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Global Impact of Antiretroviral Therapy-Associated Diarrhea

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Dear Editor,

Side effects of antiretroviral therapy (ART) still remain a formidable issue for patients globally. In resource-limited settings, side effects are a major risk for lack of treatment adherence.[1] Diarrhea remains one of the leading side effects seen in ART, and it contributes significantly to lack of treatment adherence in patients experiencing it.[2] Historically, diarrhea in HIV-positive patients was due to opportunistic infections or HIV itself.[3] However, since the advent of highly active antiretroviral therapy (HAART), diarrhea is now thought to be primarily due to antiretrovirals.[4] It is noted that among the major classes of antiretrovirals, protease inhibitors (and in particular ritonavir) seem to carry the greatest risk of for ART-induced diarrhea.[5] Two recent reviews highlight the importance of ART-associated diarrhea in HIV-infected patients, and focus on data regarding ritonavir-associated diarrhea. Macarthur and DuPont[6] found that up to 18% (range, 2–18%) of patients on ritonavir-boosted protease inhibitor regimens experience grade 2–4 diarrhea (grade 1 = mild; grade 2 = moderate; grade 3 = severe; grade 4 = life threatening). Wegzyn et al.[7] reported a diarrhea incidence of 15.5% in patients taking ritonavir-boosted lopinavir as part of their ART. These results mimic a previous review that demonstrated up to 19% (range, 2–19%) of patients experience diarrhea on similar regimens.[2] Given that none of the current recommended therapies for first-line treatment of ART-naïve patients by the World Health Organization (WHO) include protease inhibitors or ritonavir-boosted regimens, the global impact of ART-associated diarrhea remains unclear. We conducted a review of published manuscripts in PubMed to assess the rate of diarrhea associated with the six WHO-recommended HIV regimens for ART-naïve patients.

A literature search on August 1, 2012 produced 235 article titles. Search strategies used in PubMed were as follows: ("azt" or "azidothymidine" or "ZDV" or "zidovudine") and ("3TC" or "lamivudine") and ("EFV" or "efavirenz") and ("adverse events" or "side effects" or "diarrhea"); ("azt" or "azidothymidine" or "ZDV" or "zidovudine") and ("3TC" or "lamivudine") and ("NVP" or "nevirapine") and ("adverse events" or "side effects" or "diarrhea"); ("TDF" or "tenofovir") and ("3TC" or "lamivudine") and ("EFV" or "efavirenz") and ("adverse events" or "side effects" or "diarrhea"); ("TDF" or "tenofovir") and ("FTC" or "emtricitabine") and ("EFV" or "efavirenz") and ("adverse events" or "side effects" or "diarrhea"); ("TDF" or "tenofovir") and ("FTC" or "emtricitabine") and ("NVP" or "nevirapine") and ("adverse events" or "side effects" or "diarrhea"); ("TDF" or "tenofovir") and ("3TC" or "lamivudine") and ("NVP" or "nevirapine") and ("adverse events" or "side effects" or "diarrhea"). An initial screen for English and relevance of titles resulted in 133 abstracts, for which articles were retrieved and assessed for inclusion and exclusion criteria. This resulted in 13 unique articles to be included in our study. Manuscripts were excluded for the following reasons: diarrhea-specific data not provided (71), data provided as an aggregate of several treatment regimens (23), selected treatment regimens were not assessed (10), treatment regimen included additional ART drugs (5), duplicate data/article (4), time extension of previous study (4), fewer than 10 patients (1), regimen altered because of policy change (1), and article not retrievable (1). Comparative and noncomparative trials were included in the review, as were prospective and retrospective studies. All diarrheal definitions were considered. Diarrhea was assessed by physician or self-reported by patients. Authors were not contacted for additional data.

Up to 38% of subjects (range, 0–38%, weighted mean 11%, $n = 3649$) receiving one of the six WHO regimens experienced diarrhea. Regimen-specific data are as follows: zidovudine (AZT) + lamivudine (3TC) + efavirenz (EFV) (range, 4–18%, weighted mean 8%, $n = 1627$), AZT + 3TC + nevirapine (NVP) (range, 0–38%, weighted mean 7%, $n = 146$), tenofovir (TDF) + emtricitabine (FTC) + EFV (range 3–33%, weighted mean 12%, $n = 1466$), TDF + 3TC + EFV (range, 5–11%, weighted mean 6%, $n = 410$), TDF + 3TC + NVP (no data available), TDF + FTC + NVP (no data available; Table 1). When reported, study duration varied from 12 to 168 weeks. Only one study[8] was conducted in a pediatric population with the remainder conducted in adults. One study[9] was a post-exposure prophylaxis study while the others were treatment studies. The majority of study sites were in resource-wealthy settings. Six articles reported grade 1–4 diarrhea or mild to severe diarrhea (no life-threatening diarrhea emerged in the study), 4 articles reported grade 2–4 diarrhea or moderate to severe diarrhea (no life-threatening diarrhea emerged in the study), and 3 articles did not indicate what grade of diarrhea was reported.

The range of ART-associated diarrhea among the four WHO-recommended first-line regimens for which data were

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Table 1. Diarrhea Associated with WHO-Recommended HIV Regimens for ART-Naive Patients

Regimen	*Source (author, year, journal)*			*Setting*	*Study duration (in weeks)*	*Diarrhea grade reported*	N	*Number of patients with diarrhea*	*Percentage of patients with diarrhea*
AZT 3TC EFV	Tukei	2012	*J Acquir Immune Defic Syndr*	Uganda	Varied	Not reported	162	10	6%
	Currier	2008	*Antivir Ther*	Canada, European Union, USA	12	Grade 2–4	29	2	7%
	Tashima	2008	*AIDS*	Europe, North America	168	Grade 2–4	312	14	4%
	Castillo	2006	*Drug Saf*	Africa, Europe, North America, South America	≥48	Grade 1–4	325	58	18%
	Gallant	2006	*N Engl J Med*	France, Germany, Italy, Spain, United Kingdom, USA	48	Grade 2–4	254	10	4%
	DeJesus	2004	*Clin Infec Dis*	Argentina, Brazil, Canada, USA	48	Grade 1–4	272	26	10%
	DeJesus	2004	*Clin Infec Dis*	Argentina, Brazil, Canada, USA	48	Grade 1–4	273	18	7%
Total							**1627**	**138**	**8%**
AZT 3TC NVP	Tukei	2012	*J Acquir Immune Defic Syndr*	Uganda	Varied	Not reported	58	4	7%
	Podzamczer	2002	*Antivir Ther*	Argentina, Spain	52	Grade 1–4	72	0	0%
	Bernasconi	2001	*Swiss Med Weekly*	Switzerland	Not reported	Not reported	16	6	38%
Total							**146**	**10**	**7%**
TDF FTC EFV	Sax	2012	*Lancet*	North America	48	Mild, moderate, severe	352	66	19%
	Lennox	2009	*Lancet*	Australia, Brazil, Canada, Chile, Colombia, France, Germany, India, Italy, Mexico, Peru, Spain, Thailand, USA	48	Moderate to severe	282	8	3%
	DeJesus	2009	*J Acquir Immune Defic Syndr*	Puerto Rico, USA	48	Grade 1–4	203	16	8%
	DeJesus	2008	*HIV Clin Trials*	USA	24	Not reported	372	123	33%
	Gallant	2006	*N Engl J Med*	France, Germany, Italy, Spain, United Kingdom, USA	48	Grade 2–4	257	17	7%
Total							**1466**	**230**	**16%**
TDF 3TC EFV	DeJesus	2008	*HIV Clin Trials*	USA	24	Not reported	372	19	5%
	Markowitz	2007	*J Acquir Immune Defic Syndr*	Australia, Canada, Latin America, Thailand, USA	48	Mild, moderate, severe	38	4	11%
Total							**410**	**23**	**6%**
TDF 3TC NVP	N/A		N/A				N/A	N/A	
TDF FTC NVP	N/A		N/A				N/A	N/A	
Total weighted mean							**3649**	**401**	**11%**

available appears to exceed that seen in head-to-head ritonavir comparison trials. Furthermore, our data and previous reviews have likely underestimated the true incidence of ART-associated diarrhea due to reliance on clinical trial data. Community-based studies have reported an incidence of diarrhea of 25.5% and have demonstrated discordance between provider versus patient reporting of diarrhea.[10,11] The lack of data available from resource-limited settings is noteworthy, particularly given the greater reliance on these regimens in resource-limited settings. In the four trials that were excluded due to reporting of time-extended cohorts, incidence of diarrhea did not increase beyond the 48-week initial cohort assessment. Thus, it is likely that ART-associated diarrhea appears in the first year of treatment. However, it is unknown if the onset, duration, or severity of diarrhea is evenly distributed during this period or if these characteristics demonstrate other patterns of distribution. One main limitation of this review is the lack of reporting of the definition of diarrhea. It is known that lack of consistency of reporting of gastrointestinal symptoms hinders such clinical trial data.[2]

Gastrointestinal symptoms are one of the most frequent recorded side effects of ART. Elderly patients and patients taking protease inhibitors are at greater risk for diarrhea, which, in turn, is associated with loss of work productivity, worse quality of life, and increased use of health care resources.[10,12] Recent data from preexposure prophylaxis (PrEP) trials show up to 12.5% of subjects experience diarrhea.[13] Furthermore, ART-associated diarrhea may complicate concomitant treatment for multidrug-resistant tuberculosis (MDR-TB), given the high incidence of diarrhea associated with MDR-TB.[14] Our assessment indicates diarrhea is equally prevalent among ritonavir- and nonritonavir-based regimens, and has particular relevance for countries implementing WHO recommendations for ART. There are now over 7 million people worldwide on ART with a goal of having 15 million people on ART by 2015. Nonadherence is often a result of side effects of ART and diarrhea is one of the leading adverse events causing discontinuation of ART. This has significant implications for treatment efficacy and drug resistance. As the world scales up ART access to include more people through earlier treatment of HIV-positive patients and through preventative treatment of non-HIV positive patients, ART-induced diarrhea will likely need to be addressed to help ensure successful treatment outcomes.

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Author Disclosure Statement

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