < 1,000 copies/mL at baseline in all but one participant who had a VL of 1,733,025 copies/mL.

Adverse events at baseline. At baseline, 17 medical and neurological problems were elicited spontaneously from the 145 participants. Of those spontaneously reporting symptoms (N = 62; 43%), headache was the most common complaint (N = 41, 66%), followed by cough (N = 5, 8%) and localized pain (N = 5, 8%). For the baseline severity of 16 patient-reported adverse effects queried from all treatment groups, headache was the most commonly endorsed symptom by all participants (61/145, 42%), followed by irritability (36/145, 25%). Overall, participants in the cART + EI-AED group were more symptomatic at baseline than participants in the other treatment groups. A higher proportion of the cART + EI-AED group reported headache (odds ratio [OR] = 3.8; 95% confidence interval [CI] = 1.4–9.9; *P* = 0.007), generalized weakness (OR = 4.9; 95% CI = 1.8–13.5; *P* = 0.002), problems with concentration (OR = 5.1; 95% CI = 1.6–16.4; *P* = 0.006), and depression (OR: 4.7;

95% CI = 1.5–14.4; *P* = 0.008) than participants in the untreated group.

Adverse events and adherence at 2 weeks of follow-up.

All participants in the cART + EI-AED and cART-only groups completed a 2-week follow-up interview. A total of 25 (40%) participants reported symptoms at 2-week follow-up, with headache (N = 13, 21%, five cART + EI-AED, eight cART only) and localized pain (N = 5, 8%, two cART + EI-AED, three cART only) most common. Two participants in the cART + EI-AED group who had started carbamazepine 200 mg twice daily at their initial visit experienced generalized tonic-clonic seizures between visits.

A greater proportion of participants in the cART + EI-AED group reported experiencing nausea or vomiting at follow-up than at baseline (one person at initiation, six at follow-up; *P* = 0.049; Table 2). In addition, fewer participants in the cART + EI-AED group reported headaches at follow-up than at baseline (*P* = 0.007). However, a post hoc analysis comparing symptoms reported by the cART + EI-AED group based on order of medication initiation (on cART and initiating an EI-AED versus on an EI-AED and initiating cART) suggested our cohort's decreased severity of headaches might be due to the presence of postictal headache at medication initiation among cART + EI-AED participants. Among individuals on cART who were initiating an EI-AED at study enrollment, all had experienced a seizure in the 24 hours prior to the baseline interview. These individuals reported a decrease in headache severity at follow-up (*P* < 0.01). However, there was no change among individuals on an EI-AED who were initiating cART (*P* = 0.343). This post hoc sensitivity analysis also suggested a decrease in numbness and

TABLE 2
Adverse events reported by checklist at baseline and at follow-up

Symptom	Group	None	Mild	Moderate	Severe	P value
Rash	cART + EI-AED	18 (90)/19 (95)	2 (10)/1 (5)	0 (0)/0 (0)	0 (0)/0 (0)	1.0
	cART-only	38 (88)/38 (88)	5 (12)/4 (10)	0 (0)/0 (0)	0 (0)/0 (0)	0.743
	Untreated	73 (89)	7 (9)	2 (2)	0 (0)	—
Diarrhea	cART + EI-AED	17 (85)/18 (90)	3 (15)/2 (10)	0 (0)/0 (0)	0 (0)/0 (0)	0.577
	cART-only	36 (84)/36 (84)	6 (14)/2 (10)	1 (2)/1 (2)	0 (0)/0 (0)	1.0
	Untreated	67 (82)	13 (16)	2 (2)	0 (0)	—
Nausea or Vomiting	cART + EI-AED	19 (95)/14 (70)	1 (5)/4 (20)	0 (0)/2 (2)	0 (0)/0 (0)	0.049
	cART-only	39 (91)/36 (83)	4 (9)/5 (12)	0 (0)/2 (5)	0 (0)/0 (0)	0.133
	Untreated	67 (54)	14 (17)	1 (1)	0 (0)	—
Abdominal pain	cART + EI-AED	16 (80)/15 (75)	3 (15)/4 (20)	1 (5)/1 (5)	0 (0)/0 (0)	0.789
	cART-only	34 (79)/36 (84)	8 (19)/6 (14)	1 (2)/1 (2)	0 (0)/0 (0)	0.660
	Untreated	62 (76)	16 (19)	4 (5)	0 (0)	—
Dizziness	cART + EI-AED	14 (70)/11 (55)	5 (25)/8 (40)	1 (5)/0 (0)	0 (0)/1 (5)	0.505
	cART-only	33 (77)/30 (70)	9 (21)/12 (28)	1 (2)/1 (2)	0 (0)/0 (0)	0.522
	Untreated	65 (79)	14 (17)	3 (4)	0 (0)	—
Sleepiness	cART + EI-AED	14 (70)/15 (75)	5 (25)/4 (20)	1 (5)/1 (5)	0 (0)/0 (0)	0.815
	cART-only	35 (81)/40 (93)	7 (16)/3 (7)	1 (2)/0 (0)	0 (0)/0 (0)	0.057
	Untreated	63 (77)	14 (17)	5 (6)	0 (0)	—
Headache	cART + EI-AED	6 (30)/14 (70)	10 (50)/5 (25)	3 (15)/2 (10)	1 (5)/0 (0)	0.007
	cART-only	29 (67)/32 (74)	13 (30)/10 (23)	1 (2)/1 (2)	0 (0)/0 (0)	0.555
	Untreated	49 (60)	28 (34)	5 (6)	0 (0)	—
Ataxia	cART + EI-AED	15 (75)/16 (80)	3 (15)/2 (10)	1 (5)/1 (5)	1 (5)/1 (5)	0.789
	cART-only	41 (95)/40 (93)	2 (5)/3 (7)	0 (0)/0 (0)	0 (0)/0 (0)	0.660
	Untreated	70 (85)	11 (13)	1 (1)	0 (0)	—
Blurred vision	cART + EI-AED	19 (95)/18 (90)	1 (5)/2 (10)	0 (0)/0 (0)	0 (0)/0 (0)	0.577
	cART-only	42 (98)/41 (95)	1 (2)/2 (5)	0 (0)/0 (0)	0 (0)/0 (0)	0.569
	Untreated	77 (94)	5 (6)	0 (0)	0 (0)	—
Weakness in arms or legs	cART + EI-AED	13 (65)/12 (60)	5 (25)/6 (30)	1 (5)/2 (10)	1 (5)/0 (0)	1.0
	cART-only	34 (79)/39 (91)	8 (19)/4 (9)	1 (2)/0 (0)	0 (0)/0 (0)	0.083
	Untreated	64 (78)	18 (22)	0 (0)	0 (0)	—
Numbness Tingling	cART + EI-AED	15 (75)/19 (95)	5 (25)/1 (5)	1 (5)/0 (0)	0 (0)/0 (0)	0.104
	cART-only	34 (79)/39 (91)	8 (19)/4 (9)	1 (2)/0 (0)	0 (0)/0 (0)	0.660
	Untreated	66 (80)	12 (15)	4 (5)	0 (0)	—
Generalized fatigue	cART + EI-AED	9 (45)/16 (8)	10 (50)/0 (0)	0 (0)/4 (20)	1 (5)/0 (0)	0.204
	cART-only	36 (83)/37 (86)	5 (12)/6 (14)	2 (5)/0 (0)	0 (0)/0 (0)	0.323
	Untreated	67 (82)	13 (16)	2 (2)	0 (0)	—
Problems Thinking	cART + EI-AED	13 (65)/15 (75)	4 (20)/3 (15)	3 (15)/2 (10)	0 (0)/0 (0)	0.572
	cART-only	40 (93)/41 (95)	2 (5)/1 (2)	1 (2)/1 (2)	0 (0)/0 (0)	0.277
	Untreated	74 (90)	6 (7)	2 (2)	0 (0)	—
Memory Problems	cART + EI-AED	15 (75)/13 (65)	5 (25)/6 (30)	0 (0)/1 (5)	0 (0)/0 (0)	0.330
	cART-only	36 (84)/29 (91)	6 (14)/3 (7)	1 (2)/1 (2)	0 (0)/0 (0)	0.445
	Untreated	65 (79)	14 (17)	3 (4)	0 (0)	—
Irritability/ aggression	cART + EI-AED	13 (65)/13 (65)	3 (15)/5 (25)	4 (20)/2 (10)	0 (0)/0 (0)	0.649
	cART-only	35 (81)/36 (84)	8 (19)/7 (14)	0 (0)/0 (0)	0 (0)/0 (0)	0.710
	Untreated	61 (74)	18 (22)	3 (4)	0 (0)	—
Depression	cART + EI-AED	13 (65)/12 (60)	4 (20)/4 (20)	3 (15)/4 (20)	0 (0)/0 (0)	0.666
	cART-only	35 (81)/38 (88)	8 (19)/3 (7)	0 (0)/2 (5)	0 (0)/0 (0)	0.799
	Untreated	73 (89)	6 (7)	3 (4)	0 (0)	—

cART = combination antiretroviral therapy; EI-AED = cytochrome P450 enzyme-inducing antiepileptic drug. Data expressed as number endorsing symptom at initiation (%) / number endorsing symptom follow-up (%).

tingling in patients on cART who were initiating an EI-AED ($P = 0.015$) without a corresponding decrease among patients on an EI-AED who were initiating cART ($P = 0.343$). No other differences were noted in symptom reporting based on order of medication initiation in the cART + EI-AED group. No significant change in adverse effects was observed among individuals in the cART-only group.

For assessment of adherence in the week prior to interview, 19 of 20 (95%) of cART + EI-AED individuals and 42 of 43 (98%) cART-only persons reported 100% adherence to cART. One person in the cART + EI-AED group missed two doses of cART, whereas one person in the cART-only group missed one dose. EI-AED adherence was also high with 100% EI-AED adherence reported in 19 of 20 (95%) of participants in the week prior to interview. Only

one person forgot to take carbamazepine for 2 days, though the participant remembered to take all cART doses.

Findings at 6-month follow-up. Six-month follow-up data was available for 38 participants, including 15 and 23 in the cART + EI-AED and cART-only groups, respectively. Individuals with follow-up data did not differ significantly in gender, age, enrollment WHO stage, CD4 count, or liver function compared with those without 6-month data (all $P > 0.05$).

Of 33 participants with adherence data, 18 (56%) had a lapse in drug acquisition that would have resulted in greater than 1 week off cART. In addition, 24 participants (73%) missed a clinic visit by 1 week or more. There was no significant difference in pill collection or clinic attendance based on treatment group (both $P > 0.05$). All participants

in the cART + EI-AED group reported that they were still taking their EI-AED at 6 months. cART treatment failure with VL > 1,000 copies/mL was documented for 2/15 (13%) cART + EI-AED participants and 4/23 (17%) cART-only participants. Of those participants exhibiting treatment failure, four had a gap in drug coverage of at least 1 week.

DISCUSSION

There can be significant challenges in the treatment of HIV and a comorbid chronic condition secondary to drug interactions, overlapping adverse effects, and poor medication adherence. These challenges may be greatest in resource-limited settings where treatment options are limited and dose adjustments with the aid of pharmacokinetic monitoring is not feasible. Providers in countries like Zambia face this challenge when caring for patients with comorbid HIV infection and epilepsy, where first-line treatments for both conditions are associated with greater CYP450 interactions and adverse effects than first-line agents in settings without resource limitations.¹³ We sought to characterize patient-reported adverse effects after initiating treatment with cART and an EI-AED as there is currently limited data regarding patient experiences managing comorbid HIV and epilepsy in this setting. In addition, we reported 6-month VL responses in a subset of our population since a major concern of cotreatment with cART and an EI-AED is loss of virologic suppression leading to the development of drug-resistant HIV mutations.

The identification and interpretation of symptoms, including adverse effects, is unique to the individual and is mediated by social and cultural constructs.^{39–42} Participant-reported adverse effects can be influenced by how symptoms are queried⁴³ as well as the significance of symptoms to participants.⁴⁴ In addition, adverse effects may be underreported when participants are aware that treatment options are limited either by availability²⁰ or cost.⁴⁵ In this study, co-usage of cART and an EI-AED was associated with increased nausea and vomiting after 2 weeks on treatment. This suggests that adverse effects may be more severe among HIV-positive individuals taking medication for comorbid seizure disorders, as a similar change was not seen among individuals taking only cART.

In addition to experiencing increased nausea and vomiting, participants taking cART with an EI-AED were generally more symptomatic at baseline than those initiating cART with untreated HIV infection. Baseline ill health may have modified participant-reported severity of adverse effects in the cART + EI-AED group. For example, Allen and others found that South African participants involved in cART trials often underreported adverse effects as they compared their severity to illness experienced prior to initiating treatment.⁴⁴ As such, the impact of adverse effects secondary to cART and EI-AED co-usage may be underappreciated in our study due to the presence of baseline symptoms prior to treatment.

Although adverse effects for cART and EI-AEDs have been well reported in the literature, there is no uniform method for assessing and reporting these symptoms in clinical settings or for research purposes.^{46–48} Many studies examining cART-related adverse effects do not report the method by which they were assessed, and studies relying

on chart documentation of symptoms may underestimate adverse events.^{2,7,8} We evaluated patient symptoms and adverse effects by two methods in our current study: spontaneous patient report and symptom checklist. We observed that more participants reported adverse effects via the checklist method than when asked to report them spontaneously. This may be due to increased recognition of symptom significance with the checklist method, as shown previously.^{43,44} Additional studies evaluating the collection of symptoms and adverse effects are necessary to evaluate the best methods for collection in patients with HIV and other comorbidities requiring treatment.

Adverse effects have been repeatedly associated with decreased medication adherence.^{2,49,50} In our study, short-term medication adherence did not appear to be impacted by adverse effects with only three participants failing to take medications in the week prior to assessment. However, previous research in sub-Saharan Africa suggests that individuals taking cART and EI-AEDs continue to experience adverse effects long after initiating treatment which may impact long-term adherence.^{8,20} A subset of participants followed for 6 months had decreased medication adherence and often missed clinic visits, which raise concerns about the long-term efficacy and tolerability of HIV and epilepsy cotreatment in resource-limited settings.

There are multiple potential limitations to this study. The concurrent use of medications such as TMP/SMX, ATT, or fluconazole by some study participants may have affected reported adverse effects, though this was mitigated by the requirement for greater than 2–4 weeks of treatment with these agents prior to study entry. It was not feasible to exclude persons taking these medications due to their common use for disease prophylaxis and/or treatment. We were also unable to rule out the impact of immune reconstitution on patients' reported symptoms or compare across all possible treatment groups due to an insufficient number of HIV-positive individuals initiating only EI-AEDs in the study population. The impact of EI-AED co-usage on cART efficacy could not be ascertained and long-term adherence data was not available for many participants whose care was transferred to a local clinic after treatment stabilization. The inability to obtain VL studies in most participants limited the ability to analyze VL as a marker of ART adherence.

Ample opportunity exists for HIV and epilepsy to co-occur, especially in sub-Saharan Africa where the prevalence of both conditions is high.^{51,52} Treatment-related adverse effects have been shown to compound the disabling features of these conditions and adversely impact quality of life.^{53,54} As individuals with HIV infection continue to live longer and access to epilepsy treatment improves in low-income settings, co-usage of cART and EI-AEDs will increase the likelihood for adverse effects. Counseling patients about the potential for these side effects as well as managing them when they do occur may be key to sustained medication adherence among individuals with HIV infection and comorbid conditions such as epilepsy.

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REFERENCES

- Max B, Sherer R, 2000. Management of the adverse effects of antiretroviral therapy and medication adherence. *Clin Infect Dis* 30 (Suppl 2): S96–S116.
- Monforte A, Lepri A, Rezza G, Pezzotti P, Antinori A, Philips A, Angarano G, Colanelli V, de Luca A, Ippolito G, Caggese L, Soscia F, Feilice G, Gritti F, Narciso P, Tirelli U, Moroni M, 2000. Insights into the reason for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naive patients. *Aids Alert* 14: 499–507.
- Wasti SP, Simkhada P, Randall J, Freeman JV, van Teijlingen E, 2012. Factors influencing adherence to antiretroviral treatment in Nepal: a mixed-methods study. *PLoS One* 7: e35547.
- World Health Organization, 2013. *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection. A Public Health Approach*. Geneva, Switzerland: World Health Organization.
- Justice AC, Holmes W, Gifford AL, Rabeneck L, Zackin R, Sinclair G, Weissman S, Neidig J, Marcus C, Chesney M, Cohn SE, Wu AW, Adult ACTUOC, 2001. Development and validation of a self-completed HIV symptom index. *J Clin Epidemiol* 54 (Suppl 1): S77–S90.
- 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, Ad ISG, 2001. Self-reported symptoms and medication side effects influence adherence to highly active antiretroviral therapy in persons with HIV infection. *J Acquir Immune Defic Syndr* 28: 445–449.
- World Health Organization, 2013. *HIV/AIDS Programme: Surveillance of Antiretroviral Drug Toxicity within Antiretroviral Treatment Programmes*. Technical Brief: Surveillance of Antiretroviral Toxicity. Geneva, Switzerland: World Health Organization.
- Tapsfield J, Mathews T, Lungu M, Van Oosterhout JJ, 2011. Underreporting of side effects of standard first-line ART in the routine setting in Blantyre, Malawi. *Malawi Med J* 23: 115–117.
- Johnson MO, Stallworth T, Neillands TB, 2003. The drugs or the disease? Causal attributions of symptoms held by HIV-positive adults on HAART. *AIDS Behav* 7: 109–117.
- Nachega JB, Hsu AJ, Uthman OA, Spinewine A, Pham PA, 2012. Antiretroviral therapy adherence and drug-drug interactions in the aging HIV population. *AIDS* 26 (Suppl 1): S39–S53.
- Romanelli F, Ryan M, 2002. Seizures in HIV-seropositive individuals: epidemiology and treatment. *CNS Drugs* 16: 91–98.
- Ji P, Damle B, Xie J, Unger SE, Grasela DM, Kaul S, 2008. Pharmacokinetic interaction between efavirenz and carbamazepine after multiple-dose administration in healthy subjects. *J Clin Pharmacol* 48: 948–956.
- Birbeck GL, French JA, Perucca E, Simpson DM, Fraimow H, George JM, Okulicz JF, Clifford DB, Hachad H, Levy RH; Quality Standards Subcommittee of the American Academy of Neurology; Ad Hoc Task Force of the Commission on Therapeutic Strategies of the International League Against E, 2012. Evidence-based guideline: antiepileptic drug selection for people with HIV/AIDS: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Ad Hoc Task Force of the Commission on Therapeutic Strategies of the International League Against Epilepsy. *Neurology* 78: 139–145.
- Okulicz JF, Grandits GA, French JA, George JM, Simpson DM, Birbeck GL, Ganesan A, Weintrob AC, Crum-Cianflone N, Lalani T, Landrum ML; the Infectious Disease Clinical Research Program HIV Working Group, 2011. Virologic outcomes of HAART with concurrent use of cytochrome P450 enzyme-inducing antiepileptics: a retrospective case control study. *AIDS Res Ther* 8: 18.
- Okulicz JF, Grandits GA, French JA, Perucca E, George JM, Landrum ML, Acosta EP, Birbeck GL, 2013. The impact of enzyme-inducing antiepileptic drugs on antiretroviral drug levels: a case-control study. *Epilepsy Res* 103: 245–253.
- Birbeck G, Chomba E, Ddumba E, Kauye F, Mielke J, 2007. Lack of appropriate treatment for people with comorbid HIV/AIDS and epilepsy in sub-Saharan Africa. *Epilepsia* 48: 1424–1425.
- Wright E, Brew BJ, Lal L, Ali ST, Arayawichanont A, Imran D, Kamarulzaman A, Kongsangdao S, Kruiy L, Merati TP, Samantharapanya K, Sarim C, Tau G, Thangsing C, Vin-Samnan C, Wesselingh SL, 2008. Response to Birbeck et al. *Epilepsia* 49: 541–543.
- Carpay JA, Aldenkamp AP, van Donselaar CA, 2005. Complaints associated with the use of antiepileptic drugs: results from a community-based study. *Seizure* 14: 198–206.
- Perucca P, Gilliam FG, 2012. Adverse effects of antiepileptic drugs. *Lancet Neurol* 11: 792–802.
- Elafros MA, Bui E, Birbeck GL, 2014. Medication side effects among people with epilepsy taking phenobarbital in Zambia. *Epilepsy Res* 108: 1680–1684.
- Kellinghaus C, Engbring C, Kovac S, Moddel G, Boesebeck F, Fischera M, Anneken K, Klonne K, Reichelt D, Evers S, Husstedt IW, 2008. Frequency of seizures and epilepsy in neurological HIV-infected patients. *Seizure* 17: 27–33.
- Wong MC, Suite ND, Labar DR, 1990. Seizures in human immunodeficiency virus infection. *Arch Neurol* 47: 640–642.
- Kaufman KR, 2011. Antiepileptic drugs in the treatment of psychiatric disorders. *Epilepsy Behav* 21: 1–11.
- Kvalsund MP, Haworth A, Murman DL, Velie E, Birbeck GL, 2009. Closing gaps in antiretroviral therapy access: human immunodeficiency virus-associated dementia screening instruments for non-physician healthcare workers. *Am J Trop Med Hyg* 80: 1054–1059.
- Ministry of Health, Zambia, 2007. *National Guidelines: Management of HIV Infected People*. Lusaka, Zambia: Ministry of Health.
- Wu AW, Rubin HR, Mathews WC, Ware JE Jr, Brysk LT, Hardy WD, Bozzette SA, Spector SA, Richman DD, 1991. A health status questionnaire using 30 items from the Medical Outcomes Study. Preliminary validation in persons with early HIV infection. *Med Care* 29: 786–798.
- Fellay J, Boubaker K, Ledergerber B, Bernasconi E, Furrer H, Battegay M, Hirschel B, Vernazza P, Francioli P, Greub G, Flepp M, Telenti A; Swiss HIV Cohort Study, 2001. Prevalence of adverse events associated with potent antiretroviral treatment: Swiss HIV Cohort Study. *Lancet* 358: 1322–1327.

28. Cleary PD, Fowler FJ Jr, Weissman J, Massagli MP, Wilson I, Seage GR 3rd, Gatsonis C, Epstein A, 1993. Health-related quality of life in persons with acquired immune deficiency syndrome. *Med Care* 31: 569–580.
29. Whalen CC, Antani M, Carey J, Landefeld CS, 1994. An index of symptoms for infection with human immunodeficiency virus: reliability and validity. *J Clin Epidemiol* 47: 537–546.
30. Ware JE Jr, Sherbourne CD, 1992. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 30: 473–483.
31. Holzemer WL, Hudson A, Kirksey KM, Hamilton MJ, Bakken S, 2001. The revised Sign and Symptom Check-List for HIV (SSC-HIVrev). *J Assoc Nurses AIDS Care* 12: 60–70.
32. Baker G, Jacoby A, Francis P, Chadwick D, 1994. Initial development, reliability, and validity of a patient-based adverse drug event scale. *Epilepsia* 35: 20.
33. Salinsky MC, Storzach D, 2005. The Portland Neurotoxicity Scale: validation of a brief self-report measure of antiepileptic-drug-related neurotoxicity. *Assessment* 12: 107–117.
34. Aldenkamp AP, Baker G, Pieters MS, Schoemaker HC, Cohen AF, Schwabe S, 1995. The Neurotoxicity Scale: the validity of a patient-based scale, assessing neurotoxicity. *Epilepsy Res* 20: 229–239.
35. Uijl SG, Uiterwaal CS, Aldenkamp AP, Carpay JA, Doelman JC, Keizer K, Vecht CJ, de Krom MC, van Donselaar CA, 2006. A cross-sectional study of subjective complaints in patients with epilepsy who seem to be well-controlled with antiepileptic drugs. *Seizure* 15: 242–248.
36. Birbeck G, Kvalsund M, Byers P, Bradbury R, Mang'ombe C, Organek N, Kaile T, Sinyama A, Sinyangwe S, Malama K, Malama C, 2011. Neuropsychiatric and socioeconomic status impact antiretroviral adherence and mortality in rural Zambia. *Am J Trop Med Hyg* 85: 782–789.
37. Oyugi JH, Byakika-Tusiime J, Charlebois ED, Kityo C, Mugerwa R, Mugenyi P, Bangsberg DR, 2004. Multiple validated measures of adherence indicate high levels of adherence to generic HIV antiretroviral therapy in a resource-limited setting. *J Acquir Immune Defic Syndr* 36: 1100–1102.
38. Walsh JC, Mandalia S, Gazzard BG, 2002. Responses to a 1 month self-report on adherence to antiretroviral therapy are consistent with electronic data and virological treatment outcome. *AIDS* 16: 269–277.
39. Etkin NL, 1992. Side effects: cultural constructions and reinterpretations of western pharmaceuticals. *Med Anthropol Q* 6: 99–113.
40. Juarez G, Ferrell B, Borneman T, 1998. Influence of culture on cancer pain management in Hispanic patients. *Cancer Pract* 6: 262–269.
41. Stewart SM, Lewinsohn PM, Lee PWH, Ho LM, Kennard B, Hughes CW, Emslie GJ, 2002. Symptom patterns in depression and “subthreshold” depression among adolescents in Hong Kong and the United States. *J Cross Cult Psychol* 33: 559–576.
42. Marsella AJ, Kinzie D, Gordon P, 1973. Ethnic variations in the expression of depression. *J Cross Cult Psychol* 4: 435–458.
43. Carreno M, Gil-Nagel A, Sanchez JC, Elices E, Serratosa JM, Salas-Puig J, Villanueva V, Porcel J, 2008. Strategies to detect adverse effects of antiepileptic drugs in clinical practice. *Epilepsy Behav* 13: 178–183.
44. Allen EN, Mushi AK, Massawe IS, Vestergaard LS, Lemnge M, Staedke SG, Meththa U, Barnes KI, Chandler CI, 2013. How experiences become data: the process of eliciting adverse event, medical history and concomitant medication reports in antimalarial and antiretroviral interaction trials. *BMC Med Res Methodol* 13: 1–13.
45. Kamat VR, 2009. Cultural interpretations of the efficacy and side effects of antimalarials in Tanzania. *Anthropol Med* 16: 293–305.
46. Kanters S, Mills EJ, Thorlund K, Bucher HC, Ioannidis JP, 2014. Antiretroviral therapy for initial human immunodeficiency virus/AIDS treatment: critical appraisal of the evidence from over 100 randomized trials and 400 systematic reviews and meta-analyses. *Clin Microbiol Infect* 20: 114–122.
47. Gaitatzis A, Sander JW, 2013. The long-term safety of antiepileptic drugs. *CNS Drugs* 27: 435–455.
48. World Health Organization, 2010. *Antiretroviral Therapy for HIV Infection in Infants and Children: Towards Universal Access: Recommendations for a Public Health Approach*, 2010 revision. Geneva, Switzerland: World Health Organization.
49. Catz SL, Kelly JA, Bogart LM, Benotsch EG, McAuliffe TL, 2000. Patterns, correlates, and barriers to medication adherence among persons prescribed new treatments for HIV disease. *Health Psychol* 19: 124–133.
50. Chung S, Wang N, Hank N, 2007. Comparative retention rates and long-term tolerability of new antiepileptic drugs. *Seizure* 16: 296–304.
51. Ortblad KF, Lozano R, Murray CJ, 2013. The burden of HIV: insights from the Global Burden of Disease Study 2010. *AIDS* 27: 2003–2017.
52. Newton CR, Garcia HH, 2012. Epilepsy in poor regions of the world. *Lancet* 380: 1193–1201.
53. Cramer JA, Brandenburg NA, Xu X, Vera-Llonch M, Oster G, 2007. The impact of seizures and adverse effects on global health ratings. *Epilepsy Behav* 11: 179–184.
54. Devinsky O, Westbrook L, Cramer J, Glassman M, Perrine K, Camfield C, 1999. Risk factors for poor health-related quality of life in adolescents with epilepsy. *Epilepsia* 40: 1715–1720.